

## Cholangiocarcinoma in Caroli's Disease<sup>†</sup> — Report of a Case —

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**= Abstract =** We present a case of cholangiocarcinoma arising in Caroli's disease from a 46 years old female, who was asymptomatic and incidentally found on routine examination. A large cystic dilatation of intrahepatic bile duct communicated with the secondary branch of the left lobe and accompanied a non-invasive papillary adenocarcinoma of cystic epithelial lining origin, which is, to our knowledge, the first reported case in Korea. The pathogenesis of carcinoma complicating in congenital cystic lesions of biliary system is discussed.

**Key Words:** *Cholangiocarcinoma, Intrahepatic, Caroli's Disease, Liver*

### INTRODUCTION

Caroli's disease, a congenital cystic dilatation of intrahepatic bile duct, is a rare developmental abnormality which may present at any age. It was first described by Vachell and Stevens in 1906, but was reviewed and clearly defined by Caroli *et al.* in 1958.

Since Irwin and Morrison (1944) reported the first case of carcinoma associated with cystic dilatation of the biliary tree, more than 50 cases of malignant tumors developing in the cystic lesion of the intrahepatic or extrahepatic biliary tree have been reported in the English literature. Previously we have experienced two cases of adenocarcinoma arising in the congenital extrahepatic cyst (choledochal cyst) (Youn *et al.* 1981; Park *et al.* 1978), but none from the intrahepatic cyst.

We present a case of polypoid adenocarcinoma arising within the dilated intrahepatic bile duct (Caroli's disease) for its rarity and theoretical reappraisal of its carcinogenesis.

### CASE

A forty six years old housewife was admitted to the Seoul National University Hospital on March 30, 1985 for the evaluation of intrahepatic mass

which was incidentally found on routine check by an insurance company. She was healthy prior to December 1984 when she developed easy fatigability. Thereafter, she has had neither weight loss nor jaundice.

On admission, she looked healthy and was not icteric. Physical examination revealed only hepatomegaly without tenderness. Laboratory studies showed normal liver function test. HBsAg, HBsAb and HBcAb were -/+ / +, and alpha fetoprotein was less than 5 ng/ml. Liver scintiscan exhibited a space occupying lesion in the left lobe. On abdominal ultrasonography and CT films, a mass within the localized dilatation of the left intrahepatic duct was suggested. The mass itself was hypovascular, being associated with sweeping of right and left hepatic arteries. ERCP revealed a filling defect at the left intrahepatic duct about 4 cm distal to the bifurcation site between right and left intrahepatic bile ducts. After admission, high fever and right upper quadrant tenderness developed two days after the ERCP procedure without muscle guarding. Ascending cholangitis was suspected and Cefamycin, Gentamycin and Clindamycin were administered. After three days of the medication, fever subsided and general condition was recovered. For further diagnostic clarification, surgical intervention of the intrahepatic mass was scheduled and the patient was transferred to general surgery with the diagnosis of intrahepatic bile duct stones or carcinoma. Left lateral segmentectomy with cholecystec-

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tomy was performed at the 26th hospital day. Extrahepatic biliary passage and other intraabdominal viscera were unremarkable.

After operation, she has been well for 20 months. Liver function test and liver scintiscan were normal. Serum carcinoembryonic antigen was 1.4 ng/ml (normal; below 2.5 ng/ml).

### **PATHOLOGIC FINDINGS**

The resected left lateral segment of the liver measured 11 x 8 x 4 cm and showed wrinkled Glisson's capsule. On section, the intrahepatic bile duct was markedly dilated in saccular form measuring 5 x 3 cm in maximum cross, without any narrowed connection to the draining duct of the secondary branch level. The cyst wall was thin and its inner surface was bile stained but smooth and shiny. There was found a broad-based, flat, slightly lobulated and irregularly contoured solid dark reddish tumor mass in the cyst wall, measuring 3 x 2 x 1 cm (Fig. 1). On section, the cut surface of the tumor was slightly granular, papillary and partly friable.

Microscopically, the cyst was lined by a single layer of low cuboidal cells (Fig. 2), identical to the attenuated bile duct lining, and surrounded by an even thickness of dense fibrocollagenous capsule in which were small ductal structures and mild infiltration of neutrophils and lymphocytes along the luminal side. The tumor arose from the cyst lining cells abruptly to form slender papillary fronds with thin and long fibrovascular cores (Fig. 2 and 3). Each papilla was lined by a single layer of regularly tall columnar cells with basally located ovoid or elongated nuclei (Fig. 4), and their cytoplasm contained abundant supranuclear mucin granules which gave strong alcian blue positive reaction at pH 2.5. Nuclear atypism was not prominent, showing only mild nuclear hyperchromatism and a few mitotic figures. Pseudostratification was only scatteredly found, and there was no evidence of stromal or vascular invasion. The remaining hepatic parenchyma near the cyst exhibited mild cholestasis, portal inflammation and periductal fibrosis.

### **DISCUSSION**

Congenital dilatation of biliary tree is an uncommon condition with several variations by location, degree and type of dilatation (Lorenzo *et al.* 1971). Although the lesion is called 'congenital', less than 60% are diagnosed in patients under 20 years of age and some cases may present for the first time

in sixth decade of life (MacSween *et al.* 1979). It is frequently associated with abdominal pain, mass and jaundice. In adults, symptoms usually include those of ascending cholangitis. The present case is somewhat unusual in that while most patients with Caroli's disease become symptomatic by young adulthood (Nichols and Craig 1979), our patient has remained asymptomatic until the age of 46. The antecedent asymptomatic period in this patient and other cases suggests that at least in some instances the condition may remain clinically silent throughout life, making the true incidence higher than has been recognized (Phinney *et al.* 1981).

It is appropriate that Caroli's disease is called 'developmental' rather than congenital on the ground that it is frequently associated with choledochal cysts (Gots and Zuidema 1970) or renal tubular dilatations. Bizarre distribution of the dilatations and lack of obvious acquired causes are also supportive findings.

Although cystic dilatation of the bile ducts similar to those in Caroli's disease may develop as a result of the acquired biliary obstruction, they are essentially different in that the former manifests an irregular, sometimes segmental distribution of the dilatation, and spares the interlobular ducts. But the whole biliary tree is involved uniformly in the acquired biliary obstruction (Gallagher *et al.* 1972). The inflammatory reaction in this case was relatively in the acute stage and was only confined beneath the epithelial linings of the cyst and in portal spaces of the remaining parenchyma, reflecting a recent episode of acute cholangitic process following ERCP procedure. Also, this case is an isolated form of Caroli's disease without any association of malformation of extrahepatic biliary tree or other organs.

Carcinoma is rarely associated with congenital cystic conditions of the liver and bile ducts, although the incidence of malignancy is several hundredfold higher than that of general population (Bloustein 1977). Of 16 congenital cystic lesions of the liver examined at our institution during the period from 1961 to 1986, only 2 instances of adenocarcinoma were complicated in extrahepatic choledochal cysts, and none in congenital solitary cyst or Caroli's disease (Park *et al.* 1978; Youn *et al.* 1981). This patient, to our knowledge, is the first reported case of carcinoma being associated with Caroli's disease in Korea. Despite of difficulty to assess the frequency of neoplastic transformation, it is approximated 7% of the patients with



Fig. 1. Cut surface of the liver, revealing a broad-based polypoid tumor mass (arrow) within the cystically dilated bile duct (\*).

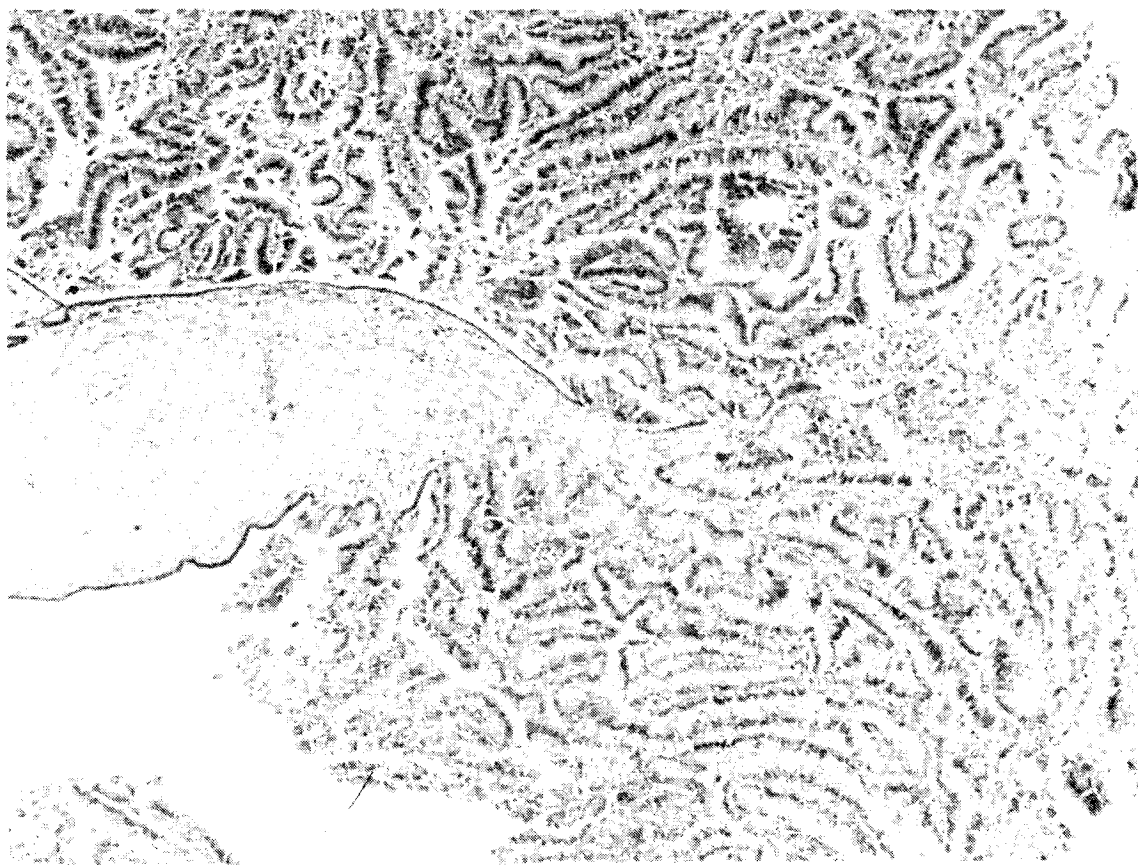


Fig. 2. Papillary adenocarcinoma is arising abruptly from bile duct epithelium. No stromal invasion is seen. H-E. x 40.

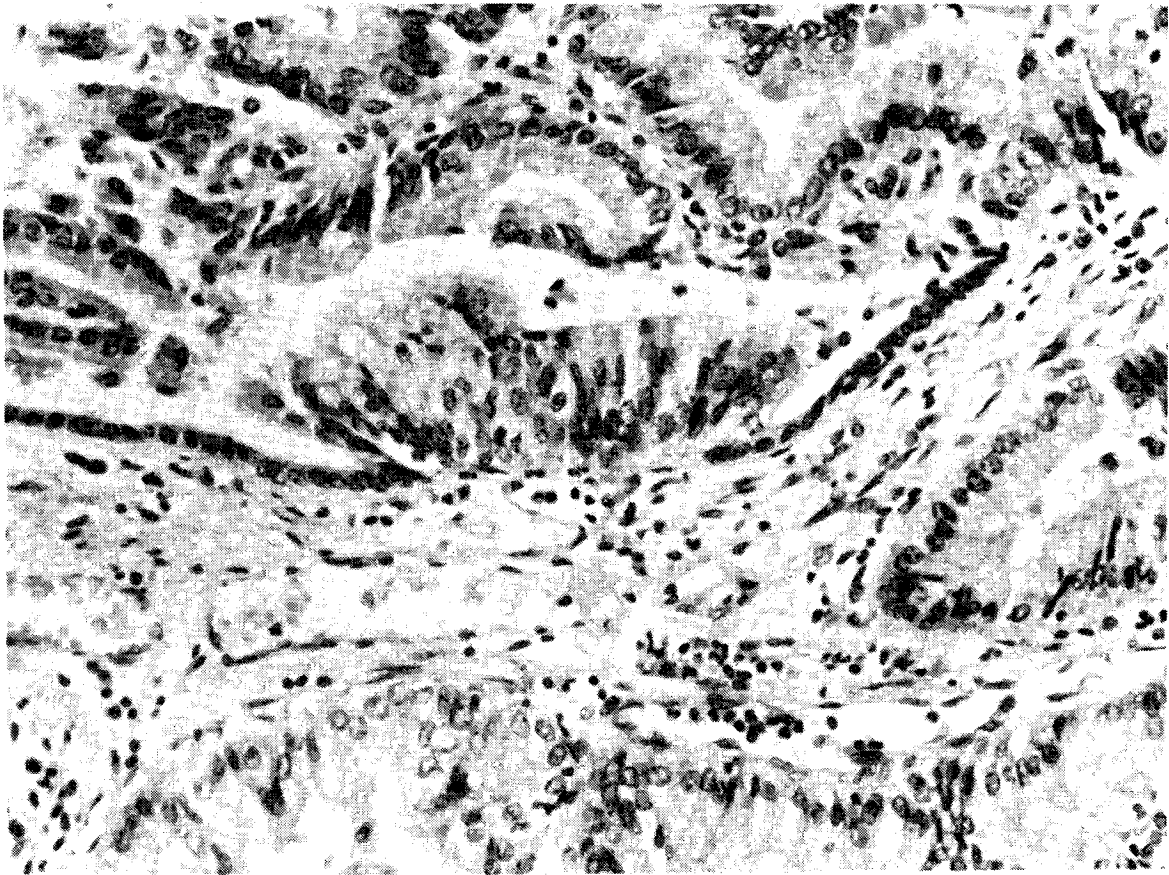


Fig. 3. Tumor island, being composed of stratified columnar cells in normal bile duct epithelium is noted. H-E, x 200.

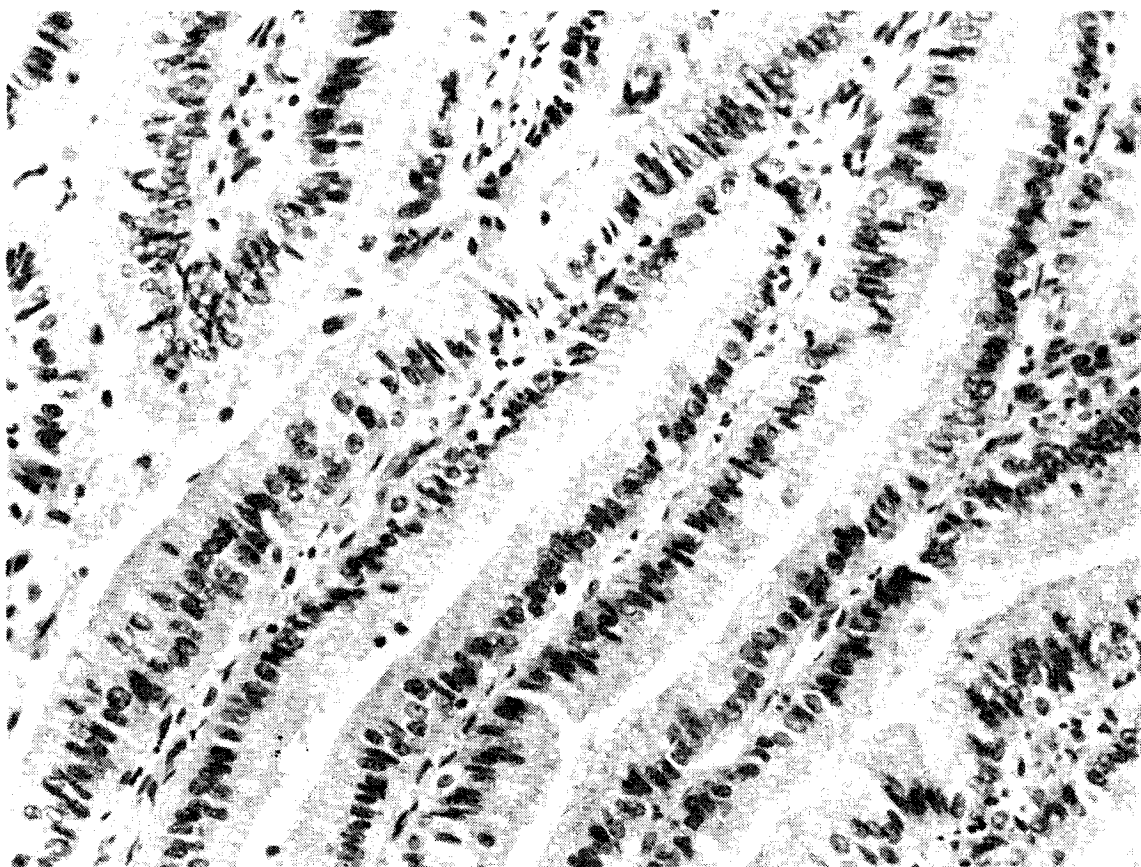


Fig. 4. Papillary adenocarcinoma consisting of tall columnar cells with moderate amount of supranuclear mucin. H-E, x 400.

congenital cystic dilatation of the intrahepatic bile ducts from the published data (Bloustein 1977; Watts *et al.* 1974). Majority of the tumors in congenital cystic lesion of biliary system are adenocarcinoma, however squamous cell carcinoma is rarely reported in intrahepatic congenital cysts (Edmonson 1958; Greenwood and Orr 1972), congenital cystic dilatation of intrahepatic bile duct (Chaudhuri *et al.* 1982) and choledochal cyst (Irwin and Morrison 1944).

Histologically the tumor infiltrates often into periductal tissue with considerable degree of desmoplasia, and metastasis is usually confined to the regional lymph nodes. However in this present case, tumor revealed polypoid growth confined to the cystically dilated intrahepatic bile duct wall. In addition, we were able to demonstrate a well differentiated papillary adenocarcinoma directly arising from bile duct lining epithelium without invasion. These gross and microscopic features are supportive for long preoperative asymptomatic course and good postoperative state in this case.

The pathogenesis of cholangiocarcinoma remains not clear, but it has long been discussed that bile juice may have a carcinogenic substance (George and Maingot 1962). The fact that cholangiocarcinomas develop more frequently in such conditions as choledochal cyst and Caroli's disease may be explained by long-term exposure of biliary epithelium to stagnated bile salts. In addition, with superimposed cholangitis, bacterial enzymes may activate procarcinogens to ultimate carcinogens, leading to increased total exposure to carcinogen (Phinney *et al.* 1981). In the analysis of 30 intrahepatic lithiasis, we found two cases of cholangiocarcinoma and over 60% of dysplastic epithelium in the dilated bile ducts away from the obstruction sites (Kim *et al.* 1986), which suggested the carcinogenetic participation of altered bile salts by intra-ductal bacterial  $\beta$ -glucuronidase derived from repeated cholangitis (Tabata and Nakayama 1981).

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= 국문초록 =

## Caroli병에 수반된 담관암종 —1증례 보고—

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저자들은 46세 여자 환자의 확장된 좌엽 간내담관(Caroli병)에 발생한 담관암종 1예를 경험하고 그 회귀성과 발암가능성을 검토하였다. 환자는 건강진단을 위해 실시한 복부 초음파검사에서 처음으로 좌엽 간내담관의 확장이 발견되었으며 그 안에 3×2×1cm 크기의 종양이 발견되었다. 이학적 검사상 환자는 건강하였고 체중 감소나 증상이 없었다. 간기능 검사는 정상이었으며 B형 간염 표면 항원은 음성이었고  $\alpha$ -fetoprotein은 5ng/ml 이하이었다. 좌외엽 절제술로 절제된 간 조직은 11×8×4cm였으며 절단면에서는 장경 5×3cm의 낭성으로 늘어난 간내 이차담관의 벽에서 넓은 기저부를 가진 폴립양 종양이 관찰되었다. 현미경적으로 정상적인 담관 상피세포에서 분화가 좋은 유두양 선암으로의 이행을 확인할 수 있었으며 주변 조직으로의 침윤은 관찰되지 않았다. 본 증례는 국내에서 처음 보고되는 Caroli병에 수반된 담관암종으로서 이미 보고된 간외 담관낭종에 생긴 선암 2예의 경우와 마찬가지로 정체된 담즙의 발암 성분이 담관암종의 발생에 관여하리라 사료된다.