

Temporal Morphologic Changes in the Mouse Liver after Common Bile Duct Ligation

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Purpose: Cholestasis is a common manifestation of biliary obstructive diseases. This study was designed to verify histopathologic manifestations of cholestatic liver injury after bile duct ligation in a murine model.

Methods: Eight-week-old female CB6 F1 mice underwent common bile duct ligation and sacrificed at various intervals after surgery. Serum samples were used for the levels of ALT, γ -GT, total bilirubin. Liver tissues were used for H&E stain for histopathologic examination, Masson's trichrome to assess fibrosis, and reticulin for evaluation of hepatic lobular framework and cell loss. Data were analyzed using the Students' t-test.

Results: In mid-duct ligated animals, marked microvesicular fatty change was noted between 1 to 2 days, which completely subsided after 3 days. Scattered variable-sized foci of hepatic cell loss were noted also, beginning at 12 hours, but becoming more prominent at 1 to 3 days. Fibrosis in larger portal tracts near the hilum was first noted through day 3, and remained at days 7 and 28. This was accompanied by marked branching and/or epithelial proliferation in the large bile ducts. Peripheral hepatic fibrosis was evident at day 5 and continued postoperatively. Liver function tests on serums showed an obstructive jaundice pattern during the first week. These values normalized by week 4. Choledochoduodenal fistulae were formed in mice surviving 4 weeks after ligation.

Conclusion: This study provides a temporally reproducible pattern of biochemical and histopathological changes in the liver, providing a useful model for studying the pathobiology

of cholestatic liver diseases secondary to extrahepatic bile duct obstruction. (J Korean Surg Soc 2002;63:99-104)

Key Words: Cholestasis, Morphologic change

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(cholestasis)
 가
 가 가 1800
 .(1-3) Cameron(1,4) 1866 1931
 1958
 . 1957
 Trams Symeondis(5)
 가 가 (inbred)
 가 가 가
 (6-11)

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1)
 8 CB6 F1 (19 23 gm) Charles River
 Co. 41% 70F°
 4 12
 24

UCSD glutamyltransferase (γ -GT) kits (Sigma, St. Louis, Mo.).

2) (4) : H

flurane methoxy- Masson's trichrome

reticulin (steatosis),

가 , 가

prolene 9.0

Sham ((-), absent; (+), <5%;

((+), 5-20%; (+++), >20%).

3) (+), (+), (+

(1) (n=60): (+) 10

20 3 30%; (+++), >30%.

((-), absent; (+), mild; (++), moderate; (+++), severe).

4) Student's t-test P 0.05

1 Vater

(2) (, n=32):

4 8 4 , 12 , 1

, 2 , 3 , 5 , 7 , 28 Sham

1

3 가 4 6 4

(3) : 가 35% (7/20) 7 7 가 13 13

total bilirubin, alanine aminotransferase (ALT), gamma-

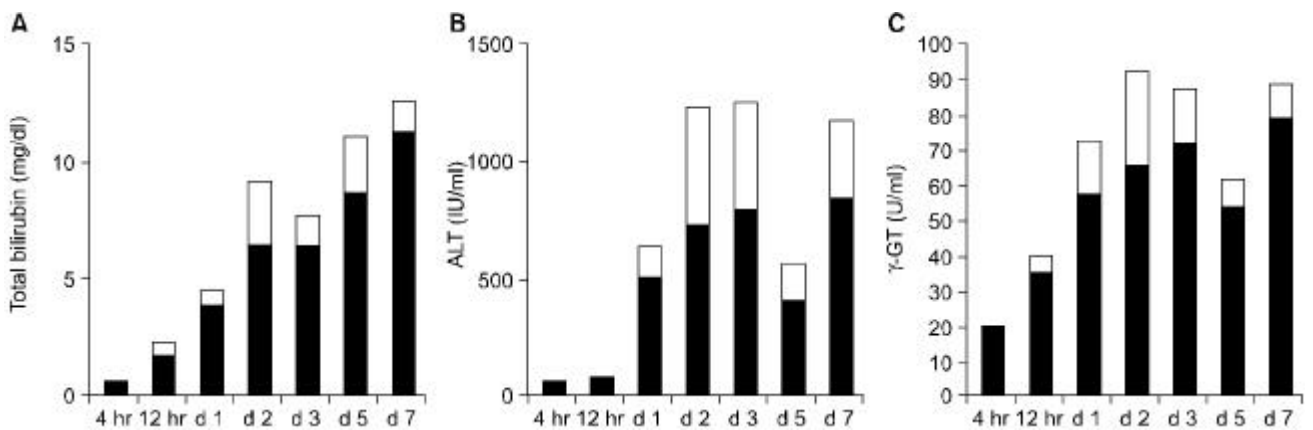


Fig. 1. Liver function tests in mice after bile duct ligation. A. total bilirubin, B. ALT, C. γ -GT, black bar; mean, white area; standard deviation.

7 95% (19/20) 가 1 4) (steatosis),
 7 25% (5/20) 가 15 4 , , 67가
 가 (saponified) (Table 1). 가

2)
 (Fig. 1). Total bilirubin 12
 가 가 (P < 0.01), ALT
 -GT 가 가
 (P > 0.1). 4
 3) (Recanalization)
 4

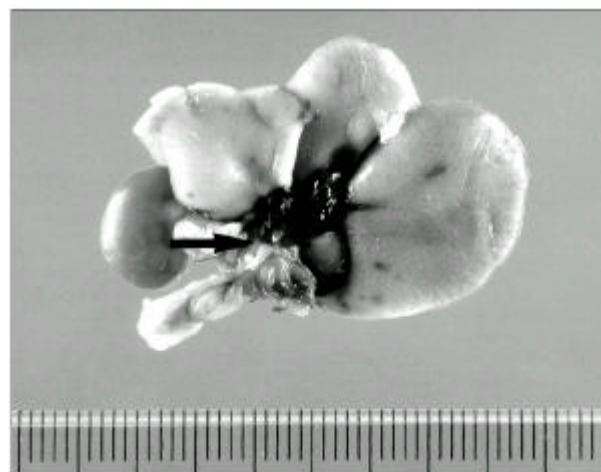


Fig. 2. Choledochoduodenal fistula, 4 weeks post-ligation. A grossly normal liver with internal communication between the biliary tract and intestine. The choledochoduodenal fistula (black arrow) was confirmed by ink injection on the proximal side of the ligature which tracked to the side distal to the ligature, into the duodenum.

Table 1. Summary of histopathologic changes after bile duct ligation

	4 hr	12 hr	1 hr	2 hr	3 hr	5 hr	7 hr	4 week
Bile duct proliferation grade	- (0/11)	- (0/8)	+ (1/9)	+++ (3/8)	+++ (5/12)	+++ (4/8)	+++ (6/8)	+++ (15/37)
Proliferated duct/total duct	- (0/15)	- (0/11)	+ (1/12)	++ (1/8)	+++ (4/11)	+++ (7/14)	+++ (15/19)	+++ (18/28)
	- (0/10)	- (0/9)	++ (1/7)	+++ (2/7)	+++ (3/8)	+++ (4/8)	+++ (6/11)	+++ (19/31)
Loss of cell mass	-	++	+	++	++	+	+	+
	-	+	+++	+	+	+++	+	+
	-	+	++	+	+	+	+	+
Steatosis	-	+	+	+	-	-	-	-
	-	-	+	+	-	-	-	-
	-	-	+	+	-	-	-	-
Fibrosis (central)	-	-	-	+	+	+++	+++	+++
	-	-	-	+	+	+++	+++	+++
	-	-	-	+	++	++	+++	+++
Fibrosis (peripheral)	-	-	-	-	-	++	++	+++
	-	-	-	-	-	++	+++	++
	-	-	-	-	-	++	++	+++

12
 (microvesicular fatty change)
 (Fig. 3).
 가 (zonal distribution)
 가
 1 5 4
 (infarction) (apoptosis)
 (Fig. 4A, B).
 가 ballooning degeneration

(eosinophilic material)
 (organelles)
 가 가
 (basement membrane)
 2
 5
 (dysplastic change)
 (hilum)
 5
 가 28

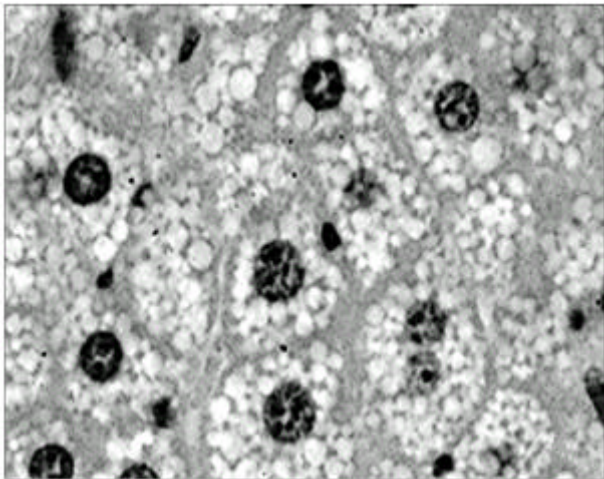


Fig. 3. Steatosis, 24 hours after ligation. The earliest changes occurred at 24 hour after common bile duct ligation. They were characterized by diffuse microvesicular steatosis, which was no longer present by day 3 (H&E stain, $\times 400$).

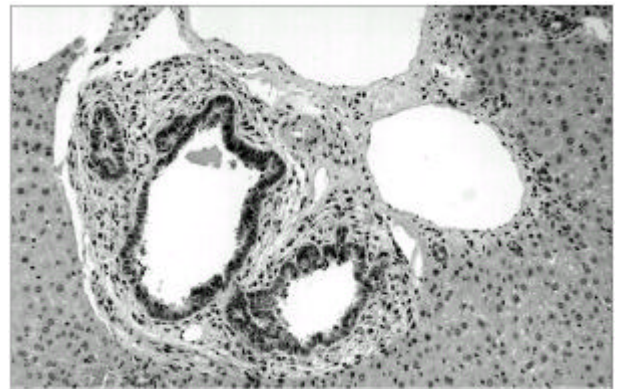


Fig. 5. Fibrosis. Fibrosis in large portal tracts was first noted at day 3, which was accompanied by marked branching and/or epithelial proliferation of the large bile ducts within the fibrotic spaces (H&E stain, $\times 200$).

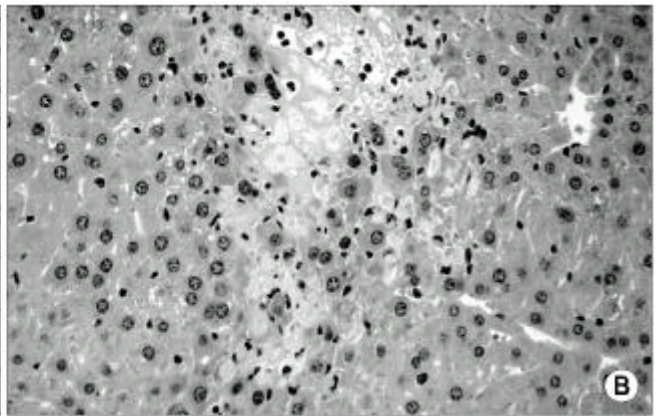
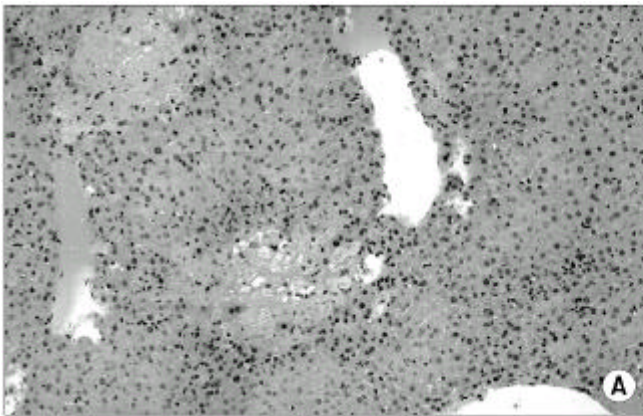


Fig. 4. Hepatic cell loss. Scattered foci of hepatic cell loss were seen as early as 12 hours, but became more apparent at day 1 to 3, and persisted to day 5. Histopathologic features in these foci appeared distinct from typical apoptosis or infarction; A, day 3 (H&E stain, $\times 200$); B, day 5 (H&E stain, $\times 400$).

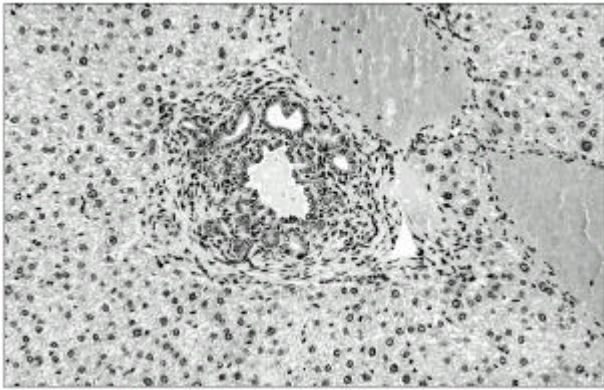


Fig. 6. Fibrosis. Fibrosis in smaller portal tracts was seen after day 5, and was also accompanied by bile duct proliferation as was in larger tracts. A section from a mice sacrificed at day 7 was illustrated (H&E stain, ×200).

(Fig. 5). 5

(Fig. 6).

(5)
 (12, 13)
 (feathery degeneration),
 (acidophilic bodies) 가 (single cell
 necrosis), 가
 (12-14)
 가 (pseudoglandular formation) liver
 plates (bile infarct),
 (confluent degeneration)
 (mixed portal inflammatory infiltrates),
 가 (15-19)
 bile plug
 bile plug (12, 17)
 bile plug

3

bile lake가

(1-5)

가

가

가

가

가 4

4 가

8 (5) Cameron Hasan(4)

가

8

가

(internal fistulization)

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