

An Autopsy Case of Biliary Cystadenocarcinoma of the Liver

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Summary : An autopsy case of a 58-year-old female with biliary cystadenocarcinoma is presented. A large cyst occupied the entire left lobe of the liver associating with multilocular daughter cysts and solid lesion. Histologically, tumor showed papillary, back-to-back glandular, cribriform pattern in the inner surface of the cysts with stromal invasion. Polygonal atypical cells were arranged in cords and adenoid cystic pattern in the solid lesion. Immunohistochemically, EMA was stained in the tumor cells as well as normal hepatocytes. CEA was diffusely stained in the cytoplasm and luminal surfaces of the tumor cells, while CEA was stained only in the luminal surfaces of benign-appearing epithelial cells of the cysts. Keratin and α -fetoprotein were not stained in the tumor cells. The origin of this tumor remains unknown, although transformation from congenital solitary cyst, biliary cystadenoma and reminiscence of cystadenoma of the pancreas or originally occurrence of cystadenocarcinoma in the liver are considered the basic histogenesis of cystadenocarcinoma of this case.

INTRODUCTION

It has been said that biliary cystadenocarcinoma is a rare tumor, but the rate of discovery and diagnosis of it seems to have risen up by means of recent sophisticated medical instruments and technique such as scintigram, CT scan, ultrasonography^{5,8)} and angiography. It is comparatively easy to evaluate the cystic lesion associated with solid areas using them. But it seems to be difficult to differentiate cystadenocarcinomas from cystadenomas not only in the liver but also in the pancreas and the ovary. In general, many authors consider that biliary cystadenocarcinomas arise in preexisting cystadenomas during a long period of years on the basis of occurrence age and histological features presenting transition from

cystadenomas to cystadenocarcinomas in the same section^{1,9,10,12,15,18, 19, 20)}. Although some other possibilities on its histogenesis are published^{3,4,15)}, exact origin remains unclear and has been controversial. In this paper, immunohistochemical stains such as EMA, CEA, keratin and α -fetoprotein were applied to investigate the histogenesis of cystadenocarcinomas.

CLINICAL COURSE

A 55-year-old woman was admitted to Sasebo General Hospital in May 1983 with a chief complaint of abdominal mass in the left upper quadrant. She had experienced piercing pain in the abdomen right side to navel in the midnight once a year since about 20 years ago. She had noticed the same piercing pain more frequently about four times a year since 1980.

On admission, barium gastrointestinal tract studies showed no deformity. Ultrasonography and computed tomographic (CT) scan revealed a large encapsulated cystic mass associated with papillary ingrowth tumor, necrosis, dilatation of the bile duct in the left lobe, two small cysts in the right lobe of the liver (**Fig. 1**) and a cyst in the left kidney.

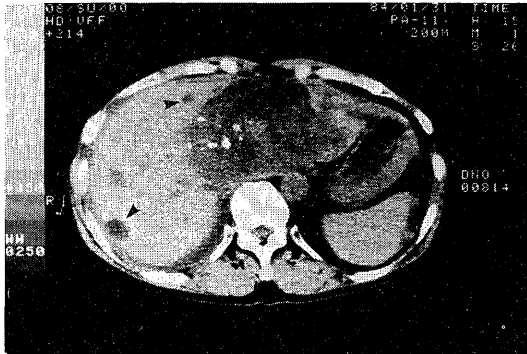


Fig. 1. Abdominal CT scan image on admission, May, 1983.

A large cystic mass occupies the entire left lobe of the liver, which is expressed as low-density area. Papillary projections with low-density areas originate from the inner surface of the cyst. Two small cysts are presented in the right lobe (arrowhead).

She was hospitalized on June 14, 1983 on suspicion of polycystic disease. Results of a physical examination revealed a small abdominal mass in the epigastric region, whose surface was smooth and elastic hard in consistency. A liver scintigram using ^{99m}Tm -phytate showed large defects occupying the left lobe and a part of the right lobe of the liver. Selective superior mesenteric and celiac angiography showed stretching of left hepatic arteries around a large avascular mass. Many tortuous, fluffy vessels arose from the left hepatic artery branches. In the late venous phase of the injection, irregular stains and a radiopaque rim appeared at the periphery of the most of the hepatic lesion. Laparoscopy revealed the swelling of the liver and a large mass near falciform ligament in the left lobe of the liver.

Adenocarcinoma (Class IV) was suspected by cytological examination from the liver cyst

puncture, ascites and right pleural effusion. Liver biopsy on June 20, 1983 revealed papillary proliferation of atypical cuboidal cells lining within the fibrous cyst wall. Mucinous cyst adenocarcinoma was suspected best of all. Mitomycin C (MMC) was injected locally because there was no indication for surgical operation.

She was discharged from November 4, 1983 to January 19, 1984 but rehospitalized from January 20 to March 20, 1984 because of increased pleural effusion, then followed up at the outpatient clinic. She repeated hospitalization three times between May 23, 1985 and November 12, 1986 in order to take the transarterial embolization (TAE) therapy.

She was hospitalized on her sixth time on May 1, 1987 because of aggravated epigastralgia and general malaise. She developed fever, abdominal pain and appetite loss after taking TAE therapy on May 27, 1987. On June 17, 1987, she became unconscious suddenly after vomiting and got into coma without voluntary respiration. CT scan revealed the subarchnoideal hemorrhage by rupture of cerebral artery aneurysm. She remained comatous and died on June 26, 1987.

AUTOPSY FINDINGS

The autopsy was performed approximately 44 minutes post mortem. Moderate jaundice was observed on bulber conjunctiva and sclera but not on the skin. The abdominal cavity contained approximately 250 ml of straw-coloured ascites. The liver weighed 2870 gm, measuring $28 \times 22 \times 9$ cm and the surface of the left lobe was multicystic, smooth and indented by cysts of varying size bulging. On cut surface, large solitary cyst measuring 9×5 cm in the greatest diameter was observed occupying entire left lobe of the liver, and was largely encapsulated by 1-2 mm grayish white thick wall (**Fig. 2**). Some small daughter cysts measuring 1 to 5 cm, which were multilocular separated by several thin intersepta, were located at the periphery of the large cyst in the left lobe. Moreover, slightly elevated, grayish and solid tumor measuring 11×3 cm was observed surrounding the right side of the large cyst, extending to the right lobe



Fig. 2. Cut surface of the liver
A large cyst is surrounded by thick capsule and contain central necrosis, mucinous and friable material. Some daughter cysts containing mucious material surround the large cyst. Slightly elevated solid mass exists right side to the large cyst extending to the right lobe. Two small cysts containing serous fluid are seen in the right lobe (arrowhead).

at part. The solid tumor was associated with necrosis (**Fig. 2**). The large cyst was completely filled with large amounts of necrosis in the center, surrounded by hemorrhage, fibrosis, greenish friable and mucinous or gelatinous material, and yellow-whitish papillo-verrucous tumor contiguous with internal surface of the cyst (**Fig. 2**). Multiloculation was not observed apparently within the large cyst. Small daughter cysts contained clear, glairy and mucinous material, and solid papillary tumor at part. Some 2 cm-cysts containing serous fluid were observed in the right lobe of the liver (**Fig. 2**). Metastasis was found in lymphnodes of the peripancreas, hilus of the liver and right adrenal gland on gross inspection.

The heart and adventitia of the esophagus were associated with petechiae and focal hemorrhage. The lungs showed congestion, edema and focal hemorrhage with scattered foci of bronchopneumonia. 200 ml, straw-coloured left pleural effusion and right fibrinous pleuritis were observed. Other findings were splenomegaly weighing 170 gm, cholecystolithiasis and 2 cm-cyst containing yellow-whitish necrotic material in the upper pole of the left kidney. Brain was not examined because of the refusal of autopsy.

MICROSCOPIC FINDINGS

Large liver cysts were encapsulated by thick, fibrous connective tissues and daughter cysts were particularly multilocular intersected by thin connective tissue (**Fig. 3**). The lining



Fig. 3. A cyst is intersected by thin fibrovascular septi. Tumor grows from the intersected septi presenting papillary projection. (H. E stain, $\times 5$)

epithelium of both large cyst and daughter cysts showed multistratification, arborizing papillary infoldings with fibrovascular stalk, back-to-back glandular formations and cribriform patterns associated with atypia and loss of polarity of nuclei, thick nucleolus and coarse granular chromatines (**Fig. 3, 4**). In a number of areas cysts contained mucinous material and demonstrated transition from a single cuboidal or ciliated columnar epithelial cells to papillary or cribriform arrangements (**Fig. 4**). A great number of hyperemic neovascularization, lymphangiectasia, dilatation of the portal vein and dispersed foci of calcification were observed in the fibrous capsule, which was invaded by large dilated cysts and clustering of small atypical glands. Moreover, neural invasion was observed. Benign-appearing epithelium and malignant-appearing epithelium were found within a single layer of cysts: a single flattened or single cuboidal to columnar epithelium with round to oval nuclei situated regularly at the base of cytoplasm, which were seemingly benign, but the other showed unequal size and loss of polarity of nuclei with coarse granular chromatines, which were seemingly malignant.

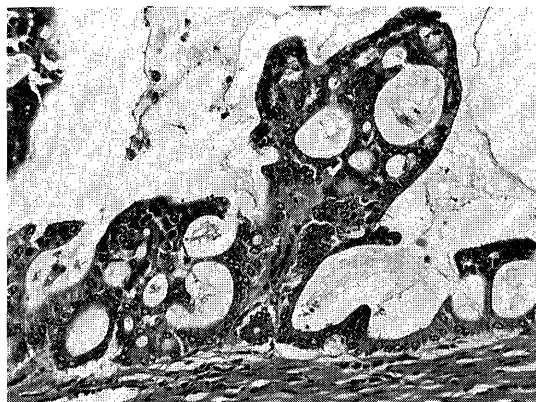


Fig. 4. High-power view of the Fig. 4. Tumor cells which arrange in the inner surface of the cyst show a single layer of cuboidal cells and papillary or cribriform pattern. (H.E stain, $\times 100$)

Solid lesion showed compact, solid cords of polygonal atypical cells with adenoid cystic pattern containing mucinous material (**Fig. 5**). These histological findings on autopsy were not prominently different from that of the liver biopsy material on June 20, 1983. Multiple tumor emboli were found in the intrahepatic portal vein, lymphatic vessels and capillaries of middle lobe of the right lung.

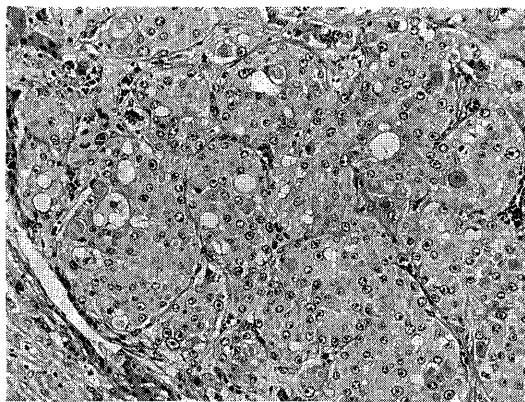


Fig. 5. Solid lesion shows the compact nests intersected by delicate fibrous stroma. Compact nests are composed of polygonal cells, presenting adenoid cystic pattern which contains mucinous material. (H.E stain, $\times 100$)

Intestinal metaplasia with both goblet and argentaffin cells was not detected by Grimelius staining. PAS and mucicarmine stains were

intensely positive in both cystic and solid lesions. No smooth muscle was detected in the fibrous capsule by Elastica Van Gieson stain. The capsule of the cyst was almost collagenous with small amount of elastic fibers.

Immunohistochemically, EMA (epithelial membrane antigen) was positive not only in tumor cells but also in the normal hepatocytes and bile duct epithelium. Intense reactivity to CEA (carcinoembryonic antigen) was detected diffusely both in the cilia or luminal surfaces of cells and the cytoplasm of cells in papillary or cribriform lesions, multistratified epithelial cells of the cyst, and cells in the solid lesion as well as a single-layer flattened epithelium or a single layer cuboidal to columnar epithelium of the cysts (**Fig. 6, 7, 8**). The nuclei of CEA positive cells in those lesion were large, revealing nuclear atypia and loss of polarity. On the other hand, only linear stain of CEA was detected in cilia or luminal surfaces of single-layer flattened cells, or single-layer cuboidal to columnar epithelial cells of the cyst, which did not associate with nuclear atypia.

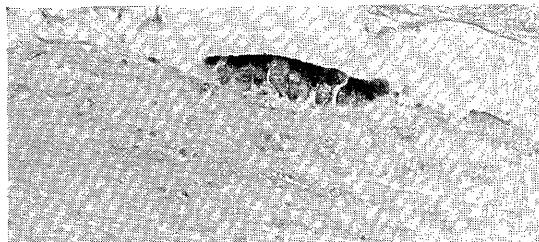


Fig. 6. CEA is stained diffusely in the cytoplasm of the cuboidal cells. (CEA stain, $\times 100$)

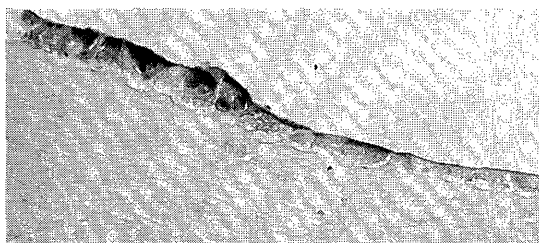


Fig. 7. Transition zone showing biphasic reactivity to CEA. Single layer of the cuboidal cells show the reactivity to CEA both in the diffuse way within cytoplasm and linear way in the luminal surfaces. (CEA $\times 100$)

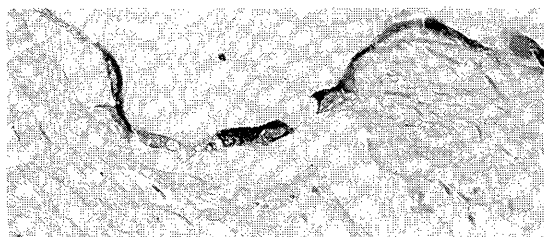


Fig. 8. Single layer of the flattened cells show the diffuse reactivity to CEA in the cytoplasm. (CEA stain, $\times 100$)

In those areas, faint staining of CEA was observed in the cytoplasm at part. Keratin and α -fetoprotein were not stained at all in the tumor cells and normal hepatocytes. Moreover, CEA was not detected in the normal hepatocytes.

As other findings, multiple fibrin thrombi were found in the small vessels in both lungs, liver, both kidneys, pancreas and ovaries, suggesting the presence of disseminated intravascular coagulopathy (DIC). Small necrotic cyst in the left kidney was angiomyolipoma.

DISCUSSION

Biliary cystadenocarcinoma in the liver is a rare multilocular tumor with cystic and solid areas. It is reported to occur predominantly in female presenting enlargement of abdomen, a palpable mass or hepatomegaly, right upper quadrant abdominal pain and tenderness. Favorable lobe of occurrence does not seem to present, although Iemoto reported the tumor arose in the left lobe (14 cases), in the right lobe (9 cases), or both lobes (4 cases)¹¹.

Roentgenograms usually have been non-specific, but displacement of the structures surrounding the liver such as stomach, colon, kidney, and ureter has been demonstrated by contrast studies. Liver scan would demonstrate the filling defect. In this case, the presence of clusters of abnormal vessels in the cyst wall and septa or within the solid lesions indicates a neoplasm. Moreover, papillary projections within the cyst, which were typical features of cystadenomas or cystadenocarcinomas, were demonstrated by CT scan. Carroll⁵, Forrest and Cho *et al.*⁸) describe ultrasonographic feature of cystic lesion and their differentiation in detail.

Histogenesis of biliary cystadenocarcinoma remains unknown and various hypotheses have been proposed as follows: ① malignant transformation from congenital cystic disease^{3, 6, 11, 13}); ② malignant transformation from biliary cystadenoma of the liver^{1, 9, 10, 12, 15, 18, 19, 20}), ③ malignant transformation from the hepatic hamartomas and aberrant bile ducts^{3, 4}), or from the reminiscence of cystadenomas of the pancreas¹⁶); ④ biliary cystadenocarcinomas per se may arise in the liver originally without association of above-mentioned lesions¹⁴). According to the discription by Bloustein³), the incidence of carcinoma in solitary non-parasitic cysts of the liver or polycystic liver disease is distinctly low, while the carcinoma may arise with a higher incidence, 1 % in congenital hepatic fibrosis, 4 % in choledochal cyst and 7 % in congenital cystic dilatation of the intrahepatic bile ducts. As the reason for the higher risk of malignant transformation in the latter three diseases, Bloustein suggests something in the bile may play a role as carcinogen. Edmondson⁷), Bloustein and Silverberg²) attribute the squamous metaplasia of the cyst epithelium to the developmental base of carcinoma. Cahill *et al.*⁴) demonstrates the frequent argentaffin cells in the gland of biliary cystadnomas, and More¹⁶) describes the goblet cells and argentaffin cells in biliary cystadenocarcinoma. In our case, preexisting polycystic liver disease, congenital hepatic fibrosis, intrahepatic bile ducts and other hamartomatous or aberrant bile ducts were not observed. Further, goblet cells and argentaffin cells, which derived from foregut endoderm, were not detected in our case. Thompson and Wolff¹⁷) paralleled the relationship between biliary cystadenoma/cystadenocarcinoma and pancreatic cystadenoma/cystadenocarcinoma because the embryological origin of the hepatic and pancreatic ducts are very similar and closely related. Therefore, as the origin of cystadenocarcinoma in our case, congenital solitary cysts, biliary cystadenomas, reminiscence of cystadenocarcinoma of the pancreas, and the original appearance of cystadenocarcinoma in the liver are enumerated.

Majority of authors consider biliary cystadenocarcinoma arise in preexisting biliary

cystadenomas on the fact that the mean age of the cystadenomas occurrence is in forties, while the mean age of cystadenocarcinomas occurrence is in fifties^{1, 9, 10, 12, 15, 18, 19, 20}. Malignant transformation of the epithelium is now considered to occur over a period of many years. Tomioka *et al.*¹⁸) propose the helpful usage of CEA immunohistochemically to differentiate biliary cystadenocarcinomas from biliary cystadenomas on the basis of different staining patterns of CEA. Our results concerning CEA staining was almost identical to that of Tomioka *et al.* They suggest that the epithelium, whose luminal surfaces stained with CEA in linear way, is cystadenoma, while the papillary projected epithelium, whose cytoplasm stained with CEA in a diffuse pattern, is cystadenocarcinoma. In our case, transition from benign-appearing epithelium presenting cystadenoma to cystadenocarcinoma was demonstrated.

Arrangements of multilayered cuboidal and columnar cells, multiple papillary projections into the lumen, marked nuclear atypia, breaks and invasion of the underlying fibrous stroma are now believed to be the evidence of cystadenocarcinoma to differentiate cystadenomas. Though, Iemoto describes that those findings per se are not so diagnostic for malignancy because they can be observed in benign cystadenomas¹⁰). Therefore, the differentiation between cystadenomas and cystadenocarcinomas is difficult by means of the conventional H.E stain, moreover, their diagnostic standard seems to be vague. Some authors believe that the single cuboidal to high columnar epithelium are all benign cystadenomas. However, in our result, single flattened epithelium, single cuboidal and columnar epithelium with nuclear atypia and pleomorphism were suspected malignant because their cytoplasm was diffusely stained with CEA. Therefore, it is suggested that single cuboidal or columnar epitheliums are not always benign. The mixture of CEA positive and negative lesion existed both in papillary and single layered epithelium. The staining for CEA may be helpful to diagnose the malignant lesion in the single layered epithelium as well as papillary, cribriform and solid lesion.

In addition, a question concerning the origin

of this case still remains, because the smooth muscle fibers could not be detected in spite of the emphasis of Tomioka *et al.*¹⁸). They demonstrated the presence of smooth muscle fibers in the cystic wall of cystadenoma and its absence in the cystic wall of solitary cysts. The fact that there were two small retention cysts in the right lobe of the liver in our case may be a suggestive evidence of transformation from congenital cysts to cystadenocarcinoma. It is conceivable that the tumor of our patient has gradually developed for a long years considering from her noticeable abdominal pain since about 20 years ago.

The real origin of this case is not known definitely. More investigation is necessary to define the exact histogenesis of cystadenocarcinoma in this case.

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