www.jmscr.igmpublication.org
Impact Factor (SJIF): 6.379
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v6i6.148

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Original Article

Histopathological Analysis of Liver Lesions in 80 Liver Biopsy Specimens

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Abstract
Background: *Liver biopsy serves an important role in the definitive diagnosis of liver diseases, determining the grade and stage of the disease and also in evaluating the effect of therapy. It is particularly useful in the diagnosis of biliary atresia.*
Material and Methods: *80 percutaneous liver biopsy specimens received in our department over a period of August 2014 to Jan 2018 were studied. Biopsy findings were correlated with biochemical investigations and clinical features.*
Result: *59 out of 80 cases were neoplasms with 35 metastatic tumors, 22 hepatocellular carcinomas and one case each of non Hodgkin lymphoma and hemangioma. Out of 35 metastatic tumors, 28 were adenocarcinomas along with two cases each of gastrointestinal stromal tumors and squamous cell carcinoma and one case each of malignant melanoma, adenosquamous carcinoma and malignant small round cell tumor. Non neoplastic lesions included seven cases of cirrhosis and four congenital lesions consisting of three cases of biliary atresia and one case of neonatal hepatitis. We had two cases of glycogen storage disease and one case each of fatty change and abscess.*
Conclusion: *The present study showed that hepatic tumors are the most common lesions encountered on liver biopsy. Metastatic tumors especially adenocarcinomas are much more frequent than primary hepatic tumors. Biopsy of the liver is considered gold standard for histopathological characterization of congenital lesions like biliary atresia and storage disorders.*

Introduction

Liver biopsy is a cornerstone in the evaluation and management of patients with liver disease and has long been considered to be an integral component of the clinician's diagnostic armamentarium. Even with the advent of new and sensitive blood tests, liver biopsy still remains a valuable diagnostic tool.[1] It is commonly used in disease monitoring in patients with autoimmune hepatitis and primary biliary cirrhosis as well as for assessment of fibrosis in patients with hepatitis C. It is crucial in the diagnosis of neoplasms, both primary and metastatic. Indications of liver biopsy are varied and include evaluation of abnormal liver function tests, diagnosis of neoplasms, grading and staging

of chronic hepatitis, unexplained hepatomegaly etc.[2] Hence this study was undertaken to analyze the histopathological features of liver biopsies received in Pathology Department of our hospital.

Materials and Methods

In this study, 80 percutaneous liver biopsy specimens were included. Tissue was fixed in 10% formalin and submitted for paraffin embedding. Sections were stained by routine hematoxylin and eosin stain. Special stains were used wherever necessary. Sections were studied under light microscope and diagnosis was reached correlating the history, biochemical and radiological investigations.

Results

The total number of percutaneous liver biopsies received was 80. The age group ranged from less than 1 to 90 years. Maximum number of liver biopsies were seen in the age group 61 – 70 years (21 cases i.e.26.25%). Total number of males was 46 (57.5%) and females 34(42.5%) giving M:F ratio of 1.35:1 (Table no.1)

The various lesions encountered are shown in Table no. 2.

The most frequently encountered lesion was neoplasms in 59 cases with 58 malignant and one benign tumor. Of these, 35 were metastatic tumors comprising of 28 adenocarcinomas, two cases each of gastrointestinal stromal tumors (GIST) and squamous cell carcinoma (SCC) and one case each of adenosquamous carcinoma, malignant melanoma and malignant small round cell tumor. On microscopy, the adenocarcinomas showed tubular or papillary architecture, cuboidal to columnar tumor cells with vesicular nuclei, prominent nucleoli and variable mucin production. Out of 28 cases, primary tumor was in the stomach in three cases, in lung and gall bladder in two cases each and in pancreas in one case. In remaining 20 cases, the primary was unknown.

There were 22 cases of hepatocellular carcinoma (HCC) affecting 15 males and seven females. Eleven were well differentiated, six moderately differentiated and two poorly differentiated tumors. Well differentiated HCCs showed polygonal tumor cells resembling hepatocytes arranged in trabeculae separated by sinusoids. Cells had moderate to abundant granular eosinophilic cytoplasm and vesicular nuclei. Intranuclear inclusions were seen in two cases and intracytoplasmic bile pigment in four cases. Three cases of clear cell variant of HCC were observed. Two cases of HCC showed association with cirrhosis. There was one case of NHL affecting a 60 years old female.

One case of hemangioma was encountered. Biopsy revealed cavernous spaces lined by endothelium and filled with red blood cells.

Cirrhosis was encountered in seven cases, six adult and one infant. Two cases were associated with HCC. Four patients were adult males and in all, biopsy revealed loss of architecture of liver and replacement by variably sized nodules composed of regenerating hepatocytes seperated by thick fibrous septa. The septae showed lymphocytic infiltration. A single case of biliary cirrhosis was seen in an infant with biliary atresia.

We had three cases of biliary atresia. Two were five month old males and one 46 days female. In two cases there was marked ductular proliferation and ballooning degeneration of hepatocytes with intracytoplasmic cholestasis. The portal tracts were expanded and showed mononuclear cell infiltration. The only case of neonatal hepatitis in our study was a one month old female child with complaint of dark coloured urine since eight days. Liver biopsy showed lobular disarray, intracytoplasmic and canalicular cholestasis and prominent giant cell transformation. Foci of extramedullary hematopoiesis were also seen.

In the present study, there were two cases of glycogen storage disease (GSD). As the diagnosis was suspected clinically, biopsy was sent in alcohol. On microscopy the hepatocytes were swollen, enlarged and appeared rarefied. Cell membranes were thickened and sinusoids were compressed resulting in a mosaic pattern

characteristic of GSD. On PAS staining, the hepatocytes showed intracytoplasmic PAS positive material. With these biopsy features and clinical findings diagnosis of GSD was suggested.

One case each of pyogenic abscess and fatty change was observed. No specific lesion was seen in five cases while the biopsy was inadequate in one case.

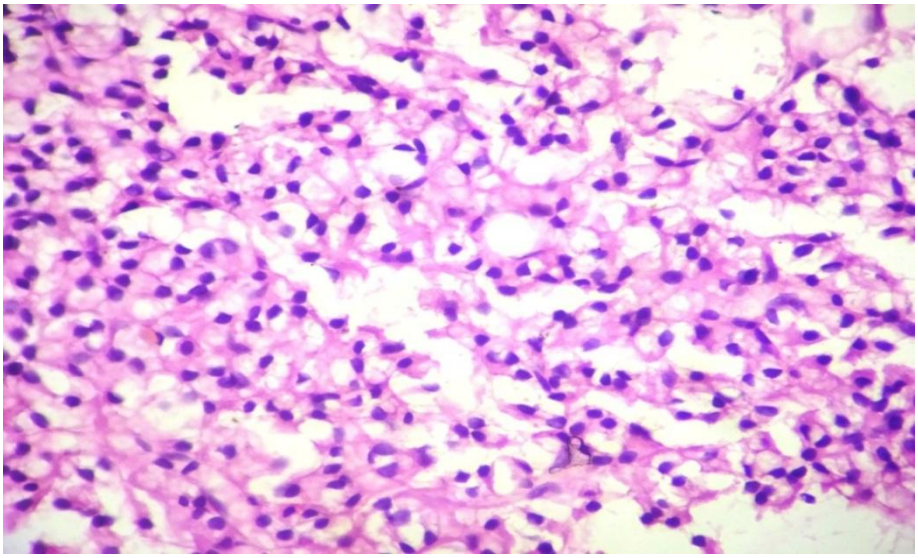

Figure I Photomicrograph showing clear cell variant of HCC. (H & E,x100)

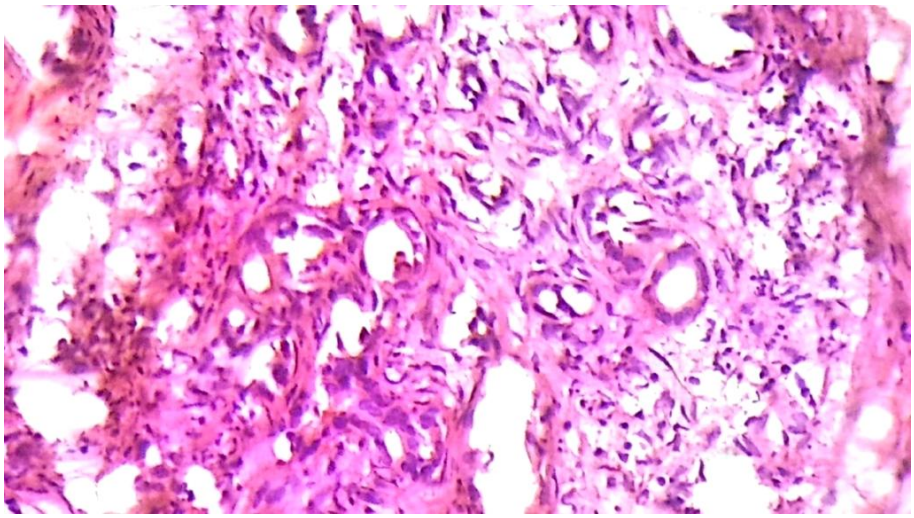

Figure II - Photomicrograph showing prominent ductular proliferation in biliary atresia (H & E,x400)

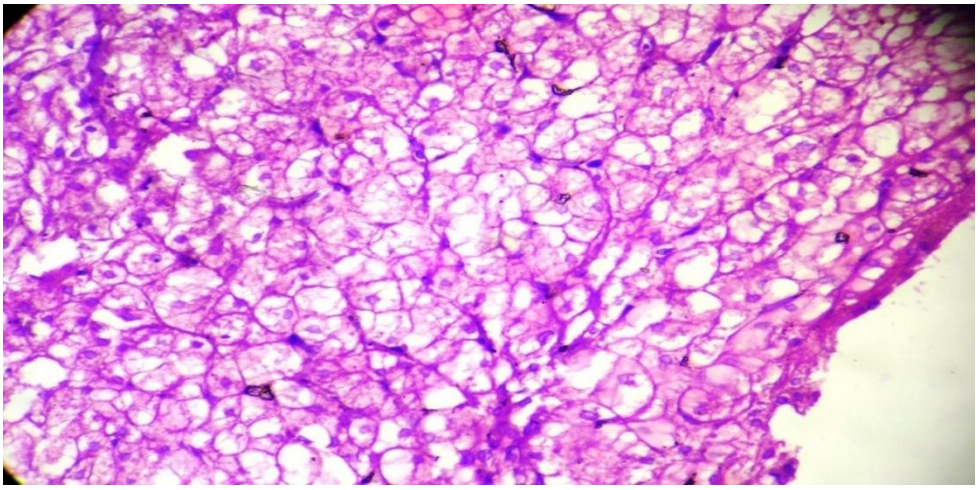

Figure III Photomicrograph showing characteristic mosaic pattern in glycogen storage disease. (H & E,x400)

Table I. Showing age & sex distribution of liver biopsies

Age groups (years)	Males	Females	Total	Percentage
<1 year	2	2	4	5
1-10	0	1	1	6.25
11-20	3	0	3	3.75
21-30	0	1	1	6.25
31-40	1	3	4	5
41-50	10	5	15	18.75
51-60	9	9	18	22.5
61-70	**14**	**7**	**21**	**26.25**
71-80	7	5	12	15
81-90	0	1	1	6.25
Total	46	34	80	100

Table II. Showing various histopathological findings on liver biopsies

Serial No	Pathology	No of cases (%)
1.	Tumors of liver	**59(73.75%)**
2.	Cirrhosis	7(8.75%)
3.	Congenital lesions	4(5%)
4.	Metabolic diseases	2 (2.5%)
5	Infectious disease	1(1.25%)
6.	Fatty change	1(1.25%)
7.	No specific lesion	5(6.25%)
8.	Inadequate	1(1.25%)

Table no III Showing the comparison with other authors

Liver disease	**Chawla N et al (2013)[7]**	**Zahir ST et al[8](2015)**	**Ugiagbe EE etal (2016)[9]**	**Present study**
Hepatic tumors	**17 (26.15%)**	164	18 (22.5%)	**59(73.39%)**
Cirrhosis	15 (23.08%)	-	5 (6.3%)	7(8.75%)
Fatty change	13 (20%)	-	6 (7.5%)	1(1.25%)
Hepatitis	4 (6.15%)	-	**50 (62.5%)**	-
Neonatal hepatitis	01 (1.54%)	-	1(1.3%)	1(1.25%)
Biliary atresia	01 (1.54%)	-	-	3(3.75%)
Storage disorders	01 (1.54%)	-	-	2(2.5%)
Abscess				1 (1.25%)
Inadequate				1(1.25%)
No specific lesion	9(13.85%)	-	-	5 (6.25%)

Table IV: Showing comparison of tumors by various authors

	Total cases	Tumors	Benign	Malignant Metastatic	HCC	Others
Chawla N et al[7]	65	17	-	3	14	-
Zahir ST et al[8]	164	164	15	115	9	13
Ugiagbe EE et al[9]	80	18	-	6	10	-
Present study	80	59	1	35	22	1

Discussion

Rich systemic and portal blood supply make liver a fertile soil for metastasis. There is a wide variation in the ratio of metastatic to primary liver tumors; 40: 1 in Europe and South America to 2.6: 1 in Japan. In order of frequency the primary sites are upper GIT, colon, lung, breast, esophagus and genitourinary organs. 2/3rd of patients with hepatic metastases produce clinical manifestation like ascites, jaundice, anorexia and weight loss.[3] A percutaneous liver biopsy is positive in about 75% of the cases with widespread metastatic liver disease.[4]

In our study 59 out of 80 cases were tumors. The commonest complaint with liver tumors was abdominal pain in 34 patients, loss of weight and

appetite in 17 patients followed by palpable abdominal mass in 8 patients.

HCC represents the most common primary malignant epithelial tumors of the liver. Men are at higher risk than women with ratio varying from 1.3 to 3.6. WHO classification divides tumors into well, moderately, poorly differentiated and undifferentiated grades. Presence of bile within neoplastic cells or tubular lumina is pathognomic of HCC, but is seen in less than one third of cases.[3]

We had 22 cases of HCC affecting 15 males and seven females with a male to female ratio of 2.14:1. There were 11 well differentiated, six moderately differentiated and two poorly differentiated tumors. Three cases of clear cell variant of HCC were encountered.

Clear cell HCC comprises about 9% of all malignant hepatocellular neoplasms. It shows marked female predominance and high association with cirrhosis. Cytoplasmic clearing is due to the accumulation of glycogen and /or fat. Differential diagnosis includes metastatic renal or adrenal cortical carcinoma and is facilitated by immune staining by Hep par 1 and polyclonal CEA.[4] In the current study two out of three cases of clear cell HCC were females. However none of the cases showed cirrhosis.

Twenty eight out of 35 metastatic tumors were adenocarcinomas. In three cases, primary tumor was in stomach, two each had primary in the lung and gall bladder while one had primary in pancreas. In 20 cases the primary was unknown. Metastses of two cases each of GIST and SCC was observed. One of the two patients with metastatic SCC had a previous history of SCC of cervix. Remaining metastatic tumors included one case each of adenosquamous carcinoma, malignant melanoma and malignant small round cell tumor. A single case of NHL was also encountered.

Chawla Net al[7] studied 65 cases of liver biopsy.17 were tumors (26.15%) out of which 14 (82.35%) were HCC. Two cases of metastatic adenocarcinoma with primary in the stomach in one and prostate in other were reported. There was one case of metastatic squamous cell carcinoma with primary in the esophagus.

Zahir ST et al[8] studied 164 liver tumors over a period of ten years. There were 147(89.6%) malignant tumors, out of which 115 (73.2%) were metastatic. These included five squamous cell carcinomas with primary in uterine cervix, five malignant lymphomas and three cases each of renal cell carcinoma and gastric carcinoma. Two cases each of neuroendocrine tumors from GIT and cutaneous malignant melanoma and one case each of carcinoma colon, breast, pancreas, small intestine and anal basaloid carcinoma were noted. The primary was unknown in 85 cases. HCC accounted for 19 (12.9%) cases. They have also reported 11 cases of hemangioma.

Ugiagbe EE et al [9] have reported their study of 80 liver biopsies. There were 18 (22.5%) tumors, 10 HCCs (55.6%) and six metastatic tumors (33.3%). Almost half of HCCs occurred between 4th to 6th decade and male : female ratio was 4:1.

There is strong evidence of the pathogenetic role of both hepatitis B and hepatitis C virus in the development of HCC in both cirrhotic and non cirrhotic liver. Overall 50 – 55 % cases of HCC are attributed to HBV.[5]In our study five cases of HCC were positive for hepatitis B surface antigen. In four of these the tumor was well differentiated while in one case it was clear cell variant.

Cirrhosis is defined as a diffuse nodulation of the liver resulting from fibrous bands subdividing the liver into regenerating nodules.[5,6] Biopsy of cirrhotic liver sometimes shows marked fragmentation with the needle retrieving only parenchyma and no fibrosis. The reticulin stain is of help in this setting, both by demonstrating regenerative activity and by identifying delicate layer of reticulin surrounding the nodules. Fragments of normal liver on the other hand consist of hepatocytes at their edges without the rim of collagen. Also, the cirrhotic fragments tend to have a rounded contour as against the angular nature of normal liver fragments.[5] Cirrhosis is also associated with an increased risk of

developing HCC . In our study two cases of HCC showed associated cirrhosis.

We had seven cases of cirrhosis. Two cases were associated with HCC. Four were seen in adult males and one case of biliary cirrhosis was noted in an infant.

Cavernous hamangioma is the most frequently occurring benign tumor of the liver.[3] We had a single case of hemangioma. Patient was a 65 year male. Biopsy showed a mass composed of variably sized endothelium lined cavernous spaces containing red blood cells. Zahir et al studied 164 liver tumors and reported hemangioma to be the most prevalent benign tumor of liver accounting for 11 cases.

Biliary atresia is the most common cause of pathologic jaundice in infants. The clinical trial of persistant neonatal jaundice beyond two weeks of life, dark urine and pale stool and hepatomegaly is characteristic of biliary atresia. Liver biopsy with ductular proliferation is the most diagnostic feature.[10,11]

In all three cases of biliary atresia in our study, total bilirubin, ALT and AST levels were markedly increased and HIDA scan revealed absent radiotrace excretion in the intestine. On microscopy, two cases showed features of biliary atresia while one showed biliary cirrhosis.

Neonatal hepatitis is a general term for clinical condition manifested by prolonged jaundice in neonates with variable but definable histologic picture.[10] We had only one case of neonatal hepatitis in our study.

Dehghani et al[12] studied 308 pediatric liver biopsies out of which 14 showed biliary atresia and 22 neonatal hepatitis. Panchal et al[13] have reported on 25 liver biopsies with two cases of neonatal hepatitis and no case of biliary atresia.

Glycogen storage disorder is an inherited disorder of glycogen metabolism predominantly affecting infants and children. GSD types involving the liver are I, III, IV, VI and IX. Although the presence of characteristic clinical and histologic features may suggest the type of GSD, diagnosis is confirmed by enzymatic assay on liver and DNA mutational analysis.[11] In our study diagnosis of GSD was suggested in two cases. The first patient was two years old female with complaints of early morning hypoglycemia and delayed milestones. The other patient was one and half years male child with history of abdominal distention and facial puffiness. Both the patients had huge hepatomegaly. With characteristic biopsy features and clinical findings diagnosis of GSD was suggested. Koshy A et al[14] had 17 cases of confirmed GSD in their study. The median age at presentation was 15 months and presenting complaints were hypoglycemia, hepatomegaly and delayed milestones. Dehghani et al[12] have reported nine cases of GSD out of total 308 pediatric liver biopsies in children less than two years old.

Steatosis or fatty change is characterized by accumulation of lipid within the cytoplasm of hepatocytes. Histologically two major patterns are recognized macrovesicular and microvesicular. Uncomplicated macrovesicular steatosis has generally been regarded as benign and fully reversible condition while microvesicular steatosis is a serious condition with hepatic dysfunction and coma.

We had a single case of fatty change. Patient was a 13 years old boy: a known case of primary peritoneal tuberculosis with ruptured liver abscess. Ascitic fluid ADA level was high. Microscopically, the liver architecture was preserved. Hepatocytes revealed grade II macrovesicular steatosis.[15]

Steatosis is a common finding in tuberculosis. This may be due to malnutrition, starvation and tuberculous toxicity itself. Frequency of fatty change in pulmonary and extra pulmonary tuberculosis in various studies ranges from 20 – 44 %.[16,17]

A multitude of organisms can infect the liver and biliary tree including bacteria, fungi, helminth and parasites. Factors predisposing to liver abscess include biliary tract obstruction, direct extension from a contiguous infection, penetrating/ non penetrating trauma and pyelephlebitis. Hepatic

abscesses vary considerably in size. Multiplicity of lesions is seen in about half of pyogenic abscesses and one fourth of amoebic abscesses. Clinically patients may present with fever and in many instances, right upper quadrant pain and tender hepatomegaly.[4]

We had a single case of liver abscess in our study. The patient was a 62 years diabetic male with chief complaint of pain in right hypochondriac region. He had a history of lung abscess. Biopsy showed liver with diffuse and dense infiltration by numerous, viable and degenerated polymorphs, admixed with fibrin and bile.

Conclusion

Liver biopsy plays an important role in the diagnosis of liver diseases. Prevalence of metastatic tumors is much higher than primary hepatic tumors. It is considered the gold standard for histopathological characterization of congenital lesions like biliary atresia. It is also useful in the diagnosis of storage disorders like glycogen storage disease.

Source of support: nil

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