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Review

Clinical aspects of intraductal papillary mucinous neoplasm of the pancreas

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Intraductal papillary mucinous neoplasm (IPMN) is a spectrum of neoplasia in the pancreatic duct epithelium characterized by cystic dilation of the main and/or branch pancreatic duct. According to the site of involvement IPMNs are classified into three categories, i.e., main duct type, branch duct type, and combined type. Most branch duct IPMNs are benign, whereas the other two types are often malignant. A large size of branch duct IPMN and marked dilation of the main pancreatic duct indicate the presence of adenoma at least. The additional existence of large mural nodules increases the possibility of malignancy in all types. Of recent interest is the relatively high prevalence of synchronous and/or metachronous malignancy in various organs, including the pancreas. The prognosis is favorable after complete resection of benign and noninvasive malignant IPMNs. Malignant IPMNs acquiring aggressiveness after parenchymal invasion necessitate adequate lymph node dissection. On the other hand, asymptomatic branch duct IPMNs without mural nodules can be observed without resection for a considerably long time. This review addresses available data, current understanding, controversy, and future directions.

Key words: intraductal papillary mucinous neoplasm, pancreatic cancer

Introduction

Intraductal papillary mucinous neoplasm (IPMN) is characterized by cystic dilation of the main and/or branch pancreatic duct. This neoplasm was histologically defined by the World Health Organization as "intraductal mucin-produing neoplasm with tall columnar mucin-containing epithelium with or without papillary projections, involving the main pancreatic duct and/or major side branches, and lacking ovarian-type stroma characteristic of mucinous cystic neoplasm (MCN)" in 1996.[1] IPMN shows a wide spectrum of histological differentiation from hyperplasia, adenoma, and borderline neoplasm to carcinoma.[2,3] The natural history of IPMN has been documented as a so-called adenoma–carcinoma sequence, where the ultimate form of malignant progression is invasive carcinoma.[2,4–6]

Although IPMN is a rare tumor, it is becoming increasingly recognized, probably due to the increased awareness of this entity, accounting for 0.5% of all pancreatic neoplasms found in autopsy specimens, 7.5% of pancreatic neoplasms clinically diagnosed, and 16.3% of pancreatic neoplasms surgically resected.[7] IPMN is not infrequently found in the head of the pancreas of elderly men. In a collective review of 259 patients with mucin-producing neoplasms of the pancreas, Kimura et al.[8] reported a male preponderance (male 177, female 82; ratio 2.2:1) and a mean age of 65.5 years (range 30–94). We also demonstrated similar age and sex distribution.[9]

The differentiation of IPMN from MCN has been the most controversial point but has been clarified to a considerable extent by the definition and classification proposed by the World Health Organization[1] and the Armed Forces Institute of Pathology.[10] Although IPMN and MCN similarly produce a large amount of mucin and are sometimes difficult to distinguish, these are certainly separate entities. Although the presence of ovarian-type stroma is the only histological feature to definitively differentiate MCN from IPMN,[1,10] there are many other clinical characteristics to suggest the diagnosis of each entity (Table 1).

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Table 1. Clinical features for differentiation of MCN and branch duct IPMN

Feature	MCN	Branch duct IPMN
Age	Perimenopausal	Elderly
Sex (% female)	>95%	Around 30%
Location	Mostly in the body and tail	>60% in the head
Calcification	Rare	No
Common thick capsule	Yes	No
Macroscopic appearance	Orange-like	Grape-like
Communication with pancreatic duct	Rare	Yes, but not always demonstrable
Main pancreatic duct	Normal or deviated	Normal or dilated

MCN, mucinous cystic neoplasm; IPMN, intraductal papillary mucinous neoplasm

Presentation

Patients with IPMN often present with acute pancreatitis of mild to moderate severity. Up to 70%–80% of patients with IPMN present with abdominal symptoms such as epigastric discomfort and/or pain, backache, weight loss, and jaundice.[11–15] In addition, long-standing hyperamylasemia is often present.[12,16] These are due to partial or complete occlusion of the main pancreatic duct with viscid mucin. Chronic persistent occlusion may result in pancreatic insufficiency, presenting with diabetes and/or steatorrhea. Jaundice may be due to viscid mucin obliterating the ampulla, compression of the common bile duct by a large, mostly malignant IPMN, or involvement of the common bile duct and/or ampulla by mural nodules. Two-thirds to three-fourths of patients with IPMN, however, are asymptomatic, due to relatively inactive production of mucin and/or the location of the tumor away from the head of the pancreas. In these cases, IPMNs may be incidentally diagnosed during routine work-up for other diseases or at autopsy.

Classification

IPMNs are usually classified as main duct type, branch duct type, and combined type according to the site and extent of involvement based on imaging findings and/or by histology.[17] Most, if not all, branch duct IPMNs are benign, while main duct IPMN and combined type are frequently malignant. Although the combined type seems to be an advanced form of branch duct IPMN, whether this category can be neglected or not has not been determined yet. Main duct IPMN and branch duct IPMN show a significant difference in the prevalence of malignancy. Moreover, main duct IPMN and probably combined type are more frequently associated with invasive carcinoma. Sugiyama and Atomi[18] reported that 54% of 13 main duct IPMNs and 58% of 12 combined type IPMNs showed invasion. Since the presence of invasive carcinoma is of pivotal importance in the outcome of resection of IPMN,[19] the classification plays important roles in the prediction of the prognosis.

The preoperative classification of IPMN is based on imaging studies. Histological examinations of surgical specimens of branch duct IPMN, however, may prove some degree of main duct involvement, thus putting many branch duct IPMNs into the combined category. Criteria for the definition of IPMNs in the international consensus manuscript published in 2004[20] may be useful for the differentiation, but many IPMNs would still be categorized as combined from a histological viewpoint. In practice, therefore, the clinical classification of the type of IPMN must be based on imaging findings. Pathological reports should include more detailed description of distribution of IPMN.

Diagnosis

The most characteristic endoscopic finding often observed in patients with IPMN is mucin extrusion from the patulous ampulla of Vater[21] (Fig. 1). This unique finding initially brought this disease to our attention.[21–23] The widening of the ampullary orifice can be seen at the minor papilla and/or the major papilla. An increased awareness of this feature of IPMN is leading to an increasing number of patients being diagnosed during routine upper gastrointestinal endoscopy.

Ultrasonography (US), endoscopic ultra sonography (EUS),[24] and computed tomography (CT)[12,25] would demonstrate one or more cystic lesions in the pancreas (branch duct IPMN), or diffuse or segmental dilation of the main pancreatic duct (main duct IPMN), with or without mural nodules (Fig. 2). Since EUS and CT are among routine examinations for work-up of abdominal diseases, cystic lesions have become a frequent incidental finding. Magnetic resonance (MR) cholangiopancreatography (MRCP) is the best method to outline the entire lesion regardless of the type of IPMN (Fig. 3).[26,27] Endoscopic retrograde pancreatography (ERP) is a

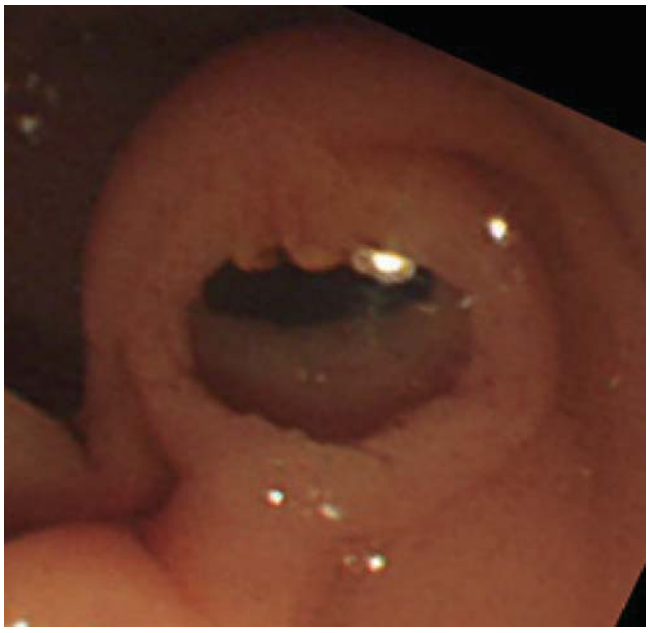

Fig. 1. Widely dilated ampulla of Vater with extrusion of mucin

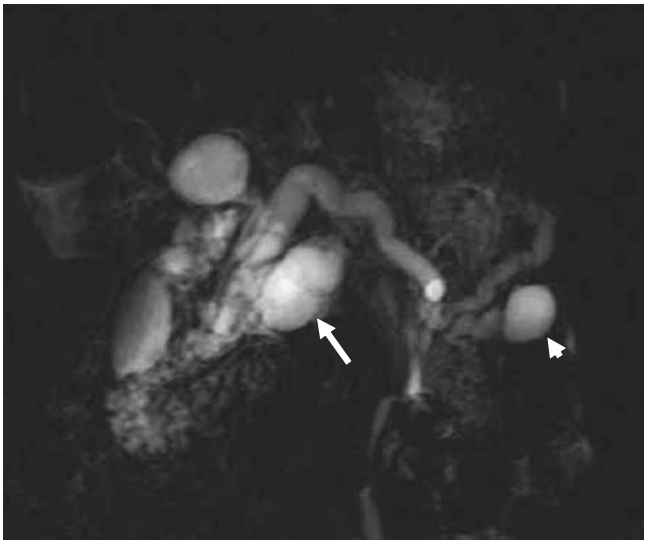

Fig. 3. Magnetic resonance cholangiopancreatogram outlining two branch duct intraductal papillary mucinous neoplasms (IPMNs) in the head (*arrow*) and tail (*arrowhead*) of the pancreas

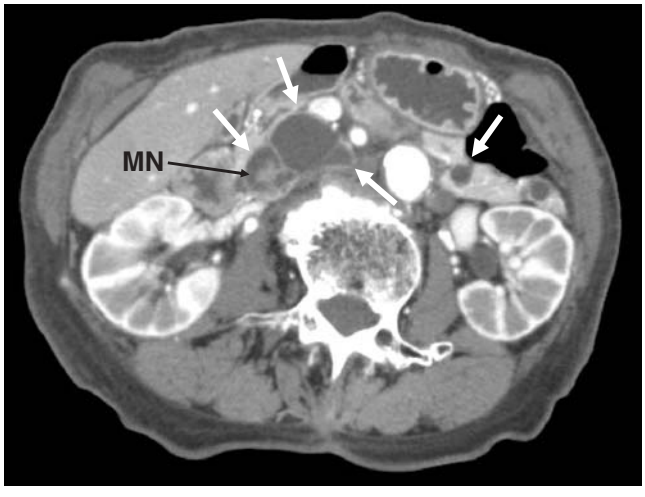

Fig. 2. Contrast-enhanced computed tomogram of the abdomen showing a multilocular cystic lesion in the head and a unilocular cyst in the tail of the pancreas (*white arrows*). A mural nodule (*MN*) is seen in a locule of the head lesion (*black arrow*)

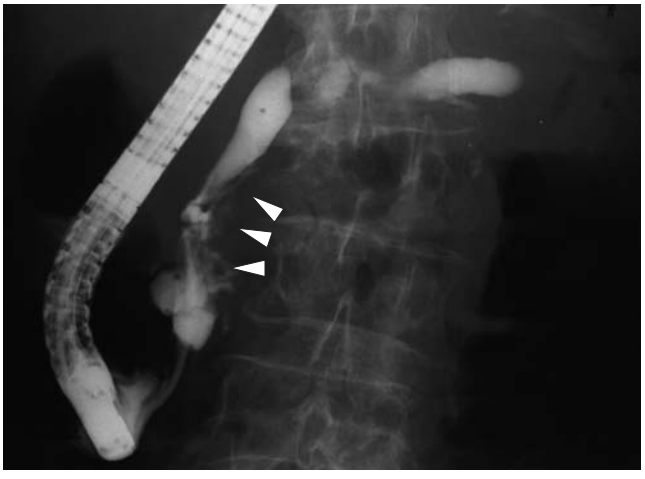

Fig. 4. Endoscopic retrograde pancreatogram showing dilated main pancreatic duct with a sign of compression (*arrowheads*) by a branch duct IPMN in the head of the pancreas in the same patient as in Fig. 3. The IPMN is not visualized due to obliteration of the communicating duct with viscid mucin and/or a mural nodule

more sophisticated method to reveal dilation of the main pancreatic duct and/or branches with filling defects due to mural nodules or viscid mucin (Fig. 4). Communication between branch duct IPMN and the main pancreatic duct is usually evident, but not always demonstrable due to mucin obliterating the communication. The ductal communication was seen in only 45 (85%) of our series of 53 patients with branch duct IPMN.[9]

Diagnosis of malignant IPMN

The diagnosis of malignancy in IPMN is often difficult, even with current advanced imaging modalities. Several indirect markers are used to suggest the presence of malignancy. First of all, the presence of main duct IPMN per se indicates the possible existence of malignant changes in more than half of the patients. Salvia et al.[14] reported a collective experience of 140 patients

with main duct IPMN, 18% and 41% of whom had in situ and invasive carcinoma in their IPMN, respectively. In addition, marked dilation (>1 cm) of the main pancreatic duct, and the presence of mural nodules (>1 cm) are highly suggestive of malignancy regarding branch duct IPMN as well as main duct IPMN.[11]

The diameter of a dilated main pancreatic duct can be determined by US, CT, MR, and EUS. The presence or absence of mural nodules or solid components can be confirmed preoperatively by EUS, which is superior to any other diagnostic modalities in this respect but not always correct. Kubo et al.[24] reported an 86% accuracy of EUS in differentiating malignant IPMN from benign IPMN. Although main pancreatic duct aspiration at ERP may be positive for malignant cells by cytology and/or shows high levels of CEA and CA19-9,[28] the rate of positivity of transpapillary biopsy and cytology is less than 50%.[16,29] EUS-guided fine needle aspiration (EUS-FNA) is now under investigation to determine the accuracy of the malignant diagnosis.[30] However, its significance must be meticulously evaluated and balanced against the possible risk of seeding and disseminating of malignant IPMNs. Peroral pancreatoscopy may reveal the fish-egg appearance of papillary growths in main duct IPMN and may help us determine the extent of the spread of IPMN and thus the site of resection.[31,32] Extrapancreatic invasion and resectability of invasive IPMNs are most efficiently determined by enhanced CT (Fig. 5). Although intraductal probe ultrasonography (IDUS) also appears to be useful in demonstrating mural nodules,[33] distinction of mucin plugs from mural nodules often remains difficult.

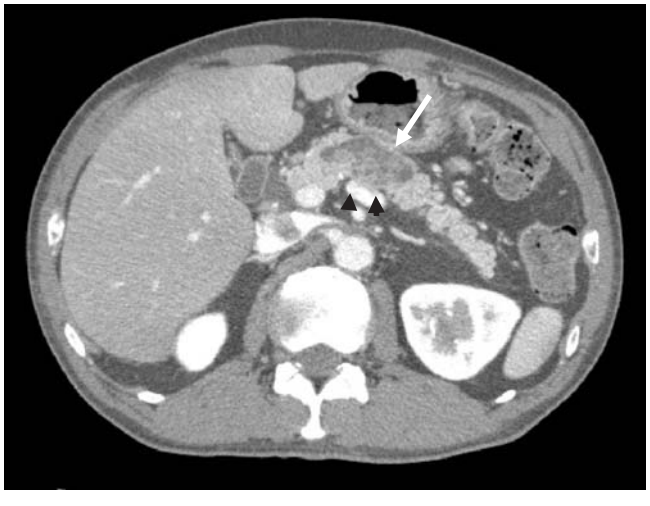

Fig. 5. Enhanced computed tomogram demonstrating a main duct IPMN with mural nodules (*arrow*) and parenchymal and retropancreatic invasion to the splenic vein (*arrowheads*)

Simultaneous and metachronous association with other malignancy

Another unique characteristic of IPMN is its synchronous or metachronous association with malignant neoplasms in other organs. It has been reported that the rate of the association of IPMN and extrapancreatic malignant neoplasms ranges from 23.6% to 32%.[9,34,35] Yamaguchi et al.[9] found nonpancreatic malignancies in 18 of 56 patients (32%) with IPMNs who underwent surgical resection. Sugiyama and Atomi[34] also reported that 15 of 42 patients (32%) with benign and malignant IPMNs resected had gastric, biliary, and colorectal neoplasms either synchronously or metachronously. Osanai et al.[35] recently described that 35 of 148 surgical or nonsurgical patients (23.6%) with IPMNs experienced malignancies of the colon, stomach, or lung before (13 patients), at (12 patients), or after (10 patients) the diagnosis of IPMN. Because the age of patients with IPMN is relatively old (mean 65 years), whether the association of nonpancreatic malignancy in those with IPMN is really more frequent than in ordinary populations must await further evaluation.

Of particular interest is the potentially high prevalence of pancreatic cancer in patients with IPMN. Yamaguchi et al.[36] reported that seven of 76 patients (9.2%) with branch duct IPMN had independent usual type pancreatic cancer, which was synchronous (5 patients), metachronous (one patient), or both synchronous and metachronous (one patient) with resection of IPMN. The seven patients included two with in situ carcinoma, one with minimally invasive carcinoma, and four with invasive carcinoma. The fact that the presence of IPMN has led to the diagnosis of concomitant pancreatic cancer in four of these seven patients is of paramount importance. All seven IPMNs associated with pancreatic cancer were branch duct IPMN of adenoma with mild dysplasia. Nakaizumi et al.[37] also reported the same combination of branch duct IPMN and common-type pancreatic carcinoma in five male patients. Whether the association of IPMN and malignancy in various organs suggests some genetic defects for neoplasm formation deserves further investigation. For the present, we should be well aware of the possibility that an IPMN may be an indicator of development of pancreatic and nonpancreatic cancers.[38]

Treatment

The long-term prognosis of patients with benign IPMNs and malignant yet noninvasive IPMNs is excellent after complete resection.[39–42] Although only around 40% of all malignant IPMNs are invasive,[8] and the 5-year survival rate is around 80% in malignant IPMNs,[39] inappro-

priate and/or incomplete resection may still lead to recurrence. The frequency of recurrence after resection of noninvasive IPMN was reported to be at least 7% but its relationship to surgical margins is unclear.[14,43,44] The prognosis of an invasive malignant IPMN depends on its histological type and the extent of invasion and metastasis.[2] In our previous series, reported in 2000, the 3-year survival rate for 10 patients with malignant IPMN was 48% after curative resection.[9]

D1 lymph node dissection is sufficient in most patients with malignant IPMN without massive parenchymal invasion.[45,46] However, malignant IPMN was reported to acquire aggressive behavior similar to usual pancreatic carcinoma once it has invaded the pancreatic parenchyma.[47] Adequate pancreatic resection should be performed with D1 plus alpha or preferably D2 lymph node dissection in such patients. Accurate preoperative or intraoperative determination of the degree of parenchymal invasion can be obtained by EUS, dynamic CT, and intraoperative US.[48]

Main duct IPMN

Main duct IPMN is frequently malignant and requires adequate resection as soon as possible. Careful evaluation is needed as to the presence of mural nodules, possible parenchymal and extrapancreatic invasion, and the area and extent of resection. Intraoperative US[48] and pancreatoscopy may be helpful to determine the site of resection, but actual localization of IPMN may still be different from the dilated ductal segment.[3] In addition to all preoperative and intraoperative procedures to locate the resection line, frozen section diagnosis should be properly utilized, although diagnosis by frozen section histology is not always accurate. Although some patients may need total pancreatectomy, the benefits of such an aggressive treatment must be balanced against severe and permanent endocrine and exocrine pancreatic insufficiency because IPMN is a slow-growing disease of elderly people and the prognosis is relatively good even in malignant IPMNs.[15,39,41]

Branch duct IPMN

An asymptomatic branch duct IPMN without mural nodules may not require immediate resection. On rare occasions, however, even an IPMN without mural nodules has in situ carcinoma or minimally invasive carcinoma. Maguchi et al.[49] recommended that branch duct IPMN be excised when it is ≥25 mm in size, has mural nodules ≥6 mm in diameter, and/or the main pancreatic duct is dilated ≥7 mm. The same group stated that branch duct IPMNs with mural nodules of ≥6 mm in diameter are most likely to have carcinoma, and that IPMNs showing branch dilation of ≥25 mm or main duct dilation of ≥7 mm are frequently adenoma.[50] They emphasized the importance of the "initial" diagnosis to determine indications for surgery. When branch duct IPMNs are to be followed up without resection, they recommended meticulous screenings by CT or US at 3, 6, and 12 months to check potentially rapid changes, and yearly MRCP thereafter. When a branch duct IPMN causes acute pancreatitis or other symptoms, or when it has mural nodules suggesting malignancy, complete surgical resection must be performed. If a symptomatic IPMN appears benign, a variety of limited pancreatic resections may be attempted, preferably by experienced pancreatic surgeons.[51–57]

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