

Liver changes associated with cholecystitis

J M Geraghty, R D Goldin

Abstract

Aims—To investigate the histopathological changes in the livers of patients undergoing cholecystectomy and to relate these changes to the underlying biliary tract pathology.

Methods—Liver changes in 67 patients undergoing cholecystectomy were investigated. Sixty three had gall stones, one cholesterosis only, and there were three cases of acute acalculous cholecystitis.

Results—Only 34% of the patients had completely normal liver biopsy specimens. The most clinically important pathology was found in 11 of the 14 patients with choledocholithiasis: three of these had cholangitis and eight had features of large bile duct obstruction (four also had chronic cholestasis and portal-portal linking fibrosis). Non-specific reactive hepatitis was the most common abnormality in the remaining 53 patients with cholecystitis alone, and was found in 18. A further four patients had chronic cholestasis without fibrosis and early primary biliary cirrhosis was a coincidental finding in another. Clinical symptoms were poorly correlated with gall bladder and liver pathology apart from an association between jaundice and choledocholithiasis. Liver function tests of obstructive pattern were noted in 23 of 58 patients, most of whom had choledocholithiasis or non-specific reactive hepatitis. Bile cultures were positive in 10 of 42 patients, predominantly in cases of cholangitis and acute cholecystitis.

Conclusions—Cholangitis and extensive fibrosis associated with large bile duct obstruction are common findings in patients with choledocholithiasis. The liver disease may progress to secondary biliary cirrhosis if the obstruction is not relieved, emphasising the need for early surgery. A peroperative liver biopsy may be useful to exclude cirrhosis in these patients, but is unlikely to be informative in those with cholecystitis alone.

Previous studies correlating the presence of gall stones with changes in liver histology have given conflicting results.⁴⁻⁹ In particular, the reported incidences of portal tract fibrosis differed considerably, and its association with the localisation of gall stones has been poorly defined. More importantly, the histological changes have not been described in detail.

The aim of this study, therefore, was to determine the prevalence and extent of liver disease, and to assess the value of peroperative liver biopsy specimens in patients undergoing cholecystectomy for gall stones and cholecystitis. Clinical assessment, liver function tests and biliary microbiology were correlated with liver and gall bladder histology and the distribution of gall stones in the biliary tree.

Methods

Peroperative protocol liver biopsy specimens distal to the gall bladder bed were obtained from 67 consecutive patients undergoing cholecystectomy at St Mary's Hospital, London, between January 1984 and March 1989. The series included 41 women, mean age 47.6 years (range 18 to 83 years), and 26 men, mean age 57.6 years (range 32 to 75 years), a distribution similar to that expected for the British population.^{10 11}

Forty patients presented with acute symptoms and underwent emergency cholecystectomy. Twenty one of these had had a history of gall stone related disease of between four weeks' and 10 years' duration. Elective surgery was carried out in the remaining 27 patients, who had histories of gall stone related disease of between eight weeks and 15 years. None of the patients was alcoholic, had viral hepatitis, or was known to be taking drugs associated with liver damage. The results of preoperative liver function tests (serum bilirubin, aspartate amino transferase, and alkaline phosphatase), taken within three days before surgery, were available in 53 patients.

The distribution of gall stones within the biliary tree was determined by a combination of radiological and ultrasound findings before surgery and those at surgery including peroperative cholangiography and exploration of the common bile duct. Peroperative bile swabs from the gall bladder and common bile duct were cultured aerobically and anaerobically by standard methods, and results were available for 42 patients.

The liver biopsy specimens (stained with haematoxylin and eosin, reticulin, and orcein stains) and blocks from the gall bladders

Department of
Histopathology, St
Mary's Hospital
Medical School,
Norfolk Place, London
W2 1PG

J M Geraghty
R D Goldin

Correspondence to:
Dr R D Goldin

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Liver damage in patients with gall stones is thought to be the result of chronic extra-hepatic large bile duct obstruction with or without repeated episodes of cholangitis^{1 2} and may ultimately progress to secondary biliary cirrhosis.³

Table 1 Gall bladder histology in 67 patients undergoing cholecystectomy, with percentages of the total in parentheses

Normal	2(3.0)
Acute cholecystitis	8(11.9)
Acute-on-chronic cholecystitis	22(32.8)
Chronic cholecystitis	34(50.7)
Cholesterosis only	1(1.5)

(fundus, neck, and body) were assessed independently by both authors and designated histological categories according to standard texts.^{1,12} Discrepancies were settled by consensus.

Results

GALL BLADDER HISTOLOGY AND DISTRIBUTION OF GALL STONES

Histological changes in the gall bladder are documented in table 1. Cholelithiasis was present in 63 patients, 14 of whom also had choledocholithiasis. Three had acute acalculous cholecystitis and another only cholesterosis. The distribution of stones and the gall bladder histology were similar in men and women (results not shown).

LIVER HISTOLOGY (TABLE 2)

Although minor differences were seen in the frequency of histological changes between men and women, these were not significant (results not shown). Liver histology was normal in 23 (34%) patients. The commonest abnormalities were non-specific reactive hepatitis and large droplet fatty change. Of the 18 patients (27%) with reactive hepatitis seven also had acute inflammatory cells in portal tracts not involving the bile ducts.

More clinically important pathology in the form of cholestasis, cholangitis, or large duct obstruction was present in 18 patients. Extensive fibrosis with portal-portal linking was confined to the four patients with acute large duct obstruction who also showed features of chronic cholestasis, including the accumulation of copper associated protein in periportal hepatocytes.¹³ None of the patients had secondary biliary cirrhosis. The liver biopsy specimen from one woman displayed the features of primary biliary cirrhosis (stage 2), subsequently confirmed by a positive test for serum mitochondrial antibodies.

A frequent observation was the presence of focal necroses and collections of neutrophils in the sinusoids, which are generally accepted to be the result of surgery and anaesthesia.¹

Table 2 Liver histology in 67 patients undergoing cholecystectomy with percentages of the total

Normal	23(34.3)
Large droplet fatty change only	7(10.4)
Non-specific reactive hepatitis	18(26.8)
Acute cholestasis only	3(4.5)
Chronic cholestasis only	4(6.0)
Acute cholangitis	3(4.5)
Acute large duct obstruction	4(6.0)
Acute large duct obstruction with chronic cholestasis	3(6.0)
Primary biliary cirrhosis	1(1.5)

CORRELATION BETWEEN LIVER AND GALL BLADDER HISTOLOGY

Normal liver histology and reactive hepatitis were common in all categories of gall bladder disease. Large droplet fatty change and acute or chronic large duct obstruction were seen mainly in cases of acute-on-chronic or chronic cholecystitis. All those patients with cholangitis or reactive hepatitis with acute inflammatory cells in portal tracts had either acute or acute-on-chronic cholecystitis.

CLINICAL SYMPTOMS

The most common symptoms were abdominal pain with or without jaundice. There was no correlation between the timing of the pain and gall bladder or liver histology.

Thirteen (19%) patients presented with acute abdominal pain and jaundice, with the following liver histology: acute cholangitis (n = 3); acute large duct obstruction (n = 4); acute large duct obstruction with chronic cholestasis (n = 2); non-specific reactive hepatitis (n = 1); and cholestasis only (n = 3). None had normal liver histology. All three patients with cholangitis had swinging fever in addition to abdominal pain and jaundice.

Forty two patients had no history of jaundice, including two with the changes of acute large duct obstruction with chronic cholestasis, both of whom had histories of abdominal pain of more than two years.

All four patients with only chronic cholestasis had histories of recurrent abdominal pain, of at least three months' duration, but none had had jaundice before.

In general, there was poor correlation between symptoms and gall bladder pathology.

CHOLEDOCHOLITHIASIS

The results of liver histology for the 14 patients with choledocholithiasis are given in table 3.

LIVER FUNCTION TESTS

Abnormal preoperative liver function tests are correlated with liver histology in table 4. Twenty eight of the 53 (53%) patients in whom results were available had abnormal liver function tests. The most sensitive indicator of clinically important liver pathology was a raised serum alkaline phosphatase value, present in 23 (43%) patients. None of the patients with acalculous cholecystitis had a raised alkaline phosphatase activity.

BILIARY MICROBIOLOGY

Of the 42 patients in whom the results of peroperative bile swab microbiology were

Table 3 Liver histology in 14 patients with choledocholithiasis

Liver histology	No. of cases
Normal	3
Acute cholangitis	3
Acute large duct obstruction	4
Acute large duct obstruction with chronic cholestasis	4
Total	14

Table 4 Abnormal liver function tests in patients undergoing cholecystectomy

	Raised bilirubin (>17mmol/l)	Raised AST (>40 U/l)	Raised alkaline phosphatase (>130 U/l)	Total (total No of patients tested)
Normal	1	1	1	3(18)
Large droplet fatty change only	0	0	0	0(1)
Non-specific reactive hepatitis	5	6	7	9(16)
Acute cholestasis only	3	2	2	3(3)
Chronic cholestasis only	0	0	2	2(3)
Acute cholangitis	3	3	3	3(3)
Acute large duct obstruction	4	3	4	4(4)
Acute large duct obstruction with chronic cholestasis	2	3	3	3(4)
Primary biliary cirrhosis	0	1	1	1(1)
Total	18	19	23	28(53)

available, 10 (24%) had positive cultures of one or more organisms, including six of the 14 with choledocholithiasis (results were unavailable in two of these). Infected bile was seen mainly in acute or acute-on-chronic cholecystitis. Only two of these patients had chronic cholecystitis with no acute inflammatory component.

Liver histology in these patients was as follows: acute cholangitis (n = 3); reactive hepatitis (n = 3, two with an acute inflammatory component); acute large duct obstruction with chronic cholestasis (n = 1); acute cholestasis only (n = 1); and normal (n = 2). Bacterial isolates comprised *Escherichia coli* (six patients), *Streptococcus faecalis* (three patients), *Bacteroides fragilis* (one patient), *Pseudomonas aeruginosa* (one patient), and *Clostridium perfringens* (one patient).

All categories of gall bladder and liver histology, apart from cholangitis, were represented among the 32 patients with sterile bile cultures.

Discussion

This study has shown that a high proportion (66%) of patients with gall stones and cholecystitis had abnormal liver histology. The most common findings were non-specific reactive hepatitis and large droplet fatty change. More clinically important liver pathology, in the form of large duct obstruction or cholangitis, was associated with choledocholithiasis, which is similar to the findings of others.^{2,6,7}

Extensive fibrosis with portal-portal linking was present in four of the patients with large duct obstruction. This was shown to be the result of chronic biliary disease by the demonstration of chronic cholestasis in each case. This observation is important because the fibrosis could ultimately progress to irreversible secondary biliary cirrhosis.^{2,3,6} The mean interval between the onset of partial biliary obstruction by gall stones and the confirmation of cirrhosis has been estimated at 4.6 years.³ Considerable resolution may still be possible at the stage of portal-portal linking if

the obstruction is relieved,¹⁴ which emphasises the importance of early surgery.

Others have reported minor degrees of fibrosis or the prominence of acute inflammatory cells in portal tracts in patients with cholecystitis or choledocholithiasis, but the presence or absence of the changes of large duct obstruction, cholangitis, and cholestasis were not emphasised in these studies.^{5,8,9}

The presence of acute and chronic cholestasis alone in two and four patients, respectively, with cholelithiasis, is most likely related to previous choledocholithiasis with expulsion of the stone before surgery. This is supported by the obstructive pattern of liver function tests present in four of these cases. None of these patients had extensive fibrosis.

Non-specific reactive hepatitis was a frequent finding in this study and was confined to patients with acute or chronic cholecystitis. None had choledocholithiasis, but nine had abnormal liver function tests, most of obstructive pattern. Reactive hepatitis might, therefore, be the result of a recent episode of common bile duct obstruction in some patients. Chronic inflammation in portal tracts, with or without large droplet fatty change, has been reported by others with similar frequency.^{4,5,8} Reactive hepatitis has been described in patients with a variety of conditions, including febrile illnesses, hepatic space-occupying lesions, venous outflow obstruction and intestinal infections.¹ As a common disease, cholecystitis should be regarded as an important additional cause. Some patients with reactive hepatitis also had acute inflammatory cells in portal tracts and this correlated with acute inflammation in the gall bladder.

The finding of a single case of primary biliary cirrhosis among these patients should be regarded as coincidental. There is no known association between the two diseases.

Clinical symptoms were of poor discriminative value in predicting the underlying pathology, in accordance with the findings of others.⁹ The duration of abdominal pain could not be correlated with either liver or gall bladder pathology. Jaundice was often present in patients with cholangitis or large duct obstruction, but the association was not invariable. A previous history of jaundice was not correlated with extensive liver pathology. Conversely, six of the eight patients with chronic cholestasis had never been jaundiced, similar to the findings in the early stages of primary biliary cirrhosis.¹⁵

Abnormal liver function tests were most common in patients with choledocholithiasis. An obstructive pattern with raised alkaline phosphatase values was the most frequent abnormality, which was similar to the findings of others.¹⁶

The noted high incidence of positive bile cultures in patients with choledocholithiasis, cholangitis, and acute cholecystitis and the spectrum of bacterial isolates was as expected from other series.^{8,17-20}

This study has shown that cholangitis and extensive fibrosis associated with large bile

duct obstruction are common in patients with choledocholithiasis. The liver disease may progress to secondary biliary cirrhosis if the obstruction is not relieved, emphasising the need for early surgery. A peroperative liver biopsy may be useful to exclude cirrhosis in these patients, but is unlikely to be informative in those with cholecystitis alone.

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