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Pathology of Gallbladder Diseases

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ABSTRACT

Various diseases are frequently found in the gallbladder. Cholesterolosis is one of the most common diseases of gallbladder. Acute and chronic cholecystitis are inflammatory disorders, associated with gall stones and metaplasia. Tumor-like lesions include adenomyomatosis, many types of polyps, and heterotopic tissues. WHO classification of tumors defines not only benign and malignant tumors, but also precursor lesions of gallbladder such as intracholecystic papillary neoplasm. Most malignancies are adenocarcinoma, which are aggressive phenotypes with lymphatic/venous/perineural invasion.

Keywords: Cholecystitis, Metaplasia, Polyp, Tumor, Adenocarcinoma

HISTOLOGY OF GALLBLADDER

The biliary tract (also biliary system) refers to the liver, gallbladder, and bile ducts, and works to make, store, and secrete bile. The gallbladder is a pear-shaped hollow organ, measuring 7 to 10 cm in length, and 3 to 4 cm in width. Normal gallbladder wall is approximately 1 to 2 mm thick [1].

Histologically, the gallbladder wall is divided into the three layers: (1) mucosa, (2) muscular layer, and subserosa. The mucosa is subdivided into the two components: the columnar epithelium, and lamina propria mucosae. The muscular layer consists of the thin layer of smooth muscle bundles. The subserosa is composed of loose connective tissue, including medium-sized arteries/veins/nerves.

There are small tubulo-alveolar glands in the wall of the gallbladder neck and the cystic duct. The gallbladder wall frequently shows Rokitansky-Aschoff sinuses which are diverticulum-like structure of mucosal epithelium into and through the muscular layer.

ANOMALOUS PANCREATICOBILIARY DUCTAL UNION (APBDU)

In the APBDU cases, the junction of the common bile duct and pancreatic duct lies outside the duodenal wall (sphincter of Oddi) and is frequently associated with congenital choledochal cyst/dilatation [2]. The gallbladder with APBDU shows mucosal hyperplasia, one of the high-risk lesions of gallbladder adenocarcinoma.

CHOLESTEROLOSIS

Cholesterolosis refers to lipid deposition within macrophages in the lamina propria mucosae and is one of the most common diseases of gallbladder (**Figure 1**). Macroscopically, the gallbladder mucosa shows granular or reticular pattern of cholesterolosis in golden-yellow to white-yellow color. Microscopically, numerous lipid-laden macrophages aggregate in the lamina propria mucosae.

A. Acute cholecystitis

Acute cholecystitis is caused by inflammation, blood circular disturbance such as ischemia, and chemicals. The gallbladder wall exhibits mucosal edema, congestion/hemorrhage, and erosion. Edema, congestion/hemorrhage, fibrinous exudates are associated with ischemic changes, and inflammatory cells such as neutrophils are related to the infection.

A-1. Acute gangrenous cholecystitis

Acute gangrenous cholecystitis is caused by circular disturbance, and characterized by extensive transmural necrosis with edema, congestion/hemorrhage, erosion/ulceration, and inflammatory exudates. Transmural ghost-like necrosis is caused by severe ischemia and infarction.

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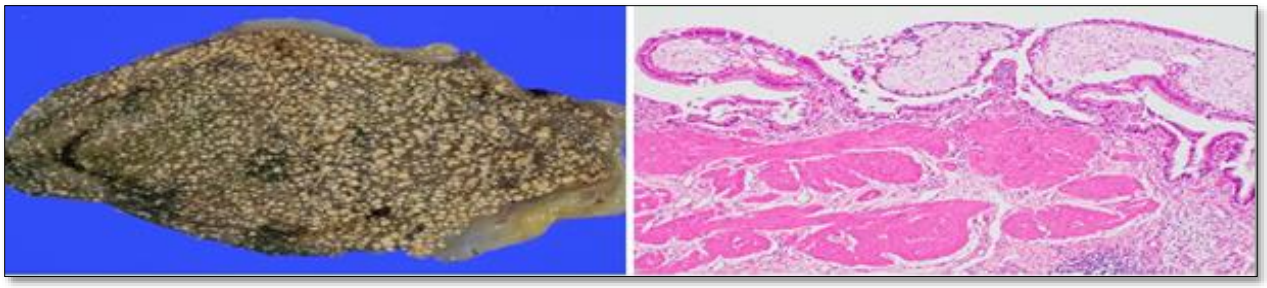

Figure 1. Cholestrolosis. Gross finding (Left) and histopathology (Right).

INFLAMMATION

A-2. Xanthogranulomatous cholecystitis (XGC)

XGC is a rare type of gallbladder inflammation and is characterized by xanthogranuloma formation with lipid-laden macrophages and granulation tissue. XGC occasionally forms pseudo-tumoral lesion with adjacent organ involvement, mimicking gallbladder cancer (**Figure 2**).

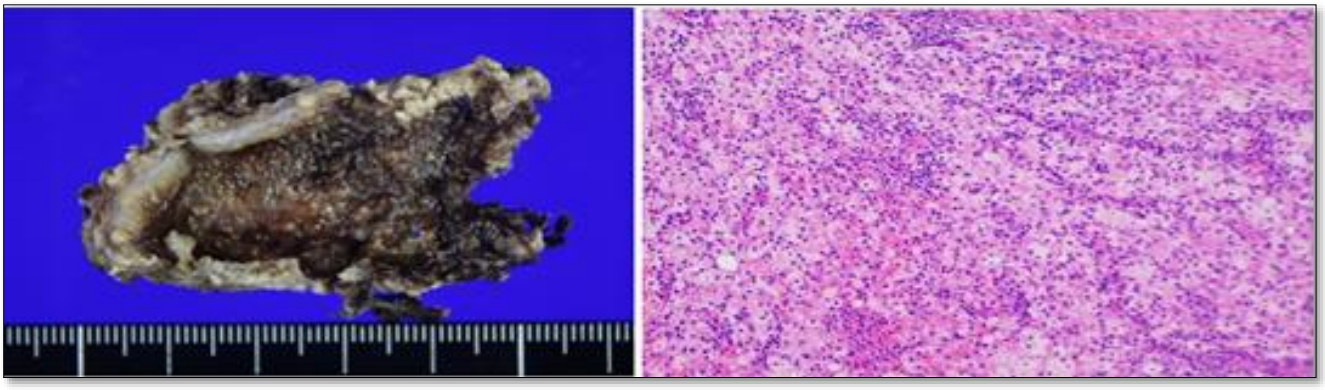

Figure 2. Xantogranulomatous cholecystitis. Gross findings (Left) and histopathology (Right).

B. Chronic cholecystitis

Chronic cholecystitis results from chronic persistent inflammation of the gallstones, and/or prolonged state of acute cholecystitis. Histologically, chronic cholecystitis is characterized by (1) inflammatory cell infiltration occasionally with lymphoid follicle formation, (2) fibrosis with gallbladder wall thickening, and (3) changes of mucosal epithelium frequently with metaplasia.

B-1. Metaplasia

Various metaplastic changes are present in gallbladder mucosa, including pyloric gland metaplasia (gastric metaplasia), goblet cell metaplasia (intestinal metaplasia), and surface cell mucous metaplasia (**Figure 3**) [3].

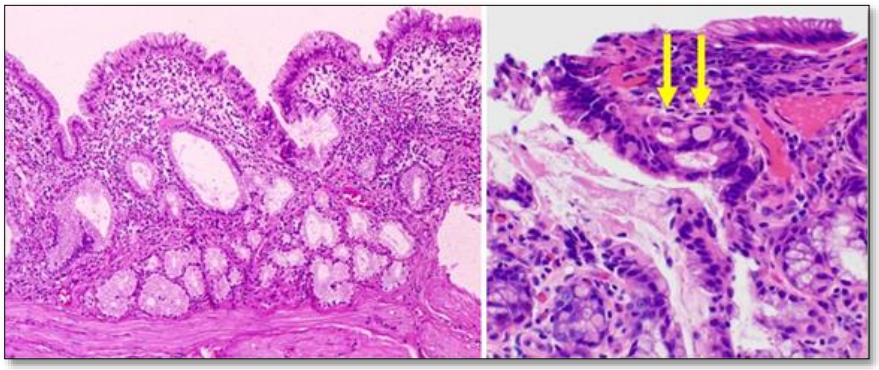

Figure 3. Metaplasia. Gallbladder mucosa shows surface cell mucous metaplasia at the mucosal surface and pyloric gland metaplasia in the lamina propria mucosa (Left)/ Goblet cell metaplasia is noted in the epithelium (Right, arrows).

Pyloric gland metaplasia, also known as gastric metaplasia, results from chronic inflammation and forms tubule-alveolar mucous glands similar to the gastric pyloric glands. Goblet cell metaplasia, also intestinal metaplasia, is characterized by goblet cells in the mucosal epithelium. Intestinal metaplasia is infrequently associated with Paneth cell and brush border formation.

Immunohistochemically, the gallbladder epithelium without metaplasia is positive for CD10 and CA19-9 at the epithelial luminal surface. MUC5AC-positive cells are present at the mucosal surface epithelium with pyloric gland metaplasia and/or surface cell mucous metaplasia. In addition, MUC-6 immunoreactivity is noted in the metaplastic pyloric glands. Intestinal metaplasia shows MUC2-positive goblet cells in the epithelium.

TUMOR-LIKE LESIONS, INCLUDING ADENOMYOMATOSIS AND POLYPS

A. Adenomyomatosis

Adenomyomatosis, also known as adenomyomatous hyperplasia, is hyperplastic changes of Rokitansky-Aschoff sinuses in the gallbladder wall, frequently related to fibromuscular thickening of gallbladder wall (**Figure 4**) [3]. Macroscopically, adenomyomatosis is usually divided into three types. (1) fundal type (local type), adenomyomatosis forms a tumorous lesion mimicking true neoplasia; (2) segmental type (annular type), adenomyomatosis deforms the gallbladder in an hourglass-like shape; and (3) diffuse type.

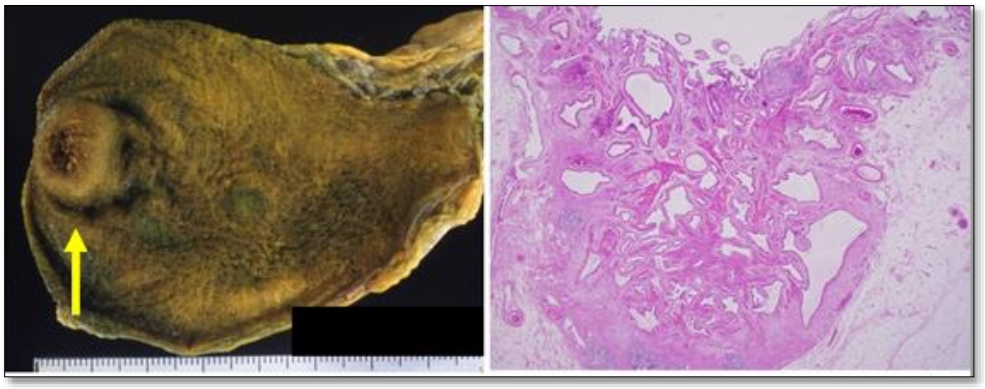

Figure 4. Adenomyomatosis, fungal type. Gross findings (Left, arrow) and histopathology (Right).

B. Polyps

Gallbladder polypoid lesions include neoplastic lesions such as adenoma and adenocarcinoma (intramucosal), and non-neoplastic polyps such as cholesterol polyp, hyperplastic polyp, and granulation tissue polyps (**Figure 5**) [3].

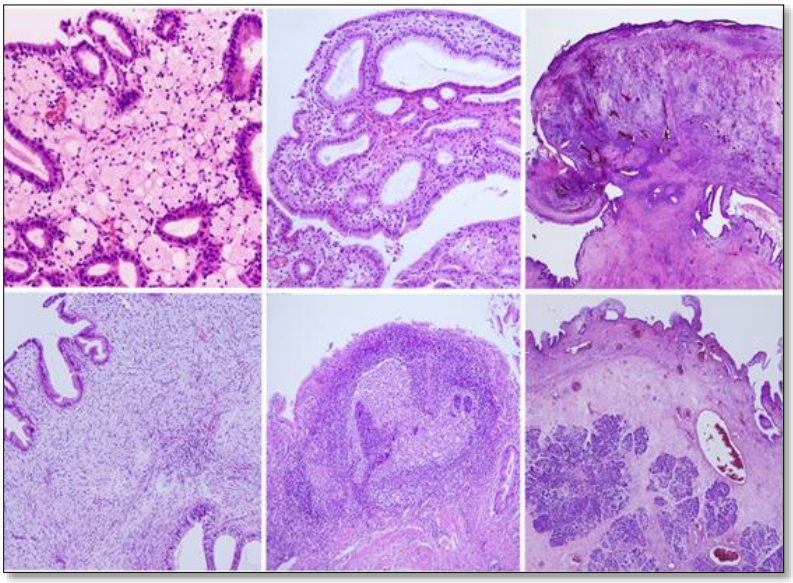

Figure 5. Polyps and ectopic tissue. Cholesterol poly (Top left), Hyperplastic polyp (Top middle), Granulation tissue polyp (Top right), Fibrous polyp (Bottom left), Lymphoid polyp (Bottom middle), and Ectopic liver (Bottom right).

Cholesterol polyp is the most common type of gallbladder polyps and is characterized by lipid-laden macrophages and hyperplastic epithelium. Hyperplastic polyp consists of epithelial or glandular hyperplasia without atypia. Granulation tissue consists of granulation tissue with inflammation and is frequently related to the acute cholecystitis. Fibrous polyp and inflammatory polyp are composed of loose connective tissue and are associated with resolving stage of acute inflammation. Lymphoid polyp consists of hyperplastic lymphoid tissue with germinal centers (**Table 1**).

Table 1. Morphological characteristics of gallbladder polyps.

Non-neoplastic polyps	
Cholesterol polyp	Mulberry-like yellowish-white polyp with a thin stalk. The polyp consists of lipid-laden macrophages.
Hyperplastic polyp	Papillary or nodular polyp. The polyp consists of hyperplastic epithelium or glands.
Granulation tissue polyp	Brownish polyp with necrotic tissue. The polyp consists of granulation tissue with inflammation.
Fibrous polyp	Polyp consists of fibrous/fibrovascular tissue.
Inflammatory polyp	Polyp consists of loose/fibrous connective tissue with inflammation.
Lymphoid polyp	Polyp consists of hyperplastic lymphoid tissue.
Neoplastic polyps	
Adenoma	Benign neoplasm of pyloric glands phenotype.
Intracholecystic papillary neoplasm	Papillary non-invasive epithelial neoplasm.
Adenocarcinoma	Epithelial neoplasm with/without invasion.
Neuroendocrine tumor	Neoplasm with neuroendocrine differentiation.

C. Ectopic tissues

Several types of ectopic tissue, such as liver, pancreas, and gastric mucosa, are noted in and attached to the gallbladder wall.

TUMORS

The most of gallbladder tumors are epithelial neoplasms and are divided into the three categories: benign epithelial tumors, borderline epithelial tumors (precursors), and malignant epithelial tumors [4] (**Table 2**).

Table 2. Non-invasive neoplasms of gallbladder, bile duct, and ampullary region.

	Gallbladder	**Bile duct**	**Duodenal ampulla**
Papillary neoplasm	Intracholecystic papillary neoplasm (ICPN)	Intraductal papillary neoplasm of bile duct (IPNB)	Intra-ampullary papillary-tubular neoplasm (IAPN)
Flat neoplasia	Biliary intraepithelial neoplasia (BilIN)		
Benign neoplasm	Pyloric gland adenoma		Ampullary adenoma

A. Benign epithelial tumor

A-1. Pyloric gland adenoma

Pyloric gland adenoma is recognized as nodular polyp and is histologically composed of packed small pyloric-type glands with minimal stroma [3,5]. MUC-6 immunoreactivity is noted in the pyloric-type glands.

B. Borderline epithelial tumor (precursors)

Borderline epithelial tumors are classified as the two categories: intracholecystic papillary neoplasm (ICPN) and biliary intraepithelial neoplasia (BilIN).

B-1. Intracholecystic papillary neoplasm (ICPN)

ICPN is grossly recognized as mass forming, non-invasive epithelial neoplasm arising from the gallbladder lumen (**Figure 6**). ICPN forms an exophytic (papillary or polypoid) company lesion, frequently more than 1 cm in a size [4,6]. According to the histopathological findings, ICPN is divided into the three groups: ICPN with low-grade intraepithelial neoplasia, ICPN with high-grade intraepithelial neoplasia, and ICPN with associated with invasive carcinoma. Four morphological phenotypes are recognized: (1) biliary type (frequently positive for CK7, MUC1), (2) gastric type (frequently positive for MUC5AC, MUC6), (3) intestinal type (frequently positive for CK20, CDX2, MUC2), and (4) oncocytic type (rare).

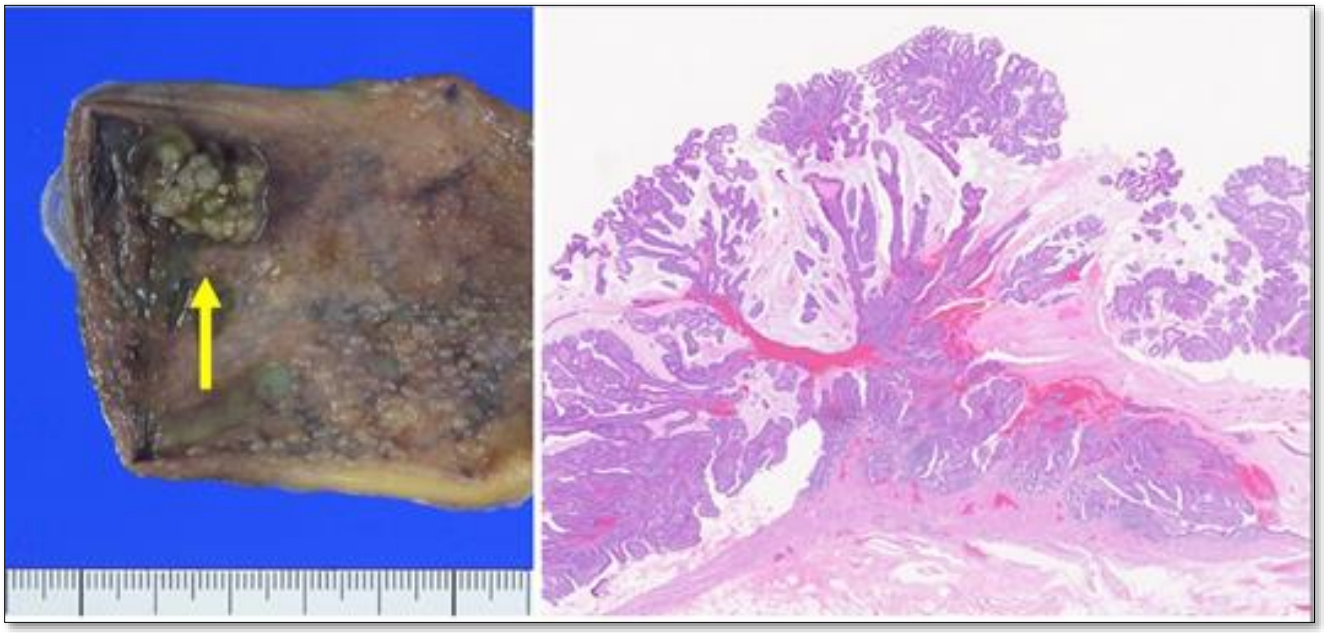

Figure 6. Intracholecystic papillary neoplasm (ICPN). Gross findings (Left, arrow) and histopathology (Right).

B-2. Biliary intraepithelial neoplasia (BilIN)

BilIN is microscopically recognized as non-invasive flat (or micropapillary) neoplastic lesion of gallbladder lumen [3, 4]. According to the histopathological atypia, BilIN is divided into the two groups: low-grade BilIN and high-grade BilIN. High-grade BilIN shows neoplastic atypia with nuclear pleomorphism. Differential diagnosis between low-grade BilIN and reactive epithelial atypia, as well as differential diagnosis between high-grade BilIN and carcinoma *in situ*, are difficult.

C. Malignant epithelial tumor

C-1. Adenocarcinoma

Adenocarcinoma is the most common histological type of gallbladder carcinoma [3]. The adenocarcinomas frequently show invasive growth in the gallbladder wall, characterized by well differentiated type at the superficial part of tumor, and moderately to poorly differentiated type at the invasive front of tumor. The invasive carcinoma induces stromal desmoplasia (irregular fibrosis) in the gallbladder wall and is associated with frequent lymphatic/venous/perineural invasion [7-9].

The various patterns of adenocarcinoma are noted as follows: biliary-type adenocarcinoma (frequently positive for CK7, MUC1), intestinal-type adenocarcinoma (frequently positive for CK20, CDX2, MUC2), gastric-type adenocarcinoma (frequently positive for MUC5AC, MUC6), and mucinous adenocarcinoma [10, 11]. Invasive micropapillary carcinoma (IMPC) is one of the specific adenocarcinomas with aggressive clinicopathological behavior and is characterized by micropapillary clusters within clear stromal spaces (**Figure 7**) [12]. The clusters are composed of tumor cells with pleomorphic nuclei.

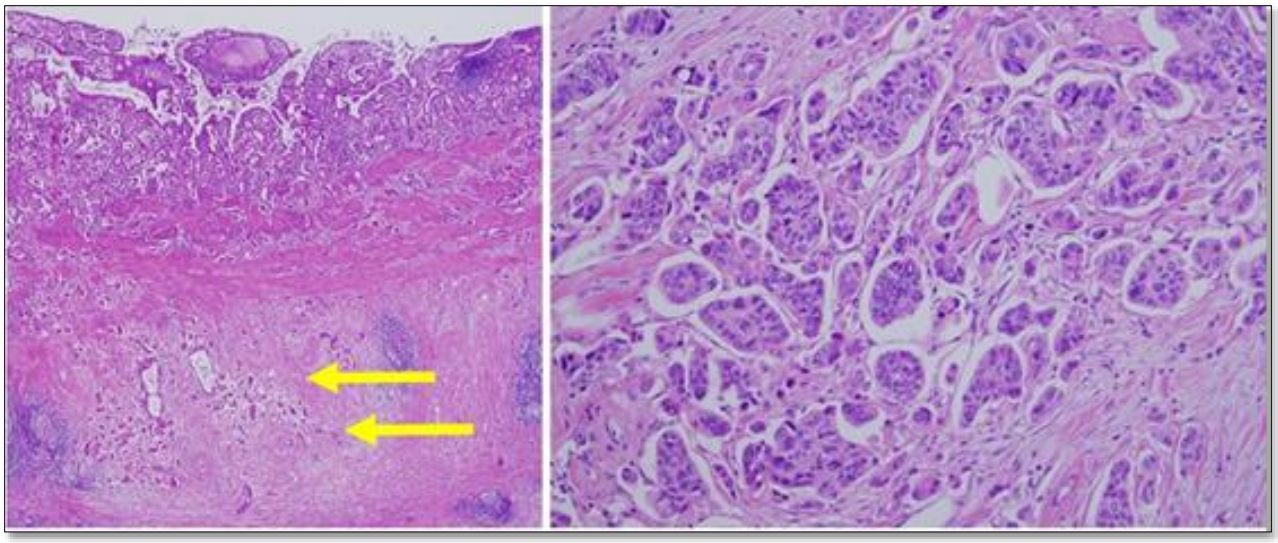

Figure 7. Invasive micropapillary carcinoma. Histopathology, low magnification (Left, arrow) and high magnification (Right).

C-2. Adenosquamous carcinoma, Squamous cell carcinoma

Adenosquamous carcinoma consists of two substantial components (more than 25% of tumor): adenocarcinoma part, and squamous cell carcinoma part. Pure squamous cell carcinoma is rare and shows aggressive behavior.

C-3. Undifferentiated carcinoma

Undifferentiated carcinoma is rare and has non-glandular, non-descript morphology with high cellular pleomorphism.

C-4. Neuroeodocrine neoplasm (NEN)

Neuroendocrine neoplasm (NEN) is divided into the two categories: neuroendocrine tumor (NET), and neuroendocrine carcinoma (NEC) [4]. NET consists of tumor cells with well differentiated endocrine phenotype and is graded as G1, G2, and G3. NEC is composed of carcinoma cells with poorly differentiated endocrine phenotype and subdivided into the small cell type SCNEC), and large cell type (LCNEC). Many cases of NEC have non-neuroendocrine component such as adenocarcinoma and are recognized as mixed neuroendocrine - non-neuroendocrine neoplasm (MiNEN).

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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