Serrated Adenoma of the Gallbladder: A Case Report

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Abstract. *A case of serrated adenomatous polyp found in a cholecystectomy specimen is reported. The adenoma was built with mucosal crypts exhibiting unlocked serrations lined with up to high-grade dysplastic cells. A desmoplastic sclerotic tissue having multiple stromal hubs with branched thin spokes replaced the subjacent lamina propia, muscularis mucosae, and submucosa. The generous serrated configurations covering a multi-branched sclerotic stroma, gave the adenoma a papillary appearance. Review of the literature indicates that this appears to be the first reported case of serrated adenoma of the gallbladder.*

Most adenocarcinomas of the lower digestive tract evolve from foci of dysplastic mucosa, currently named conventional colorectal adenomas, through the (conventional) adenoma-carcinoma sequence (1). At histology, conventional colorectal adenomas usually exhibit tubular or villous configurations, with either low- or high-grade dysplasia (2). In this paradigm, hyperplastic polyps were considered innocuous.

In 1990, Longacre and Fenoglio-Preisser described the serrated adenoma, a novel colonic adenoma phenotype characterized by villous-like outgrowths displaying lengthwise, unlocked serrations (3). Subsequently, another adenoma phenotype was reported, the villo-microglandular adenoma, typified by microtubules found sideways and within villous-like outgrowths (4); this adenoma phenotype was re-named by the WHO in 2000 as microtubular adenoma (5).

In 2001, Jass postulated that the traditional adenoma-carcinoma sequence might not apply to sporadic Microsatellite instability (MSI)-High colorectal cancer and that the serrated pathway could be the missing link (6). Serrated colorectal polyps are presently classified into hyperplastic polyps, sessile serrated adenoma/polyps and traditional serrated adenomas (TSA) (7). Two phenotypes of TSA are recognized: one with dysplastic crypts depicting unlocked serrations, as described by Longacre and Fenoglio-Preisser (3), and the other revealing villous-like outgrowths with microtubules as described by Kubo *et al.* (4), or with ectopic crypt formations as described by Torlakovic *et al.* (8). In this paradigm, hyperplastic polyps, sessile serrated adenoma/polyps and TSA are regarded early histological precursors of serrated carcinoma (7).

The estimated frequency of the serrated pathway is approximately 15 to 30% of all colorectal cancers (9). Colonic cancer *via* the serrated pathway may occur at a faster rate than *via* the conventional adenoma-carcinoma pathway (10).

In previous publications, we reported serrated adenomas in other organs of the digestive tract, such as the esophagus (11), stomach (12), duodenum (13), pancreatic duct (14), the appendix (15) and the colorectum (16). Herein, I report a case of serrated adenoma of the gallbladder.

Case Report

The patient. A 75-year-old male had been treated for Crohn's colitis since 1982. In 2002, he complained of right upper quadrant pain. An ultrasound and a computed tomographic scan of the abdomen suggested a primary gallbladder wall malignancy. An open cholecystectomy was performed.

Gross examination of the gallbladder. The gallbladder measured 8 cm in length; an ulcerated tumor measuring 22×25 mm was found in the body. In addition, a 9×5 mm polyp was found in the fundus. No stones were identified.

Histological examination of the gallbladder. Low-power examination of the lesion in the fundus revealed a papillary polyp (Figure 1b). Closer examination disclosed an adenoma with papillary outgrowths built by dysplastic crypts with saw tooth-like configurations lined with up to high-grade dysplastic cells (Figure 1b and c). The subjacent *lamina propria*, muscularis mucosae and submucosa lengths of the entire papillary adenoma were replaced by sclerotic

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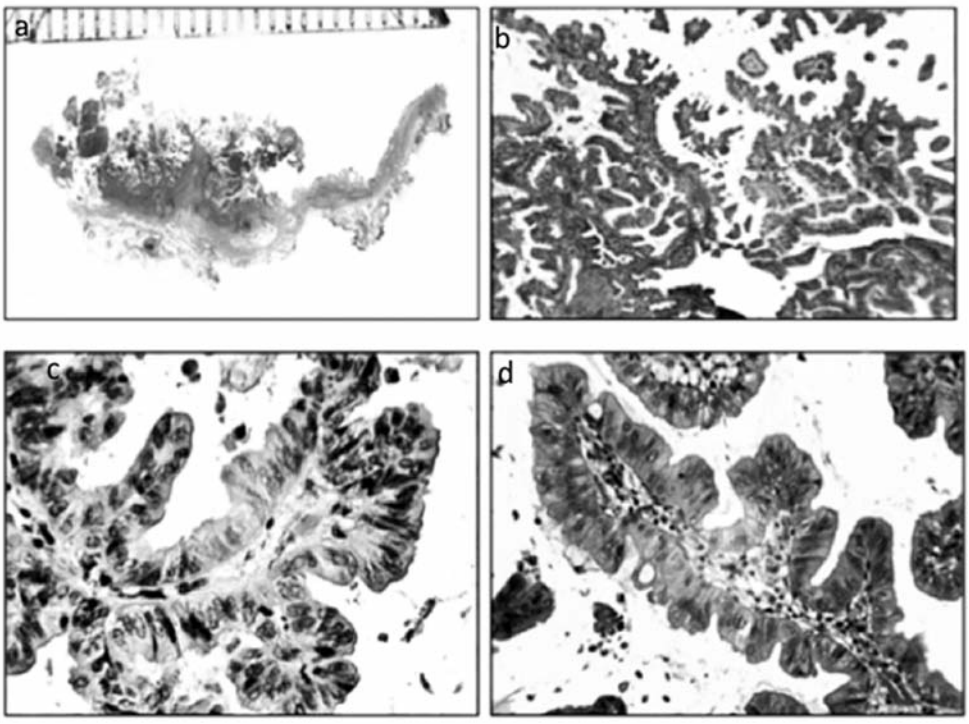

Figure 1. *Serrated adenoma of the gallbladder (surgical specimen). a: Overview of the papillary polyp (haematoxylin and eosin, section scanned with EPSON Perfection 4990; scale in mm). b: Low-power microscopical view showing the serrated pattern of the adenoma (haematoxylin and eosin, ×4), c, d: Detail showing the unlocked serrated crypts lined with high-grade dysplastic cells (haematoxylin and eosin, ×20).*

desmoplastic tissue with low cellularity. Detailed examination revealed a series of sclerotic hubs with branched spokes (Figure 1a). This setting was interpreted as papillary when examined under low-power microscopy.

Sections from the ulcerated area in the body disclosed a moderately differentiated adenocarcinoma. The tumor penetrated through the *muscularis propria,* and invaded the surrounding adipose tissue; no invasion of the liver bed was found. No perineural or intravascular tumor was identified. The intervening mucosa between the papillary serrated adenoma and the adenocarcinoma showed chronic inflammation; no dysplastic elements were found.

Follow-up. The patient underwent re-operation one month after cholecystectomy. The remnant fat, the ductus cysticus and the liver bed (corresponding to the previously removed gallbladder) were excised. The histological examination of the surgical specimen showed no remnant tumor.

In 2005, a liver biopsy revealed primary sclerosing cholangitis. In 2006 and in 2008, colonoscopical/histological examinations showed Inflammatory Bowel Disease in remission. In 2013, a computed tomographic scan revealed two tumors, one in the liver and the other in the hilus hepaticus. A liver biopsy disclosed a cholangiocarcinoma.

The patient died two months later. Autopsy was not performed.

Discussion

A low-power view of the gallbladder adenoma reported revealed an exuberant papillary polyp. Closer examination revealed serrated crypts lined with dysplastic epithelial cells. A similar histological pattern was described by Longacre and Fenoglio-Preiser (3) in the colon as serrated adenoma.

It was impossible to assess whether the invasive carcinoma in the body had evolved from a conventional adenoma or from a serrated adenoma similar to that in the fundus, since the adenocarcinoma showed no remnant adenoma. The intervening mucosa between the serrated adenoma in the fundus and the carcinoma in the body showed non-dysplastic chronic inflammation, indicating that the two neoplasias in the gallbladder were growing independently.

Underneath the exuberant papillary serrated adenoma, a larger sclerotic core sided by a successive collection of tiny sclerotic hubs was found. The luminal aspect of these hubs displayed branched sclerotic spokes. Papillary neoplasias occur in the gallbladder and extrahepatic bile ducts (17) and the pancreatic duct (18), but are extremely rare in other

adenomas of the digestive tract. The question arises: Why do papillary adenomas have a collection of multiple stromal cores with branched sclerotic spokes, while the majority of the conventional adenomas of the digestive tract have a single stromal core? One possible explanation may be that the molecular signals that choreograph the different stromal modalities (19) are organ-dependant.

In sum, a case of serrated adenoma of the gallbladder is reported. The histological characteristics of the epithelial component at high-power examination permitted to classify this lesion as serrated adenoma. Papillary adenomas should be classified, not by their appearance at low-power examination, but by the histological pattern of the dysplastic epithelium at higher examination, a microscopic criterion applied to classify other adenomas of the digestive tract (2).

The review of the literature indicates that this appears to be the first case of serrated adenoma of the gallbladder ever reported. Increased awareness of the existence of serrated intraepithelial neoplasias in the gallbladder may result in the report of similar cases from other Institutions in the future.

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