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Original Research Article

Histopathological spectrum of liver lesions at autopsy: A cross sectional study

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ABSTRACT

Background: Liver is the principal site of many metabolic activities and is vulnerable to many metabolic, toxic, microbial and circulatory insults. It is frequently involved in metastatic spread of malignancies from all parts of body.

Aims: This study aimed to analyze histopathological spectrum of liver diseases in autopsy cases, and correlate with the clinical findings wherever available.

Materials and Methods: It was an observational study conducted over a period of 2 years on 283 autopsy cases in department of Pathology of a tertiary care teaching institute in central India. Liver specimens were included in study irrespective of age, sex and cause of death. After fixation in 10% formalin the sections from representative area were submitted for processing, Hematoxylin and Eosin-stained sections were subjected for microscopic examination.

Results: Total 283 liver autopsy cases studied showed predominance of male (68.65%). Maximum cases were in the age group of 21 to 30 years (20.14%) followed by 31 to 40 years (18.28%). Fatty change was evident in a majority (32.08%) of the cases while a remarkable (26.49%) number of cases showed changes of congestion on histological examination. Massive hepatocellular necrosis and midzonal necrosis were seen in 2 cases each. Tubercular granulomas and metastasis of adenocarcinoma were seen in 3 cases each.

Conclusion: Histological analysis of liver is important learning objective for pathologists to study silent diseases of liver which are incidentally seen in histopathology.

1. Introduction

The main purpose of autopsy is to know the exact cause of death and it provides valuable information about the disease. Liver, being the principal site of many metabolic activities, is vulnerable to many metabolic, toxic, microbial and circulatory insults and is the most frequently affected organ in the body. It is also frequently involved in the metastatic spread of malignancies from all parts of the body.[1]

Sometimes, the disease is primary, while in others, the hepatic involvement is secondary to disease elsewhere in the body, for example, cardiac decompensation, alcoholism, extrahepatic infections, etcetera. Liver cell involvement may be focal, diffuse or zonal. A number of abnormal histological lesions may be encountered at autopsy. Fatty change (steatosis) is a very common finding both in biopsies and at postmortem. One of the commonest liver disorders are due to alcohol abuse, generally leading to three pathologically distinct entities fatty liver, hepatitis and cirrhosis. Chronic hepatitis can be due to hepatotropic viruses, drug-induced or autoimmune etiology. It varies in different geographic areas and is based on various factors such as socioeconomic status, lifestyle, diet, local or regional infections, and other endemic disease.[2]

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Liver diseases and cirrhosis contribute to 23.59% of mortality and ranks 27^{th} as cause of death, in the world and it constitutes 2.74% of all the causes of death in India. However, the exact prevalence of cirrhosis is unknown because the disease is often silent. About 30% to 40% of cases are incidentally discovered at autopsy, indicating that in substantial proportion of people, the disease goes undetected during life. There are various etiologies of cirrhosis and all these causes leave specific imprints upon the liver, so as to be identified histologically. Histology remains the only fool proof diagnostic tool that identifies various liver pathologies.[3]

Extra hepatic bacterial infections, particularly sepsis can induce mild hepatic inflammation and varying degrees of hepatocellular cholestasis. Many chemicals including drugs and toxins can produce liver damage. Acute injury may produce parenchymal damage, arrested blood flow and jaundice. Drugs can also produce chronic active hepatitis, fatty liver, cirrhosis, several vascular lesions and, rarely, neoplastic lesions of the liver.[4]

Hepatocellular necrosis may be focal, diffuse, massive, or zonal. Zonal patterns, characterized as centrilobular, midzonal, or periportal, appear to be related to the mechanism of hepatocellular injury. Centrilobular necrosis is the most common form of zonal necrosis, and is usually associated with profound hypotension, but may also be caused by a number of drugs. Periportal necrosis is characteristically produced by certain toxins like elemental phosphorous, allyl alcohol. Midzonal necrosis is rarely observed in the human liver, except in cases of yellow fever.[5]

Liver diseases are, most of the time, silent due to the vast reserves of the organ. Even in symptomatic cases, biopsies are rarely performed in our setup. Hence many of the typical histological changes like zonal necrosis are not seen in routine practice. This study, therefore, fulfills an urgent need to familiarize budding pathologists to the whole spectrum of liver histopathology.

2. Aims and Objectives

To study histopathological spectrum of liver diseases in autopsy cases, and correlate with the clinical findings, wherever available.

3. Materials and Methods

It was a cross-sectional study conducted in the department of Pathology of a tertiary care teaching hospital located in Central India, over a period of 2 years from January 2018 to December 2019 on 283 autopsy cases.

3.1. Inclusion criteria

All autopsy cases, where the liver was received, irrespective of age, sex and cause of death, were included in the study.

3.2. Exclusion criteria

Autolyzed specimens were excluded from the study.

Clinical history and diagnosis were elicited from the records whenever available.

Liver specimens were mostly received in small pieces, as a part of multiple viscera. In an occasional case the whole liver was received. The liver was grossly examined for any focal or diffuse changes, like infarction, fibrosis, nodules, tumors, abscesses, hemorrhagic areas, cholestasis etcetera. Weight of each liver specimen was measured in grams during the autopsy.

Sections from representative areas were submitted, fixed in 10% formalin, for tissue processing. Processed tissues were sectioned, and Hematoxylin and Eosin (H and E) stained slides were subjected to microscopic examination. Special stains were carried out, when indicated, in a few cases.

4. Results

A total of 283 liver specimens were examined, out of which 15 showed autolysis, which were excluded from study. In this study, there was a male predominance, with males forming 68.65% of all cases while females were 31.34%. Maximum (20.14%) cases were from the age group of 21 to 30 years followed by 18.28% cases from 31 to 40 years. (Table 1).

A large number of the autopsy cases (20.89%) had a clinical history of chronic alcohol use. There were cases with history of poisoning, hepatobiliary symptoms, neurological symptoms like paralysis or coma, pregnancy associated complications, known cases of primary malignancy. In a large number of cases (40.29%), the diagnosis was not specified as they were brought dead. A remarkable number of cases (17.91%) had a diagnosis of cardio-respiratory arrest, while 13.05% of cases had a diagnosis of shock. (Table 2)

In most of the cases, (31.44%) liver weight was in the range of 1000 to 1500 grams. 22.79% cases had liver weight between 1501 to 2000 grams, while 24.73% cases had weight less than 1000grams. In 10.95% cases liver weight was between 2000 to 2500 grams, while only 1.86% cases had liver weight more than 2500 grams. In a significant number of cases (33.20%), the liver showed pale yellow appearance on gross examination. Other gross examination findings included various types of nodules, nutmeg appearance, secondaries, shrunken liver and millet sized lesions.

Histopathological examination revealed fatty change in a majority of the cases (32.08%), while a remarkable number of cases (26.49%) showed congestion in the form of acute sinusoidal congestion and chronic venous congestion. Portal tract inflammation was in the form of mild to moderate mononuclear inflammatory infiltrate,

Table 1: Age and Gender wise distribution of autopsy cases (n=268)

Age group (Years)	Male	Female	Total (%)
0 - 10	12	12	24 (8.95)
11 - 20	10	23	33 (12.31)
21 - 30	29	25	54 (20.14)
31 – 40	39	10	49 (18.28)
41 - 50	37	05	42 (15.67)
51 - 60	29	03	32 (11.94)
61 - 70	20	05	25 (9.32)
71 - 80	08	01	09 (3.35)
Total (%)	184 (68.65)	84 (31.34)	268 (100)

Table 2: Clinical diagnosis in autopsy cases (n=268)

Clinical diagnosis	Male	Female	Total (%)
Brought dead	84	24	108 (40.29)
Cardio-respiratory arrest	27	21	48 (17.91)
Shock	13	22	35 (13.05)
Hepatobiliary involvement	22	1	23 (8.58)
Neurological involvement	10	2	12 (4.47)
Metabolic disorders	9	2	11 (4.10)
Unknown poisoning	7	2	9 (3.35)
Infections	5	4	9 (3.35)
Acute abdomen	5	0	5 (1.86)
Secondaries	0	3	3 (1.11)
Eclampsia	0	3	3 (1.11)
Congenital anomalies	2	0	2 (0.74)

Table 3: Histopathological findings in liver of autopsy cases (n=268)

Histopathological findings	Male	Female	Total (%)
Fatty change	71	15	86 (32.08)
Circulatory disorders (Acute sinusoidal congestion/CVC)	47	24	71 (26.49)
Cirrhosis	19	3	22 (8.20)
Unremarkable	4	14	18 (6.71))
Portal tract inflammation	10	7	17 (6.34)
Cholestasis	4	5	9 (3.35)
Acute viral hepatitis	5	4	9 (3.35)
Extramedullary hematopoiesis	4	2	6 (2.23)
Acute alcoholic steatohepatitis	5	0	5 (1.86)
Chronic viral hepatitis	3	1	4 (1.49)
Massive hepatocellular necrosis	2	2	4 (1.49)
Micro abscesses	2	1	3 (1.11)
Metastasis	0	3	3 (1.11)
Tubercular granulomas	3	0	3 (1.11)
Sickle cells	1	2	3 (1.11)
Mid-zonal necrosis	2	0	2 (0.74)
Microthrombi	1	0	1 (0.37)
Cavernous hemangioma	0	1	1 (0.37)
Elongation & duplication of bile ducts, perivenular fibrosis	1	0	1 (0.37)

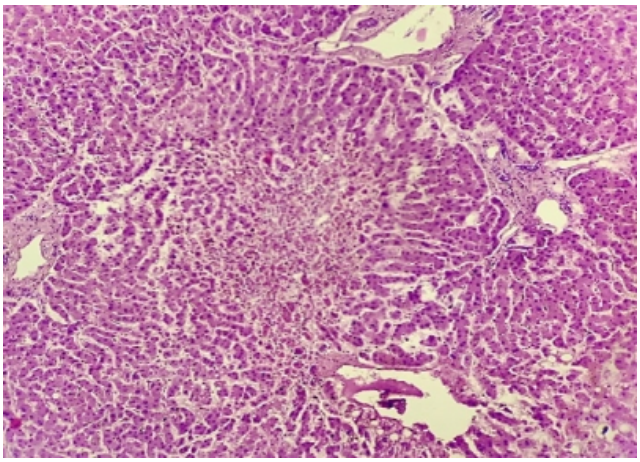

Fig. 1: (H and E Stain, 20X) Mid-zonal necrosis with bridging fibrosis showing early changes of cirrhosis

Fig. 2: Liver shows multiple variable sized necrotic nodules with surrounding normal liver parenchyma.

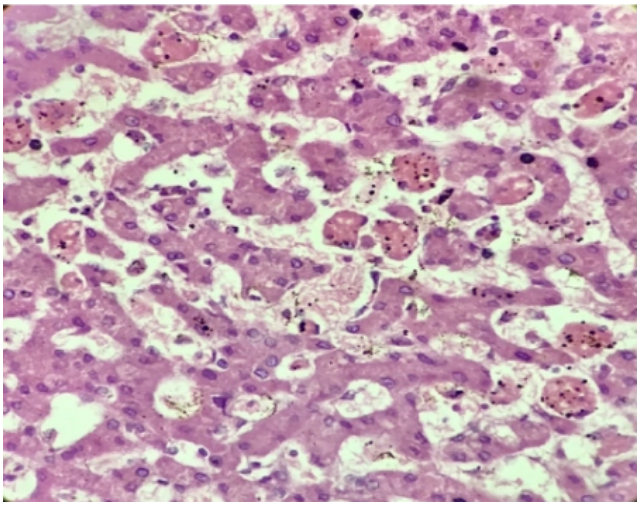

Fig. 3: (H and E Stain, 40X) Sinusoids showing multiple microthrombi in a case of unknown bite.

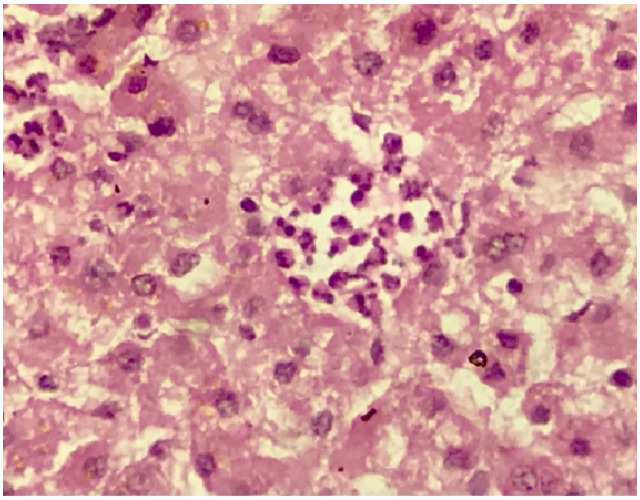

Fig. 4: (H and E Stain, 40X) Multiple micro abscesses seen in a case of septic shock.

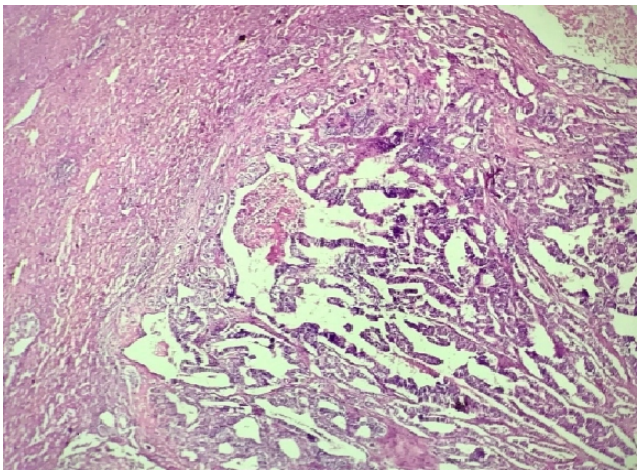

Fig. 5: (H and E Stain,40X) Metastasis of adenocarcinoma of stomach in the liver

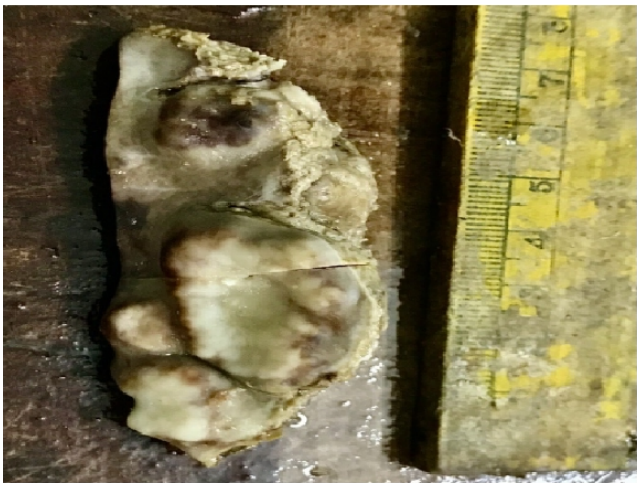

Fig. 6: Liver showing multiple metastatic nodules with central necrosis in a case of adenocarcinoma of stomach

without fibrosis. In cases of alcoholic hepatitis, fatty change, cluster of inflammatory cells around necrotic hepatocytes and Mallory-Denk bodies were evident. In cases of acute viral hepatitis, the portal tract showed scant to moderate mononuclear infiltrate, ballooning degeneration, apoptotic bodies, lobular inflammation and drop out of hepatocytes. In cases of chronic viral hepatitis, dense mononuclear portal inflammation with portal fibrosis, bridging necrosis and fibrosis were seen, while in some cases bile duct proliferation was noted and many of these had early cirrhotic changes. We had 3 cases showing epithelioid cell granulomas, without necrosis. Granulomas were confirmed to be tubercular after Acid Fast staining. These cases had widespread miliary tuberculosis. Mid zonal necrosis was seen in two cases of shock (Figure 1), while massive hepatocellular necrosis was seen in two known cases of eclampsia. Gross morphology of midzonal necrosis cases showed diffuse pale areas in between normal appearing liver. Grossly massive hepatocellular necrosis showed, multiple, variable sized focal pale nodules all over the external and cut surfaces of liver (Figure 2). In one case of unknown bite, multiple microthrombi were seen in hepatic sinusoids (Figure 3), as well as in the lungs and kidneys. All cases of extramedullary hematopoiesis were seen in neonates. Both the cases with micro abscesses were found in middle aged males, with a history of severe diabetes mellitus, with ketoacidosis, septic shock, and respiratory failure (Figure 4). Metastases of adenocarcinoma were found in females, all three were known cases of carcinoma stomach (Figure 5). Grossly these metastatic nodules were multiple, greyish white with central area of necrosis (Figure 6). The cases with sickle cells in the sinusoids and central veins, had associated findings of portal mononuclear infiltrate, fatty change and perivenular necrosis. (Table 3)

5. Discussion

Male cases were predominant in our study, similar to Bhagat R et al, Singal P et al and Patel PR et al.[2,6,7] In the present study maximum number of cases (38.42%) were in the age group of 21 to 30 years and 31 to 40 years. Similarly, predominance of cases in the age group of 31 to 40 years was found by Patel PR et al and Porwal V et al.[7,8]

Fatty liver was the commonest finding in most of the studies, and our findings compare well with those of Bhagat R et al, Singal P et al and Patel P R et al.[2,6,7]

Circulatory disturbances, including acute and chronic congestion were seen in a significant number of cases comparable to the findings of Singhal et al. Porwal V et al had a much higher incidence, and some of the studies had a much lower incidence.[6,8] Most studies have commonly reported congestion in autopsied livers, probably as a terminal event, in otherwise normal histology.

We found acute hepatitis in 3.35% of cases, similar to Bal MS et al, whereas most of the others had a much higher incidence.[9] Our incidence of chronic hepatitis at 1.49% stands much lower than other studies. These had dense portal inflammation, lobular involvement, bridging necrosis and variable amounts of fibrosis and bile duct reduplication.

Most of the studies had a much higher incidence of unremarkable histology than our study, however, it compares well with that of Porwal V et al.[8] Full blown cirrhosis was seen in 8.2% of cases, similar to the findings of Sameer MA et al, Bhagat R et al and Behera A et al.[1,2,10] However early changes of cirrhosis were seen in 22 cases. Some of these had associated fatty change, necrosis and Mallory-Denk bodies. Steatohepatitis is a stage in the progression of alcoholic liver disease to cirrhosis. It could also be seen in non-alcoholic steatohepatitis (NASH). Experimental studies have implicated steatosis itself as a direct cause of more advanced pathology. The mere presence of oxidisable fat within the liver is enough to trigger lipid peroxidation. Nevertheless, many patients with steatosis never progress to necroinflammation or fibrosis. These observations led to the ”two hit ”hypothesis. In addition to steatosis (the first “hit”), development of steatohepatitis requires the presence of some other factor(s) (second “hit”).[11]

Granulomatous lesions were found in 3 of the livers, all were part of a miliary process. Singal P and Bhagat R et al found caseating granulomas, which was not seen in our cases.[2,6] Liver is involved in a large proportion of cases of miliary tuberculosis. Primary hepatic tuberculosis is rare, postulated to be due to its low oxygen tension. Granulomas are commonly seen in drug reactions; they may be the only manifestation. It could be a cause of, otherwise unexplained, granulomas.

In the present study, massive necrosis was seen in 2 women with eclampsia. Das P et al found 61 pregnant women and total 170 women, in their study of 224 cases of fulminant hepatic failure, 8 of which tested positive for HBsAg.[12] Singal P et al had one case in their study who was a young pregnant woman who had consumed some quack medicine to terminate the pregnancy.[6] Midzonal necrosis is rarely observed in the human liver, except in patients with yellow fever. Suzanne M et al, in a retrospective analysis of livers from 1000 adult autopsies, found 18 cases of shock with midzonal necrosis. These patients had no history of yellow fever or drug induced hepatotoxicity.[5] In the present study, we found 2 cases of midzonal necrosis, who had a clinical diagnosis of shock.

We had 2 cases of severe diabetes mellitus (DM), in our study, with multiple microabscesses in the liver. Porwal V et al found intranuclear vacuolation in their cases of DM.[8] This was, however, not seen in our cases. Non-alcoholic fatty liver disease (NAFLD) is highly prevalent in type 2 diabetes mellitus, likely reflecting the frequent occurrence of obesity and insulin resistance in type 2 diabetes mellitus.[13] In present study cholestasis was seen in

3.35% of cases which is in concordance with Konjengbam R et al who found 3.2% of cases of cholestasis. [14]

Both benign and malignant tumors, tumors of epithelial or mesenchymal origin, occur in the liver. Metastatic tumors are more common than the primary hepatic tumors. In our study, we observed 3 cases (1.11%) of liver metastasis, all were females with a history of adenocarcinoma of stomach. Similarly metastatic deposits were found by Sameer MA et al in 1.33%, Patel PR et al in 0.48% and Bal MS et al in 3% cases. [1,7,9]

6. Conclusion

From our study we concluded that incidence of liver diseases was more common in males. Most affected age group was between 21 to 30 years (20.14%) followed by 31 to 40 years. Steatosis (32.08%) was the most common histological finding. Most of the cases with steatosis had a history of chronic alcohol consumption, which indicates that alcohol is a major culprit in the pathogenesis of fatty liver. Hence, awareness about adverse effects of alcohol use is necessary in the community. Other major histological findings were circulatory disturbances (26.49%) followed by cirrhosis (8.20%).

Out of 268 liver autopsy cases which we studied only 18 cases were unremarkable on histology while rest of the cases (250) had various pathological findings. Thus, our study concluded that liver is directly or indirectly involved in majority of medical conditions irrespective of patient's clinical symptoms. Since liver biopsy was not done in theses cases, the findings were found only after histological examination of autopsy liver specimens.

Histological examination of the liver specimens at autopsy is an important learning tool for pathologists as well as clinicians to study silent liver diseases. Liver autopsy studies can thus improve diagnostic and clinical approach towards liver diseases.

7. Conflict of Interest

The authors declare that they have no conflict of interest.

8. Source of Funding

None.

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