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Case Report

Primary Papillary Hyperplasia of the Gallbladder Mimicking Gallbladder Cancer

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Primary papillary hyperplasia of the gallbladder (PPHG) is a rare entity. PPHG is a benign diffuse mucosal projection without any background chronic inflammation-related disease of the gallbladder or bile ducts. Reported cases of PPHG are limited in that its characteristics are not well defined. We herein report a case of PPHG mimicking gallbladder cancer in radiologic investigations and present a review of the literature. Also coincident erythroderma is discussed.

Key words: Primary papillary hyperplasia – Gallbladder – Erythroderma – Carcinoembryonic antigen – Prophylactic surgery

A 63-year-old male visited our dermatology clinic, presenting with skin rash widely occupying the body (Fig. 1a). He was not allergic to anything and had no particular past history. Blood tests were carried out but detected no particular antigen related to skin rash. However, serum carcinoembryonic antigen (CEA) was above the normal limit (8.3 ng/mL) and the patient was referred to our department for further investigation of gastrointestinal malignancy. Gastroduodenoscopy and colonoscopy were performed but did not detect any malignancy. CT scan revealed a relatively small gallbladder, measuring 3 cm in maximum length, adjacent to the duodenum and its lumen, which was invisible due to the fulfilling tumor. The tumor was well enhanced by the contrast medium (Fig. 1b). Direct invasion to the nearby organs was absent and distant metastases were not detected. Magnetic resonance cholangiopancreatography showed normal biliary tree and the cystic duct was disrupted (Fig. 1c). With the diagnosis of T3N0 gallbladder cancer, we performed segmentectomy of 4a and 5 along with extrahepatic biliary duct resection, regional lymph node dissection and biliary reconstruction. Grossly, resected gallbladder was rather small measuring $2.5 \times 1.5 \times 1.5$ cm. No calculi were found inside the lumen. Diffuse thickening of the epithelium was noted and its color was

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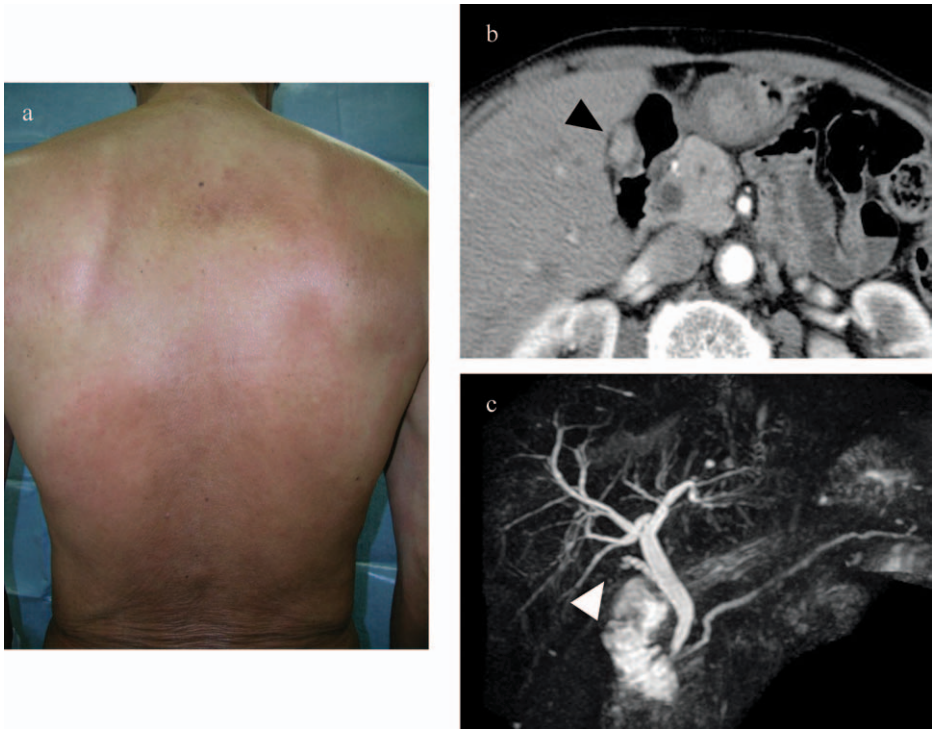

Fig. 1 (A) Erythema and scaling involving more than 80% of total body surface. (B) Enhanced CT scan showing hypervascular mass full filling the lumen of the small gallbladder. The air density area beside the gallbladder is the gas within the duodenum. (C) Magnetic resonance pancreatocholangiography revealed absence of pancreaticobiliary maljunction. Note gallbladder lumen is not visualized and other bile ducts are normal.

documented as light brownish. The whole gallbladder lumen was occupied by this epithelium. The thickness was limited within the gallbladder and was not seen at the continuing cystic duct (Fig. 2a). Microscopic examination revealed diffuse papillary projection of the mucosa without any structural abnormality, suggesting neoplasm (Figs. 2b, 2c). Some tubular structure continuing from the papillary folds were found in the proper muscular layer but they were considered as results of hyperplastic change of the mucosa within the Rokitansky-Aschoff sinus. Cells composing the papillary structure are single-layered, tall columnar cells without mitosis (Fig. 2d). Fibrosis was rarely seen nor was the infiltration of inflammatory cells. The final pathologic diagnosis was primary papillary hyperplasia of the gallbladder (PPHG). The patient was discharged from the hospital on the 10th postoperative day. His CEA value did not normalize until 1 year after the operation. However, erythroderma gradually improved during the 1-year period. He is free of related disease after 5 years' follow-up.

Discussion

In this report, we have demonstrated the radiologic resemblance of PPHG and gallbladder cancer. They are both apt to be solid tumor filling the gallbladder lumen and vascular rich. However, invasive findings directly to the liver or to the perihilar lesion of the liver were absent in this case, which may have served as the critical findings for differential diagnosis. Slight elevation of serum CEA may also have led to misdiagnosis. CEA did not associate with the treatment of PPHG, but rather it followed the condition of erythroderma. Pathologic confirmation by frozen section during surgery may have helped to avoid excessive surgical resection. Nevertheless, PPHG was too rare to give diagnosis even upon laparotomy.

PPHG is defined as "exceedingly rare" in AFIP that it occurs without coexisting inflammation-related disease such as cholelithiasis, cholecystitis, primary sclerosing cholangitis, or inflammatory bowel disease.[1] Elfving *et al* reported that 5.9% of predominantly adult cholecystectomy specimens

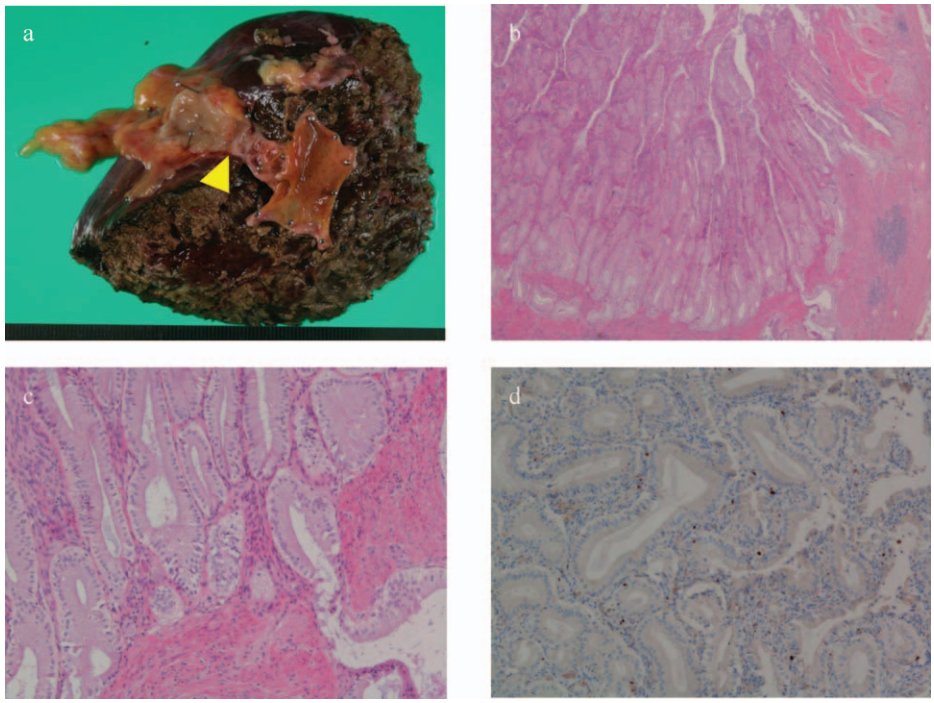

Fig. 2 (A) Resected specimen. Mucosal thickening of gallbladder is clearly shown. Note the thickness ends with clear margin at the neck of the gallbladder (arrow), cystic duct and common bile duct showing macroscopically normal epithelium. (B) Microscopic findings; low power view. Papillary folds and projections are dense and thick. (C) Microscopic findings; high power view. Close view of the papillary structure. Single-layer tall columnar cells and thin fibroblastic stroma are shown. (D) Immunohistochemical staining of Ki-67. Positive cells are rarely found.

have these histologic findings.[2] However, his definition of primary hyperplasia is that it is of a rather villous or spongioid structure, different from that of AFIP. Pediatric case is also reported.[3] The present case lacks previously known coexisting diseases, but had erythroderma (exfoliative dermatitis), known as an inflammation-related skin disease. We were interested to determine whether erythroderma was related to PPHG.

Although uncommon, erythroderma is known to associate with hematologic malignancies, mostly cutaneous T-cell lymphoma.[4–6] Few studies in the literature have described the relationship of erythroderma with gastrointestinal malignancies.[7–11] They all have reported spontaneous recovery from erythroderma after curative resection. Unfortunately, our patient did not have the same course, indicating that erythroderma was not caused by PPHG. On the other hand, serum CEA was associated with the improvement of erythroderma, signifying serum CEA had nothing to do with PPHG. Therefore, high serum CEA value was due to the condition of erythroderma. We have monitored CA19-9 as well during the whole clinical course but it remained within the normal limit.

The pathologic findings were nothing different from the previously reported PPHG.[1,12,13] Grossly thick, elevated lesions were covering the whole gallbladder. Cystic duct as well as the common bile duct showed normal mucosa. Microscopic findings were crowded papillary folds and projections with no dysplastic change. Epithelial cells were single-layered columnar cells, and their nucleus lacked mitosis. The potential of cell activity was checked by immunohistochemical staining (Ki-67; Fig. 2d). Ectatic capillaries in the stroma at the tips of the papillary projections are pointed out by Umudum and his colleagues,[14] but we were unable to identify such histologic findings in our case. However, the radiologic finding of well enhanced gallbladder by CT may be explained by the association of capillary ectasis.

We often encounter papillary hyperplasia of the mucosa secondary to chronic inflammatory disease related to gallbladder. Histologically, continuous stimulation to the bile duct epithelium generates hyperplastic change. In cholelithiasis, regardless of

infection, hyperplastic change may be focal or segmental according to the location of the stone. However, in pancreaticobiliary maljunction (PBM), an anatomic anomaly causing reflux of pancreatic juice into the bile duct is said to be associated with diffuse change. This phenomenon is caused by activation of bile acids and pancreatic enzymes.[15] Other causes of secondary papillary hyperplasia are ulcerative colitis and primary sclerosing cholangitis.[16,17] They are said to have mucinous-secreting columnar cells that may present nuclear atypia. It is also interesting to learn that tuberculosis of the gallbladder shows similar histologic changes.[18]

Our surgical procedure may have been too aggressive as a result. Granted that the diagnosis was gallbladder cancer, preoperative radiologic findings were basically noninvasive. Therefore, an option to perform cholecystectomy and make the most of pathologic confirmation by frozen biopsy for further surgical procedure should have been considered in this case. However, upon laparotomy, the tumor was elastic soft in tactile sensation and subserosa infiltration was considered if it was to be a carcinoma and if so, microscopic spread to the hepatoduodenal ligament and liver were of great concern. This unusual gallbladder tumor led us to perform extended surgery, which would be a complete treatment even if the pathology turns out to be malignant. We humbly regret our decision for extensive surgery and together with the acknowledgment of PPHG, we would like to emphasize that intraoperative frozen biopsy should always be carried out for undiagnosed gallbladder tumor to avoid unnecessary surgical procedure.

Hyperplastic change of the bile duct epithelium has recently been considered as a precursor of bile duct malignancies. Seki and his colleagues have investigated the bile duct epithelium of the patients who underwent biliary resection for PBM.[15] They have shown that papillary hyperplasia of the biliary epithelium occur in PBM patients, regardless of the maljunction type and concluded that the risk of cancer, especially gallbladder cancer, becomes greater in proportion to age. Yamato and colleagues have found frequent papillary hyperplasia and higher proliferative activities compared to control in series of PBM patients studied.[19] Furthermore, they found mucin core protein MUC1 expression at dedifferentiated and invasive areas of the gallbladder cancer associated in PMJ patients and MUC1 was variably expressed on the luminal surface of the non-neoplastic epithelium of the PBM patients. Sugiyama *et al* have investigated the risk factors of carcinogenesis in a series of PBM patients and have concluded that elevation of lysolecithin concentration is one of the factors for cancer development.[20] Yamaguchi and his coworkers have demonstrated *in vivo* that papillary hyperplasia of the gallbladder in PBM may represent a senescent-related lesion induced by lysolecithin.[21] Given these reports suggesting papillary hyperplasia of the biliary epithelium being a precursor of carcinoma, prophylactic surgery is recommended.[22] Unfortunately, PPHG and other primary papillary hyperplasia of the biliary epithelium cannot be detected easily by radiologic or other alternative examinations in practice that performing prophylactic surgery is not a realistic matter. We need to accumulate more PPHG patients to define its characteristics for future diagnosis and treatment.

In conclusion, PPHG is a rare entity among the diseases concerning gallbladder. Radiologic findings of PPHG mimicked gallbladder cancer, making differential diagnosis difficult. Coexistence of erythroderma showed slight high value of serum CEA, which gave an opportunity for investigating malignancy and accordingly discovering PPHG. Pathophysiology of PPHG is still undefined and accumulation of cases is necessary. Investigations are ongoing and recent findings are in favor of primary hyperplasia of the biliary epithelium as a precursor of cancer for which prophylactic surgery is recommended.

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