Commentary

Organ-specific concept and controversy for premalignant lesions and carcinogenesis of gallbladder cancer

Keita Kai

Department of Pathology, Saga University Hospital, Saga 849-8501, Japan

Correspondence to: Keita Kai. Department of Pathology, Saga University Hospital, Nabesima 5-1-1, Saga City, Saga 849-8501, Japan. Email: kaikeit@cc.saga-u.ac.jp.

Abstract: An analysis of premalignant lesions, risk factors and models of carcinogenesis of gallbladder cancer (GBC) involves the concept of organ specificity. In GBC, the dysplasia-carcinoma sequence and metaplasia-dysplasia-carcinoma sequence are considered to be more important models of carcinogenesis than the adenoma-carcinoma sequence. Cholecystectomy is recommended for gallbladder polyps ≥1.0 cm, and all pre-invasive adenomas and papillary neoplasms ≥1.0 cm are defined as intracholecystic papillary-tubular neoplasms (ICPTNs). Although adenomyomatosis (ADM) and xanthogranulomatous cholecystitis (XGC) are controversial lesions, a knowledge of their clinicopathological features would help clinicians to manage gallbladder lesions associated with ADM or XCG.

Keywords: Gallbladder cancer (GBC); premalignant lesion; adenoma; intracholecystic papillary-tubular neoplasms (ICPTNs); adenomyomatosis (ADM); xanthogranulomatous cholecystitis (XGC)

Submitted Dec 01, 2015. Accepted for publication Dec 04, 2015.
doi: 10.3978/j.issn.2304-3881.2016.01.03
View this article at: http://dx.doi.org/10.3978/j.issn.2304-3881.2016.01.03

Gallbladder cancer (GBC) is generally considered to be a rare malignant neoplasm, and there has been no definitive definition to date of its premalignant lesions, risk factors or models of carcinogenesis. Barreto *et al.* recently reviewed models of the pathways of carcinogenesis of GBC (1). Stepwise development via adenoma/dysplasia to carcinoma is the most classical model of GBC carcinogenesis. Adenoma of the gallbladder typically presents as well-demarcated polypoid lesions. It is classified into three histological subtypes: the pyloric gland type, the intestinal type and the foveolar type (2). Pyloric gland-type adenoma is the most common variant. In colorectal cancer, the adenoma-carcinoma sequence proposed by Fearon and Vogelstein (3) is widely accepted as a major model of carcinogenesis, while in GBC, the malignant transformation of adenoma or the co-existence of adenoma with GBC is very rare (4). Therefore, the dysplasia-carcinoma sequence (5) or the metaplasia-dysplasia-carcinoma sequence (6) is considered to be more important models of gallbladder carcinogenesis than the adenoma-carcinoma sequence. Generally, a pathological diagnosis of dysplasia depends primarily on nuclear atypia, and a diagnosis of metaplasia depends primarily on features of cytoplasm.

The decision for or against surgical intervention is important in the clinical management of gallbladder polyps, and pathologists agree that, after cholecystectomy, routine pathological examination or extensive pathological examination of whole sections of the resected gallbladder is important. A consensus meeting of the Americas Hepato-Pancreato-Biliary Association (AHPBA) recommends surgery for gallbladder polyps ≥1.0 cm because polyps of this size are more frequently associated with cancer than smaller ones. The AHPBA also recommends extensive pathological examination of the remaining whole gallbladder when high-grade dysplasia is pathologically found in the polyp because carcinomatous changes frequently occur in the background gallbladder in that situation (7). Adsay *et al.* propose the term "intracholecystic papillary-tubular neoplasms" (ICPTNs) for all pre-invasive adenomas and papillary neoplasms of the gallbladder that are ≥1.0 cm,

regardless of the phenotype of tumor cells (8). By definition, ICPTNs embrace all subtypes of adenomas and intracystic papillary neoplasms in the WHO-2010 classification (2). Although intracholecystic papillary-tubular neoplasm was originally abbreviated as "ICPN" (8), "ICPTN" was used in the report on the AHPBA consensus meeting (7), probably to clearly distinguish "ICPTNs" from "intracystic papillary neoplasms".

Adenomyomatosis (ADM) and xanthogranulomatous cholecystitis (XGC) are controversial lesions. Although ADM is not generally considered a premalignant lesion, previous studies and case reports suggest the malignant potential of ADM, and segmental-type ADM is known to have an increased risk of carcinogenesis (9-12). It is difficult to prove whether a cancer truly arose from rokitansky-aschoff sinus (RAS) or surface *in situ* cancer extended into RAS. In addition, as the carcinogenesis of GBC correlates with the presence of gallstones and/or inflammation, the accompanying gallstones and/or inflammation tend to be considered responsible for the carcinogenesis rather than the presence of ADM itself. Although the malignant potential of ADM remains unclear, the clinician should keep in mind that a diagnosis of early GBC is very difficult in the context of preceding ADM (13). Actually, in our previous series of invasive GBCs, approximately 25% were grossly associated with ADM and all of these cases were diagnosed at the advanced (≥ T2) stage (14).

As XGC often coexists with GBC, the malignant potential of XGC is disputed. One study suggests the malignant potential of XGC for its upregulated oncogenes (BCL-2, c-Myc) (15), while another study suggests the inflammatory nature of XGC through the expression of p53, proliferating cell nuclear antigen (PCNA) and beta-catenin (16). It is of clinical importance that XGC often mimics GBC and rarely involves adjacent organs (17). Therefore, clinicians should include XGC among the possible differential diagnoses of masses in the liver hilum.

In summary, a thorough understanding of precancerous lesions of the gallbladder, adenoma, dysplasia, and ICPTNs requires organ specificity. Although ADM and XGC remain controversial, a knowledge of their clinicopathological features would help clinicians to better manage gallbladder lesions associated with ADM or XCG.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Commentary commissioned by the Deputy Editor-in-Chief Haitao Zhao (Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, China).
Conflicts of Interest: The author has no conflicts of interest to declare.

Comment on: Barreto SG, Dutt A, Chaudhary A. A genetic model for gallbladder carcinogenesis and its dissemination. Ann Oncol 2014;25:1086-97.

References

1. Barreto SG, Dutt A, Chaudhary A. A genetic model for gallbladder carcinogenesis and its dissemination. Ann Oncol 2014;25:1086-97.
2. Bosman FT, Carnerio F, Hruban RH, et al, editors. WHO Classification of Tumors of the Digestive System. Lyon: IARC Press, 2010:269-70.
3. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990;61:759-67.
4. Goldin RD, Roa JC. Gallbladder cancer: a morphological and molecular update. Histopathology 2009;55:218-29.
5. Wistuba II, Albores-Saavedra J. Genetic abnormalities involved in the pathogenesis of gallbladder carcinoma. J Hepatobiliary Pancreat Surg 1999;6:237-44.
6. Yamagiwa H, Tomiyama H. Intestinal metaplasia-dysplasia-carcinoma sequence of the gallbladder. Acta Pathol Jpn 1986;36:989-97.
7. Adsay V, Jang KT, Roa JC, et al. Intracholecystic papillary-tubular neoplasms (ICPN) of the gallbladder (neoplastic polyps, adenomas, and papillary neoplasms that are ≥1.0 cm): clinicopathologic and immunohistochemical analysis of 123 cases. Am J Surg Pathol 2012;36:1279-301.
8. Aloia TA, Járufe N, Javle M, et al. Gallbladder cancer: expert consensus statement. HPB (Oxford) 2015;17:681-90.
9. Ootani T, Shirai Y, Tsukada K, et al. Relationship between gallbladder carcinoma and the segmental type of adenomyomatosis of the gallbladder. Cancer 1992;69:2647-52.
10. Nabatame N, Shirai Y, Nishimura A, et al. High risk of gallbladder carcinoma in elderly patients with segmental adenomyomatosis of the gallbladder. J Exp Clin Cancer Res 2004;23:593-8.

11. Albores-Saavedra J, Shukla D, Carrick K, et al. In situ and invasive adenocarcinomas of the gallbladder extending into or arising from Rokitansky-Aschoff sinuses: a clinicopathologic study of 49 cases. Am J Surg Pathol 2004;28:621-8.
12. Funabiki T, Matsumoto S, Tsukada N, et al. A patient with early gallbladder cancer derived from a Rokitanski-Aschoff sinus. Surg Today 1993;23:350-5.
13. Kai K, Irie H, Ide T, et al. Actual status of clinical diagnosis in patients with primary gallbladder cancer associated with adenomyomatosis. Indian J Gastroenterol 2013;32:386-91.
14. Kai K, Ide T, Masuda M, et al. Clinicopathologic features of advanced gallbladder cancer associated with adenomyomatosis. Virchows Arch 2011;459:573-80.
15. Zhuang PY, Zhu MJ, Wang JD, et al. Xanthogranulomatous cholecystitis: a clinicopathological study of its association with gallbladder carcinoma. J Dig Dis 2013;14:45-50.
16. Ghosh M, Sakhuja P, Agarwal AK. Xanthogranulomatous cholecystitis: a premalignant condition? Hepatobiliary Pancreat Dis Int 2011;10:179-84.
17. Spinelli A, Schumacher G, Pascher A, et al. Extended surgical resection for xanthogranulomatous cholecystitis mimicking advanced gallbladder carcinoma: A case report and review of literature. World J Gastroenterol 2006;12:2293-6.

Cite this article as: Kai K. Organ-specific concept and controversy for premalignant lesions and carcinogenesis of gallbladder cancer. Hepatobiliary Surg Nutr 2016;5(1):85-87. doi: 10.3978/j.issn.2304-3881.2016.01.03

