Involvement of Peribiliary Glands in Primary Sclerosing Cholangitis: A Histopathologic Study

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We examined the histological changes of the peribiliary glands (PBGs), a hitherto pooly recognized anatomical element around the biliary tree, in 7 cases of primary sclerosing cholangitis (PSC). These glands showed proliferation, and nonspecific inflammation with lymphoplasmacytic infiltration, fibrosis, and destruction. In addition, there were cystic lesions around the bile ducts, and they were considered to reflect dilatation of the PBGs. These changes were found around the intrahepatic and extrahepatic bile ducts in the cases examined. It is of interest that changes in the PBGs tended to correlate with the inflammatory changes of the bile duct wall itself, though 2 cases showed changes in the duct walls and PBGs unrelated to their distribution along the biliary tree. These findings suggest that the PBGs are also a target structure in addition to the bile ducts themselves in PSC.

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Key words: biliary tree, peribiliary cyst

Introduction

Primary sclerosing cholangitis (PSC), a rare disease of unknown etiology, is characterized by chronic nonspecific and fibrosing inflammation and obliteration of the bile ducts, usually affecting both the extrahepatic and intrahepatic bile ducts (1, 2). In addition to the pathological changes of bile ducts, hepatic parenchyma also showed nonspecific changes and features of chronic cholestasis and chronic active hepatitis, which were followed by biliary cirrhosis.

It has been recently reported that there are peribiliary glands (PBGs) around the extrahepatic bile ducts (3) and also intrahepatic bile ducts (4). Histologically, PBGs are classified into intramural and extramural according to their location. The intramural PBGs are scattered within the bile duct walls, few in number, and are simple tubular mucinous glands. In contrast, the extramural PBGs are more abundant, located in the periductal connective tissue, and are branched tubuloalveolar seromucinous glands. Although their physiological functions remain unclarified, they show variable pathological changes in hepatobiliary diseases (4–8). However, there are no reports of pathological findings of PBGs in PSC, except for one case report in which PBGs in the extrahepatic bile ducts in PSC showed marked proliferation: cholangitis glandularis proliferans (9).

Here, we report that nonspecific inflammatory changes of PBGs are frequently found in PSC and raise the possibility that PBGs are also a target structure in PSC in addition to the bile duct itself.

Materials and Methods

Patients and specimens

We studied 7 cases of PSC, which were treated in our laboratory and several affiliated hospitals from 1986 to 1991 (Table 1). These cases presented the biliary imaging and biochemical data and histological findings, consistent with a diagnosis of PSC (1, 2). The diagnostic criteria which were applied in this study, are generalized beading and stenosis of the biliary tree on cholangiography with absence of either choledocholithiasis or a history of bile duct surgery or bile duct cancer. They consisted of 5 males and 2 females, and all but case 7 were intra- and extrahepatic type of PSC (1, 2). Case 7 was the intrahepatic type. As to the histologic stage of liver in PSC (10), 3 cases were of stage I, 1 of stage III, and 3 of stage IV.

The specimens of the liver tissues, intrahepatic large bile ducts and/or extrahepatic bile ducts were fixed in 10% neutral formalin and embedded in paraffin. Several sections were cut, in 3 μm thickness, and were stained by hematoxylin and eosin, Azan-Mallory and reticulin stains.

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Table 1. Characteristics of Patients with Primary Sclerosing Cholangitis (PSC)

Case	Age	Sex	Type of PSC	Stage	Specimens
1	42	M	IE	IV	Autopsy
2	62	F	IE	IV	Autopsy
3	67	M	IE	I	Surgical specimen
4	16	F	IE	IV	Surgical specimen
5	66	M	IE	I	Surgical specimen
6	65	M	IE	III	Surgical specimen
7	53	F	E	I	Surgical specimen

IE: intra and extrahepatic type, E: extrahepatic.

Histological evaluation

Histopathologic changes such as inflammation and proliferation of PBGs and inflammation of bile duct wall were estimated semiquantitatively as mild or severe by two pathologists.

Classification of peribiliary glands and adenitis

The glandular structures within the duct wall were called the intramural glands and those in the connective tissue around the duct wall as the extramural glands (4). The inflammatory changes of PBGs (adenitis) were classified into suppurative, lymphocytic, edematous and necrodegenerative types, according to our previous proposal (6). The suppurative and lymphocytic types characteristically show prominent infiltration of neutrophils and lymphocytes, respectively. Both are consistently associated with variable glandular abnormalities such as swollen or acidophilic cytoplasm or even necrosis. The edematous type is characterized by prominent edema of the glandular lobules and minimal inflammatory cell infiltration, with the biliary epithelial damage being mild. The necrodegenerative type is characterized by marked necrodegeneration of the glandular epithelia with minimal inflammation.

Result

Pathologic findings of the bile ducts

In the wall of bile ducts, inflammatory reactions were seen in both intra- and extrahepatic bile ducts in all cases. Nonspecific inflammation and fibrosis were found, accompanied by lymphoplasmacytic infiltration, causing thickening of the bile duct wall. The nonspecific inflammation and fibrosis extended into the periductal tissue to a varied degree and extent, making the margin of the bile duct wall unclear in places.

Pathologic findings of PBGs (Table 2)

Proliferation of glandular acini with mild ectasia and inflammatory reaction of PBGs to various degrees were found around the intra- and extrahepatic bile ducts. The infiltrated leukocytes were mainly lymphocytes and plasma cells, and there was occasional lymph follicle formation with a germinal center. These changes were lymphocytic or edematous types, according to our classification (6). Many glands became mucinous, particularly in the extrahepatic biliary tree. These findings were seen in the intramural as well as extramural glands (Figs. 1–5). In case 2, PBGs in the thickened duct wall showed pyknotic and

Table 2. Changes in the Bile Duct Wall and Peribiliary Glands of PSC Patients

Case	Type of PSC	Intrahepatic bile ducts			Extrahepatic bile ducts		
		Bile duct wall	Peribiliary glands		Bile duct wall	Peribiliary glands	
		Inflammation	Proliferation	Inflammation	Inflammation	Proliferation	Inflammation
1	IE	+	+	+	++	+	+
2	IE	++	++	++	++	++	++
3	IE	++	++	++	++	++	++
4	IE	++	++	++	NE	NE	NE
5	IE	NE	NE	NE	++	++	++
6	IE	++	++	++	NE	NE	NE
7	E	NE	NE	NE	+	+	+

IE: intra and extrahepatic type, E: extrahepatic, NE: not examined, +: mild change, ++: severe change.

eosinophilic cells, resembling oncocytic changes (Fig. 6). Several cases showed more necroinflammatory changes in PBGs than in the bile duct walls (Fig. 1). In all cases, the degree of inflammatory change of PBGs tended to be parallel with that of the bile duct wall, although two cases showed unrelated distribution of inflammation of bile ducts (cholangitis) and inflammation of PBGs (adenitis) along the biliary tree. There was no correlation between the histologic stage of PSC and the degree of inflammatory change of PBGs.

In addition, in 6 of 7 cases, variable sized epithelial cysts were found adjacent to the intra- and extrahepatic bile duct wall (Fig. 4). The distribution of these cysts varied from case to case. The wall of these cysts consisted of columnar or cubic lining cells surrounded by variable fibrous tissue. They were adjacent to or admixed with the PBGs (Fig. 7), and the latter also showed intermediate size microcysts or cystic dilatation. Therefore, the cystic lesions were thought to be due to dilatation of PBGs.

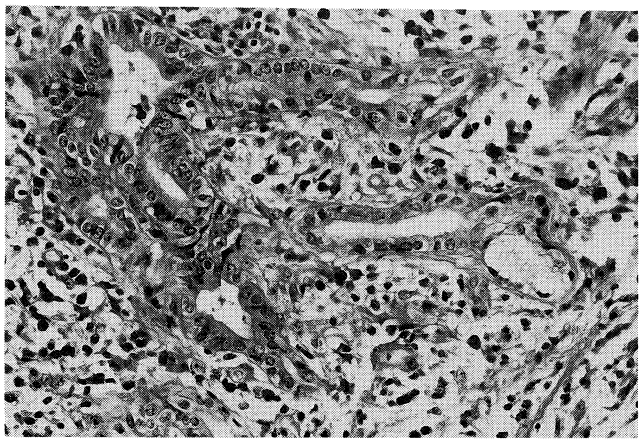

Figure 3. Lymphoplasmacytes infiltrate around the peribiliary gland and some also infiltrate into the glandular epithelial layer (HE stain, ×400, Case 3).

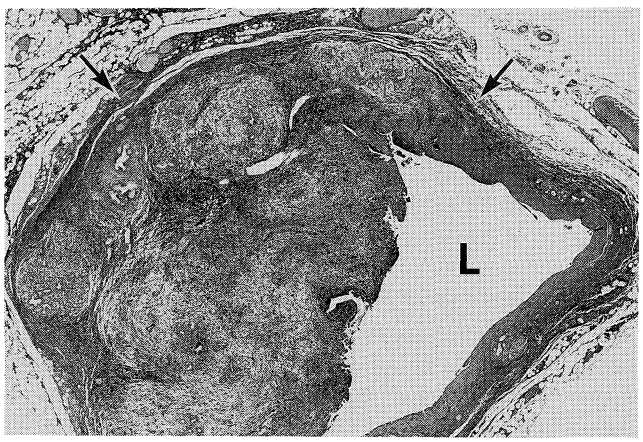

Figure 1. Approximately one-half of the circumference of the extrahepatic bile duct (arrows) is markedly thickened and its layered structure is destroyed. L: lumen (HE stain, ×40, Case 3).

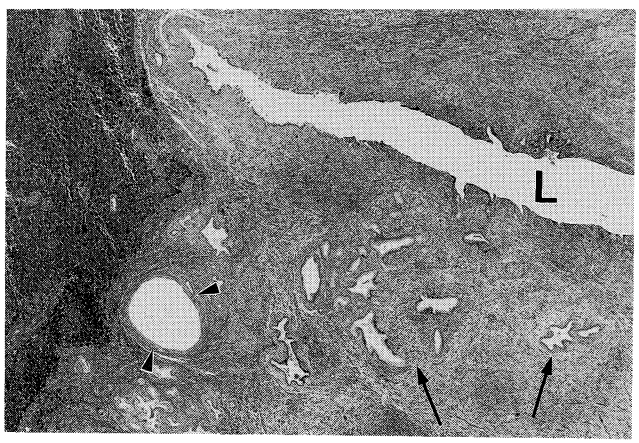

Figure 4. An intrahepatic large bile duct which is markedly thickened and irregular with proliferation of peribiliary glands (arrows) are seen. There is a cystic lesion beside the bile duct (arrowheads). L: lumen of the bile duct (HE stain, ×40, Case 3).

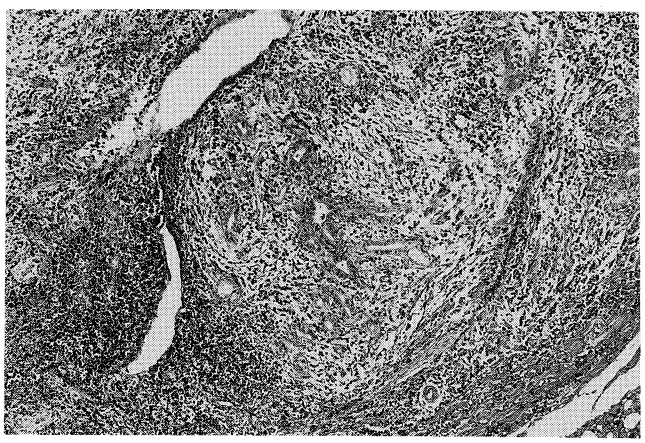

Figure 2. Peribiliary glands of extrahepatic bile ducts show severe inflammatory cell infiltration mainly lymphoplasmacytic and edematous change around and within them (HE stain, ×130, Case 3).

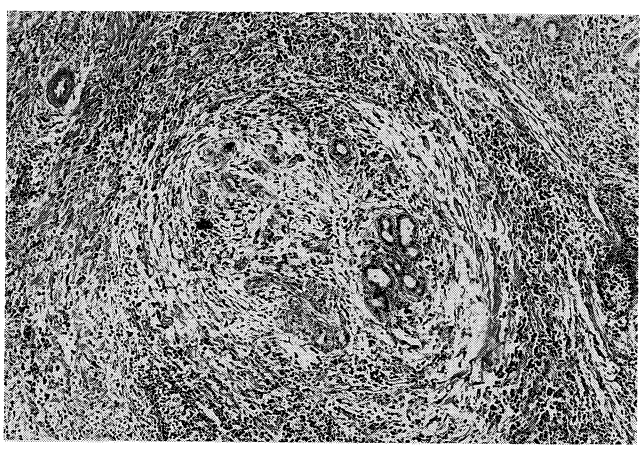

Figure 5. Peribiliary glands of the intrahepatic bile duct also show severe inflammatory reaction with destruction of glandular acini (HE stain, ×130, Case 3).

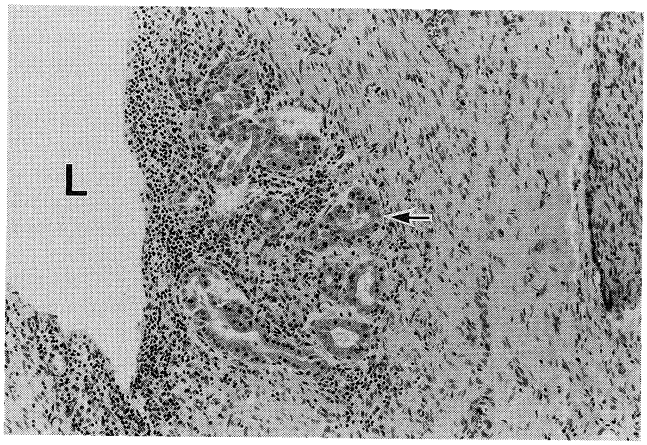

Figure 6. Oncocytic changes of the glandular element (arrow) are seen in the intramural glands. The glandular cells are pyknotic and eosinophilic. L: bile duct lumen (HE stain, ×130, Case 3).

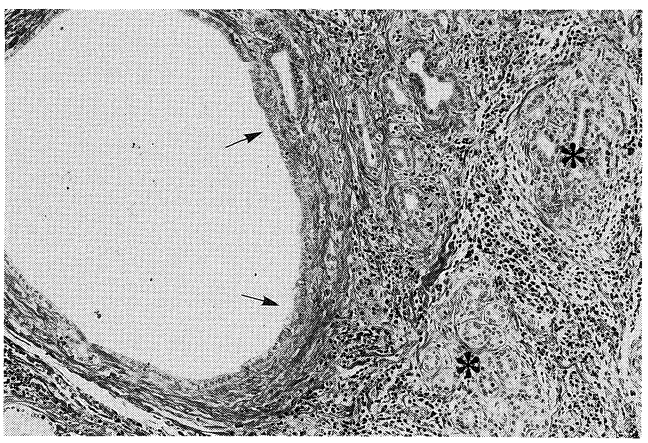

Figure 7. A cystic lesion (arrows) is adjacent to peribiliary glands (*). The wall of this lesion consists of columnar or cubic cells. There is also lymphoplasmacytic infiltration around the peribiliary glands (HE stain, ×130, Case 3).

Discussion

To date, there have been several reports on the pathological changes of the bile duct wall and hepatic parenchyma in PSC (11, 12). However, no reports state whether or not PBGs are involved in PSC. It was found in this study that the PBGs in PSC showed proliferation and necroinflammatory reaction [mainly, lymphocytic type of adenitis (6)] in and around both intra- and extrahepatic bile duct. Edematous changes were also found [edematous adenitis (6)]. It is of interest that the degree of inflammation of PBGs tended to be parallel to that of the bile duct wall. All of these findings suggest that the changes of PBGs may be related to the inflammatory process itself of PSC, while it remains unclear whether the changes of PBGs are a secondary or primary phenomena of inflammation of the bile duct wall. Our previous study disclosed that necroinflammatory changes of PBGs are nonspecifically found in a number of hepatobiliary diseases (7). Therefore, the findings obtained in this study simply reflect an extension of the inflammatory process of bile duct walls to the PBGs in PSC. However, two cases showed predominant involvement of PBGs compared to duct walls in some places and vice versa in another, suggesting that PBGs are a target tissue separate from the bile ducts themselves in PSC. There was no correlation between the histologic stage of PSC and the degree of inflammatory change of PBGs. This finding suggested that some degree of inflammatory changes of PBG continues throughout the course of PSC.

In this study, some glands showing oncocytic change are seen in the thickened bile duct wall. This finding may suggest that an autoimmune mechanism is associated with this condition, because such an oncocytic change of glandular tissue is thought to be seen in autoimmune diseases such as chronic thyroiditis and primary biliary cirrhosis (13, 14). Immunological mechanisms have been suggested in the pathogenesis of bile duct injury in PSC (15–17) and may also be responsible for the damage of PBGs in PSC.

In cholangiography, diverticulum-like out-pouchings are often seen in PSC (18). In the present study, cystic lesions were detected around the large bile duct in 6 of 7 cases. These lesions seem to be a result of dilatation of PBGs. Nakanuma et al first reported that cystic change of PBGs could occur as a result of the disturbance of intrahepatic circulation or as a result of inflammatory destruction of the glandular conduits (19). So, large sized cysts which can be detected radiologically, may form the out-pouchings or dilatation of PBGs in PSC.

In conclusion, our study strongly suggested that 1) the PBGs are a target tissue in PSC and immunological reaction may be associated with this condition, and 2) radiologists should make special note of these changes in PBGs, particularly the cystic ones, in the evaluation of cholangiography of PSC.

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