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Intraductal papillary mucinous neoplasm (IPMN): UPDATE

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Abstract

At present, IPMN is broadly divided into two main types: main duct and branch duct. However, as discussed below, the definition of mixed-type IPMN is gradually becoming accepted. In main duct IPMN, the main pancreatic duct is very dilated, while in branch duct IPMN, the branches of the pancreatic duct are dilated, resembling a bunch of grapes.

IPMN is most frequently diagnosed in the elderly (around 65 years old), and the male to female ratio is 2:1, indicating that the incidence of the disease is twofold higher in males than in females. IPMN most commonly originates in the head of the pancreas, and approximately 70% of IPMN lesions are found in the head of the pancreas. It also tends to occur in multiple sites.

With regard to imaging, endoscopy has revealed that the opening of the papilla of Vater, located in the duodenum close to the stomach, is dilated by mucus. This dilation of the papillary opening of Vater by mucus is a key characteristic of IPMN. When directly viewed by pancreatoscopy, IPMN appears as small protrusions similar to salmon roe.

Key words: IPMN, main duct type, branch duct type, Pancreas, cyst

1. IPMN as a cystic disease of the pancreas: classifications and status

Conventionally, the term 'cyst' is clinicopathologically defined as 'a closed cavity containing a liquid or semi-solid substance'. Therefore, by definition, a pancreatic cyst has no communication with the pancreatic duct, and this has been considered as an important element in the concept of cystic disease of the pancreas. However, even typical pancreatic 'cysts' may exhibit communication with the pancreatic duct that increases the intraductal pressure either during endoscopic retrograde pancreatography (ERP) or during pancreatography of a resected specimen. Moreover, it is justifiable to consider the pancreatic duct as the origin of retention cysts, cystic neoplasms and cystic disease of the pancreas. Therefore, it can be assumed that originally, there was communication with the pancreatic duct, which means that the status of communication with the pancreatic duct may not always be necessary in defining cysts.

Furthermore, advances in imaging diagnosis over the past 20 years have enabled extensive visualisation of cystic dilatory lesions of the pancreas. Consequently, these lesions are now treated as cystic lesions of the pancreas, regardless of the status of communication with the pancreatic

duct [1, 2].

Cysts with an epithelial lining of the cystic lumen are true cysts, while those without an epithelial lining are pseudocysts. Neoplastic cysts (cystic neoplasms of the pancreas) are true cysts and include serous cystic neoplasm (SCN), mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN) [3,4].

From a clinicopathological perspective, IPMN is now more widely accepted than the mucus-producing pancreatic cancer proposed by Ohashi et al. in 1982 [5], and such cases were later reported in the 1980s. There have been several debates on the establishment of the concept of IPMN as a disease in Japan. Thereafter, around 1990, the concept became established worldwide following the publication of the fourth edition of the regulations on handling pancreatic cancer in Japan [6], the Armed Forces Institute of Pathology (AFIP) publication on tumours of the pancreas [7] and the World Health Organization (WHO) classification of pancreatic tumours [8]. As a result of establishing the concept of the disease and the frequent discovery of the disease in clinicopathological practice in Japan, IPMN is considered to have originated in Japan and gradually been recognised internationally. Following various international debates, the first version of the IPMN/MCN international consensus guidelines [9] was published in 2006. Six years later, in 2012, the second version [10] was published. International awareness of IPMN with regard to its course, classification, definition and surgical indications continues to develop with new reviews and revisions.

In the past, there have been a number of classifications of pancreatic cysts, including those by Howard and Jordan [11], Strodel and Eckhauser [12], Cubilla and Fitzgerald [13], Bradley [14], Howard [15] and Kuroda and Morioka [16]. However, the concept of IPMN as a dilated lesion of the pancreatic duct, which has now been established, does not incorporate the classification of a pancreatic cyst, which is now considered outdated. Instead, the latter is considered a practical classification that incorporates the concept of IPMN.

2. Diagnosis and challenges of IPMN

To improve the understanding of cystic neoplasms of the pancreas and IPMN, it is important to clarify differences in the concepts of IPMN and MCN and to differentiate between the two. Until the latter half of the 1990s, there was ongoing debate on where to draw the line between main duct and branch duct IPMNs and MCN and no consensus was reached regarding the diagnosis and treatment of cystic neoplasms of the pancreas.

There have been a number of discussions, including whether IPMN and MCN should be considered as different diseases or congeneric diseases. In both MCN and IPMN, the pancreatic duct is dilated to form a cyst and mucus is produced (Fig. 1) [1]. In addition, both are derived from the pancreatic duct epithelium and therefore exhibit the same

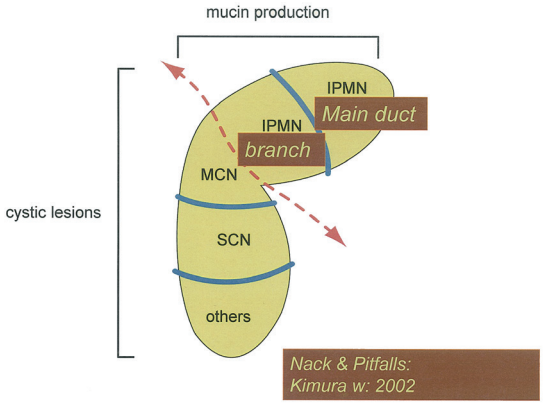

Fig. 1 Demarcation between MCN and branch duct IPMN

Similar to MCN and serous cystic tumour, branch duct IPMN is often treated as a cystic disease of the pancreas. However, there has been resistance against placing main duct IPMN in the class of cystic disease of the pancreas. Moreover, IPMN and MCN have the common attribute of mucus production; however, MCN and IPMN are clearly different diseases clinicopathologically. Therefore, it is very important to differentiate and draw a line between MCN and branch duct IPMN. The lack of consensus on where to place the line of differentiation between MCN and branch duct IPMN has been a cause of confusion [1].

histology. However, there are marked differences in the clinicopathological characteristics, such as age of onset, gender, site of onset, presence or absence of ovary-like stroma, capsule structure, communication with the pancreatic duct and concomitant pancreatitis. In other words, as the Japan Pancreas Society Subcommittee has clearly stated with regard to pancreatic cyst classification, MCN and IPMN are clearly different diseases clinicopathologically. In particular, the presence of fibrous membranes and ovary-like stroma in the septal wall, as revealed histologically, has been reported in many cases of MCN (86%) [17]. Therefore, the fact that ovary-like stroma is never observed in IPMN has become recognised as a definitive finding that shows that IPMN and MCN are different diseases. Following this, another issue was the clarification of where the line should be drawn between branch duct IPMN and MCN (Fig. 1) [1] and where the two are positioned in the classification of pancreatic cysts and the classification of exocrine pancreatic tumours [1].

Moreover, whether the presence of ovary-like stroma is an absolute requirement in the definition of MCN remained a topic of discussion. In medical practice, differential diagnosis should be made before surgery, following which indications for surgery are decided. In addition, it has been suggested that it is better to differentiate IPMN from MCN by imaging. In other words, the tumours should be defined on the basis of diagnostic imaging or macroscopically as follows: 'macroscopically, MCN is spherically shaped and has a characteristic fibrous capsule where the entire cyst is enclosed, and branch duct IPMN consists of a collection of dilated pancreatic duct branches where the outline is not spherical but irregular' [18]. In other words, in terms of imaging diagnostics, MCN can be characterised as 'a summer orange' and branch duct IPMN as 'a cluster of grapes' (Fig. 2) [19].

Zamboni et al. [17], who suggested a strong relationship between MCN and ovary-like stroma, also reported that 14% of MCNs do not have an ovary-like stroma and that these MCNs have a stronger tendency to infiltrate than those with an ovary-like stroma. The opinion that 'the classifications must be performed by diagnostic imaging before surgery' was not clearly documented in the first published IPMN/MCN international guidelines [9] on whether macroscopic classification of main duct, branch duct and mixed-type IPMNs should be performed by diagnostic imaging or histologically but it is documented in the second edition [10]. Because this is important while establishing a treatment policy, it is stipulated that macroscopic classification must be performed by diagnostic imaging before surgery.

For MCNs without an ovary-like stroma clinicopathologically, the expression 'indeterminate mucin-producing cystic neoplasm

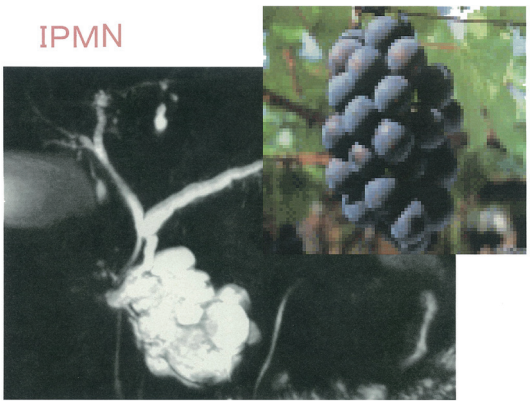

Fig. 2 MRCP image of branch duct IPMN showing how it resembles a bunch of grapes.

Fig. 3 MRCP image of main duct IPMN.

of the pancreas' was proposed on the basis of our recommendation currently in preparation by the First Department of Surgery team.

3. At present, IPMN is mainly divided into two types: main duct (Fig.3) and branch duct. However, as discussed below, the definition of mixed-type IPMN is gradually being accepted. In main duct IPMN, the entire main pancreatic duct is very dilated, whereas in branch duct IPMN, the branches of the pancreatic duct are dilated, resembling a bunch of grapes. IPMN is most frequently diagnosed in the elderly, aged around 65 years, and the male to female ratio is 2:1, indicating that its incidence is twofold higher in males than in females. IPMN most commonly originates in the head of the pancreas, and approximately 70% of tumours are found in the head of the pancreas. It can also occur in multiple sites.

Endoscopy has revealed that the opening of the papilla of Vater, located in the duodenum close to the stomach, is dilated by mucus. This dilation of the papillary opening by mucus is a key characteristic of IPMN. When directly viewed by pancreatoscopy, IPMN appears as small protrusions similar to salmon roe. Findings of endoscopic retrograde cholangiopancreatography (ERCP) have revealed a radiolucent image of mucus in the main pancreatic duct. Magnetic resonance imaging (MRI) may reveal a mass resembling a bunch of grapes, as described previously, indicating branch duct IPMN. Observation of the interior of the cyst by endoscopic ultrasound (EUS) may reveal nodular protruded lesions in the cyst, and these findings indicate the need for surgery. Incision of the pancreas during surgery is known to result in leakage of copious amounts of mucus from the main pancreatic duct. This mucus is collected and placed into a Petri dish, where it can be examined. The clinical confirmation of the presence of mucus is an important marker in the diagnosis of IPMN.

With regard to symptoms and complications associated with IPMN, acute pancreatitis accounts for approximately 18% of complications, multiple-organ malignancies for 18% − 30% and conventional pancreatic cancer for approximately 3%. In addition, IPMN tends to recur in the remaining pancreas after surgery. Furthermore, when there is disease progression with infiltration of the periphery, IPMN can present as jaundice.

IPMN can be divided into four tissue subtypes, namely gastric, intestinal, biliopancreatic ductal and neoplastic cell types. Of these, the prognosis after tumour resection is known to be comparatively favourable for the gastric and intestinal cell types.

The correlation between the grade of IPMN and cellular proliferation factor is indicated by the expression of Ki-67. The lower the IPMN grade, the lower is the level of Ki-67. On the other hand, the greater the seriousness of the condition, the higher is the level of Ki-67.

With regard to the correlation between IPMN intraductal volume and the grade of malignancy, when the intraductal volume is determined by CT, the larger the volume, the higher is the grade of malignancy.

Our experience in cases of IPMN resection is now discussed. We have performed IPMN resection on 109 patients. Of these, 21 (approximately 20%) had IPMN-induced infiltrative cancer and three (approximately 3%) had concomitant conventional pancreatic cancer.

After IPMN resection, the overall 5-year survival rate was approximately 90%, which is a very good survival rate. However, when the condition had progressed to IPMN-induced infiltrative cancer, the 5-year survival rate was considerably worse (less than 60%). Therefore, it is important to resect IMPN before it becomes infiltrative. In addition, IPMN removed at the pre-infiltrative stage might also fall into the category of early pancreatic cancer. Surgery of the pancreas is divided into two main types: pancreaticoduodenectomy, in which surgery is performed on pancreatic head lesions,

and distal pancreatectomy, in which surgery is performed on lesions in the distal part of the pancreas.

4. Future advances and challenges of IPMN

The revised version of the international guidelines on IPMN/MCN (2nd edition) was published in 2012[10], and important clinical research on IPMN is ongoing.

1. The incorporation of tissue subtypes in the 2012 guidelines [10] has increased the possibility of predicting the grade of malignancy in the future using the pancreatic fluid obtained during ERCP as a test sample. Till date, there is no decisive guideline for judging the grade from examination of the pancreatic fluid. Moreover, with regard to pancreatic fluid carcinoembryonic antigen (CEA), the concentration in the pancreatic fluid flowing in the pancreatic duct differs from that in the fluid present in the cyst. The significance of diagnosing malignancy on the basis of these findings is an issue for future research.

2. As usual, nodular protrusion of the cyst wall is an important index of malignancy.

3. To stratify the risk of malignancy, worrisome features that lead to suspicion of malignancy (obscure diagnostic findings) have been newly defined in addition to high-risk stigmata (clear diagnostic findings), which is strongly suggestive of malignancy [10]. In the first edition, mural nodules, dilatation of the main pancreatic duct and positive cytodiagnosis were documented as high-risk stigmata [9]. In the 2012 edition, the content of the cyst on imaging, a main pancreatic duct diameter ≥10 mm and cystic lesions of the pancreatic head as a result of obstructive jaundice were added to the list of high-risk stigmata.

The first edition of the guidelines stated that the question of whether branch duct IPMN with a cyst diameter of at least 30 mm and without mural nodules should be immediately considered for surgery was an issue for future investigation (Fig. 3) [9]. However, in the 2012 edition, this stage of disease has been defined as a worrisome feature, which should be observed (it has dropped one step below an indication for surgery). In addition, with regard to the indications for main duct surgery, in the 2012 edition, a dilation of the main pancreatic duct of at least 6 mm is defined as main duct. A main pancreatic duct diameter of at least 10 mm is defined as a high-risk stigmata and considered as an indication for surgery. IPMN with a main pancreatic duct diameter of 5 − 9 mm is defined as a worrisome feature, for which closer examination is recommended.

With regard to the definition of malignancy, in the WHO classification revised in 2010, in situ carcinoma has been defined as IPMN with high-grade dysplasia [23]. Similarly, in the 2012 version of the guidelines, in situ carcinoma has been defined as IPMN with high-grade dysplasia. Although the guidelines do not state that IPMN with high-grade dysplasia is in situ carcinoma or noninvasive carcinoma, caution is required because it could be interpreted that only infiltrative cancer is malignant. As clinicians, our aim is to resect as many malignant tumours as possible. Based on the prognosis, the best approach is to diagnose IPMN at the in situ carcinoma or noninvasive carcinoma stage and to perform early resection.

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