Neoplastic precursors (dysplasia, intraepithelial neoplasia) of the gallbladder and biliary tract: terminology, classification, pathologic diagnosis, and clinical significance

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Abstract

In the past decade, there have been significant developments in the terminology, classification and understanding of the precursor neoplastic lesions of the gallbladder and bile ducts. Many analogies with their pancreatic counterparts have been identified. Multiple cell lineages (biliary, intestinal, foveolar, pyloric, and oncocytic) are recognized, with differential molecular/genetic fingerprints. Two distinct types have been characterized: (1) Non-tumour forming ("flat") type dysplasia, now also recognized under the heading of biliary intraepithelial neoplasia (BilIN). As in other organs, low-grade BilINs seem to be negligible. High-grade BilINs of the bile ducts seldom are encountered outside the setting of adenocarcinoma and thus also typically clinically irrelevant, perhaps except when they involve the margins. In the gallbladder, low-grade dysplasia is believed to be clinically inconsequential. Cases with gallbladder high-grade dysplasia (also known as "carcinoma in situ") also are often cured, although some may have recurrence/metastasis attributable to missed invasion or field-defect/field-effect emphasizing the crucial nature of total sampling. (2) Polypoid/papillary preinvasive neoplasms (tumoural intraepithelial neoplasia; TINs; i.e., adenoma–carcinoma sequence), for which, in the bile ducts, two distinct entities have been characterized, intraductal papillary neoplasms, and intraductal tubular/tubulopapillary neoplasms. In the gallbladder, all TINs have been proposed to be unified under the umbrella of intracholecystic papillary-tubular neoplasms. Non-invasive TINs are often curable if invasion is excluded definitively, although some exhibit recurrence/metastasis (due to missed invasion and/or field phenomenon). Invasive carcinomas arising in TINs appear to have less aggressive behaviour than ordinary invasive carcinomas. It is important to appreciate the clinicopathologic characteristics of these precursor lesions, both for management purposes and as invaluable models of carcinogenesis.

Keywords biliary intraepithelial neoplasia; dysplasia; intracholecystic papillary-tubular neoplasm; intraductal papillary neoplasm; intraductal tubulopapillary neoplasm

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Introduction

The incidence of carcinoma of the biliary tract varies in different geographical areas: intrahepatic carcinoma has the highest incidence in Asian countries, while gallbladder carcinoma is more frequent in parts of India and South America, reaching the highest incidence in Chile. In the USA, cancer of the gallbladder accounts for 0.17% of all cancers in males and 0.49% in females, while extrahepatic bile duct carcinoma accounts for 0.16% of all invasive cancers in males and 0.15% in females.[1] Biliary cancer frequently arises in the setting of chronic inflammation. In the large majority of patients with gallbladder carcinoma, the origin of chronic inflammation is represented by cholesterol gallstones. The presence of stones increases the risk of cancer four to five-fold. Additional risk factors include primary sclerosing cholangitis, ulcerative colitis, liver flukes, and *Helicobacter pylori* infection. Hepatitis virus B and C infections, heavy alcohol consumption, and hepatolithiasis may also play an important role in the pathogenesis of biliary cancer.[1]

In recent years it has been shown that invasive biliary carcinomas are preceded by two types of precancerous lesions: the 'flat' (non-mass-forming), and the mass-forming type (tumoural intraepithelial neoplasms). The flat type, a microscopically defined flat or at most micropapillary lesion, has been named 'biliary intraepithelial neoplasia (BilIN)'.[2,3] In contrast, the papillary and/or tubular mass-forming type is composed of macroscopically visible, intraductal growing mucosal proliferations, and has been named 'intraductal papillary neoplasms of the bile duct (IPNBs)'.[3] The more tubular examples are now being recognized separately and called 'intraductal tubular (or tubulopapillary) neoplasms of bile ducts (ITPNs-B)'.[3] In addition, the rare biliary mucinous cystic neoplasms (MCN) may also give rise to invasive adenocarcinomas.[3,4]

Precursor lesions of the bile ducts

Biliary intraepithelial neoplasia

Definition: microscopic, incidental, preinvasive neoplasia of the bile ducts are considered "flat" lesions. These often also have some papilla formation, but usually stubby, and by definition, the process does not form a grossly or radiographically recognizable mass. In the current WHO (2010 edition), the term "biliary intraepithelial neoplasia" (BilIN) has been proposed for these non-tumoural dysplastic lesions.[2,3] The BilIN classification scheme[3] employed a three-tiered approach as BilIN 1, 2 and 3.[3]

However, it is becoming clear that both biologically and for management purposes, a two-tiered system is more applicable. In fact, for the biliary tract, many pathologists have always maintained usage of dysplasia terminology in two tiers, low- and high-grade dysplasia.[5]

Clinical features: endoscopically, these "flat" lesions may be recognizable as a hyperemic zone or granular mucosa, depending on the type and degree of proliferation, but typically, they are detected incidentally in resection specimens. High-grade BilIN is detected in the adjacent mucosa of patients with invasive carcinoma in 40–60% of the cases.[5] However, the true incidence is difficult to determine due to definitional issues, and challenges in distinguishing from mucosal colonization and pagetoid spread of invasive carcinoma.

Pathologic features: flat precursor neoplasms do not form identifiable tumour, but some manifest as surface granularity or congestion. Microscopically, low-grade BilINs (grades 1 and 2; low-grade dysplasia) are characterized by the presence of disorderly atypical columnar, cuboidal, or elongated biliary type cells. High-grade BilINs correspond to carcinoma in situ, and consist of marked diffuse disturbance of cell polarity with tufting, papilla formation and detachment of cells into the lumen, nuclear atypia, and necrotic cells (Figure 1).

Differential diagnosis: the main differential diagnosis is with reactive epithelial atypia. In fact, low-grade BilINs (1 and 2) are virtually indistinguishable from hyperplastic/metaplastic changes with regenerative atypia.[2] For the distinction of high-grade dysplasia (BilIN-3/CIS) from reactive atypia, the features of architectural complexity, nuclear stratification, enlargement, hyperchromasia, and nuclear irregularity are helpful, while reactive changes are favoured by maturation toward the surface, evenness of nuclear chromatin, the presence of sharp and smooth chromatin, and lack of marked nuclear enlargement. In areas of active inflammation or ulceration, one should be cautious in diagnosing BilIN, since regenerative changes may also show substantial atypia, including nuclear crowding, enlargement, and sometimes even hyperchromasia, although in many cases the chromatin can display a pale pattern. A history of instrumentation or stent placement should also raise the bar significantly for a diagnosis of dysplasia.

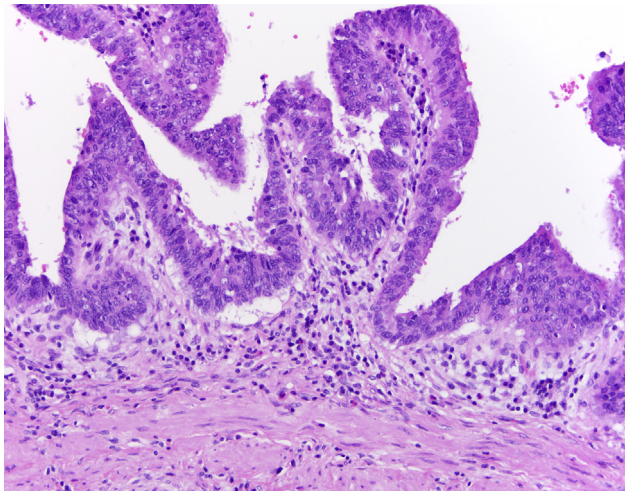

Figure 1 Biliary intraepithelial neoplasia with high-grade dysplasia. High-grade dysplasia (carcinoma in-situ) of bile duct (BilIN-3) is characterized by disorganized pleomorphic cells with nuclear enlargement and hyperchromasia.

BilIN-3 may also be difficult to distinguish from mucosal involvement by invasive carcinoma, referred to as cancerization/colonization of surface epithelium. If the mucosal neoplastic process shows direct spatial continuity and histologic similarity with the underlying invasive carcinoma, it is best regarded as cancerization rather than high-grade dysplasia.

BilIN that extends into accessory (peribiliary) mucous glands can result in a pseudoinfiltrative appearance. Preservation of a lobular architecture is a helpful clue of benignity, while carcinomas show more signs of dispersion. Additionally, peribiliary glands tend to have a small round appearance with narrow lumens, whereas invasive glands vary considerably in size and shape, and show contour irregularity and open and round lumens.

Natural history: since BilIN of bile ducts is most commonly detected incidentally in association with invasive carcinoma, its biologic behaviour and natural history have been difficult to evaluate. There are no data regarding the risk of progression of BilIN in the absence of invasive carcinoma. Low-grade dysplasias (BilINs 1 and 2), by themselves, are largely believed to be clinically inconsequential; their risk of progression has not been established, but is presumed to be low. However, high-grade dysplasia (BilIN-3; carcinoma in-situ) is believed to be a significant lesion that may be associated with (or progress into) invasive carcinoma with relatively high risk, and thus warrants careful clinical attention.

Intraductal papillary neoplasm

Definition: recently, the category of intraductal papillary neoplasms of the bile ducts (IPNBs) was proposed in order to encompass all tumours that used to be termed papillary adenomas, papillomas, papillary adenocarcinomas, intraductal papillary mucinous neoplasms of the bile ducts, and biliary papillomatosis.[3] The tubular mucin-poor cases are now being recognized separately as "intraductal tubulopapillary neoplasms",[6,7] discussed below.

This category is applicable to both the intra-hepatic and extra-hepatic bile duct system. Those occurring in the intra-ampullary segment of the common bile duct (CBD) (arising in the very distal aspect of the CBD within the duodenal wall) are termed intra-ampullary papillary-tubular neoplasms[8] and classified separately.

Clinical features: these tumours account for 10% of bile duct cancers.[9,10] The mean age of the patients is in the early 60s. Abdominal pain, jaundice, and cholangitis are the main symptoms and signs. Some cases are detected incidentally. In some studies, cases that are multifocal and show extensive examples with a florid papillary pattern, also called "*papillomatosis*," were detected in patients of younger age (mean, 50s).[1] Both sexes are affected equally. The incidence of high-grade dysplasia is quite high, and an association with invasive carcinoma is very strong.