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Histopathological Findings of Liver Autopsy Cases: Study at a Tertiary Care Hospital

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Abstract

Background and objective: Liver diseases are common health problems throughout the world. Most of the chronic liver diseases, even in advanced stages, may cause no prominent clinical signs or symptoms. They either go undiagnosed or are found incidentally during general health check-ups, investigations for other diseases, surgery, or autopsy. This study will provide important information about the frequency of undiagnosed chronic hepatic lesions in autopsy specimens in this area and incidental autopsy findings can contribute to discovering many of the common liver diseases which will provide a framework for the clinician to pursue further diagnostic studies. **Methods:** This descriptive cross-sectional study was conducted at the Department of Pathology, Mymensingh Medical College (MMC) from March 2017 to December 2018. The specimens were from medicolegal autopsies, as clinical autopsies are not done in Bangladesh. The autopsy cases that fulfilled the selection criteria were enrolled as the study samples. After the exclusion of decomposed and extensive necrosed samples, 171 cases were included in the study. After routine tissue processing, all slides were stained with Hematoxylin & Eosin (H/E) stains. A special stain with Masson's trichrome was done to evaluate the liver architecture and pattern of fibrosis, whenever necessary. After that histopathological evaluation was done and diagnosis was made. The data was tabulated and statistical analysis was performed. **Results:** Out of 171 cases, 151 cases had normal histological findings and only 11.7% had pathological findings. Of them, the most common changes were steatosis, which was in twelve (7%), chronic hepatitis in four (2.3%) and congestion in three (1.8%) cases. Secondary malignancy was found in one (0.6%) case. The most common lesion observed in the 5th decade was steatosis. While chronic hepatitis was not observed before the age of 30 years. It was seen in equal distribution in the 4th decade and the 5th decade. One case of congestion was seen in the 4th decade while two cases were observed in the 5th decade. Also, one case of secondary malignancy was seen in the 5th decade. **Conclusion:** The study result will be beneficial for the medical community by providing information regarding the reliable frequency of hepatic disease in this region of our country.

Keywords: Histopathology, Liver autopsy

Introduction

The liver is one of the major and most vital organs in our body. The term "liver disease" applies to many diseases and disorders that cause the liver to function improperly or to stop functioning. Wide varieties of metabolic, toxic, microbial, circulatory and neoplastic insults are seen in the liver. Sometimes, the disease is primary while in others there is secondary involvement of the liver to cardiac de-compensation, alcoholism or

extrahepatic infections.¹ Liver diseases are common health problems seen throughout the world. According to WHO, about 46 % of global diseases and 59 % of mortality are because of chronic diseases, and around 35 million people in the world die of chronic diseases.² Silent liver diseases are not uncommon and histology is the unique method for diagnosis. Abnormal findings in the autopsy of the liver can be fatty change, glycogen storage disease, hemosiderosis, tuberculosis, cirrhosis,

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acute and chronic passive hyperemia, amyloidosis, abscess, hydatid cyst, malignancy (primary and secondary) hemangioma, granuloma, chronic congestion, cystic lesions and others.¹ So, the importance of silent liver disease in the overall perspective of pathology and clinical medicine cannot be overemphasized.³

The underlying causes of chronic liver diseases usually vary in different geographic areas and are commonly based on various factors such as age, sex, socioeconomic status, lifestyle, diet, local or regional infections and other endemic diseases.⁴ The major primary diseases of the liver are viral hepatitis, nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease and hepatocellular carcinoma (HCC). Alcohol use is estimated to contribute to 2.5 million deaths globally and 2.3% of all deaths in the Southeast Asia Region. Whereas alcohol accounts for 80% of cirrhosis in the United States, the predominant cause of cirrhosis in China, Southeast Asia and Africa is hepatitis B (WHO 2018). Alcohol abuse generally leads to three pathologically distinct liver diseases; those are hepatocellular steatosis or fatty liver, alcoholic (or steato-) hepatitis and alcoholic cirrhosis or steatofibrosis. Any one or all the three can occur at the same time; in the same patient.⁵

HBV and HCV-related liver diseases are a huge burden to Bangladesh for its economy and health care delivery system. It has been estimated that the prevalence of HBV and HCV in Bangladesh maybe 5.4% and 0.84% respectively. More than 10 million Bangladeshis are chronically infected with either of these two viruses. The main risk factors for the transmission of HBV and HCV in Bangladesh have been identified as treatment from quacks, shaving and haircuts in barber shops, ear piercing dental procedures, etc.⁶

HBV is still the leading cause of acute and chronic liver disease (CLD) in Bangladesh. It is responsible for approximately 30% of cases of acute hepatitis, 75% of cases of chronic hepatitis, 60% of cases of liver cirrhosis and 65% of cases of hepatocellular carcinoma (HCC) in Bangladesh and HCC is the third most common cause of cancer deaths in our country, next only to deaths from cancer from lungs and stomach.⁶

The liver is one of the most common sites for metastatic disease, accounting for 25 % of all metastases from solid organs. Metastatic involvement of the liver is far more common than hepatocellular carcinoma. The incidence of metastases is 20 times higher than primary malignant liver tumors.⁷

Diagnostic liver biopsy is only performed in selected cases in our daily clinical practice which does not

reflect the true frequency of various hepatic lesions in the general population.

Many liver diseases are symptomatic while some are diagnosed only in autopsy. Autopsy is one of the most useful tools to validate clinical diagnosis. So, an autopsy study is useful to monitor the cause of death and to plan medical strategies.¹ Therefore, autopsies performed for those who have passed away for reasons other than liver disease are certainly a better source of determining the frequency of various hepatic diseases. The most common lesion observed in the 5th decade was steatosis.

There have been few works in this field. So, the study aimed to determine the pathological findings of liver in autopsy cases which will certainly determine the undiagnosed liver diseases that should seriously be considered as an important threat to the health of the general populations of Bangladesh.

Materials and methods

This was a cross-sectional observational study carried out at the Department of Pathology, Mymensingh Medical College, Mymensingh from March 2017 to December 2018. The sample size was 200 initially. Seventeen were excluded from the study having gross extensive decomposition due to autolytic change. Again twelve cases were excluded as they showed extensive necrosis on microscopic examination. So, finally, the sample size was 171. The study population was autopsy specimens of the liver that were received at the Department of Pathology for histopathological examination. These specimens were all from medico-legal autopsy, as clinical autopsy is not done in Bangladesh.

Collection of samples

To do this study ethical clearance was taken from the Institutional Review Board (IRB) of Mymensingh Medical College, Mymensingh. Liver tissue samples were received either as a part of the examination of multiple viscera or were collected from unidentified postmortem cases with permission of the Department of Forensic Medicine, MMC.

The age and sex of the deceased were recorded from the documents that were provided along with the specimen. The heights and weights of many of the deceased were not mentioned in the provided documents; therefore, the basal metabolic index (BMI) could not be calculated. The gross weight of the liver could not be taken as some specimens were represented by only part of the liver. A naked eye

examination was done and gross findings like autolytic change, color, consistency and nodularity were noted.

Routine processing and staining for light microscopy

Tissues were fixed in 10% formalin and kept for overnight fixation. Tissue processing was performed manually following the standard protocol for paraffin embedding in the Pathology laboratory of MMC. Resected samples measuring (2 x 2 x 2 cm) were obtained from the right and left lobes in each case. The paraffin blocks were sectioned with a rotary manual microtome at 4-5 micrometer thickness. After deparaffinization with xylene, the slides were dehydrated with decreasing graded alcohol. The slides were stained with routine hematoxylin and eosin (H & E stain).

A special stain with Masson's trichrome was done to evaluate the liver architecture and pattern of fibrosis, whenever necessary.

Microscopic evaluation

All the microscopy was done and photomicrographs were taken by Olympus multi-head microscope, Model U-MDO10R3, T5 SN 5J42483 201509, Olympus Corporation, Tokyo-163-0914, Japan.

Statistical analysis

The statistical analysis was carried out using the Statistical Package for Social Sciences for Windows (SPSS Inc., Chicago, Illinois, USA, version 23).

Histopathological evaluation of liver biopsy

Liver tissues were stained with hematoxylin and eosin and evaluated by light microscope. In hematoxylin and eosin stain the following points like lobular architecture, presence and pattern of fat droplets within hepatocytes, hepatocyte ballooning, apoptosis/necrosis, parenchymal inflammation, the extent of fibrosis, nodularity and liver cell dysplasia, etc. were noted. In Masson's trichrome stain, the pattern of fibrosis was noted. Based on these findings following diagnoses were made.

- Steatosis (Fatty change)
- Steatohepatitis
- Chronic hepatitis
- Cirrhosis
- Hepatic granuloma
- Hepatocellular carcinoma
- Malignancy (Secondary)

Steatosis (Fatty change):

Steatosis was characterized by intracytoplasmic lipid

droplets which in H&E stained sections were seen as cytoplasmic vacuoles.^{8,9} They were recognized either as microvesicular or macrovesicular, though often seen in mixed pattern.¹⁰ Its severity was generally determined by estimating the proportion of hepatocytes containing fat droplets in lobules.¹¹

Steatohepatitis:

Steatohepatitis was identified by steatosis, parenchymal inflammatory cells infiltrate, hepatocellular injury in the form of ballooning degeneration, perisinusoidal and perivenular fibrosis. Fibrosis was also detected in periportal areas and some cases progressed to cirrhosis.¹²

Chronic hepatitis:

Diagnosis of chronic hepatitis was made by varying degrees of hepatocellular necrosis, portal inflammation, interface hepatitis, or piecemeal necrosis and fibrosis.^{8,9} The hallmark of chronic liver damage is deposition of fibrous tissue. In the more severe form, necroinflammation, associated with progressive fibrosis and parenchymal regeneration leading to cirrhosis was noted.¹³

Cirrhosis:

Cirrhosis was diagnosed based on three main morphological features, the regenerating nodules, bridging fibrous septa and disruption of the architecture of the entire liver.¹³

For grading and staging of chronic hepatitis, steatohepatitis, and cirrhosis the histological activity index (HAI) of Knodell¹⁴ was applied.

Correlation between semiquantitative grading and verbal assessment of tissue samples.⁸

HAI	Brief Description
1-3	Minimal chronic hepatitis
4-8	Mild chronic hepatitis
9-12	Moderate chronic hepatitis
13-18	Severe chronic hepatitis

Congestion:

Diagnostic features of congestion were sinusoidal dilation and blood-filled central veins.

Hepatocellular carcinoma:

The important diagnostic features of hepatocellular carcinoma include cellular and nuclear pleomorphism in the hepatocytes, dysplastic change in the form of small cell or large cell dysplasia, prominent nucleoli, bizarre

mitotic figures, tumor giant cells and thickness of the trabeculae.^{8,9}

Malignancy (Secondary):

Metastatic tumor in the liver was diagnosed by anaplastic epithelial cells forming acinar structures, which recapitulate the gland formation within the normal organ.^{8,9} In typical adenocarcinoma, focal mucin production within either the cytoplasm or lumen was noted and may be correctly diagnosed using standard morphological techniques.

Results

The present study was carried out to reveal the morphological spectrum of silent liver disease by histological examination of autopsy specimens of the liver. So, from the selected 171 cases of autopsy specimens, 151 cases had normal histological findings and only 11.7% had pathological findings. Of them, the most common changes were steatosis, which was in 12 (7%), chronic hepatitis in 4 (2.3%), and congestion in 3 (1.8%) cases. Secondary malignancy was found in 1 (0.6%) case.

In this study, steatosis was not seen before 20 years of age. In the 3rd decade steatosis was seen in three cases, while only one case was seen in the 4th decade. The most common lesion observed in the 5th decade was steatosis. With time some of this steatosis might have progressed to steatohepatitis. While chronic hepatitis was not observed before the age of 30 years. It was seen in equal distribution in the 4th decade and in the 5th decade, which were two cases each. The cause of this chronic liver disease may be due to hepatitis B, hepatitis C viral infection, alcohol, drugs, toxins, and metabolic storage disorders like hemochromatosis, and Wilson's disease, which need special attention. One case of congestion was seen in the 4th decade while two cases were observed in the 5th decade. Also, one case of secondary malignancy was seen in the 5th decade.

Table 01: Distribution of different hepatic lesions according to age

Diagnosis	Age (Years)							
	10-20		21-30		31-40		41-55	
	n	%	n	%	N	%	n	%
Normal	34	100	36	92.3	48	92.3	33	71.7
Steatosis, Mild	-	-	3	7.7	1	1.9	7	15.2

Diagnosis	Age (Years)							
	10-20		21-30		31-40		41-55	
	n	%	n	%	N	%	n	%
Steatosis, moderate	-	-	-	-	-	-	1	2.2
Chronic hepatitis	-	-	-	-	2	3.8	2	4.3
Congestion	-	-	-	-	1	1.9	2	4.3
Secondary malignancy	-	-	-	-	-	-	1	2.2
Total	34	100	39	100	52	100	46	100

Table 02: Frequency of different hepatic lesions observed by histologic evaluation in autopsy series

Diagnosis	Frequency	Percent
Normal	151	88.3
Steatosis, Mild	11	6.4
Steatosis, moderate	1	0.6
Chronic hepatitis	4	2.3
Congestion	3	1.8
Secondary malignancy	1	0.6
Total	171	100.0

Table 03: Distribution of fatty change

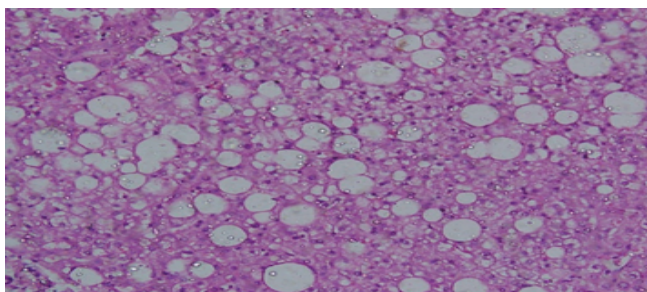
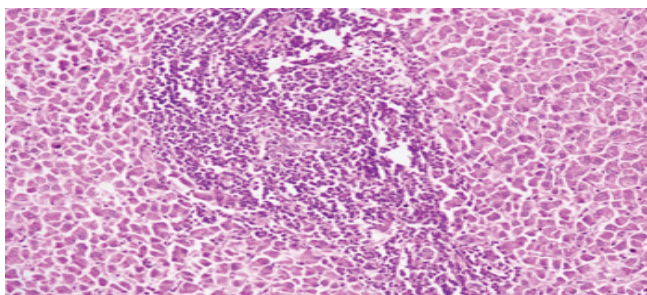
Fatty change	Frequency	Percent
Absent	159	92.98
<1/3rd hepatocytes involved lobules	8	4.67
1/3rd-2/3rd hepatocytes involved lobules	4	0.23
Total	171	100.0

Table 04: Distribution of diagnosis of pattern of fat droplets in hepatocytes

Diagnosis	Droplets in hepatocytes					
	Absence of fat droplet		Predominantly macrovesicular		Predominantly microvesicular	
	n	%	n	%	n	%
Normal	151	95.0	-	-	-	-
Steatosis, Mild	-	-	11	100	-	-
Steatosis, moderate	-	-	-	-	1	100
Chronic hepatitis	4	2.5	-	-	-	-
Congestion	3	1.9	-	-	-	-
Secondary malignancy	1	0.6	-	-	-	-
Total	159	100	11	100	1	100

Table 05: HAI for numerical scoring of liver specimens

Case	I. Periportal ± Bridging Necrosis	II. Intralobular Degeneration and Focal Necrosis	III. Portal Inflammation	Total Score (I+II+III)	IV. Fibrosis
1	1	1	1	3	0
2	3	1	1	5	0
3	1	1	1	3	0
4	3	1	1	5	0

**Figure 01: Photomicrograph shows hepatocytes with large and small fat vacuoles (H & E X 200).****Figure 02: Photomicrograph shows the portal tract is heavily infiltrated by lymphocytes, extending irregularly into the adjacent tissue. A lymphoid follicle with germinal center is formed (H & E X 400).**

Discussion

Autopsy findings of the liver, incidentally discovered, can contribute to many of the common liver diseases. The present study was carried out at the Department of Pathology, Mymensingh Medical College to evaluate the frequency of undiagnosed hepatic lesions existing in the general population of Bangladesh, especially in the Mymensingh district areas.

In this present study, the mean age was 32.80 ± 11.61 years and the age ranged from 10 to 55 years. The majority of the studied subjects had an age range from 31-40 years (53%). Similarly, another study showed a mean age of 43.8 ± 19.7 years.⁴ Another group of

authors in Salem district, Tamil Nadu had found a mean age of 46.9 ± 5.28 years which was in a higher range.³ The mean age is influenced by the life expectancy of that particular country.

In this present study, 126 were male (73.7%) and female were 45(26.5%). The male-female ratio was 2.80:1. Some other researchers have studied autopsy specimen of the liver and their series also had male predominance.^{1,3,4,15,16} It is to be mentioned that most of the cases in this study were anonymous and unidentified and the cause of death was mostly unnatural type, like road traffic accident (29.24%), organophosphorus poisoning (18.13%), homicidal (10.54%), suicidal hanging (64.68%), etc. The records of the last two years of the Department of Pathology have also shown that there is a male predominance in overall autopsy cases received which reflects that males are involved in more outdoor activities. Similarly, another study showed the major cases of death were trauma (35%).⁴

Autopsy performed for those who have passed away for reasons other than liver disease are certainly better sources for the determination of silent liver disease. The true incidence and prevalence of many silent liver diseases in different populations are largely unknown. In the present study, histologic changes were seen in twenty (11.7 %) cases. The most common changes were steatosis, which was in 12 (7%), chronic hepatitis in 4 (2.3%) and congestion in 3 (1.8%) cases. Secondary malignancy was found in 1 (0.6%) case. It is believed that steatosis and steatohepatitis which includes both alcoholic steatohepatitis and non-alcoholic steatohepatitis are the most common liver disease in the general population.¹¹ In Bangladesh non-alcoholic fatty liver disease (NAFLD) is the most common disease observed in clinical practice affecting approximately 20% of the general population.¹⁷ In the current study the most common lesion was steatosis which was found in twelve (7%) cases. In India, a study showed steatosis in 39% of cases¹, and in Tehran, another study also showed steatosis as the most common lesion (31.16%).⁴ Similar findings were observed in some other studies.^{18,19} A group of authors observed fatty liver as the most common (20.96%) cases.¹⁶ But in the current study the frequency of steatosis was much lower than the study mentioned above. This may be due to less consumption habits of alcohol intake in our Muslims due to religious constraints which is only 0.2% of the population over 15 years, lesser consumption of fatty diet, and lower prevalence of obesity which is 3.6%.²⁰

In the current study, no steatohepatitis was observed. However, some author showed 39.8% steatohepatitis in their study.¹⁹ These can be explained as all cases of steatosis do not progress to steatohepatitis. Lack of influencing factors like low consumption of alcohol due to religious restriction and the lower prevalence of obesity may be the case why steatohepatitis was not observed in the study. All these influencing factors prevail in Greece and also it may be the cause of a higher incidence of steatohepatitis in that country.¹⁹

Considering the low intake of alcohol, we can say that in our country the majority of cases of steatosis are not alcohol-related.²⁰ So, it can be assumed that concealed ASH in the present study was very minimal. These may represent as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

Chronic hepatitis can present with or without symptoms. Even when it is symptomatic, the symptoms can be non-specific.⁸ In this current series, it was observed that chronic hepatitis was found in four cases (2.3%). In another study, the frequency of chronic hepatitis observed by histological evaluation of the liver was 2.6%.⁴ It may be due to the prevalence of hepatitis B virus, and hepatitis C virus infection in our country and the lack of adequate preventive measures, screening, and vaccination programs.

According to Knodell's score, the first three parameters i.e. periportal necrosis with or without bridging necrosis, intralobular degeneration, focal necrosis and portal inflammation are the components of necroinflammation. The total score for necroinflammation is 18, which indicates the grade of the disease. The last parameter i.e. fibrosis, the total score is 4, which indicates the stage of the disease.¹⁴ In this present study out of a total of four cases of chronic hepatitis two showed minimal chronic hepatitis and two cases showed mild chronic hepatitis without any fibrosis.

Congestion is not an uncommon finding in the autopsy of the liver of any age and is of uncertain significance in many instances.²¹ In this current study, it was observed that congestion was present in three cases (1.8%). Another study showed congestion in 9 % of cases.²²

Liver cirrhosis is often undiagnosed (23.7%) in the elderly.²³ The reported incidence of hepatocellular carcinoma development in patients with cirrhosis ranges from 2-6.5% per year.²⁴ The etiology of hepatocellular carcinoma varies in different geographic areas. Even among Asian countries, the proportion of viral etiology is different. The Hepatitis C virus plays a

major role in Japan, whereas the Hepatitis B virus predominates in other Asian countries.²⁵ In this current study no cases of liver cirrhosis and hepatocellular carcinoma were found probably due to a relatively low incidence of this condition in our region and maybe because of the early age group in the autopsy series and the highest age was only 55 years and the majority was by accidental deaths. The prevalence of cirrhosis and hepatocellular carcinoma associated with cirrhosis was absent may be due to low consumption of alcohol, and lack of exposure to food contaminants like Aflatoxin B in our country. However, no study has been done on exposure to this carcinogen.

In this current series, metastatic adenocarcinoma was found in only one case (0.6%). Another study revealed secondary malignancy in 2% of cases.¹ Secondary liver neoplasm is far more common than primary hepatic neoplasm.⁷ Carcinomas from the lung, colon, pancreas, breast and stomach are the most frequent sources of metastases to the liver, but eventually, any cancer in any site of the body may spread to the liver including leukemia, lymphomas and rarely sarcomas.²² In this study the primary source could not be investigated due to the minimum history supplied.

In this study, it was observed that steatosis was not seen before 20 years of age. In the 3rd decade steatosis was seen in three cases, while eight cases were seen in the 4th decade. The most common lesions observed in the 5th decade were steatosis. While chronic hepatitis was not observed before the age of 30 years. It was seen in equal distribution in the 4th decade and in the 5th decade, there were two cases each. One case of congestion was seen in the 4th decade while two cases were observed in the 5th decade. Also, one case of secondary malignancy was seen in the 5th decade. The proportion of steatosis was higher than in the previous decade. This can be explained that with age the frequency of this lesion increases.

This current study showed in the 5th decade, the commonest lesion was steatosis and then chronic hepatitis. Another group of authors showed in their study that the major incidence of steatosis aged between 41 to 50 years with male predominance.¹ In our study, three cases of steatosis were seen in the 3rd decade. This may be due to lower life expectancy in Bangladesh. In the present study, there is a rise of hepatic lesions like steatosis, chronic hepatitis and congestion in the 5th decade. Many of the history are lacking such as drug, alcohol, hyperlipidemia, dietary history, smoking history and other history which are taken to be the predisposing cause of alcoholic or non-

alcoholic steatohepatitis. A large population-based cohort study of healthy individuals may give the true prevalence of steatosis and steatohepatitis and it will also help to evaluate what proportion of steatosis progresses to steatohepatitis.

Conclusion and Limitations

In a developing country like Bangladesh, where limited funding is a constant problem to do an epidemiology survey for the prevalence of steatosis and its related disorders, an autopsy specimen can be an alternative to biopsy. The result of this study can be regarded as a reflection of the epidemiological survey.

Some of the received autopsy specimens were in partial and many of them were in gross decomposition state. So, it is recommended that the autopsy specimens sent from the Department of Forensic Medicine and those that were brought by the police should have adequate preservatives (10% formalin) in them to prevent autolysis. It is also recommended that further studies be conducted using whole specimens and as fresh state as possible. As steatosis and steatohepatitis can have serious clinical consequences, patients presenting with high-risk factors for fatty liver disease such as obesity, type 2 diabetes, family history of fatty liver disease, hyperlipidemia, and raised blood pressure should be considered for further investigations. Samples were collected only from the Mymensingh region. So, it does not reflect the picture of the whole country and a short period of study was another limitation.

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