Review of: "Traditional Serrated Adenoma of the Gallbladder, a Case Report"

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The gallbladder is an organ of foregut derivative. Metaplasia of cholecystic epithelium into gastric foveolar, pyloric and intestinal lineages can be seen in diseased states. However, neoplastic precursors especially polypoid proliferation are relatively low in prevalence in the gallbladder, probably due to its smaller organ size and less accessibility than other gastrointestinal (GI) tract. Pyloric gland adenoma and intracholecystic papillary neoplasm (ICPN) are the most common types recognized by WHO classification(1). They are characterized by their architectural morphology, either back-to-back tubules or arborizing papillae, and a spectrum of cell types from foveolar, pyloric, biliary, intestinal and oncocytic types(2). Some of the serrated polyps were categorized into ICPN based on the complex villiform/papillary structure. In contrast, traditional serrated adenoma (TSA) is extremely rare in the gallbladder.

Micsik et al. reported a TSA of the gallbladder without malignant transformation in a patient with chronic cholecystitis and cholelithiasis(3). This polypoid lesion, like other cholecystic preinvasive neoplasm, was large in size more than 1 cm. Morphologically, it demonstrated salient features of colonic TSA including villous/papillary structures, eosinophilic cytoplasm with pencillate nuclei, slit-like serration and ectopic foci formation. Mismatch repair proteins were retained in the lesion. Molecular assays identified *KRAS* G12D mutation, whereas *BRAF* was wild type. The case showed convincing morphology of TSA, distinguishing it from oncocytic variant of ICPN and tubulovillous adenoma.

Gallbladder TSA along with other upper gastrointestinal TSAs are relatively rare compared to colonic ones. Eosinophilic cytoplasm and slit-like serration in TSA are reminiscent of small intestinal mucosa. Thus the question is why TSA is not common in upper GI and pancreatobiliary tract, given its close developmental lineage. To answer this question, we need to understand how TSA grows from its normal epithelium. Although not completely understood, it is believed that at least some of the colonic TSAs are developed from hyperplastic polyp and sessile serrated lesion. DNA methylation, mitogen-activated protein kinase pathway (*KRAS/BRAF* mutation), WNT and possibly other signalings are the molecular underpinnings that dictate the cytological and architectural changes of TSA(4, 5). It is therefore possible that the rarity of upper GI and pancreatobiliary TSA is due to lack of signalings and/or interacting environmental factors, which function as the fostering soil for TSA in the colon. One obvious example would be colonic microbiota which is absent in upper GI and pancreatobiliary tract.

Another intriguing feature of upper GI and pancreatobiliary TSA is that it associates with a higher rate of invasive carcinoma, over 50%(6). It cannot be explained simply by amenability of precursor lesions or the size of the lesion (ICPN>1 cm is seen in 6.4% of carcinoma (2)). The intrinsic molecular alterations accounting for the aggressive behavior of gallbladder and other upper GI TSAs need to be explored in future studies.

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