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Peripheral hepatolithiasis incidentally found at autopsy

A morphological study

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Summary. Hepatolithiasis is a common disease in East Asia though very rare in the West. Four cases of hepatolithiasis in which calculi were incidentally found in the peripheral branches of the intrahepatic biliary tree at autopsy are described and compared with hepatolithiasis involving the major branches of the intrahepatic biliary tree. These four cases were all elderly, three patients were male and one female. The calculi were brown pigment stones in each case, as seen in the major branch type. The stone-containing ducts showed mild fibrosis and glandular proliferation with inflammatory changes in three cases; these changes were marked in the fourth case. The hepatic parenchyma around the stone-containing ducts was atrophic or collapsed in all four cases. The major branches of the intrahepatic biliary tree as well as the extrahepatic tree failed to show findings suggestive of bacterial infections or biliary anomalies. These data suggest that brown pigment stones develop primarily in the peripheral ducts in the liver. It remains uncertain whether the peripheral type eventually progresses to the major type or not.

Key words: Hepatolithiasis – Intrahepatic biliary tree – Bacterial infection

Introduction

It is well known that the incidence of hepatolithiasis is high in East Asia in comparison with the West. The relative incidence of hepatolithiasis among all cholelithiasis cases in most parts of East Asia ranges from 4.1% to 51.7% but that in the West is less than 1% (Nakayama 1984b), respectively. It remains unclear whether the aetiology and pathogenesis of the condition in different Asian countries are identical. In Hong Kong and Phillipines, bacterial infection (especially by enteric bacteria) and inflammation occur primarily in the bile ducts, leading to stricture and calculus formation. This condition is known as recurrent pyogenic cholangitis (RPC), and RPC involving the entire liver or localized segments is known to occur (Ong et al. 1962), though its exact pathogenesis remains unclear. A majority of calculi in hepatolithiasis are brown pigment stones (Nakayama et al. 1984a; Ong et al. 1962).

In Japan, parasitic infection of the biliary tree complicated by secondary bacterial infection has also been suggested as a primary and causative event in hepatolithiasis (Maki 1966), though such event is now an unlikely predisposing factor (Nakayama et al. 1984a). Recently advanced imaging modalities lead us to believe that stones are formed primarily within the intrahepatic biliary lumena (primary hepatolithiasis) in a majority of patients with hepatolithiasis (Kimura et al. 1984; Nakayama et al. 1984; Ohto et al. 1982). A national survey of hepatolithiasis with an emphasis on its pathology, conducted by the Japanese Hepatolithiasis Study Group (Chairman: Prof. Fumio Nakayama, Fukuoka) in 1983 and 1987 (Ohta et al. 1987), showed that the great majority of cases of primary hepatolithiasis showed multiple brown pigment stones within the major as well as the peripheral branches of the left hepatic lobe. Changes were more marked in the left lobe, there was female predominance and a prediliction for middle and old age. The stone-containing bile ducts were variably dilated or stenotic and their walls were fibrous. Histologically, the stone-containing ducts showed a variable degree of fibrosis, numerous glandular elements and inflammatory cell infiltration, and the term "chronic proliferative cholangi-

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tis" was coined by us for these lesions (Ohta et al. 1984 and 1987). The hepatic parenchyma peripheral to and surrounding the stones, showed atrophy and a variable fibrosis. However, the pathogenesis of the major type (that involving the major and minor ducts) of hepatolithiasis remains unclear.

Hepatolithiasis confined to the peripheral branches of intrahepatic biliary tree (the peripheral type) was originally described by Ohto et al. (1982), and this type is now increasing in Japan (Kimura et al. 1984; Ohto et al. 1982). The peripheral type is not usually associated with severe clinical signs or symptoms so that surgical resection of the affected part of the liver is not indicated. Thus, no detailed histopathological assessment is available. The present study is aimed at describing the histopathological features of the peripheral type when found incidentally at autopsy. A comparison with the major type (Ohta et al. 1984, 1987; Terada and Nakanuma 1988) is made.

Materials and Methods

Autopsy reports of our Department from 1977 to 1986 (total number of autopsied cases in this period were 954) were reviewed, and 4 cases of the peripheral type of hepatolithiasis were collected. The stone-containing bile duct and its neighborhood and other hepatobiliary areas including the hepatic hilus, were prepared and fixed in 10% formalin. Approximately 5 μm paraffin sections were processed for conventional staining including H & E, Azan-Mallory, elastica van Gieson, periodic acid Schiff (PAS), alcian blue (pH 2.5) and mucicarmine stains.

The intrahepatic bile ducts were defined as including right and left hepatic ducts distal to their junction and their branches, and were classified according to Healey and Schroy (1953) into: hepatic (right and left hepatic duct), segmental (the first major branches of each hepatic duct: left medial and lateral, and right anterior and posterior) and area ducts (the first major branches of each segment duct: anterior and inferior). In this study, both hepatic ducts and the four segment ducts were termed as "major intrahepatic bile ducts" and the area ducts and their finer branches as "peripheral intrahepatic bile ducts". The septal and interlobular bile ducts and bile ductules were identified microscopically (Masuko et al. 1964). The bile duct wall was defined as a dense fibrous band encircling the lumen, and the surrounding loose connective tissue was termed periductal tissue. The intrahepatic peribiliary glands which are normally present along the hilar and area ducts of the biliary tree (Terada et al. 1987), were also evaluated.

Hepatolithiasis was said to exist when calculi were found in the right and/or left hepatic ducts and/or their branches irrespective of coexistence of choledocholithiasis or cholecystolithiasis (Nakanuma et al. 1985; Ohta et al. 1984, 1987; Simi et al. 1979; Yamamoto 1982). It was divided into the peripheral type (stones confined to the peripheral intrahepatic bile duct) and major type (stones in the peripheral as well as major intrahepatic bile ducts) according to Kimura et al. (1984) and Ohto et al. (1982). Gallstones were classified by visual inspection (Maki 1982; Sato and Takahashi 1983). Brown pigment stones have a rough, light to dark brown surface and on cross section exhibited multiple concentric layers of varying shades of brown or rather black color. Black stones are black and have an uneven surface and a cross-sectional appearance lacked a lamellar pattern. Cholesterol stones have a smooth surface and radial pattern with a small dark center.

Results

The main clinical features are shown in Table 1. The peripheral type of hepatolithiasis was an incidental finding at autopsy in these 4 cases and the present illness and past medical history failed to show distinct symptoms or signs related to the hepatobiliary system. All were elderly, three were male and one female. There was no history or clinical symptoms suggestive of ulcerative colitis, and the gastrointestinal tracts failed to show findings of ulcerative colitis at autopsy.

The calculi were found focally in the area ducts and finer branches of the left lobe (cases 1, 2 and 4) and of the right lobe (case 3) (see Table 2). Calculi were found in the area ducts and/or their branches (Figs. 1, 2 and 3). Both right and left hepatic ducts and the segment duct were free of calculi and of pathological changes. The stone-containing ducts disclosed focal spindle-shaped or saccular dilatation in each case. In case 4, a considerable length of the duct (in which many stones were impacted) showed irregular saccular dilatations and tortuosities interspersed with relative stenoses (Fig. 3). The stone-containing ducts showed a vari-

Table 1. Presentation of four cases with peripheral hepatolithiasis

Case	Age	Sex	Main disease	Hepatobiliary symptoms and signs	Other cholelithiasis	Liver weight
1	70	female	Recurrence of breast ca.	–	–	940 g
2	76	male	Pulmonary tuberculosis	–	Cholecystolithiasis (cholesterol stone)	1310 g
3	73	male	Pulmonary ca.	–	–	2025 g
4	68	male	Intracerebral haemorrhage	–	–	1295 g

Table 2. Macroscopic findings

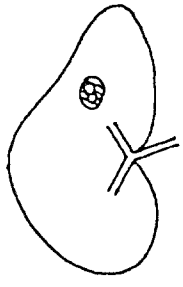
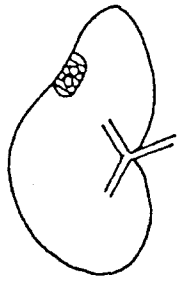
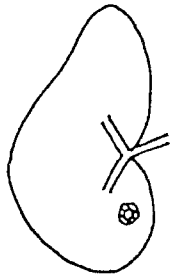
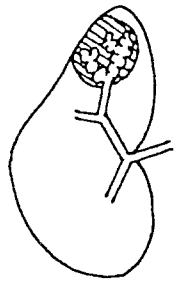
	Case 1	Case 2	Case 3	Case 4
Distribution of intrahepatic calculi				
Size of stones and their character	0.1 cm brown pigment stone	0.1~0.2 cm brown pigment stone	0.1~0.3 cm brown pigment stone	0.3~0.4 cm brown pigment stone
Thickening of stone-containing ducts	+	+	+	+ + +
Dilatation of stone-containing ducts	+	+	+	+ + +
Dilatation and tortuosity of the ducts distal to the stone	−	−	−	+ +
Atrophy and/or dropout hepatic parenchyma distal to and/or surrounding the stone-containing ducts	−	+	+	+ +

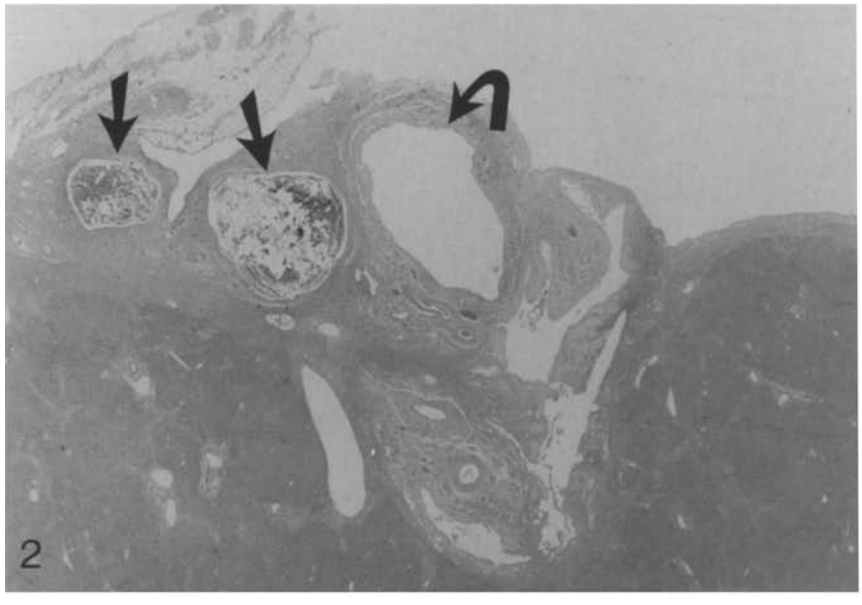
Table 3. Histologic findings

	Case 1	Case 2	Case 3	Case 4
Stone-containing ducts				
Fibrous thickening	±	+	+	+ + +
Proliferation of glandular elements	+	+	+	+ + +
Inflammatory cell infiltration	±	+	+ +	+
Atrophy of hepatic lobules surrounding stone-containing ducts	±	+	+	+ +
Other hepatic lesions	mild hepatic fibrosis	mild hepatic fibrosis	fatty liver	NS

±: minimum, +: mild, + +: moderate, + + +: marked, NS: not significant

able fibrous thickening, and the parenchyma adjacent or distal to the stones was atrophic or dropped out (Fig. 1, 2). These changes were prominent in case 4 (Fig. 3). There were more than 2 calculi in every case, case 4 disclosed numerous stones. All of these ranged in size from 0.1 to 0.5 cm in diameter and fulfilled the visual characteristics of brown pigment stones (Fig. 1–3), though chemical analysis was not done. The major intrahepatic bile ducts as well as the extrahepatic biliary tree were free of pathological changes (abnormal pancreaticobiliary ductal union, cystic changes, carcinoma or parasitic infection) except for mild chronic cholecystitis due to cholecystolithiasis (cholesterol stone) in case 2.

Cases 1–3 showed mild fibrosis and minimum to mild glandular proliferation in the ductal wall and periductal tissue (see Table 3). There were minimum inflammatory cell infiltration in the stone containing ducts (Fig. 4). Case 4, however, showed moderate ductal and periductal fibrosis as well as glandular proliferation with inflammatory cell infiltration (Figs. 5, 6). The proliferated glandular elements were composed of mucous and serous acini. The hepatic parenchyma around the stone-containing ducts was mildly atrophic with approximation of adjoining portal tracts (Benz et al. 1952) in cases 1–3 and actual collapse in case 4. Other hepatic changes included mild portal fibrosis and periductal fibrosis (cases 1, 2 and 4) and fatty change (case 2). Infiltration of hepatic sinusoids by neutrophils, microabscess or bile plug formation were not found. The extrahepatic and major intrahepatic biliary tree failed to show histopathological changes suggestive of preceding infection.



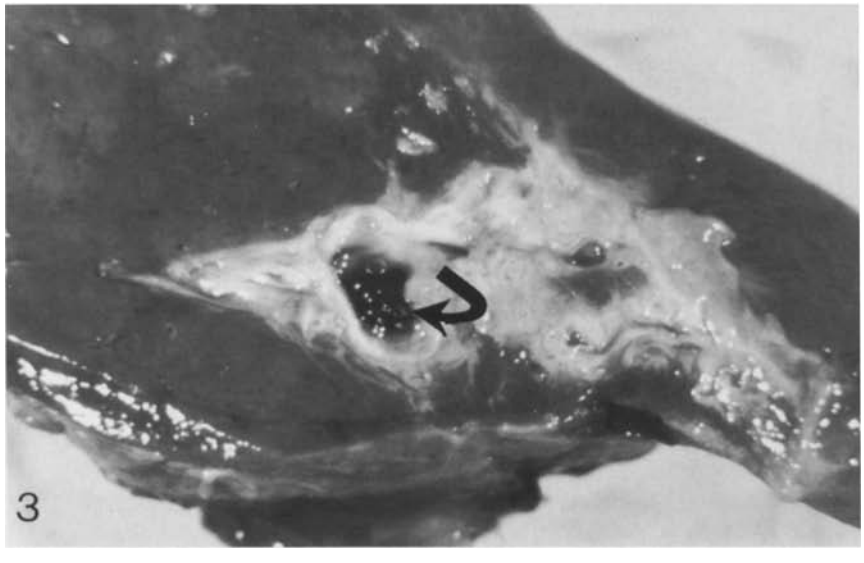
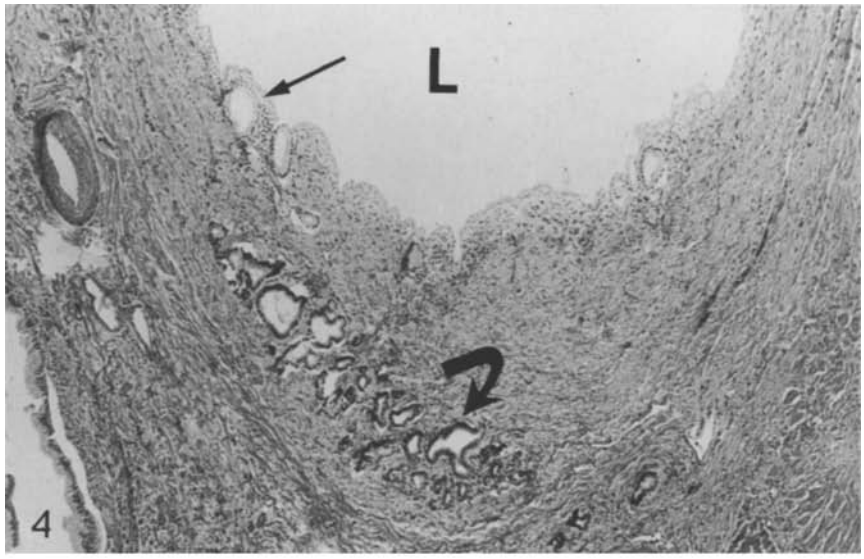


Fig. 1. Calculi (*arrows*) are seen in the branch of left segmental duct. Case 1. Surrounding hepatic parenchyma was slightly atrophic

Fig. 2. Calculi (*straight arrows*) in the peripheral ducts in the subcapsular region. *Curved arrow* denotes a bile duct in which calculi were artificially removed. The surrounding parenchyma had dropped out. Case 2

Fig. 3. Calculi (*arrow*) are seen in the branch of left segmental duct. Stone containing ducts are fibrously thickened and dilated. The surrounding parenchyma is collapsed. Case 4



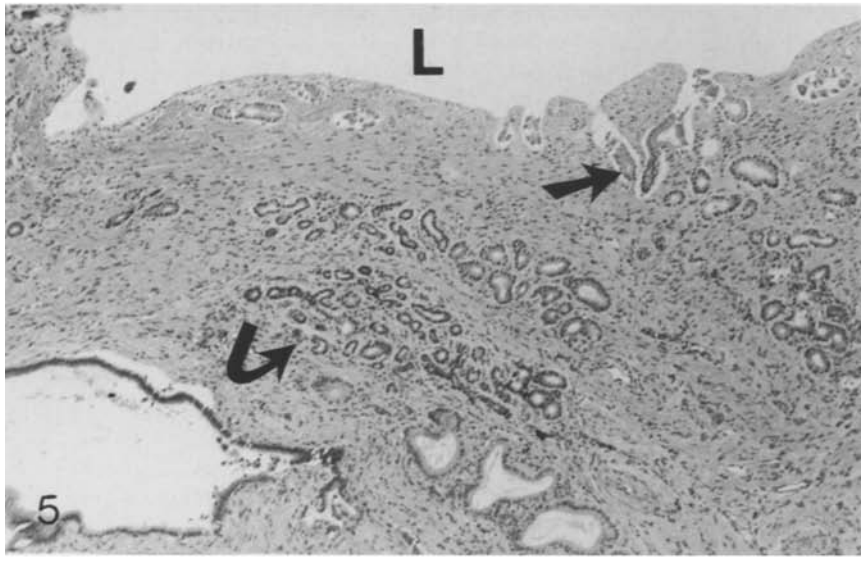


Fig. 4. Stone-containing duct shows fibrosis and glandular elements in the ductal wall and periductal tissue. *Straight arrow* shows single nonbranched glands in the ductal wall and the *curved arrow* shows glands arranged in a lobule. *L*: ductal lumen. Case 1: HE ×80

Fig. 5. Stone-containing ducts show fibrosis and glandular elements in the ductal wall and periductal tissue. *Straight arrow* shows single nonbranched gland and *curved arrow* shows glands arranged in a lobule. Case 4. HE ×80

Fig. 6. There is mild to moderate lymphocytic infiltration (*arrows*) in the stone-containing bile duct wall. Case 3. HE ×80

Discussion

The present study revealed that the calculi of the peripheral type were of a brown pigment stone as seen in the major type of hepatolithiasis (Ohta et al. 1984, 1986; Terada and Nakanuma 1988). Stagnation of bile with bacterial infection of the biliary tree and the action of β-glucuronidase on conjugated bilirubin followed by deconjugation and combination with calcium, are thought to be important preceding events in the formation of brown pigment stones (Maki et al. 1984; Masuda et al. 1979). Therefore, this sequence might also have been present in the development of intrahepatic calculi in the present cases. However, the major intrahepatic and extrahepatic biliary tree failed to show inflammation or any histopathological changes which were known to predispose to bacterial infections. As speculated in RPC (Ong 1962), bacteria carried by the portal blood might have led to focal infection of the peripheral branches of the biliary tree. However, there was no evidence suggesting portal bacteraemia in our cases.

In addition to these bacterial factors, factors such as activation of intrinsic β-glucuronidase, alteration of bile composition, anomalies in the biliary tree or focal preceding cholangitis may also have played a part in stone formation in the peripheral ducts. No morphological biliary anomalies were found in the present cases. However, minor anomalies such as unusual branching pattern or branching angle of the peripheral bile ducts might have been related to calculi formation cannot be excluded. All of our 4 cases showed mild dilatation of biliary tree where stones were impacted. It is unclear whether this ductal dilatation preceded the stone formation or have occurred after stone formation. It seems possible that an unusual intrahepatic localization of primary sclerosing cholangitis (PSC) is associated with peripheral type of hepatolithiasis, because intraductal stone is a well known complication of PSC (Lindor et al. 1987). However, this localized form of PSC has not well established (LaRusso et al. 1984; Lindor et al. 1987). Furthermore, the stones were localized only in the affected ducts and no patients had ulcerative colitis in this present series, so that this possibility is unlikely.

The stone-containing ducts of the peripheral type showed fibrosis, inflammatory cell infiltration and a variable proliferation of glandular elements in the ductal wall and periductal tissues. This suggests that the histopathology of the stone containing ductal lesions was basically identical to those of the major type (chronic proliferative cholangitis) (Ohta et al. 1984, 1987), though their degree was considerably milder except for case 4. This implies that these cases are at an early stage and may eventually progress to the major type presenting fully developed "chronic proliferative cholangitis". An alternative explanation is that the peripheral type remains non-progressive. This issue is very important in evaluating the mechanism and progression of intrahepatic calculi in Japan. Follow-up of the cases of the peripheral type is mandatory to clarify this issue.

The present study showed that brown pigment stones can arise in the peripheral branches in the liver as a primary event. In addition, there have been recently several reports concerning the intrahepatic cholesterol stones which might have developed primarily in the peripheral ducts (Akiyama et al. 1987). Factors including biliary physiology, anatomical change and pathology leading to calculus formation in the peripheral bile ducts should be carefully evaluated, as it has been in the gallbladder and major intrahepatic bile ducts (LaMont et al. 1983; Messing et al. 1983).

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