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Clinicopathological correlation in liver biopsy of cirrhosis

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Abstract
Background: Liver disease has steadily gained recognition as a major health problem principally because of the world wide epidemic of hepatitis and ubiquity of cirrhosis of liver. Alcohol is considered to be a major etiological factor in western world, whereas viral etiology is considered to be predominant cause of cirrhosis in Indian subcontinent. Early diagnosis and specific treatment for etiology can reverse the cirrhosis.
Material & Methods: This retrospective study was carried out in the Department of Pathology, Government Medical College, and Aurangabad. Tissue bits from liver biopsy were preserved in 10% formalin. These were processed and paraffin sectioning was done followed by Haematoxylin and Eosin staining. The sections were then examined microscopically.
Results: Out of 60 cases of cirrhosis, 47 cases (78.33%) were males and 13 cases (21.66%) were females with maximum numbers of cases, in age group of 31-60 years were 43 cases (71.66%). The most common presentation were ascites, oedema and abdominal distention. Predominant morphological pattern was micronodular cirrhosis (76.66%) and least type was mix pattern. (3.31%)
Conclusion: Alcohol remained the most common etiology of cirrhosis most commonly in males. The early diagnosis of liver disease may prevent the progression of disease severity and may also prevents the cirrhosis. Therefore, if there is no contraindication, for confirmation of diagnosis liver biopsy still remains a useful diagnostic tool modality, even in the era of advanced virological, immunological and molecular genetic testing.

Keywords: Haematoxylin and eosin, liver biopsy

Introduction
Liver disease has steadily gained recognition as a major health problem principally because of the world wide epidemic of hepatitis and ubiquity of cirrhosis of liver. The term cirrhosis first used by Laennec in 1826 to described the colour of cirrhotic liver and he was the first investigator who had documented the clinical and pathological feature of cirrhosis observed in chronic alcoholic. Cirrhosis has become a common disease due to heavy intake of alcohol in most countries, high prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections; and new epidemic of nonalcoholic fatty liver disease (NAFLD) [1]. There is a trend towards increase in prevalence of cirrhosis and subsequent morbidity and mortality worldwide [1, 2]. Alcohol consumption and subsequent cirrhosis is increasingly seen in countries such as Japan and India which traditionally had a low prevalence of the disease [3, 4]. Classically, cirrhosis is defined by its histological hallmark findings on liver biopsy (regenerative nodules surrounded by fibrotic tissue) and is considered as the final evolution stage of any progressive liver disease, irrespective of its etiology. The advances in diagnostic methods allow now early diagnosis, even before the development of complications, which are mostly related to development of portal hypertension [5]. Liver biopsies are important for many reasons, such as accurate diagnosis or ruling out any coexisting liver diseases, staging and grading the severity of liver disease, treatment decisions, patient and provider reassurance, and as a benchmark for gauging future progression [6]. There are many different types of liver biopsies, such as the percutaneous, transjugular, laparoscopic, fine needle aspiration and open surgery liver biopsy [7]. Liver biopsy is the only investigation for the confirmatory diagnosis of chronic liver disease in spite of tremendous advancement in diagnostic procedures [8].

Aims and objectives
The aim of this study was to find out incidence and possible etiological factors of cirrhosis. To find out types of cirrhosis and their histopathological features in biopsy material.

Materials and methods
The study was conducted on 60 liver biopsies retrospectively in the Department of Pathology Government Medical College and Hospital, Aurangabad over a period of six year (January 2013 to December 2018). The clinical history were recorded in all cases. Formalin fixed liver biopsy tissues were submitted for routine paraffine processing. The slides were stained with Haematoxylin and Eosin (H&E) and were examined under the microscope. Some special stains like Reticulin, Periodic Acid Schiff (PAS), Orcein were used in selected cases. The findings were recorded and analysed.

Results
In the present study a total of 60 cases of hepatic cirrhosis were studied during a period of January 2013 to December 2018 for clinical and histopathological examination. Out of 60 cases, 54 percutaneous needle biopsy and remaining 6 cases were open liver biopsy specimens. During the 6 years period total 204 liver biopsies were done and cirrhosis of liver were observed in 60 cases. The incidence of hepatic cirrhosis observed in present study was 29.4%.

Out of total 60 cases, 47 cases (78.33%) were males and 13 cases (21.66%) were females. The male to female ratio was 3.6:1. The age ranged from 14 to 70 years. Maximum numbers of cases, in age group of 41-50 years were 15 cases (25%) followed by in age group 31-40 years and 51-60 years with 14 cases (23.33%) each. The age group of 31 -60 years were showed maximum cases in present study, that is 43 cases (71.66%) (Table I)

Clinical Presentation of 60 cases were studied (Table II) which included ascites, oedema and abdominal distention as the most constant presentations (100%), seen in all cases. The next common presentation were loss of appetite 91.66%, weight loss 86.66% and splenomegaly 83.33%. Anaemia was seen in all the cases of cirrhosis with reduction in haemoglobin between 4-8 gm% in 20 cases (33.33%). Microcytic anaemia observed in 16 cases (26.66%) while macrocytic anaemia in 44 cases (73.33%). From above data it can be stated that macrocytic anaemia is more frequently present in cases of cirrhosis.

The histopathological criteria were applied to classify cirrhosis morphologically. (Table III) Out of 60 cases of cirrhosis, micronodular cirrhosis were observed in 46 cases (76.66%), macronodular cirrhosis were observed in 12 cases (20%) and mix patter were observed only in 2 cases (3.31%). The histopathological pattern of cirrhosis shows that maximum cases were of portal cirrhosis 48 cases (80%) followed by post necrotic cirrhosis 12 cases (20%). Biliary cirrhosis, cardiac cirrhosis and haemochromatic were not detected in present study. In present study Hepatocellular carcinoma was observed in 10 cases (16.6%) all the cases showed postnecrotic cirrhosis on histopathological examination.

The detailed past history shows that excessive alcohol consumption over a prolonged duration were observed in 23 cases (38%). All these cases histologically showed portal cirrhosis (micronodular). The remaining 25 cases out of 48 portal cirrhosis were not associated with alcohol consumption. Past history of jaundice were recorded in 19 cases (31.66%), out of these 12 showed postnecrotic cirrhosis (Macronodular) and remaining 7 cases showed portal cirrhosis. Out of 12 cases of postnecrotic cirrhosis 4 cases were diagnosed as hepatitis B. Remaining 30% cases of cirrhosis in present study appear to be idiopathic cirrhosis or cirrhosis of unknown etiology.

Table 1: Age and Sex wise distribution of liver cirrhosis

SN	Age group	Sex		No of cases (%)
		Male	Female	
1.	Below 10	0	0	0
2.	11-20	4	2	6 (10%)
3.	21-30	6	3	9 (15%)
4.	31-40	11	3	14 (23.33%)
5.	41-50	12	3	15 (25%)
6.	51-60	12	2	14 (23.33%)
7.	61-70	2	0	2 (3.33%)
	Total	47 (78.33%)	13 (21.66%)	60

Table 2: Clinical presentation of liver cirrhosis

Sr. No.	Signs and symptoms	No of cases (%)	Sr. No	Investigation	No of cases (%)
1	Fever	10 (16.66%)	1.	Peripheral smear	
2	Loss of appetite	55 (91.66%)		-Microcytic anaemia	16(26%)
3	Loss of weight	52(86.66%)		-Macrocytic anaemia	44(73%)
4	Distention of abdomen	60(100%)	2.	TLC	
5	Oedema	60 (100%)		Normal	50(83.33%)
				Raised	10(16%)
6	Pain in abdomen	40 (66.66%)	3.	Serun bilirubin	
7	Vomitting	20 (33.33%)		0-1mg%	7(7(11.66%)
8	Haematemesis	7 (11.66%)		1-3mg%	53(88.33%)
9	Bleeding piles	4 (6.66%)			
10	Ascitis	60 (100%)	4.	ALP,SGOT,SGPT Raised	60(100%)
11	Splenomegaly	50 (83.33%)	5.	Urobilinogen	
12	Caput Medusae	40 (66.66%)		Normal	7(7(11.66%)
13	Testicular atrophy	6 (10%)		Raised	53(88.33%)
14	Gynaecomastia	1 (3.33%)			

Table 3: Morphological and histological types of cirrhosis

SN	Morphological types cirrhosis	No of cases (%)	Histological types	No of cases (%)
1.	Micronodular	46 (76.66%)	Portal	48 (80%)
2.	Macronodular	12 (20%)	Post necrotic	12 (20%)
3.	Mixed	2 (3.33%)	Other	0
	Total	60	Total	60

Discussion

According to recent WHO estimate, end-stage liver disease is responsible for one in forty deaths (2.5%) throughout the World.[9] In India, mortality due to liver cirrhosis increased from 77,741 (95% uncertainty levels 52,196-116,746) in 1980 to 188,575 (95% uncertainty levels 109,748-303,989) in 2010.[10] Moreover, most cases of hepatocellular carcinoma (HCC) arise in a cirrhotic liver, so cirrhosis prevention is, in fact, also HCC prevention. The risk of developing HCC depends on the underlying disease: It is low, for example, when the underlying disease is autoimmune hepatitis (2.9% in 10 years) [11], and high when the underlying disease is chronic hepatitis B with a viral burden greater than 107 copies/mL (19.8% in 13 years) [12]. Liver cirrhosis is largely preventable. Identifying and subsequently controlling the risk factors for cirrhosis have been recognized. The various etiologies of cirrhosis are alcohol, hepatitis B, hepatitis C, autoimmune, NASH, biliary cirrhosis, cardiac cirrhosis, inherited metabolic liver diseases including hemochromatosis, Wilson's disease, α1 antitrypsin deficiency and finally cryptogenic cirrhosis for which no underlying cause has been identified [13].

The Liver biopsy (LB) is the gold standard method for assessment of liver histology. It provides valuable,

otherwise unobtainable information, regarding the degree of fibrosis, parenchymal integrity, degree and pattern of inflammation, bile duct status and deposition of materials and minerals in the liver. This information provides immense help in the diagnosis and prognostication of a variety of liver diseases. With careful selection of patients, and performance of the procedure appropriately, the complications become exceptionally rare in current clinical practice [14]. A number of non-invasive techniques have been developed which can be used instead of liver biopsy to assess liver disease severity, including serum markers and transient elastography [15, 16]. However, most non-invasive tests fail to differentiate between adjacent stages of fibrosis, and are generally only accurate when distinguishing cirrhosis from no or minimal fibrosis [17].

In the present study the higher incidence of cirrhosis observed that is 29.4% same as found in Mukherjee PS *et al* study 33.9% [18] The predominant age group was between 41-50 years (25%) followed by (23.3%) in the age group of 31-40 and 51-60 years. These observations are consistent with the study of Sharma B *et al*. [19] In our study, most of the patients were male 47 (78.33%) and only 13 (21.66%) were female with a male to female ratio 3.6:1 which were correlated with previous study of Solanki S *et al*. [20].

In Dhaka *et al* study [6], the commonest clinical presentations were loss of appetite (82%), Jaundice (74%), weight loss (68%), hepatic facies (54%), Splenomegaly (44%), ascites (40%) and hepatomegaly (38%) whereas in our study ascites, oedema and abdominal distention as the most constant presentations (100%), seen in all cases. The next common presentation were loss of appetite 91.66%, weight loss 86.66% and splenomegaly 83.33%.

In present study predomoinant morphological pattern was micronodular cirrhosis (76.66%) and least type was mix pattern. (3.31%) consistent with findings of Gall *et al* study [21]. MacSween and Scott *et al*. [22] study reported macronodular cirrhosis in 71.8%, micronodular cirrhosis were observed in 16% and mix patter were observed in 12.2%.

The excessive alcohol consumption over a prolonged duration was observed in 38% in this study and it was 34.5% in Solanki S *et al*. [20] In India, the recorded alcohol per capita (15+ age in years) consumption (in liters of pure alcohol) was 4.3 in 2010 as reported by the WHO. In 2012, the age standardized death rates (ASDR), as per WHO, due to liver cirrhosis in India among males and females were 39.5 and 19.6 respectively, out of which alcohol attributable fractions (AAF) constituted 62.9% and 33.2% respectively [23].

Past history of hepatitis B was seen in 2.09% cases in our study where as in Solanki S *et al.* [20] study it was 11.35% and in Sharma B *et al*. [19] study it was 10.2%. Hepatitis B is not a common cause of cirrhosis in this region possibly because of low prevalence.

Remaining 30% cases of cirrhosis in present study appear to be idiopathic cirrhosis or cirrhosis of unknown etiology or cryptogenic cirrhosis. This category, i.e. cirrhosis of unknown etiology, is found in 3-30% of patients with cirrhosis [24, 25]. NASH is considered the commonest cause of cryptogenic cirrhosis [26-28]. Other possible causes are silent or "burnt out" AIH, occult viral infection and covert alcoholism. The so-called residual histological findings such as foci of autoimmune-like inflammatory infiltrates versus NASH-like foci of steatosis, cellular ballooning, and glycogenated nuclei may help in defining the underlying cause of cryptogenic cirrhosis [29, 30].

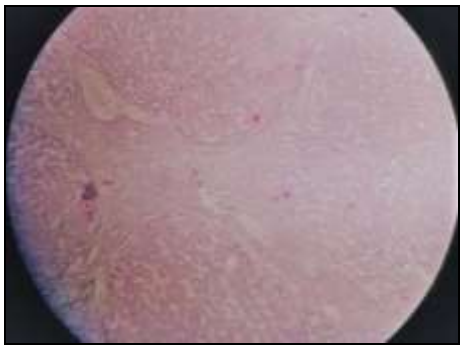

Fig 1: Micronodular cirrhosis shows small size regenerating nodules with surrounding thin fibrous stand. (H & E: 20x)

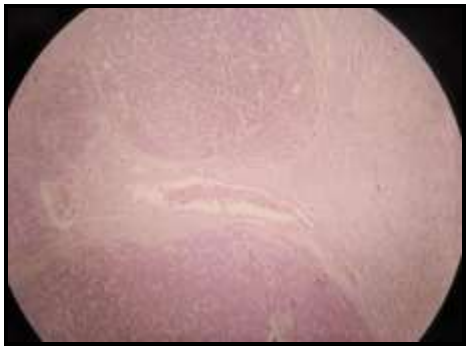

Fig 2: Macronodular cirrhosis shows regenerating nodules with surrounding thick fibrous band and sparse inflammatory infiltrate.. (H & E: 20x)

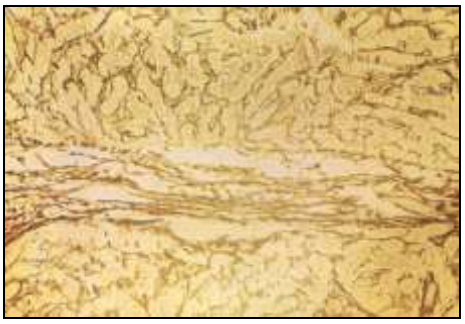

Fig 3: Macronodular cirrhosis shows reticulin pattern. (Reticulin stain: 40x)

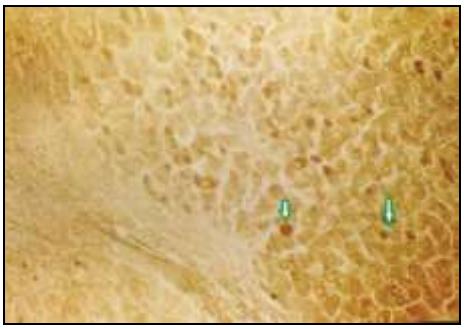

Fig 4: Postnecrotic cirrhosis shows cytoplasmic orcein positive material. (Orcein Stain 40x)

Conclusion

Alcohol intake was the most frequent etiologic factor for the development of cirrhosis, mostly in men as compared to female. Patient may develop Hepatocellular Carcinoma in

later stages. Therefore, awareness must be created to avoid alcohol intake. It would be helpful in prevention of any type of liver disease including cirrhosis and HCC. The early diagnosis of above mentioned disease conditions may prevent the progression of disease severity and may also prevents the cirrhosis. For the establishment of diagnosis and treatment it is mandatory to have a good correlation between clinical features and histopathological finding. Therefore, if there is no contraindication, for confirmation of diagnosis liver biopsy still remains a useful diagnostic tool modality, even in the era of advanced virological, immunological and molecular genetic testing.

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