Cystic Neoplasms of the Pancreas

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OBJECTIVES:

- ***Recognize the diagnostic criteria of common cystic pancreatic neoplasms.***
- ***Understand the clinical behavior of these lesions***
- ***Develop recommendations to be provided to the surgeons***

PANCREATIC SEROUS CYSTADENOMA

Definition, Epidemiology and Etiology:

Serous cystic neoplasms of the pancreas are benign lesions composed of various numbers of cystic structures uniformly lined by glycogen-rich cuboidal epithelium.[7]
Well characterized for the first time in the seminal paper of Compagno & Oertel published in 1978,[4] serous cystic neoplasms are estimated to account for about 25% of all pancreatic cystic tumors.[20, 21]

Serous cystic neoplasms essentially occur only in adult patients, with a marked female predominance representing up to 70% of the cases. The age of the patients range, depending on the series, from 18 to 91 years old, with a median age in the seventh decade.[14, 17]

The etiology and pathogenesis of serous cystadenoma remains unknown. An association with Von Hippel-Lindau has been reported, and genetic molecular studies have confirmed that the chromosomal alterations (deletion and mutation) seen in Von Hippel-Lindau (located on 3p25) are been found in the majority of microcystic serous adenomas.[4, 19]

Clinical features:

Generally, a third of the patients are asymptomatic, and the neoplasms are incidental findings at routine physical examination, on imaging studies, or

autopsy.[6] (Egawa 1994, Dyke 1992) However, the majority of patients present with nonspecific symptoms related to local mass effects. The usual complaints include abdominal or epigastric pain, dyspepsia, nausea, and weight loss.[15] Less common presentations include jaundice due to obstruction, portal hypertension secondary to splenic vein occlusion, recurrent pancreatitis, acute gastrointestinal hemorrhage due to ulceration of the duodenum by the tumor, or hemoperitoneum due to erosion of tumor into neighboring vessels.[7]

Gross pathology:

Serous pancreatic neoplasm usually occurs as single tumors, and most frequently in the body or tail of the gland.[2, 4]

They are well-circumscribed, bosselated, round lesions. They vary in size, ranging from 1 to 30 cm, with a mean between 6 and 11 cm.[1, 2, 4, 8, 15, 16] Few reports of multiple separate synchronous tumors, as well as confluent tumors involving the entire pancreas, can be found in the literature.[4, 9, 10, 18]

The cut surface of serous cystadenomas is variable, depending on the tumor subtype. The macrocystic subtype (or serous oligocystic adenoma) appear to be composed of a few relatively large cystic structures[3, 11] whose cysts are relatively large in size, sometimes up to several centimeters. The cysts usually display a thin watery-colored fluid with rare examples of frankly bloody or hemosiderin-laden fluid.

The central aspect of the serous cystadenoma is usually composed of a large stellate area of fibrosis (central scar), sometimes with microcalcifications that represent the counterpart of the "sunburst" pattern identified on imaging studies.[1, 2, 4]

The interface formed between the tumor and the surrounding pancreatic parenchyma is a pushing interface, with a few cases demonstrating a thick fibrous capsule or only a thin fibrous rim.[11, 12]

Histopathology:

The low-power examination demonstrates a sponge-like or honeycomb-like appearance. The cysts are lined by an inconspicuous single layer of either cuboidal or flattened cells. The cytoplasm of the cells is either clear or eosinophilic, and the nuclei are usually centrally located, small, and hyperchromatic. PAS stain demonstrates the presence of abundant intracytoplasmic glycogen. At times, rare short intracystic papillary structures

lined by the typical cellular elements are present.[5] Mitoses are conspicuously absent.[5]

The surrounding stroma is uniformly dense and fibrous with areas of hyalinization. Dystrophic calcifications also can be present, as well as cholesterol clefts and hemosiderin-laden macrophages. Islets of Langerhans, scattered pancreatic acini, and nerves may also be seen.

Immunohistochemical studies are essentially of no value, with the epithelioid lining positive for CK7, 18, and 19, as well as focally for CA19.9, but characteristically negative for CEA.[5]

Variants of Pancreatic Serous Cystadenoma

Serous oligocystic adenoma is much less common than the microcystic variant.[6, 11] Notably, there is no sex predilection. The tumor has been seen in pediatric populations.[17] Most serous oligocystic adenomas are located in the head and the body of the pancreas, where they can obstruct the periampullary portion of the common bile duct.[17]

A noncystic variant, *"solid" serous adenoma*, has been recognized.[13] The solid variant is believed to be small, ranging between 2 and 4 cm in greatest dimension. Differential diagnosis, because of the compact arrangements of small acini with a limited or no lumen and clear cytoplasm, include "sugar" tumor of the pancreas and metastatic renal cell carcinoma, as well as pancreatic endocrine tumors with clear cell.

Serous cystadenocarcinoma

Rare examples of malignant cystic neoplasm composed of glycogen-rich cells have been reported. Those patients presented with symptoms ranging from bleeding of gastric varices to invasion of the stomach and splenic vein, jaundice, and palpable abdominal masses.

The size of these tumors varies between 2.5 and 12 cm. On gross section, the neoplasms maintain a spongy appearance.

The histologic appearance is deceptively benign, with a marked resemblance to the benign counterpart, although mild focal nuclear pleomorphism can be found. Perineural invasion, vascular and perivascular invasion, and lymph node metastasis have been reported. Those lesions are slow-growing and compatible with prolonged survival.

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INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM

Definition, Epidemiology and Etiology:

Intraductal papillary mucin-producing neoplasms (IPMNs) are composed of papillary proliferations of neoplastic mucin secretory cells that arise in the main pancreatic duct or its major branches.[16]

IPMNs are usually diagnosed in adults with a median age at diagnosis in the sixth to seventh decade and a mean age of 68 years.[2, 15, 25, 34] The actual incidence of IPMN is not precisely known. The recent increase in diagnosis has paralleled the wider use of sophisticated imaging modalities. It is likely that many lesions diagnosed currently may have been undiagnosed in the past. IPMNs have been estimated to amount to about 1 to 3% of exocrine pancreatic neoplasms, with an incidence rate of less than 1 per 100,000.[23]

Clinical features:

The clinical presentation is varied, including epigastric pain, pancreatitis, weight loss, diabetes, and jaundice. However, many small and asymptomatic cases are found during CT scans done for other reasons.[17, 32, 36] Another feature usually diagnostic of this lesion is the abundant mucin extrusion from the ampulla of Vater, although it is not always recognized. A patulous ampullary opening was reported in 55% of the patients in one series.[8, 35]

In practice, endoscopic ultrasound, ERCP, and CT scan, sometimes associated with cytologic examination and examination of fluid biochemical content, frequently lead to a preoperative diagnosis.[10, 33]

Gross Pathology:

Most IPMNs arise in the main pancreatic duct and its branches in the head of the pancreas.[7, 13, 29] It may be unifocal or diffusely involve the duct or multifocal.[19, 27, 32] Multicentricity has been suspected because of recurrence in pancreatic remnants following surgical removal of IPMN.[18]

The reported size of IPMN varies from about 1 cm to over 10 cm. However, the dimension is difficult to evaluate, given that the measurements also may include secondary cystic distension of ducts that are not involved by the tumor per se.[1]

The distended duct(s) is/are filled by a usually sticky or viscous pale yellowish material which may be difficult to remove. The mucosal lining may appear smooth and glistening or granular and reflecting papillary growth. In some cases (up to 35%, according to some), a small focus of adenocarcinoma may be identified.[8, 11, 14, 18, 24, 26, 34]

Histopathology:

The distended ductal structures are lined by papillary epithelium that may be divided into three categories based on the degree of atypia: Benign (adenoma), borderline, and malignant (either invasive or noninvasive).[16] In addition, emphasis has been placed recently on the recognition of two different types of mucinous epithelium.

The first, gastric/foveolar, usually shows low grade dysplasia (adenoma). The intestinal type resembles the colonic epithelium of villous adenomas[2] although in fact it usually is combined with epithelium also resembling gastric foveolar. It may show typical goblet cells and display moderate to high grade dysplasia.[16] The third histologic type is the pancreaticobiliary type. It is characterized by a

higher degree of architectural complexity and composed of small cuboidal cells with higher nuclear atypia.[16]

Goblet and Paneth cells may be present as a manifestation of intestinal metaplasia. Neuroendocrine cells also can be noted.[16] An oncocytic variant, IPMN, also has been described.[22, 30] This variant is rare and presents grossly with an appearance similar to typical IPMN. The lining epithelium is composed of stratified oncocytic cells with pale pink cytoplasm granules and sometimes scattered goblet cells. A characteristic feature of oncocytic IPMN is the formation of intraepithelial lumina. The clinical history appears similar to typical IPMNs.

Grading of IPMN: IPMNs should be graded in three groups: *adenoma, borderline,* or *carcinoma invasive or noninvasive*. In adenoma, the epithelium shows simple mucin-secreting cells with low N/C ratio, minimal cytologic atypia, and no or limited stratification. *Borderline lesions* are characterized by increased nuclear atypia, stratification of nuclei, and hyperchromicity. *IPMN with carcinoma in situ* demonstrates a significant nuclear atypia with prominent nucleoli, loss of mucin, and loss of nuclear polarity. Intraepithelial, micropapillary, and cribiform architecture also can be seen.

About 35% of IPMNs are associated with invasive adenocarcinoma.[28] The invasive neoplasm can be a typical ductal adenocarcinoma, although recent evidence suggests that a significant number of those cancers are colloid-type carcinomas, which have been associated with a better prognosis.[3, 4]

Immunohistochemical characteristics:

Much interest has been taken recently in the evaluation of mucin expression as evidence of differentiation and as a marker of progression.[5, 20] The intestinal type is associated with MUC2 expression and not MUC1 (92% and 8% respectively), while the pancreaticobiliary type (seen only in a minority of cases) shows a lesser degree of MUC2 expression (19%) but often shows MUC1 immunolabeling (44%) The gastric type is positive for MUC5AC.[5, 20] Interestingly, in the same series, a significant number of the cases were "null" for MUC1 and MUC2. The significance of these findings remains to be elucidated with regard to prognostication of patients.

Genetic susceptibility:

Some have reported excessive rates of colonic and gastric epithelial neoplasm in patients with IPMN, although no specific hereditary syndrome has been identified initially.[9] However, two cases of IPMNs have been reported, in two males with well documented histories of FAP. In one of the patients, genetic

analysis demonstrated loss of the wild allele of the APC gene in IPMT with inactivation of both alleles, thus suggesting that IPMT may represent an extracolonic localization of FAP.[12, 21]

Prognosis:

The overall five-year survival rate is good compared to other pancreatic neoplasm (60 to 83% at five years).[9, 34]

The prognosis is excellent for adenoma and borderline tumor with a five-year survival approaching 100%, provided that appropriate sampling has eliminated concurrent adenocarcinoma.

The survival is high for IPMN with noninvasive carcinoma, and some series have suggested that even for patients with invasive IPMN, the prognosis may be higher compared to typical ductal adenocarcinoma.[8, 34, 36] Colloid carcinoma, a variant which may be more frequently associated with IPMN, is also associated with a better prognosis.[3, 4, 6]

Side branch intraductal papillary mucin-producing neoplasms

Smaller cystic pancreatic lesions are now detected and some of them correspond to IPMNs that involve pancreatic side branches but spare the main pancreatic duct. Side branch IPMN is a controversial area with regard to its origin and prognosis. It has been reported by some that the prognosis is better with a lesser chance of malignant transformation.[31] According to one series, IPMN of the branch type corresponds to 30% of the cases. Patients with side branch IPMN were younger and the lesion were frequently located in the head and neck of the pancreas. The size of the cysts can range from 4 to 55 mm, and the major duct showed a mild dilation in most cases. Side branch IPMN were classified as adenoma (39%), borderline (46%) and in situ carcinoma (15%). No invasive carcinoma was observed. In contrast, main pancreatic duct type IPMNs showed invasive carcinoma and in situ carcinoma in 37% of the cases, thus suggesting that side branch IPMN may represent a distinctive group.[31] However, in some cases, distinguishing between side branch IPMN and distended PanIN can be difficult.

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Nomenclature and Criteria for Classification of Subtypes of IPMN

Type	Criteria	Atypia	MUC1	MUC2	MUC5AC
Gastric	Finger-like papillae, clear/eosinophilic cytoplasm, basally located nuclei.	+	-	-	+
Intestinal	Villous papillae, basophilic cytoplasm, cigar-like pseudostratified hyperchromatic nuclei.	++ to +++	-	+	+
Pancreaticobiliary	Thin branching complex papillae, moderate amphophilic cytoplasm,	++ to	+	-	+

	enlarged hyperchromatic nuclei.	+++			
Oncocytic	Thick branching complex papillae with intracellular and intraepithelial lumina, abundant eosinophilic cytoplasm, large round nuclei with prominent nucleoli.	++ to +++	+	-	+

PANCREATIC MUCINOUS CYSTIC NEOPLASM

Definition, Epidemiology and Etiology:

Mucinous cystic neoplasm (MCN), which occurs almost exclusively in women, presents as a cystic neoplasm devoid of communication with the ductal system and lined with tall columnar mucin-producing epithelium supported by ovarian-type stroma.[5] The mean age of diagnosis is usually in the 5th decade of life (range: 20 to 82).[8]

Given the changes in criteria (ovarian-type stroma), MCNs are probably rarer than initially believed. It is also likely that many cases reported in older series, as well as in men, were instead intraductal papillary mucinous neoplasms.[3, 9, 14]

The etiology of MCN is not understood. The possibility that the stromal component of MCN is derived from ovarian primordium is supported by morphologic similarities with the possibility of undergoing luteinization, the presence of hilar-like cells, and immunophenotypic sex cord-stromal differentiation. The possibility that MCN arises from ectopic ovarian stroma incorporated during embryogenesis is supported by the fact that the primordial gonad and dorsal pancreatic anlage lie side by side during the fourth to fifth weeks of development.[5, 14]

Clinical features:

Large tumors may produce vague symptoms related to the compression of adjacent organs, and may sometimes be palpable. Alternatively, smaller lesions are usually found incidentally. Mucinous cystic neoplasms are rarely associated with jaundice. Notably, an association with diabetes mellitus is relatively frequent.[8]

Increase in serum CA19.9, as well in the cyst fluid, is also suggestive of mucinous cystic neoplasm. Also, among various imaging modalities, endoscopic retrograde cholangiography (ERCP) is cardinal in showing the absence of communication between the cystic cavity and the main pancreatic duct and its displacement.[8]

Gross pathology:

MCNs have a predilection for the body and tail of the pancreas. They usually present as a round tumor with a smooth surface and fibrous capsule on section. Calcification can be observed. The size of the tumor ranges from 2 to 35 cm, with most measuring between 6 and 10 cm.[8] The cut surface demonstrates either unilocular or multilocular tumor with cystic spaces varying in size and thick mucin material.
The lining of unilocular tumors is usually smooth and glistening, whereas small papillary projections and mural nodules can be seen in multilocular MCNs. Of note, malignant MCNs are likely to show papillary projections, mural nodules, and multilocularity.[5, 14] As a rule, there is no communication between mucinous cystic neoplasms and the pancreatic duct system, although exceptions have been reported.[14]

Histopathology

MCNs are characterized by two distinct histologic components: An epithelial inner layer composed of tall mucin-secreting epithelium, and dense cellular ovarian-type stroma.

The columnar mucin-producing epithelium (d-PAS and Alcian blue positive) may be flat, or form small papillary or polypoid projections. Crypt-like invagination also can be seen. Various changes such as pseudo-pyloric, gastric foveolar, small and large intestinal, and squamous differentiation can be found. Immunohistochemical studies will demonstrate the presence of scattered neuroendocrine cells.[1-3, 12]

The epithelium may be display various degrees of dysplasia ranging from adenoma to borderline to noninvasive and invasive carcinoma.[6]
In MCN *adenoma*, the epithelium shows basally located nuclei with no increase in mitosis. In the *borderline lesion*, the epithelium may exhibit papillary projections or crypt-like invagination, some nuclear pseudostratification with crowding and slightly enlarged nuclei. Mitoses can be observed.

Mucinous *cystadenocarcinoma* can either be *invasive* or *noninvasive*. Noninvasive MCN demonstrates high-grade dysplastic epithelial changes which are usually focal and may be detected only after reviewing multiple sections. The epithelium

often forms papillae and irregular budding, as well as branching with nuclear stratification, severe nuclear atypia, and frequent mitoses.

Invasive mucinous cystadenocarcinoma usually demonstrates an invasive component similar to common ductal adenocarcinoma. In some cases, invasive adenosquamous carcinoma, osteoclast-like giant cell carcinoma, or choriocarcinoma have been reported.[3, 4, 7, 13]

The ovarian stroma is composed of densely packed spindle-shaped cells with elongated nuclei and sparse cytoplasm. It may show evidence of luteinization characterized by the presence of clusters or single epithelial cells with round to oval nuclei and abundant clear cytoplasm. Stromal luteinization is found in decreasing order from adenomatous to carcinomatous cases.[13] When the tumors are large, the stroma may be markedly fibrotic and hypocellular, and the spindle-shaped cells may be difficult to identify. Rarely, mural nodules with sarcomatous stroma or an associated sarcoma can be seen.[9, 11, 13]

Immunohistochemical phenotype:

The epithelial component is positive for various epithelial markers, including CEA and cytokeratins 7, 8, 18, and 19.[12] The stromal component expresses vimentin and alpha smooth muscle actin and in a high proportion, progesterone and estrogen receptors.[13] Luteinized cells, when present, are immunolabeled with calretinin (which recognizes testicular Leydig cells and hilar ovarian cells) and inhibin (marker of sex cord-stromal differentiation).[13, 15]

Prognosis:

Regardless of the degree of cellular atypia, the prognosis of MCN (noninvasive) is excellent if completely removed.[3, 10, 13]
The prognosis of invasive mucinous cystadenocarcinoma depends on the extent of the tumor, with poor outcome correlating with the amount of invasion of the tumor wall and peritumoral tissues.[13] Patients older than 50 years have been reported to have a lower survival rate.[13]

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SOLID PSEUDOPAPILLARY NEOPLASMS

Definition, Epidemiology and Etiology:

Solid pseudopapillary neoplasms (SPNs) are usually benign neoplasms with a predilection for young women. They are composed of monomorphic cells forming loose solid sheets and pseudopapillary structures. Various synonyms can be found in the literature, such as "solid and cystic," "papillary cystic," and also "solid and papillary epithelial" neoplasm.[1, 6]

SPNs have been recognized with increasing frequency in recent years. They account for approximately 1 to 2% of all exocrine pancreatic tumors and about 10% of cystic pancreatic neoplasm.[3, 7, 9] Predominantly recognized in adolescent girls and young women (mean age 35 years, range 8 to 67), SPNs can be recognized in the same age range in male patients, but much more rarely.[8, 15] The etiology of this neoplasm is unknown, although the striking differences in sex and age distribution point to genetic and hormonal factors.

Clinical Characteristics:

The presenting symptoms of SPNs are nonspecific, and usually the neoplasms are found incidentally. Rarely, they cause abdominal discomfort and pain. Jaundice is uncommon.[10, 11]

Imaging studies usually reveal a sharply demarcated lesion which is either solid or solid and cystic without internal septation.[2]. Sometimes calcification can be noted at the tumor margin. Angiographic studies reveal either a hypovascular or mildly hypervascular lesion with displacement of surrounding vessels.[17]

Gross Pathology:

SPNs invariably present as round large solitary masses. The tumor ranges between 3 and 18 cm in diameter, the average size between 8 and 10 cm.[4] Multiple tumors are rare.[11]

On cross-section, the surface either reveals lobulated light brown areas, but more frequently, large zones of necrosis and hemorrhage with cystic spaces filled with necrotic debris. On occasion, the lesion is entirely hemorrhagic and cystic, mimicking a pseudocyst.[4] Invasion of adjacent organs or the portal vein have been reported rarely.[12-14]

Histopathology:

In the absence of significant necrosis, SPNs usually exhibit a solid monomorphic pattern with variable sclerosis, although more frequently pseudopapillary proliferation (secondary to vascular ischemic damage) lined by small monomorphic cells is seen. The neoplastic cells usually have an eosinophilic cytoplasm, although a clear vacuolar cytoplasm also has been reported. Generally, d-PAS resistant globules of various size can be seen. Characteristically, the oval to round nuclei have a finely dispersed chromatin and are often grooved. Mitoses are rare and if numerous may indicate a poor behavior (see below). The space between pseudopapillary structures is filled by hemorrhage and scattered areas of hyalinized fibrosis with or without calcification, and cholesterol clefts can be seen.[4]

Immunohistochemistry:

The cells of SPNs are consistently positive for alpha 1-antitrypsin and alpha 1-antichymotrypsin, as well as NSE, vimentin, and progesterone receptors. Of note, the positivity for alpha 1-antitrypsin and alpha 1-antichymotrypsin, although intense, usually involves small cell clusters or single cells. In contrast, NSE and vimentin are usually diffuse. In addition, the nuclei are also consistently strongly positive for beta-catenin, a reflection of the biology of the tumor. Inconsistent results have been reported for synaptophysin, CA19.9, and cytokeratin, which is detected in 30 to 70% of the cases.[4, 5]

Prognosis:

In the majority of cases; the prognosis of SPN is extremely good. After complete resection, over 95% of patients are cured. Even if present, local spread or dissemination to the peritoneum or even hepatic metastasis are not inconsistent with a relatively indolent course with patients experiencing long disease-free periods.[4, 5, 16] However, there have been reports of patients with a dismal prognosis. The histologic features associated with a poor prognosis include

venous invasion, a high degree of nuclear atypia, increased mitotic activity, necrobiotic cell nests, extensive geographic necrosis, and sarcomatoid transformation.[4, 16].

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CYSTIC FORMS OF USUALLY SOLID PANCREATIC NEOPLASM

Excluding metastatic tumors to the pancreas which may assume a cystic appearance, primary typically solid pancreatic tumors that may become *cystic* include *pancreatic endocrine neoplasm* and cystic acinar cell neoplasms *(cystadenoma* and *cystadenocarcinoma).*

CYSTIC PANCREATIC ENDOCRINE NEOPLASM

Like their solid counterpart, cystic pancreatic endocrine neoplasms tends to be more common in females. They are usually nonfunctioning and seen in patients in the third to fourth decade of life.[1]. However, cystic insulinoma and glucagonoma have been reported.

Gross Pathology:

Usually, cystic endocrine tumors are larger than their solid counterparts. Some reports quote a size measuring up to 25 cm.[4-7] Grossly, the cyst content is clear while the wall of the cyst is composed of a well-preserved tumor.

Histopathology:

The microscopic features of the cyst wall and solid areas of the tumor reveal the characteristic features of pancreatic endocrine neoplasm, with a monotonous cell population with limited cytoplasm and a distinctive nuclear chromatin pattern. The only challenge may be the distinction, on frozen section, between cystic pancreatic endocrine neoplasm and solid pseudopapillary neoplasm. Both types of tumors are composed of uniform cells with scant cytoplasm. Appropriate immunohistochemical studies help solve the diagnostic challenge on permanent section.

CYSTIC ACINAR CELL NEOPLASMS (cystadenoma - cystadenocarcinoma).

Acinar Cell Cystadenocarcinoma

Only a handful of cases have been reported in the literature.
Most were diagnosed in adult males and the age range from 32 to 69 years.
Symptoms at presentations include epigastric pain, vomiting, weight loss and palpation of an abdominal mass. There has not been any report of associated paraneoplastic syndrome usually associated with solid acinar cell carcinoma.

The size of the reported lesions ranged from 13 to 39 cm.
Metastases were reported in all cases with available information and the liver was the most common site.

Of the 5 cases with data available, two patients were dead (at 13 and 37 months, respectively). Three patients were alive with a mean follow up of 12 months.[3]

Acinar Cell Cystadenocarcinoma

Several cases of acinar cell cystadenoma have been reported. The patients included seven women and four men (age range 16-66 years).
In five patients the lesions were incidental findings. Others complained of abdominal pain.
The cystic lesions measure between 4 and 15 cm in diameter.
Eight lesions occurred as unifocal, unilocular or multilocular cysts in the head (n = 6), body (n=1) or tail (n = 2) of the pancreas.
One case showed two independent foci (head / tail) and another involved the entire pancreas.
Their lining cells expressed pancreatic enzymes (i.e., trypsin) and lacked any cellular atypia or proliferative activity (Ki67 index <1%). All patients remained alive and well during a follow-up period of 6-84 months.[2, 8]

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