

Analysis of Morphological Changes in Liver in Obstructive Jaundice with Special Emphasis on Fibrosis

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ABSTRACT

Background: Biliary obstruction can present with distressing symptoms and increased morbidity which leads to liver fibrosis, cholestasis, portal inflammation and ductular proliferation. Experimental studies showed reversal of histological findings in liver after biliary decompression surgery; however only a limited data is available regarding the same.

Methods: Prospective observational study of 28 liver biopsies from 14 patients of obstructive jaundice, who underwent decompression surgery and showed clinical deterioration at 6 weeks with normal HIDA scan. Patients were clinically evaluated. Both intra (1st bx) and postoperative (2nd bx) liver biopsies were studied for fibrosis, cholestasis, ductular proliferation and portal inflammation.

Result: Patient's age ranged from 24 to 75 years (8 Males and females 6), commonest symptom being jaundice. In 1st bx, most of the patients showed histological evidence of obstruction, which improved at least partially after surgery. There was no definite correlation of fibrosis with etiology. Fibrosis was less commonly seen with shorter duration of symptoms and younger males had higher prevalence. Increase/static grades of fibrosis were seen in 35.71% patients each, while 28.57% showed regression. No correlation of age and etiology with status of fibrosis was observed. Regression was more common in males and with absence of cholangitis while progression was more common in females and with presence of cholangitis.

Conclusion: We wonder whether younger males are more prone for fibrosis but males in general have better prognosis regarding the reversal. Also, cholangitis could be an important factor for deciding the further course of fibrosis. However we require larger data with multivariate analysis for the confirmation of the same.

Keywords: Obstructive Jaundice, Reversal/ Regression, Liver Fibrosis

Introduction

Patients with biliary obstruction form an important subgroup presenting to gastroenterology. Its management usually depends on various factors like the cause of obstruction (benign/ malignant) and duration of symptoms, and requires a coordinated multidisciplinary approach involving gastroenterologists, radiologists, and pathologists.^[1] The benign causes of biliary obstruction include gall stone disease, chronic pancreatitis, parasitic infestation of biliary tree and strictures following trauma including iatrogenic. Strictures may be asymptomatic, but if ignored, can cause life-threatening complications, such as ascending cholangitis, liver abscess, and secondary biliary cirrhosis.^[2,3] Among malignant conditions, pancreatic cancer is the commonest cause^[4,5] however most of these patients die due to complications of tumor invasion and metastasis rather than due to strictures per se. Nonetheless, both benign and malignant bile duct strictures are associated with distressing symptoms and increased morbidity.^[6]

The liver in biliary obstruction is basically an innocent victim, suffering from the consequences of events like increased biliary pressure and bile stasis proceeding somewhere distally in the bile ducts. Over a period of time they initiate complex hepatic histopathological changes, which can result in progressive hepatic fibrosis.^[7] These changes are modified by the duration, degree, cause of the blockage and complicating factors such as biliary infection which affect the immediate and long-term outcome of definitive surgical repair, therefore have prognostic and medico legal implications.^[8]

Patient's recovery depends on the improvement in liver function, normal bile flow and reversal of pathological changes. A histological return of normal liver parenchyma is seen after relief of obstruction in both animal and human models, which correlates with the return to near-normal liver function. However, only limited data is available regarding histological findings in liver following decompression surgery.^[9,10,11,12] Hence we undertook this

study to analyze morphological changes in liver secondary to biliary obstruction and following surgical correction with special emphasis on regression of fibrosis along with its clinical correlation.

Materials and Methods

Study Design: This is a prospective observational study carried out over the period of 1 year and 10 months (September 2014 to June 2016), in the Department of Pathology at a tertiary care centre. Institutional ethics committee permission was taken.

Inclusion Criteria: Patients who underwent surgical intervention in gastrointestinal surgery department for obstructive jaundice and showed no clinical/ biochemical improvement or had deterioration after 6 weeks of decompression surgery.

Exclusion Criteria: Patients with liver parenchymal disease, other than obstructive biliary pathology or with previous history of biliary decompression surgery.

Study Procedure: Patients were evaluated for history with respect to age, gender, symptoms with duration and cause of obstruction along with detailed clinical examination. Preoperative Liver function tests (LFTs) including Serum bilirubin, Serum alanine transaminase (ALT), Serum aspartate transaminase (AST) and Serum alkaline phosphatase (ALP) were assessed along with radiological investigations. Patients underwent the required surgery, depending upon the cause and location of obstruction and an Intra-operative liver biopsy (1stBx) was taken to evaluate the morphological changes in the liver. Post-operative evaluation of LFTs was also done at various intervals up to 6 weeks as by this time maximum recovery after surgery is expected. Then a HIDA (Hepato-biliary IminoDiacetic Acid) scan was done to check the functionality of hepato-enteric anastomosis. The patients showing no evidence of biliary obstruction but having clinical/ biochemical deterioration or no improvement underwent a second percutaneous liver biopsy (2ndBx). Three to four μ m sections from the biopsy samples, fixed in 10% neutral buffered formalin solution, embedded in paraffin were obtained and stained with hematoxylin-eosin, Masson trichrome and reticulin. The histological features like fibrosis, cholestasis, ductular proliferation, portal inflammation or any other incidental pathological changes were assessed by two pathologists. (Table 1) Low grade was defined as 0-1 and higher grades as 2 and above. Findings were correlated clinically with respect to age, gender, cause and duration of symptoms. Longer duration was defined as > 6 months.

Result

Of the 24 patients who underwent decompression surgery, 15 fulfilled the inclusion criteria, of which 8 were males (M) and 7 females (F). One female expired in 2 weeks following surgery, hence was excluded from the study. Of the total 14 patients, 2 each (14.28 %) were in the age group of 3rd and 6th decade, 7(50%) in 4th decade and 3(21.42%) in 7th decade or older age group. The youngest patient was 24 years, eldest being 75 years old and 9 (64.28%) were below 40 yrs. Their presenting symptoms in decreasing order of frequency were Jaundice (85.71%), pain (64.28%), fever (57.14%) and itching (35.71%). One patient each had weight loss (7.14%) and portal hypertension (7.14%) and many had multiple symptoms. Duration between onset of symptoms and 1st biopsy ranged from 0.5 -36 months (mths) of which most patients (9/14, 64.28%) had duration of symptoms between 0-3 months, 4 (28.56%) between 3-6 months and only 1 (7.14%) had 36 months.

At least one of the LFTs (Both preoperative and 6 weeks postoperative) were deranged in all except one patient, who showed only postoperative derangement. Their range with mean values are given in Table 2. Radiological investigations like CT, MRI or MRCP were done in all.

Various causes (benign/ malignant) of obstruction found are mentioned in Table 3. An analysis of the etiology was also done with respect to age and gender. Of the total 8 patients with benign cause, 87.50% (3M, 4F) were <40yrs and 12.50% (1F) was >40yrs old. Among 6 patients with malignant cause, 33.33% (2M) were < 40yrs and 66.67% (3M, 1F) were >40yrs old.

Various surgical procedures done for relieving obstruction were hepaticojejunostomy in 12 and choledochoduodenostomy, cholecystojejunostomy and shunt surgery in 1 patient each.

Total 28 liver biopsies, including one intra-operative and post-operative each from 14 patients were studied. The histopathological analysis of the biopsies was done to look for the grade of fibrosis, ductular proliferation, inflammation and cholestasis (*Fig 1, 2*) which is given in table 4.

Fibrosis in 1stbx was low grade in 11 (78.5 %), none showed grade 2, and grade 3 was seen in 3 patients (21.42%), in 2ndbx, all patients (100%) had low grade fibrosis. Cholestasis in 1stbx was low grade in 7(50 %), rest showed grade 2, while in 2ndbx; cholestasis was low grade in all. Inflammation in 1stbx was low grade in 7(50%) while rest showed grade 2 or 3, in 2ndbx, 13 (92.85%) had low grade, one (7.14%) had grade 2 while none showed grade 3 inflammation and cholangitis was observed in 8 patients.

Ductular proliferation in 1st biopsy was low grade in 12 (85.71%) and rest had grade 2, in 2nd biopsy, all patients had low grade ductular proliferation.

The grades of fibrosis were also analyzed with respect to the age and gender of the patients, cause of obstruction and duration of symptoms (Table 5-7). In 1st biopsy, in <40yrs age group, most males (80%, 4/5) showed presence of fibrosis (grade 1), while most females (75%, 3/4) showed no fibrosis. Grade 3 fibrosis was observed only in one patient (Male). In >40yrs age group also, most males (66.66 %, 2/3) while only 1 female (50%) showed fibrosis. In 2nd biopsy, most patients (92.85%, 13/14) showed evidence of fibrosis (grade 1) except one male of > 40 yrs age group. Of the total 8 patients with benign causes, 5 (62.50%) had fibrosis in 1st while all had fibrosis in 2nd bx. Of the total 6 with malignant cause, 4 (64.28%) had fibrosis in 1st while 5 (83.33%) had fibrosis in 2nd bx. Of the total 9 patients with < 3 mnth duration of symptoms, 5 (55.55%) had fibrosis, of the 4 with 3 to 6 mnth duration 3 (75%) had fibrosis while a single patient with > 6 mnth had fibrosis which was grade 3.

Correlation of change in status of fibrosis (Regression / static/ progression) following decompression surgery was also done with respect to age, gender, cause of obstruction and cholangitis (Table 8).

Progression and static fibrosis was seen in 5 patients each (35.7%), of which 3 each showed association with benign and 2 each with malignant cause. Of those with progression of fibrosis (5), 4 were females, all showing association with cholangitis while single male had no cholangitis. Of those with static fibrosis (5), cholangitis was seen in 2 of 4 males and single female patients.

Regression was seen in 4 patients ((28.6%) of which 2 each showed association with benign and malignant cause. There were 3 males of which 1 showed cholangitis and one female with no cholangitis. Three patients showed reversals from grade 3 to grade 1 and one showed from grade 1 to grade 0.

Other incidental findings noted were, mild steatosis (*Fig 3a*) in 3 and single foreign body granuloma in portal tract (*fig 3b*) in 1 patient.

Table 1: criteria used for grading.

Grade	Fibrosis	Portal/ Periportal inflammation	Cholestasis	Ductular proliferation
0	Absent	Absent	Absence	Absent or mild
1	Portal and periportal	Mild (in < one third of portal tracts)	Bile accumulation in centrilobular hepatocytes;	Moderate
2	Presence of numerous septa	Moderate (in one third to two thirds of portal tracts)	bile accumulation in centrilobular and periportal hepatocytes or in portal tracts;	Severe
3	Cirrhosis	Severe (Dense packing of cells > two thirds of portal tracts)	the presence of bile infarcts (bile accumulation with hepatocyte necrosis surrounded by foamy histiocytes)	

Table 2: Biochemical Investigations:

Investigation	Preoperative range (mean value)	Postoperative range (mean value)
AST	28-212 IU (69.14 IU)	28-55 IU (38.07 IU)
ALT	08-478 IU (75.92 IU)	19-42 IU (29.07 IU)
ALP	152-1400 IU (665.50 IU)	90-1100 IU (376.00 IU)
Bilirubin	1-17 mg/dl (4.84 mg/dl)	0.8-2.3 mg/dl (1.30 mg/dl)

Table 3: Distribution according to the cause of obstruction:

Causes	Number of patients (n=14)
Benign	08 (57.14 %)
Benign Biliary Stricture	05 (35.71 %)
Portal Biliopathy	01 (7.14%)
Chronic Pancreatitis	01 (7.14%)
Choledocholithiasis	01 (7.14%)
Malignant	06 (42.85)
Carcinoma head of pancreas	2 (14.28%)
Ampullary carcinoma	2 (14.28%)
Distal CBD carcinoma	1 (7.14%)

Table 4: Histopathological analysis of liver biopsies

Grade	Fibrosis		Cholestasis		inflammation		Ductular proliferation	
	1 st bx (n=14)	2 nd bx (n=14)	1 st bx (n=14)	2 nd bx (n=14)	1 st bx (n=14)	2 nd bx (n=14)	1 st bx (n=14)	2 nd bx (n=14)
0	5(35.71%)	1(7.10%)	6(42.85%)	11(78.51%)	1(7.14%)	4(28.56%)	4(28.56%)	5(35.71%)
1	6(42.85%)	13(92.85%)	1(7.14%)	3(21.42%)	6(42.85%)	9(64.28%)	8(57.14%)	9(64.28%)
2	0	0	7(50.00%)	0	5(35.71%)	1(7.14%)	2(14.28%)	0
3	3(21.42%)	0	0	0	2(14.28%)	0		

Table 5: Grades of fibrosis with respect to age and gender of patients

Grades	Age < 40yrs (n=9)				Age >40yrs (n=5)			
	1 st bx		2 nd bx		1 st bx		2 nd bx	
	Males (n=5)	Females (n=4)	Males (n=5)	Female (n=4)	Males (n=3)	Females (n=2)	Male (n=3)	Female (n=2)
0	0	03 (21.42%)	0	0	01(7.14%)	01 (7.14%)	01(7.14%)	0
1	04 (28.57%)	01 (7.14%)	05(35.71%)	04 (28.57%)	01 (7.14%)	0	02(14.28%)	02 (14.28%)
2	0	0	0	0	0	0	0	0
3	01 (7.14%)	0	0	0	01 (7.14%)	01 (7.14%)	0	0

Table 6: Grades of fibrosis in relation to cause of obstruction (1st biopsy):

Grade	Benign (n=8)		Malignant (n=6)	
	1 st bx	2 nd bx	1 st bx	2 nd bx
0	03 (37.50%)	0	02 (33.33%)	01 (16.67%)
1	03 (37.50%)	08 (100%)	03(50.00%)	05 (83.33%)
2	0	0	0	0
3	02(25.00%)	0	01(16.67%)	0

Table 7: Grades of fibrosis (1stbiopsy) in relation to duration of symptoms:

Grade	<3mths (n=9)	3-6mths (n=4)	>6mths (n=1)
0	04 (28.57%)	01 (7.14%)	0
1	04 (28.57%)	02 (14.28)	0
2	0	0	0
3	01 (7.14%)	01 (7.14%)	01 (7.14%)

Table 8: Status of fibrosis after decompression surgery

Grades	Overall status (n=14)	With respect to cause(n=14)		With respect to age and gender (n=14)				cholangitis
				<40 yrs		>40 yrs		
		Benign (n=8)	Malignant (n=6)	Male (n=5)	Female (n=4)	Male (n=3)	Female (n=2)	
Regression	04 (28.57%)	2 (25.00%)	2 (33.33%)	01 (7.14%)	0	02 (14.28%)	01 (7.14%)	1
Static	05 (35.71%)	3 (37.50%)	2 (33.33%)	04 (28.57%)	01 (7.14%)	0	0	3
Progression	05 (35.71%)	3 (37.50%)	2 (33.33%)	0	03 (21.42%)	01 (7.14%)	01 (7.14%)	4

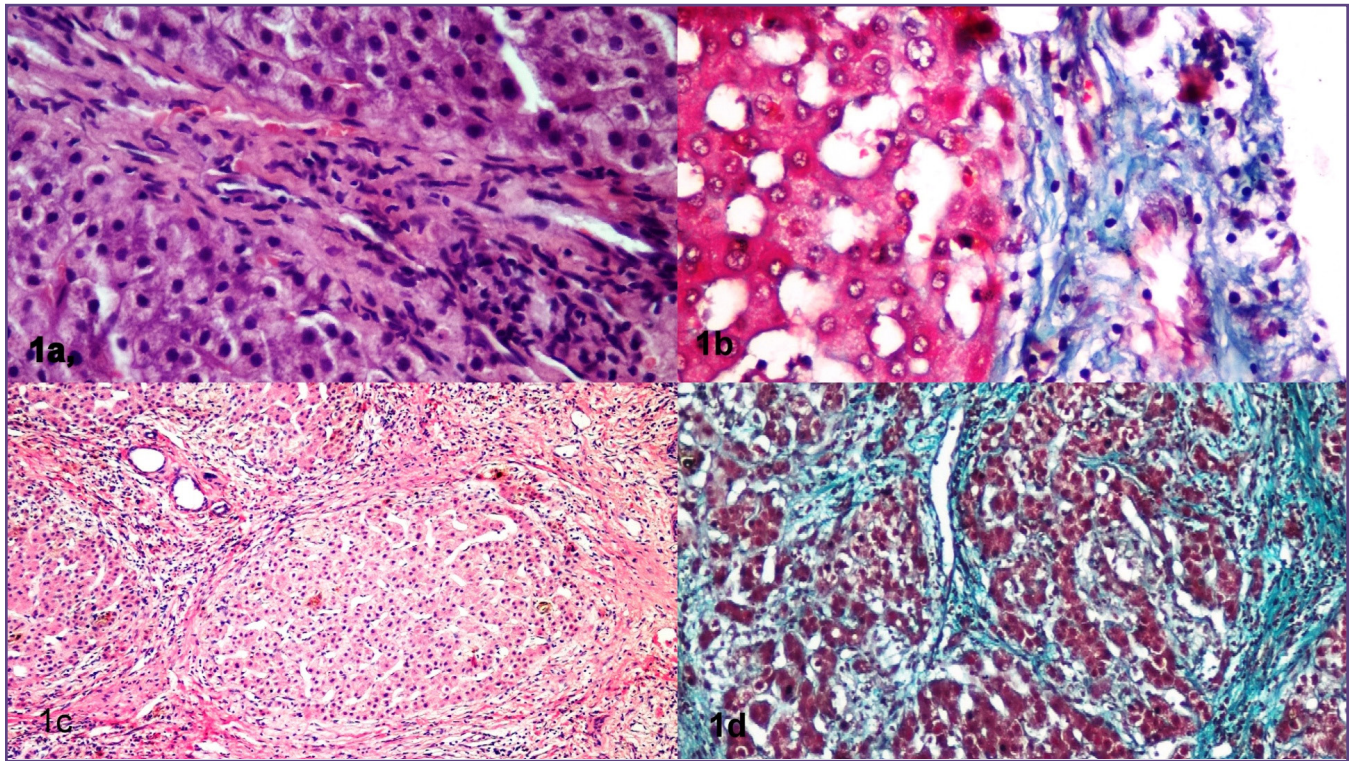


Fig. 1: Grade 1 fibrosis, H & E and Masson's Trichrome (a,b X 400) , grade 3 fibrosis, H& E and Masson's trichrome (c,d X 100)

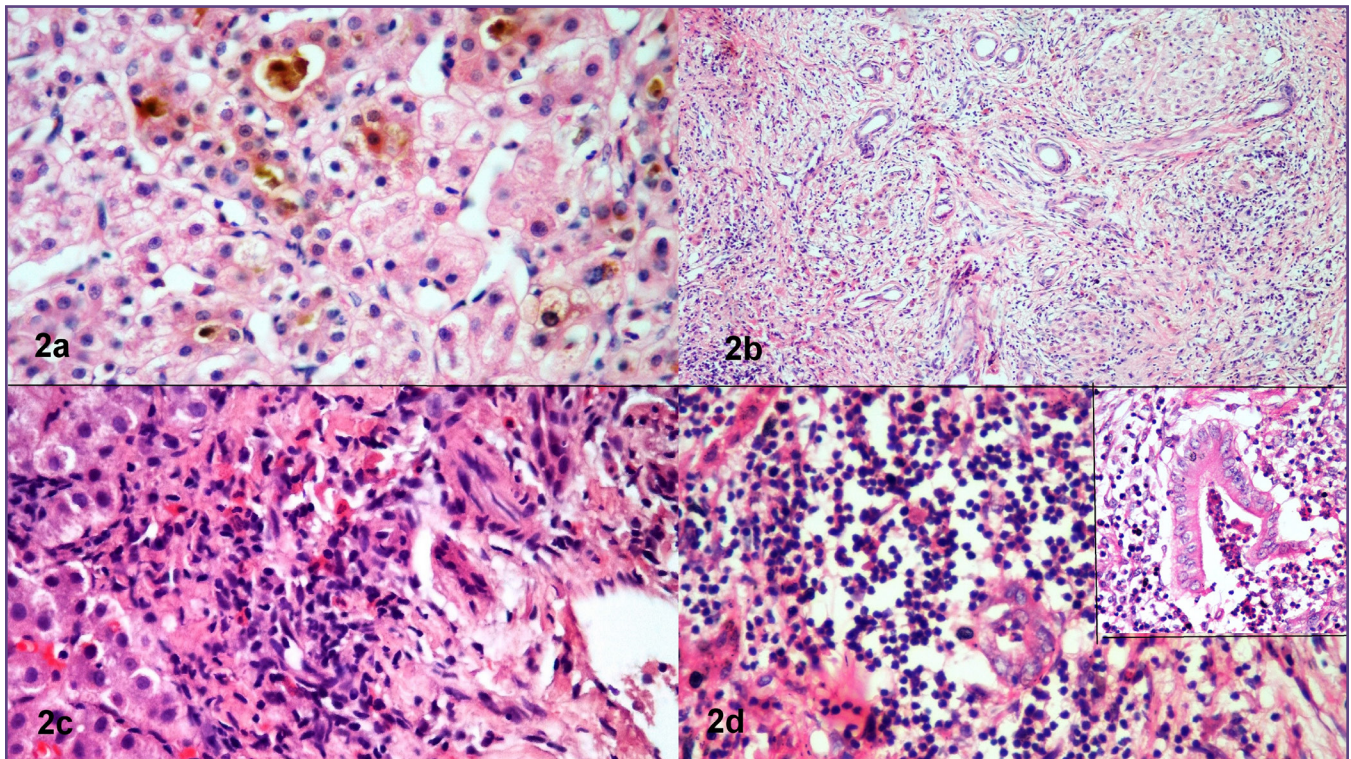


Fig. 2: (a) cholestasis (H & E X 400); (b) bile ductular proliferation (H & E X 100); (c) portal inflammation (H & E X 400) and (d) cholangitis (H&E X 400).

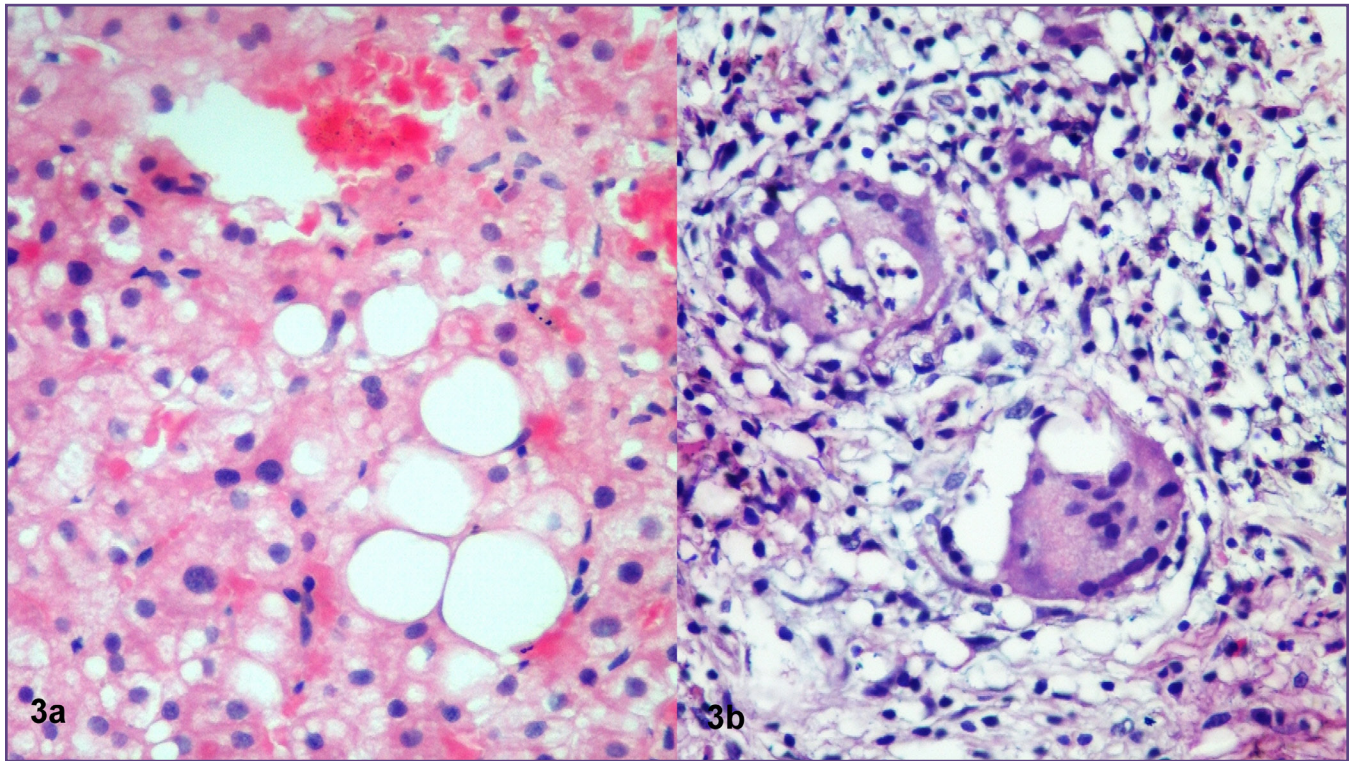


Fig. 3: (a) Incidental steatosis (H & E X 400); (b) portal foreign body granuloma (H & E X 400).

Discussion

Obstructive Jaundice is a common surgical problem that occurs due to an obstruction to the passage of conjugated bilirubin from liver into intestine and can be due to intra or extrahepatic obstruction. Early diagnosis to determine the precise etiology is of great importance because pathological changes in liver can occur if obstruction is unrelieved. Symptoms of biliary obstruction include jaundice, clay colored stools, darker urine, abdominal pain and intense itching. Other symptoms vary depending on the underlying cause of the obstruction. Patient can present early or late, depending on the severity of the disease.^[12]

In our study, 14 patients of obstructive jaundice due to various etiologies with deranged post-operative LFTs were analyzed. The morphological changes in liver, occurring secondary to biliary obstruction, as well as following surgical correction were noted, along with its clinical correlation. There was slight male preponderance (M: F 1.33:1) among the patients with wide age variation with majority being below 40 years. Most common presenting symptoms were jaundice followed by pain and fever, itching was seen in few while none had history of clay colored stool. One of our patients had associated portal hypertension. In the studies of patients of obstructive jaundice by Hammel et al,^[13] all were male between 34

to 54 yrs and in a study by Sikora et al^[9], there was a significant female preponderance (M: F ratio 1:9) with age range of 26 to 52yrs. Chalya et al^[14] also studied patients of obstructive jaundice due to various etiologies and there was a slight female preponderance (M: F, 1:1.32) with age range from 12 to 78 years. However they analyzed only preoperative biopsies. The most common symptoms in their study were jaundice (48.4%) followed by clay colored stools (36.2%), other symptoms being itching, weight loss and abdominal pain similar to our study and abdominal mass in occasional case which was not seen in our patients. Their duration of symptoms ranged from 5 to 32 days as oppose to our study where few patients had symptoms even for several months (36mths).

Elevated serum bilirubin level with a preponderance of the conjugated fraction is usually seen in obstructive jaundice. The transaminases might be raised many fold above normal and decrease rapidly once the obstruction is relieved. ALP and γ -glutamyl transferase (GGT) are markers for cholestasis.^[15] In our study too, various liver enzymes and bilirubin showed preoperative elevation in most patients and their levels significantly reduced after surgery. ALP levels reduced in most but remained significantly elevated in few patients even after surgery. However, GGT levels were not done in our study.

The causes of obstructive jaundice can be benign or malignant, stone disease being the commonest. Delay in presentation and treatment can lead to significant morbidity and mortality due to secondary infections causing cholangitis, liver abscess and systemic effect like malnutrition, weight loss, decreased immunity and renal insufficiency.^[16] In our study too, benign causes were commoner, but post cholecystectomy biliary stricture was commonest as opposed to stone disease, seen in only one. In a study of 116 patients by Chalya et al,^[14] higher number of patients (58.6%) had association with malignant etiology but choledocholithiasis was the commonest (62.5%) cause among benign (62.5%) and carcinoma of the head of pancreas (64.7%) among the malignant causes similar to our study. However, in the studies by Sikora et al,^[9] Hammel et al^[13] and Negi et al,^[17] patients with only benign etiology were included. We also analyzed the cause of obstruction with respect to age and gender, benign causes were more prevalent in females and in younger (<40yrs) age group while malignant causes were more prevalent in males and in older age group. This analysis was not done in other studies.

Surgical intervention is done with the intent to relieve obstruction and restore the normal bile flow. Various surgical procedures are done for the relief of obstruction^[14] which can result into full recovery, normalization of liver function tests, to persistent abnormality and progressive hepatic failure. In our study, most common surgical procedure done was hepatico-jejunostomy which resulted into complete correction of physical obstruction as evident on HIDA scan; however patients continued to have biochemical derangement.

Ongoing biliary obstruction is associated with progressive fibrosis leading to cirrhosis of liver.^[6] Proliferation of ductular epithelial cells and inflammation secondary to obstruction and cholestasis are responsible for activation of hepatic stellate cells which leads to deposition of collagen and matrix proteins.^[18] Various factors responsible are, cause of obstruction (benign/ malignant), associated infection and general condition of the patient. High grade fibrosis and cirrhosis at the time of surgery is considered poor prognostic indicator.^[19] In our study, in 1st biopsy, on microscopy, most of the patients showed evidence of fibrosis, cholestasis, inflammation and ductular proliferation. In addition few patients also had mild steatosis and occasional portal granuloma however, none of them showed any significant change in their clinical course on follow up thus supporting their incidental nature.

Most common grade of fibrosis was 1 followed by 3, similar to Sikora et al who studied 71 patients.^[9] However,

in a study of 11 patients by Hammel et al,^[13] most had grade 2 fibrosis followed by grade 1. The difference in prevalence of grades in above studies could be possibly due to variation in sample size, cause/ degree/ location of obstruction, associated infection or other complications.

We further analyzed fibrosis according to the age and gender of the patients which has not been reported by other researchers. In our study, in 1st bx, (in <40yrs age group), all males showed fibrosis (5/5) raising a possibility whether younger males are more prone for fibrosis following an obstruction. Nevertheless, larger studies are required for any definite conclusion.

Grade of fibrosis also depends on cause of obstruction. Scobie et al^[20] observed that cirrhosis was more commonly associated with benign etiology. In our study, in 1st bx, patients with both benign and malignant etiology showed fibrosis which was slightly more common in association with malignancy (66.66% vs. 62.50%). However in 2nd bx, all (100%) patients with benign causes showed presence of fibrosis including grade 3, which was also seen in more patients (25.00%) as compared to malignant cause (16.67%).

The duration of obstruction is as an important factor deciding the grade of fibrosis in liver. In a study by Negi et al,^[17] of 64 patients of post cholecystectomy strictures, duration of symptoms ranged from 1-120 months and a longer duration of biliary obstruction was found to be the most important predictor of advanced hepatic fibrosis. In our study, the range of duration of symptoms was shorter (0.5-36 months) and fibrosis was less commonly seen with shorter duration of symptoms similar to above study. Though there was only one patient in our study with longer duration but he showed advanced fibrosis.

Regression in fibrosis, ductular proliferation, inflammation and cholestasis is seen in patients of both benign and malignant etiology after decompression surgery.^[1, 13, 20, 21] In our study too, overall improvement of all histological parameters from was observed (Table 4), which is also observed by Sikora et al^[9] and Hammel et al.^[13] This supports the fact that decompression surgery is beneficial in obstructive jaundice.

In a study of by Hammel et al,^[13] post-surgery biopsy (2ndbx), was done in all (11) patients and majority showed regression (54.55%) followed by static (36.36%) and increased fibrosis (9%). In the study by Sikora et al,^[9] 2ndbx was done in only 5 and most patients showed either regression or static fibrosis (40% each), and only 20% showed progression. However, in our study, 2ndbx was available in more patients (14), however regression was

seen in only 4, (28.57%), increased fibrosis was seen in more patients (35.71%) while prevalence of static fibrosis was quite similar to other studies. The difference could be due to many factors as discussed earlier, including sample size. We also did analysis of status of fibrosis in relation to age, gender, cause, duration and cholangitis which was not done in other studies. No correlation of age and etiology with status of fibrosis was observed, however males appeared to show more association with regression or stasis of fibrosis while progression was more common with females. But larger studies are necessary for the confirmation. Moreover, most patients with regression (3/4) did not have cholangitis while most with progression (4/5) had associated cholangitis. Thus cholangitis appears to an important factor for deciding the course of fibrosis. Also, most patients who showed regression from grade 3 to 1 (3/4, 75%) had duration of symptom < 6 months, suggesting shorter duration is associated with higher prevalence and degree of regression.

Conclusion

It is difficult to justify multiple liver biopsies in patients, especially if there is clinical improvement. Hence a large data is not available in literature regarding histological changes in liver after surgery. However our data is one of the largest regarding availability of post operative liver biopsy in obstructive jaundice.

Our study supports the previous observation of possibility of reversal of histological changes after effective timely decompression surgery, including fibrosis which has lower prevalence when associated with shorter duration of obstructive symptoms. We observed no role of etiology for the occurrence as well as regression of fibrosis. However we wonder whether males have better prognosis regarding reversal of fibrosis and patients with cholangitis in general, as well as younger males are more prone for fibrosis. But we require larger data with multivariate analysis for the confirmation of the same.

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