Tumoral Versus Flat Intraepithelial Neoplasia of Pancreatobiliary Tract, Gallbladder, and Ampulla of Vater

Kee-Taek Jang, MD, PhD; Sangjeong Ahn, MD

• Context.—The identification of a precursor lesion is important to understanding the histopathologic and genetic alterations in carcinogenesis. There are a plethora of terminologies that describe precursor lesions of the pancreatobiliary tract, ampulla of Vater, and gallbladder. The current terminologies for precursor lesions may make it difficult to understand the tumor biology. Here, we propose the concept of tumoral and flat intraepithelial neoplasia to improve our understanding of precursor lesions of many epithelial organs, including the pancreatobiliary tract, ampulla of Vater, and gallbladder.

Objective.—To understand the dichotomous pattern of tumoral and flat intraepithelial neoplasia in carcinogenesis of pancreatobiliary tract, ampulla of Vater, and gallbladder.

Data Sources.—Review of relevant literatures indexed in PubMed.

Conclusions.—Tumoral intraepithelial neoplasia presents as an intraluminal or intraductal, mass-forming, polypoid lesion or a macroscopic, visible, cystic lesion without intracystic papillae. Microscopically, tumoral intraepithelial neoplasia shows various proportions of papillary and tubular architecture, often with a mixed pattern, such as papillary, tubular, and papillary-tubular. The malignant potential depends on the degree of dysplasia and the cell phenotype of the epithelium. Flat intraepithelial neoplasia presents as a flat or superficial, spreading, mucosal lesion that is frequently accompanied by an invasive carcinoma. Tumoral and flat intraepithelial neoplasias are not homogeneous entities and may exhibit histopathologic spectrum changes and different genetic profiles. Although intraepithelial neoplasia showed a dichotomous pattern in the tumoral versus flat types, they can coexist. Tumoral and flat intraepithelial neoplasia can be interpreted as part of a spectrum of changes in the carcinogenesis pathway of each organ.


A denoma is the prototype precursor lesion in carcinogenesis. The adenoma-carcinoma sequence is one of the well-characterized models of the carcinogenesis pathway. Through the adenoma-carcinoma sequence, many histopathologic and genetic alterations have been characterized in colorectal carcinogenesis.1,2 Another prototype precursor lesion is uterine cervix dysplasia, which also progresses to invasive squamous cell carcinoma of the uterine cervix through multistep carcinogenesis. Both colon adenoma and uterine cervix dysplasia correspond to intraepithelial neoplasia (IN), which can lead to invasive carcinoma. Most colorectal adenomas present as a polypoid lesion, whereas uterine cervix dysplasia presents as a nonpolypoid, flat, mucosal lesion. We think colon adenoma and uterine cervix dysplasia represent a mass-forming tumoral IN and a nonmass-forming, flat IN, respectively. In general, tumoral IN corresponds to a macroscopic or mass-forming lesion, and flat IN presents as invisible or microscopic lesions. Flat adenomas have been reported in the colorectum, which is much closer to a flat IN, and papillary squamous cell carcinoma of the uterine cervix, which is closer to a tumoral IN, has also been reported in the uterine cervix.3 Flat adenoma was a debatable entity to gastroenterologists for a long time because most colorectal adenomas were mass-forming, polypoid lesions.4–7 There are a plethora of terminologies describing polypoid or flat mucosal lesions of the colorectum and other organs. Various terminologies describing IN have made it difficult for clinicians and pathologists to understand the biological behavior of IN in carcinogenesis. Here, we attempt to provide a convenient explanation of IN with the concept of tumoral versus flat type to understand the biological behavior of IN in many organs with emphasis on the pancreatobiliary tract, ampulla of Vater, and gallbladder.

In this review, we will first discuss the tumoral and flat IN of the colorectum. We will then present similar examples from the pancreatobiliary tract, ampulla of Vater, and gallbladder. Finally, we will demonstrate a similar pattern of tumoral and flat IN in other epithelial organs.
TUMORAL INTRAEPITHELIAL NEOPLASM IN THE COLORECTUM

Polypoid Versus Nonpolypoid Colorectal Neoplasia

Colorectal adenoma usually presents as a polypoid lesion that is easily detected and removed by a gastroenterologist. There has been a long debate regarding nonpolypoid, flat adenoma in the colorectum. Muto et al. first described flat adenoma of the colon and emphasized the high incidence of high-grade dysplasia in flat adenomas, even in those of small size.10 Currently, flat adenomas are recognized as differing from polypoid adenoma in their malignant potential and genetic alterations during carcinogenesis.22–24 The APC and KRAS mutations, which are common in polypoid adenoma, are found less frequently in nonpolypoid and depressed lesions.18–20

Colorectal adenoma has a range of growth patterns from flat or slightly elevated lesion to large sessile or pedunculated polyps. The growth patterns of superficial, neoplastic mucosal lesions of the colorectum are divided into polypoid and nonpolypoid subtypes in the Paris classification.21 According to the Paris classification, polypoid lesions are pedunculated or sessile type (0-Ip or 0-Is), and nonpolypoid tumors are either superficial and elevated (0-IIa, <2.5 mm), flat (0-IIb), or superficial, shallow, depressed types (0-IIc). Excavated or ulcerated types are classified as 0-III and usually do not occur in the colon. We think there is a dichotomous pattern between tumoral and flat IN in colorectal, premalignant mucosal lesions. In addition to simple comparisons of polypoid versus nonpolypoid adenoma—carcinoma sequence, serrated polyps have been reported to have a different genomic profiles when compared with nonserrated adenoma—carcinoma sequence.25 Lambert et al. suggested a pragmatic classification of superficial, neoplastic colorectal lesions based on the presence or absence of serrated lesions, with additional mutation and genomic profiles that include chromosomal instability, microsatellite stability or instability, and CpG island methylator phenotype. In their pragmatic classification, nonserrated lesions were composed of polypoid adenoma, nonpolypoid and nondepressed adenomas, lateral spreading tumor adenomas, and nonpolypoid and depressed adenomas; polypoid adenomas showed a high proportion of APC and KRAS mutations, lateral spreading tumor adenomas showed a high frequency of KRAS and p53 mutation,23 and nonpolypoid and depressed adenomas showed a much higher proportion of submucosal invasion than other subtypes.24 The lateral spreading tumor adenoma was defined as a colorectal mucosal lesion larger than 10 mm with a growth pattern of superficial spreading. Lateral spreading tumor adenomas show a high frequency of high-grade dysplasia and local invasion when compared with pedunculated polyps of similar size.25,26 This mucosal spreading pattern has also been reported in bile duct carcinoma.27 The pragmatic classification of serrated lesions included hyperplastic polyps, sessile serrated lesions, mixed hyperplastic and adenomatous polyps, and traditional serrated adenoma/carcinomas. Oka et al. reported that polypoid, traditional, serrated adenomas showed more frequent intramusosal neoplasia than nonpolypoid lesions.

Through the updated classification of superficial mucosal lesions in colorectum, a trend was observed in which high-grade dysplasia and accompanying carcinoma occurred more frequently in flat mucosal lesions, whereas a polypoid mucosal lesion exhibited a relatively lower frequency of invasive carcinoma. We think colorectal mucosal lesions may show the spectrum change from nonpolypoid (flat or depressed) to polypoid growth patterns, which may correspond to flat versus tumoral IN. However, mixed patterns of polypoid and nonpolypoid lesions are present, which means tumoral and flat IN may coexist in the same lesion.

PANCREATIC INTRADUCTAL PAPILLARY-MUCINOUS NEOPLASM VERSUS PANCREATIC INTRAEPITHELIAL NEOPLASIA

Intraductal papillary-mucinous neoplasm (IPMN) is a relatively well-recognized entity characterized by intraductal neoplasm with mucin production.29–30 Although its terminology includes mucin, the mucinous component is not always present in IPMN, which presents as a dilated duct and/or mural nodules within the pancreatic duct. Histologically, IPMN presents as an intraductal papillary growth of the duct-lining epithelium, with or without mucin (Figure 1, A). The tumor biology and malignant potential depend on the degree of dysplasia and the cell-lineage phenotype of IPMN.31,32 The epithelial cell-lineage phenotype of IPMN could be classified by gastric, pancreatobiliary, intestinal, and oncocytic types. Invasive carcinoma is more frequent in the pancreatobiliary cell phenotype, and mucin-producing colloid carcinoma is frequently associated with the intestinal cell phenotype. Mucin content is associated with most intestinal and some gastric cell phenotype IPMNs. Most branch duct type IPMNs belong to the low-grade, gastric cell phenotype. In World Health Organization 2010 classification, IPMN is one of the intraductal neoplasms, and the other is intraductal tubulopapillary neoplasm (ITPN), which has been reported to be distinct from IPMN because of the lack of mucin, the uniformly high-grade nuclear atypia, and the different genetic profiles (Figure 1, B).33–35 There were some cases that showed a predominantly microscopic tubular configuration in intraductal neoplasm of the pancreas. Shahinian et al. first reported a case of tubular adenoma of the main pancreatic duct. Since that case report, some authors have also reported similar patterns in intraductal tumor of the pancreas (Figure 1, C).37–39 Tajiri et al. reported a malignant tumor of intraductal tubular neoplasm of pancreas. These tumors have been described as intraductal tubular neoplasm of the pancreas. However, intraductal tubular neoplasm is considered one variant of IPMN, rather than a separate entity, because many IPMNs exhibit tubular components in histopathologic findings, especially the branch duct type of low-grade IPMN of the pancreas. It can be confusing and difficult to differentiate and understand the intraductal neoplasms of the pancreas by IPMN, ITPN, and intraductal tubular neoplasm. Although these intraductal lesions of the pancreas have shown some differences in histopathologic and genetic profiles, we think it may be reasonable to understand that these intraductal neoplasms belong to the category of tumoral IN of the pancreas because these lesions overlap with each other in histopathologic findings, and different molecular profiles can be found within the same tumor, such as different molecular subtypes of breast cancer and malignant lymphoma.43,44 We suspect that different genetic profiles may be present in tumoral IN of the same organ. We think tumoral IN of the pancreas is not a homogeneous entity and may exhibit a histopathologic
spectrum from tubular to papillary architecture, often with mixed patterns and different genetic profiles.

Most pancreas ductal adenocarcinomas arise from pancreatic IN (PanIN), which is a microscopic precursor lesion corresponding to flat IN of the pancreas (Figure 1, D). The differentiation of IPMN and PanIN is based on size and histologic findings. However, there are gray-zone cases, which make it difficult to clearly discriminate between PanIN and IPMN. In cases of branch duct IPMN, many, small PanIN-like lesions can be found around low-grade IPMN. It is not clear whether these gray-zone cases belong to PanIN around IPMN or incipient IPMN. They can be interpreted as either small duct involvement of the IPMN or ductal spread to the PanIN. We would like to suggest an interpretation of a gradual spectrum change of the intraepithelial ductal lesion from IPMN to PanIN; in large ducts, such as the main, first, or second branch duct, it presents as IPMN, and in small, peripheral ducts, such as an interlobular duct, it may appear as PanIN.

There are differences in the genetic alterations of PanIN and IPMN, which are associated with carcinogenesis. The mutations of the KRAS gene are common in both...
 precursor lesions. Mutations of TP53 and p16/CDKN2A are much less frequent in IPMN. Overexpression of the HER2 product if often reported in IPMN, in contrast to relatively low incidence in ordinary ductal adenocarcinoma. Loss of SMAD4 is frequently associated with the PanIN pathway, whereas retained SMAD4 product is present in most IPMNs. The GNAS mutation represents colloid carcinoma arising from the intestinal type of IPMN. 46,49

ADENOMA AS TUMORAL INTRAEPITHELIAL NEOPLASIA

Adenoma is one of the most commonly used terms for precursor lesions in human carcinogenesis; it is used to describe precursor lesions in various organs. The problem is that the term adenoma gives the impression that adenoma lesions have malignant potential to progress to invasive carcinoma and should be removed by surgical procedure, which may be unsuitable in some organs because the malignant potential of adenoma lesions varies for each disease entity. In the case of pancreas serous cystadenoma, the malignant potential is extremely low; a recent international study of serous cystic neoplasm of the pancreas showed an extremely low incidence (0.1%; 3 of 2622) of malignant serous cystic neoplasm. 40 In the pancreatic mucinous cystic neoplasm (MCN), a wide range of invasive carcinomas have been reported. 31 However, a pancreas MCN study with a relatively large cohort and histologic evidence of ovarian-type stroma showed a relatively low incidence (approximately 16%; 92 of 561) of invasive carcinoma, compared with the previously reported wide range of invasive carcinoma incidence. 52–55 In pancreas IPMN, the incidence of invasive carcinoma has been reported to be approximately 30% in resected IPMNs. 56–58 As we see it, the 3 “adenomas” in serous cystic neoplasm, MCN, and IPMN of pancreas cystic tumors showed a wide range for incidence with associated invasive carcinoma, even though they are all described as adenoma. We think that if the incidence of invasive carcinoma is very low, the term cystadenoma may be inappropriate, such as in serous cystadenoma of pancreas. However, when we see a serous or mucinous cystadenoma of the pancreas, it is a single layer of epithelial lining without cellular proliferation activity, such as the nuclear pseudostratification in colorectal adenoma. We think the description of adenoma in pancreas serous cystic neoplasm or MCN may be inappropriate and overused. Thus, we insist that adenoma should be used in tumoral IN with mass-forming lesions and epithelial proliferation activity. In cystic tumors of pancreas and other organs, it may be better to describe them as cystic neoplasms with low-grade or high-grade dysplasia than as cystadenoma. Although the indication for surgical resection for these pancreatic cystic tumors is less, most clinicians, including surgeons, may feel that an adenoma lesion should be removed by surgical resection because they have a solid concept of the adenoma-carcinoma sequence. The term adenoma should be used for polypoid, mass-forming tumoral IN with at least moderate to high-grade dysplasia of the lining epithelium. The question is whether to call cases of pancreas MCN or IPMN that do not exhibit papillary nodule tumoral IN. As mentioned, tumoral IN consists of mass-forming or macroscopic, visible cystic lesion. The mucosal nodule or intracystic papillary nodule of MCN or IPMN corresponds to mass-forming tumoral IN, and MCN or IPMN without mural nodules or intracystic papillary nodules correspond to macroscopic visible tumoral IN, even without mass-forming papillary nodules within the cystic tumor.

BILIARY INTRADEPTIHAL NEOPLASMA VERSUS BILIARY INTRAEPITHELIAL NEOPLASIA

Intraductal neoplasia of the biliary tract has been called by various names: papillomatosis, papillary adenocarcinoma of bile duct, mucin-producing papillary carcinoma, and intraductal papillary-mucinous neoplasm of bile duct, among others. 59–61 Zen et al 62 proposed the diagnostic term intraductal papillary neoplasm of bile duct (IPNB), which encompasses most histopathologic aspects of the intraductal neoplasm of the bile duct (Figure 2, A). Intraductal papillary neoplasm of bile duct shares similar features with pancreatic IPMN in terms of intraductal papillary growth pattern and 4 cell lineage types; however, it differs from pancreatic IPMN with less-frequent mucin production and more-frequent invasive carcinoma. 53–55 In the bile duct, there is an intraductal neoplasm that is similar to ITPN of the pancreas. Intraductal tubulopapillary neoplasm of the bile duct has histopathologic findings similar to ITPN of the pancreas (Figure 2, B). 56,67 However, ITPN of the bile duct has a different genetic-alteration pathway than IPNB. 48 Like the pancreas, the bile duct shows a similar spectrum of intraductal neoplasms of IPNB and ITPN, which corresponds to tumoral IN of the bile duct. Most cholangiocarcinomas are preceded by flat mucosal dysplasia of the bile duct, for which the term biliary intraepithelial neoplasia (BilIN) has been suggested. 69,70 Microscopically, BilIN is characterized by atypical epithelial cells with multilayering of abnormal nuclei, often with a micropapillary configuration (Figure 2, C). Similar to PanIN of the pancreas, BilIN corresponds to flat IN of the bile duct, and it shares molecular alterations of KRAS and TP53 in multistep carcinogenesis; however, it does not harbor GNAS1 mutations, in contrast to IPNB. 71 In the biliary tract, the dichotomous pattern of tumoral and flat IN can also be observed as IPNB versus BilIN.

TUMORAL INTRAEPITHELIAL NEOPLASM OF THE GALLBLADDER AND AMPULLA OF VATER

In World Health Organization 2010 tumor categories, the classification schemes for premalignant lesion of the ampullary region and gallbladder are similar. 69 The classification scheme is basically a 3-tier system: flat dysplasia, intestinal-type adenoma (tubular, tubulovillous, villous), and noninvasive pancreatobiliary papillary neoplasm are in the ampullary region, whereas BilIN, adenoma (tubular, papillary, tubulopapillary), and intracystic papillary neoplasm are in gallbladder. Although those premalignant lesions are classified as a 3-tier group, we can find a dichotomous pattern of flat versus tumoral IN: flat dysplasia and BilIN correspond to flat IN, such as flat adenoma of colorectum and PanIN and BilIN of the pancreatobiliary tract, whereas intestinal-type adenoma, noninvasive pancreatobiliary neoplasm of the ampullary region, and adenoma, intracystic papillary neoplasm of the gallbladder may belong to tumoral IN, such as polypoid adenoma of the colorectum and IPMN or ITPN of the pancreatobiliary tract. Similar precursor lesions, with a similar histopathologic spectrum, have been reported in pancreas IPMNs and IPNBs, such as intra-ampullary papillary-tubular neoplasms (Figure 3, A) of the ampullary region 72,73 and intracholecystic papillary-tubular neoplasms of the gallbladder (Figure 3,
We can find mass-forming tumoral IN in the ampullary region and gallbladder, so it may be reasonable to consider these mass-forming precursor lesions as tumoral IN because they share similar histopathologic findings and tumor biology. The genetic profiles for premalignant lesions of the ampullary region and gallbladder are relatively limited. The microsatellite instability phenotype is an early event that develops from adenoma of the ampullary region, and only a few ampullary adenomas harbor the KRAS and BRAF mutations. β-catenin and KRAS mutations are more frequent in gallbladder adenomas than they are in carcinoma.

The flat IN of the ampullary region (Figure 4, A) has not been well characterized. This is mostly because of the small size of the ampulla of Vater, and flat mucosal lesions are usually replaced by invasive carcinoma in most surgically resected specimens. Most gallbladder cancers occur in a background of mucosal dysplasia. The dysplasia-carcinoma sequence is a main carcinogenetic pathway in gallbladder cancer, which corresponds to the flat IN pathway. In World Health Organization 2010 classification, the flat mucosal dysplasia of the gallbladder is described as BillN (Figure 4, B). It usually presents as a flat or diffuse, granular mucosal lesion, and it is frequently associated with invasive carcinoma. Biliary IN can also be found in mucosa with chronic cholecystitis and may coexist with reactive atypia of the mucosal epithelium. Genetic studies on BillN of the gallbladder have not yet, to our knowledge, been performed.

**TUMORAL INTRAEPITHELIAL NEOPLASM IN OTHER ORGANS**

**The Dual-Tract Pathway of Urinary Bladder Carcinogenesis: Papillary Versus Nonpapillary**

Koss et al introduced the dichotomous pattern of urinary bladder carcinogenesis in the 1970s. According to the dichotomy pattern of carcinogenesis, urinary bladder cancer arises via 2 distinct, but somewhat overlapping, pathways termed papillary and nonpapillary. Urothelial carcinoma arising in the background of a papillary urothelial precursor lesion showed a low tendency for invasion and metastasis. The remaining urinary bladder cancer, which originated from nonpapillary urothelial dysplasia, showed a high incidence of invasive carcinoma and distant metastasis. Spiess and Czerniak demonstrated the different genetic alterations between the papillary and nonpapillary pathways in a mouse model of carcinogenesis; the superficial papillary pathway showed a mutant H-ras or overexpression of EGFR, and the high-grade, aggressive pathway overexpressed large SV-40 T antigen. Recent molecular studies of whole genome comparative genomic hybridization and messenger RNA expression profiling have demonstrated that the dichotomous pattern of urothelial carcinoma (papillary/superficial versus nonpapillary/muscle-invasive) are truly distinct molecular entities.

We found a dichotomous pattern of tumoral versus flat IN in urinary bladder cancer, which corresponded to tumoral (papillary/superficial) and flat (nonpapillary/muscle-invasive) IN of urinary bladder carcinogenesis.

**Uterine Cervix Intraepithelial Neoplasia Versus Papillary Squamous Cell Carcinoma**

The terminology of cervical IN represents the precursor lesion of invasive squamous cell carcinoma in the uterine

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**Figure 2. Biliary intraepithelial neoplasia.** A. Mass-forming tumoral intraepithelial neoplasm of intraductal papillary neoplasm of bile duct. B. Tumoral intraepithelial neoplasia of intraductal tubulopapillary neoplasm with high-grade dysplasia. C. Microscopic, flat mucosal lesion of biliary intraepithelial neoplasia (hematoxylin-eosin, original magnifications ×10 [A], ×40 [B], and ×100 [C]).
cervix. If polyoid colorectal adenoma is the typical example of tumoral IN, cervical IN may be the prototype for flat IN. Most cervical IN presents as a flat mucosal lesion and progresses to invasive squamous cell carcinoma. Human papillomaviruses have a key role in the genetic alteration of carcinogenesis in cervical squamous cell carcinoma. The tumor suppressor proteins p53 and pRB are degraded through ubiquitination by viral oncoproteins E6 and E7 from the early phase of cervical IN.86,87 Although rare, some papillary squamous cell carcinomas of the uterine cervix have been reported, and they corresponded to the tumoral IN lesion of the uterine cervix, with a low rate of human papillomavirus DNA and TP53 mutation.3,88 We also found 2 patterns of precursor lesions in the uterine cervix that corresponded to flat and tumoral IN in this organ.

When we see many epithelial neoplasias, some are mass-forming INs, such as squamous papilloma of the oropharynx and respiratory tract, and verrucous carcinoma and condyloma accuminatum of the skin. In contrast to those lesions, Bowen disease, penile IN, and vulva IN may belong to the
flat IN category. Most tumoral IN shows exophytic, mass-forming lesions with a low tendency for invasive carcinoma, whereas flat IN have a high incidence of being accompanied by invasive carcinoma. The dichotomous pattern of tumoral and flat IN may occur in various epithelial organs. We think the tumor biology and carcinogenesis pathway can be better understood using the concept of tumoral versus flat IN, rather than that of adenoma–carcinoma and dysplasia–carcinoma sequences.

CONCLUSIONS

Tumoral and flat IN may occur in various organs, including the pancreatobiliary tract, ampulla of Vater, and gallbladder (Table). Tumoral IN usually presents as mass-forming polypoid lesions or macroscopic visible, cystic lesions without intracystic papillae, whereas flat IN present with flat or depressed growth patterns. Invasive carcinoma may occur in the background of both types of IN, but the incidence of invasive carcinoma is greater in flat IN than it is in tumoral IN in most organs. However, the malignant potential of tumoral and flat IN in the pancreatobiliary tract also depends on the cell-lineage phenotype and the grade of dysplasia of the lining epithelium. The cell phenotype of tumoral IN could be classified as a dominant cell lineage, and it may present with a mixed cell-lineage phenotype. Tumoral and flat IN may occur and coexist within the same organ. Tumoral and flat IN could also have different histologic and genetic profiles. We think the concept of tumoral and flat IN may enhance our understanding of the biologic behavior of precursor lesions in the carcinogenesis model.

References


