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Title page

A statement by the Japan-Korea expert pathologists for future clinicopathological and molecular analyses toward consensus building of intraductal papillary neoplasm of the bile duct (IPNB) through several opinions at the present stage

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Abstract

Intraductal papillary neoplasm of bile duct (IPNB) was described as a preinvasive neoplastic lesion of the biliary tract in the 2010 WHO classification. Although a number of studies have since been conducted on IPNBs, controversy remains, particularly regarding the standardization of its definition. Meetings by Japanese and Korean expert pathologists were held twice to resolve the pathological diagnostic aspects of IPNB. Through round-table discussions and histological reviews, we reached to the common understandings that IPNBs diagnosed according to the criteria of WHO 2010 are characterized by intraductal predominant papillary or villous biliary neoplasms covering delicate fibrovascular stalks and are classified into two types pathologically. One type (type 1 IPNB) is histologically similar to intraductal papillary mucinous neoplasms of pancreas, and typically develops in the intrahepatic bile ducts, while the other (type 2 IPNB) has a more complex histological architecture with irregular papillary branching or with foci of solid-tubular components and typically involves the extrahepatic bile ducts. This report states the diagnostic pathologic features of IPNB proposed by WHO 2010. Since currently, the concept of IPNB is still confusing, the proposed diagnostic pathologic features stated here will be of use for future clinicopathological and molecular analyses toward consensus building of IPNB.

Introduction

The 2010 WHO classification states that “IPNBs (intraductal papillary neoplasms of the bile duct) are characterized by dilated bile ducts filled with a non-invasive papillary or villous biliary neoplasms covering delicate fibrovascular stalks” [1,2]. While IPNBs are a pre-invasive neoplasm, it is called “IPNB associated with an invasive carcinoma” when they begin invasion. However, the prevalent location of IPNBs is highly variable among studies (~80% of tumors located in the intrahepatic bile duct in some studies; ~70% in the extrahepatic bile duct in others) [3-8]. The reported incidence of associated invasive malignancy in IPNBs also varies between 31% and 74% [3-8]. The incidence of low/intermediate dysplasia and high-grade dysplasia in IPNB are also different among the reports. Some reported that all cases were high-grade dysplasia (carcinoma in situ) with or without invasion, while others reported that about 10 to 20% of IPNB are benign (adenoma or low/intermediate dysplasia) (9-11). These discrepant findings among previous studies on IPNB could be, at least partly, due to the different diagnostic criteria applied.

Currently there is some confusion in understanding pathologic features of IPNB. One is with respect to the similarity to the intraductal papillary mucinous neoplasms (IPMNs) of the pancreas. It has been reported that IPNBs share pathological features of IPMNs of the pancreas [1,6,12-14]. IPMNs are also preinvasive intraductal papillary neoplasms of the pancreas and in addition, IPNBs and IPMNs are known to share similar subtypes [1,6,12-14]. However, there are several reports that some of IPNB were similar to IPMN and the others were not, and the differences and similarities between IPNB and IPMN have not yet been fully clarified. Another is with respect to the difference between IPNB and papillary cholangiocarcinoma. Prior to WHO 2010 proposal of IPNB, Albores-Saavedra, et al. reported invasive and non-invasive papillary carcinomas as a distinct

morphological variant of extrahepatic and gallbladder cancers based on their well-differentiated morphology and favorable prognosis [15,16]. Although in WHO 2010 proposal, papillary carcinoma reported by Albores-Saavedra, et al. [15,16] was included in IPNB of the extrahepatic bile ducts and in intracystic papillary neoplasm (ICPN) of the gallbladder [1,2], this inclusion might have not been well recognized and caused some misunderstanding [15,16]. Since most cases of IPNBs reported at that time of WHO 2010 proposal were intrahepatic tumors, only limited data were available on extrahepatic IPNBs [12-14], and pathological features had not been compared between intrahepatic and extrahepatic papillary neoplasms at that time. Therefore, it still remains to be clarified whether IPNB proposed by WHO 2010 is a single disease or is composed of several heterogeneous diseases.

Thus, it seems reasonable and timely that the pathological features of IPNB, particularly with respect to its similarities to IPMNs and also to its anatomical location along the biliary tract, should be discussed by experienced pathologists from different institutions and different countries in order to polish, refine and prevail the diagnostic pathologic criteria of IPNB originally proposed by WHO 2010, which would be a cornerstone for future clinicopathological and molecular analyses of IPNB for building consensus on what IPNB is.

A Japan-Korea study group on IPNBs jointly sponsored by the Japan Biliary Association and Korean Association of Hepato-Biliary and Pancreas Surgery was established. For clinicopathological analyses of IPNB cases collecting from many institutions, pathologic diagnostic criteria for IPNB are mandatory. For this purpose, expert pathologists of IPNB from Japan and from Korea supported by the Japan-Korea study group on IPNBs met in 2016 and again in 2017. This study protocol was approved by the institutional review board of the Dokkyo Medical University (IRB No.28059). This is a statement by experienced pathologists on characteristic and diagnostic pathologic features of

tumors currently diagnosed as IPNB and its possible subclassification.

Review of the literatures regarding the histological heterogeneity of IPNBs

Several recent studies were reviewed with respect to the heterogeneity of intraductal biliary papillary neoplasms in order to understand and share the pathologic features of IPNBs by experienced pathologists and to obtain a better pathologic diagnostic criteria of IPNBs.

Nakanuma, et al. examined IPNBs arising in the intrahepatic and extrahepatic bile ducts, and reported that approximately one half of IPNBs showed similar histopathological features to IPMNs, while the other half appeared not to be similar to IPMNs [17]. IPNBs resembling pancreatic IPMNs typically developed in the intrahepatic bile duct, and the gastric type was the most common phenotype, followed by the intestinal and oncocytic types. Mucin hypersecretion was also more frequently observed in IPMN-like cases than in IPMN-unlike cases. Most IPMN-unlike IPNBs developed in the extrahepatic bile ducts, and most were histologically the intestinal or pancreatobiliary type, and mucin secretion was occasional. IPMN-like IPNBs often contained foci of low/intermediate-grade dysplasia and not infrequently showed invasion. The most of “IPMN-unlike” tumors showed high-grade dysplasia with a few identifiable areas of low/intermediate-grade dysplasia, and had invasive frequently adenocarcinomas at the time of surgical resection. Ohtsuka et al. also reported that mucin hypersecreting IPNBs showed striking similarities to IPMN and were usually in situ or minimally invasive, but IPNBs without mucin hypersecretion showed different phenotypes and frequent p53 and MUC1 expression from the former and were always invasive [8].

Zen, et al. recently proposed stringent histological criteria for “IPNBs” in order to discriminate

IPNBs from “papillary cholangiocarcinomas” [9]; “IPNB” was re-defined as a papillary neoplasm that was usually confined to the epithelium and infrequently associated with invasion and was regularly arranged in a high-papillary architecture along thin fibrovascular stalks with an overall uniform proliferation pattern throughout the tumor and typically developed in the intrahepatic or hilar bile ducts, while the tumors with more complex papillary structures (e.g., irregular papillary branching or mixed with solid–tubular growth) were termed “papillary cholangiocarcinoma” and were most often observed in the extrahepatic bile ducts.

Common understanding the pathological features of IPNB by Japan-Korea expert pathologists

Two meetings by expert pathologists from different institutions and countries were organized by the Japan-Korea study group on IPNBs to discuss pathological aspects of IPNB based on our own experiences, and also by reviewing published English literatures, particularly WHO 2010 classification [1,2] and by observing histology of selected IPNB cases. We had round-table discussions as well as histology reviews of IPNBs using a multiheaded microscope. The first meeting was held in Sendai, Japan, on 6th, August, 2016, and three Japanese (YN, NF, and TF) and two Korean pathologists (SMH and KTJ) participated. A total of 15 representative surgical cases of IPNB (9 males and 6 females with a mean age of 65 years ranging from 40 to 76 years, 9 cases of IPNB mainly affecting the intrahepatic bile ducts and 6 cases of IPNB mainly affecting the hilar and extrahepatic bile ducts) were examined with respect to four subtypes (intestinal, gastric, pancreatobiliary and oncocytic type), grades of dysplasia, and other histology in consideration of WHO 2010 classification, height, much mucin hypersecretion, considerable tubular components, and preinvasion and invasion. All of these cases of IPNB were diagnosed as IPNB according to the

criteria of WHO 2010 [1, 2]. The intraluminal or intracystic papillary neoplasm of the gallbladder and ampulla Vater were not included. Five cases of conventional nodular/sclerosing cholangiocarcinoma of hilar regions with intraductal nodular/papillary components were used as a control. All of these cases belonged to one medical center in Japan (Shizuoka Cancer Center, Japan), and a pathologist of this center (YN) selected these IPNB cases and control cases for this meeting. In each of these cases, more than 20 tissue sections including tumor parts and adjacent non-tumorous bile ducts were prepared, and routinely stained sections including H&E, mucin and collagen fiber stainings of representative sections were available. In addition, immunostaining of several representative sections for S100P, MUC1, MUC2, MUC5AC, MUC6, CDX2, CK7, CK20, CDX2, CD10, and p53 were also available in all cases. Concise clinical data including surgical procedures and imagings were also available.

After reviewing histologic sections and thorough discussions, we reached to share the common understandings related to the characteristic and diagnostic pathologic features of IPNB and its possible subclassification, and a rough draft on these issues was written and sent to all participants.

Then, the second meeting was held in Seoul, Korea, on 11th and 12th, February, 2017, for further discussion on IPNB, focusing on validation and polishment of common understandings of the pathologic features of IPNB and subclassification in Sendai by recruiting three new pathologists. First, we generally approved the IPNB draft (the common understanding of the characteristic pathologic features of IPNB and subclassification). Then, we reviewed histologically 20 cases of IPNB of the intrahepatic and extrahepatic bile ducts under multihead microscope. In this second meeting, only one representative H&E section from each case was examined. Though there were several controversies among pathologists on diagnostic criteria of IPNB such as the mucin secretion,

height, and grade of dysplasia and also subclassification of IPNB, the second meeting was successfully finished. After then, several issues continued to be discussed by email. Eventually, the common understandings on the pathologic features of IPNB and its subclassification were obtained as follows, though actual data were not obtained through these two meetings due to unique progress of two meetings.

A. Characteristic pathologic features of IPNB

i) Gross findings: IPNBs that show predominant intraductal growth occur in the intrahepatic and extrahepatic bile ducts. The macroscopic appearance of IPNBs highly varies among cases. Intrahepatic IPNBs frequently shows cystic dilatation of the affected duct, while extrahepatic IPNBs are typically associated with cylindrical or fusiform dilatation of the affected ducts.

ii) Histological findings and subtypes: IPNBs are characterized by intraductal papillary or villous biliary neoplasms covering delicate fibrovascular stalks. Some are nearly identical to pancreatic IPMNs microscopically, while others show different features including a complex papillary architecture and association with foci of solid-tubular growth. Most IPNBs arising in the intrahepatic bile ducts share pathologic features with IPMNs, while IPNBs in the extrahepatic bile ducts are microscopically less similar to IPMN. Four histological subtypes (gastric, intestinal, pancreatobiliary, and oncocytic types) may be observed in IPNBs, particularly IPMN-like cases. However, IPNBs often comprise more than one histological subtype.

iii) Degree of dysplasia: Although most IPNBs arising in the intrahepatic bile ducts are graded as high-grade dysplasia based on the highest degree of cellular atypia, areas of low/intermediate-grade dysplasia sometimes co-exist. Actually, some intrahepatic IPNB cases are composed of

low/intermediate dysplasia (adenoma). In contrast, a majority of IPNBs arising in the extrahepatic bile ducts are typically composed of high-grade dysplasia with occasional small areas of low/intermediate-grade components.

iv) Association with invasive malignancy: Unlike intrahepatic IPNBs, which are not infrequently non-invasive at the time of resection (~50% of cases), most extrahepatic papillary neoplasms have at least focal stromal invasion. The former appears to be less aggressive than the latter. Invasive carcinomas are mainly tubular or occasionally mucinous carcinomas, though they do not show papillary structures as seen in the intraluminal papillary neoplasm.

B. Subclassification of IPNB and diagnostic pathologic features

The relation between IPNB proposed by WHO 2010 and so-called papillary carcinoma or cholangiocarcinoma of extrahepatic bile ducts reported prior to WHO 2010 proposal was also discussed in these meetings. It was concluded that papillary carcinoma reported by Albores-Saavedra et al [15,16] and papillary cholangiocarcinoma by Zen et al [9] develop in the extrahepatic bile ducts and IPNBs with more similar features to IPMN typically develop in the intrahepatic bile ducts, though there may be histological overlaps between these two neoplasms. So, it is one of our common understandings that currently diagnosed IPNBs can be heterogeneous in their morphologies and biological activities according to its similarities to IPMN and its anatomical location along the biliary tree. So, while the term IPNB was used for all intraductal papillary neoplasm arising in the bile ducts in the WHO 2010 classification, IPNB based on it could be subclassified into two types (type 1 and type 2): the prototype of type 1 is “classical IPNB”, commonly in the intrahepatic bile duct with more or less similar features of IPMN, and that of type 2 is “so called papillary carcinoma

or cholangiocarcinoma” with a more complex histologic papillary architecture typically arising in the extrahepatic bile duct. While IPNB itself is a preinvasive biliary neoplasm of the bile duct, type 2 IPNBs are mostly associated with invasion and type 1 IPNBs are also not infrequently associated with invasion at the time of surgical resection. Interestingly, invasive carcinoma areas of both types were mainly tubular and occasionally mucinous. The key gross and microscopic features of these neoplasms are summarized in Table 1. We also propose the following criteria for the pathologic diagnosis of the two types of IPNBs.

1. Type 1 IPNB (Classical IPNB)

i) This is principally a papillary neoplasm consisting of the lining neoplastic epithelium and delicate fibrovascular stalks (Figures 1A and 1B). Growth patterns vary among cases, but are relatively uniform and well organized in individual tumors.

ii) Papillary stalks are generally thin, but occasional foci of edematous broad stroma may also be present. The edematous stroma is also a microscopic change sometimes observed in pancreatic IPMNs.

iii) In addition to the papillary architecture, tubular components may co-exist, particularly in gastric-subtype neoplasms. Tubules are well organized and do not show a cribriform pattern or fused glands. Oncocytic-type tumors also show a complex growth pattern (Figure 1C).

iv) Gross mucin is common (~80%); however, the lack of mucin overproduction does not exclude the possibility of type 1 IPNB.

v) Many cases are composed of high grade dysplasia with not infrequent microscopic foci of low/intermediate-grade dysplasia, and actually, some cases are only composed of low/intermediate

dysplasia or adenoma, suggesting multi-step carcinogenesis (Figure 1D).

vi) This subtype is not infrequently associated with invasive carcinomas.

2. Type 2 IPNB (So-called papillary carcinoma or cholangiocarcinoma)

i) This is also a biliary neoplasm showing predominantly intraductal papillary growth. The papillary architecture is complex with thin and occasionally varying thick fibrovascular stalks and often associated with irregular branching (Figures 2A and 2B). Tubular, cribriform, and solid components may also be observed, but do not exceed 50% of the intraductal components (Figure 2C).

ii) Tumors show papillary growth with fibrovascular stalks typically >5 mm in the height from the adjacent biliary mucosa. This is a useful standard for the discrimination of this neoplasm from biliary intraepithelial neoplasia (BilIN), another intraepithelial neoplasm of bile duct (1), that shows micropapillary growth less than 3 mm in height.

iii) Grossly identifiable mucin overproduction is uncommon (~10%).

iv) Most cases are histologically the pancreatobiliary or intestinal type, or a mixture of the two. The gastric type is rare, while the oncocytic type is exceptional.

v) Non-invasive components are always high-grade dysplasia with a few identifiable component of low/intermediate-grade dysplasia.

vi) Most cases are associated with invasive growth (Figure 2D), at least focally, at the time of surgical resection. Extensive sampling may be required to identify small foci of invasion, particularly in tumors with extensive lateral spread.

Unanswered questions to IPNBs to be solved in future

This two-nation collaborative meeting by expert pathologists helped us to understand the characteristic pathologic features of IPNB and to share the diagnostic pathologic features of IPNB and subclassification of IPNB by discussion and reviewing histologically IPNB cases fulfilling the proposal of WHO 2010. Although we shared the idea that there are possible two types of IPNBs originated by WHO 2010 classification, currently available data are still insufficient for reaching a conclusion on how these two IPNBs are related and how these two IPNBs and ordinary bile duct cancers are different.

Some pathologists insisted that both types share one pathologic condition or stage, “preinvasive state”, thus belonging to unique concept of preinvasive intraductal papillary neoplasm of the bile duct [1,2], the only difference being that type 1 IPNBs usually arise in the intrahepatic bile ducts and type 2 in the extrahepatic bile ducts. Some cases may have overlapping features, thus, may be difficult to classify into either of the two types, and some cases present similar IPNBs synchronously and/or asynchronously in the intrahepatic as well as extrahepatic bile ducts, supporting the concept that type 1 and type 2 IPNBs comprise a spectrum of IPNB along the biliary tree. In addition, type 1 and type 2 IPNBs are also associated with invasion. In contrast, other investigators insisted that type 2 IPNB is distinct from type 1 IPNB and more likely to be an extreme papillary variant of conventional cholangiocarcinomas, as mentioned below. More clinicopathological studies and comparative molecular studies are needed in order to resolve this issue and to clarify the significance of this subclassification.

Another potential issue relates to differentiation between type 2 IPNB and ordinary bile duct cancers. While conventional cholangiocarcinomas typically present nodular/fibrosing growth of the

affected bile ducts, they can also contain variable amounts of intraductal growth components with tubular or papillotubular adenocarcinoma and fibrous stroma in addition to nodular/sclerosing growth of the affected bile ducts, the discrimination between two may not be clear in some cases. These facts raise the idea, in which type 2 IPNB is merely a variant of ordinary bile duct cancer. Furthermore, since some cases with type 1 and type 2 IPNBs may have overlapping features, as mentioned above, there is also an opinion that all types of IPNB may be simply a variant of ordinary bile duct cancers. The proposed diagnostic criteria of type 2 IPNB (papillary components comprising >50% of the intraductal tumor and papillary growth typically >5 mm in height) will be useful for discrimination between IPNB and BillIN. These separation criteria are somewhat arbitrary, but will become a reasonable scheme for future investigations. Using the same diagnostic standard is crucial for comparing findings among studies toward consensus building on what IPNB is.

Conclusions

This statement describes that Japan-Korea IPNB expert pathologists reached to the common understanding of characteristic and diagnostic pathologic features of IPNBs diagnosed on the basis of the WHO 2010 classification and in addition, proposed its possible subclassification into two types. Currently, the features of IPNB is still confusing, since there are only data obtained from tumors diagnosed as IPNB through the different pathologic criteria. Therefore, the authors hope that the proposed diagnostic pathologic features of IPNB and its subtypes stated here will be of use for future clinicopathological and molecular analyses. The feedback of the results obtained from these future analyses would be expected to lead refinement and optimization of the clinicopathological

definition of IPNB.

Conflicts of interest: None to declare

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Figure legends

Figure 1. Histopathological features of classical IPNBs. (A and B) Tumor cells are arranged in an overall well-organized, high-papillary architecture. (C) The oncocytic type shows a complex architecture with tubular structures. (D) A component of low/intermediate-grade dysplasia may also be present.

Figure 2. Histopathological features of type 2 IPNBs/papillary cholangiocarcinomas. (A and B) The papillary architecture is complex with irregular branching and thick fibrovascular stalks. (C) Cancer cells show a tubular growth with intraluminal necrosis. (D) The tumor is associated with invasive cancers.

