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Research Article

Large Cell Dysplasia and Its Relation to Liver Diseases

Shreya Maheshwari[1], Kashish Modi[2], Shreya Rana[3], Purvi Mittal[4]

[1,2,3,4]Department of Pathology, Amrita School of Medical Sciences, Faridabad, India.
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Corresponding Author:
Shreya Maheshwari, Department of Pathology, Amrita School of Medical Sciences, Faridabad, India
E-mail Id:
shreyaamrita1@gmail.com
Orcid Id:
https://orcid.org/0009-0009-5296-4788
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A B S T R A C T

Introduction: Large cell liver dysplasia is a premalignant hepatic lesion, exhibiting abnormal nuclear characteristics like cellular enlargement, nuclear polymorphism, hyperchromasia and multinucleation of hepatocytes . There is no clear consensus relating LCD as the precursor to Hepatocellular carcinoma; it results from oxidative stress.

Methods: Total of 8 liver biopsies were received from Department of Pathology , Amrita School of Medicine, Faridabad . They were microscopically reviewed over a period of 3 years for LCD, multiple microscopic fields were examined for 1000 cells over 4-5 microscopic fields at 40x .

Result: On observing the cases it was observed that LCD cases in lymphoma were of a smaller age group, adenocarcinoma was of a higher age group whereas hepatocellular carcinoma was of the highest age group.Highest percentage of LCD was seen in cases of lymphoma followed by adenocarcinoma and then hepatocellular carcinoma lowest being in hepatitis.

Discussion: LCD is a combination of sustained liver injury , chronic inflammation , oxidative stress, genetic and instability. Largest percentage of LCD was seen in lymphoma cases which is a reactive change .

The percentage of LCD in cases of adenocarcinoma was also high due to indirect effects such as chemotherapy related liver damage , metastasis induced inflammation, cytokine release, oxidative stress and malnutrition .The percentage of LCD is also increased in hepatitis and hepatocellular carcinoma due to prolonged stress and damage that chronic hepatitis inflicts on liver cells.

Keywords: Large Cell Liver Dysplasia,Hepatocellular Carcinoma, Lymphoma

Introduction

William Blake said, "The true method of knowledge is experiment," and this study seeks to refine understanding and clinical strategies.

Large cell liver dysplasia (LCLD) is thought to be a premalignant hepatic lesion, though it is highly controversial.[1] It exhibits abnormal nuclear characteristics, such as cellular enlargement, nuclear pleomorphism, hyperchromasia, and multinucleation of multinucleation of liver cells occurring in groups or occupying whole cirrhotic nodules.[2]

Lacunae

There is no clear consensus on whether large cell liver dysplasia is a precursor to hepatocellular carcinoma or merely a reactive process to liver damage.[3] No definitive morphological continuum between dysplastic hepatocytes, benign or malignant transformation has been consistently identified.[4] Liver inflammation such as from viral hepatitis is known to contribute to liver dysplasia, but the specific contribution of inflammatory mediators and immune response in LCLD is debatable.[1] The molecular markers that could distinguish between regenerative and dysplastic lesions remain poorly defined, leading to uncertainty in diagnosis and prognosis. The lack of longitudinal data on the progression of LCLD to HCC, especially in non-viral liver disease, adds to this ambiguity.[1]

Hypothesis

Large cell liver dysplasia results from chronic inflammatory signalling oxidative stress in cirrhotic livers. A plausible hypothesis might centre on specific genetic and epigenetic changes,and molecular and cellular pathways that drive its progression and link to hepatocellular carcinoma. Its heterogeneous expression and persistence over time suggest that while not all LCLD lesions are preneoplastic, certain molecular subtypes may predispose to oncogenesis.

Aims and Objectives

The aim of this study is to correlate large cell liver dysplasia with hepatocellular carcinoma and other inflammatory diseases.

Methods

A total of 8 liver biopsies were received and analysed over a period of 3 years (2022–2024).The slides and clinical details were taken from the records .The slides were microscopically reviewed and examined for large cell dysplasia (LCD).

LCD was defined as a premalignant hepatic lesion which exhibits abnormal nuclear characteristics, such as nuclear pleomorphism, hyperchromasia and multinucleation.[2] Multiple microscopic fields were examined and a total of 1000 cells were examined over 4–5 microscopic fields at 40x. The percentage of LCD cells was calculated.

Results

A total of 8 liver cases were studied, out of which, 2 cases were of viral hepatitis (hepatitis B), 2 were of hepatocellular carcinoma and 2 were of lymphoma (Table 1).

On observing the cases from 2022 to 2024, we came across the observation that LCD cases in lymphoma patients were of a smaller age group (mean: 5050), which in comparison to adenocarcinoma were higher (mean: 5700) highest age group of LCD where observed in patients of HCC followed by hepatitis. This observation sheds light on lymphoma being a high-grade malignancy at a young age, requiring extensive metabolic support, which puts the liver under stress leading to dysplastic changes,whereas adenocarcinoma often places a high metabolic demand on the liver, especially since young people have a relatively high cellular turnover and metabolic rate. The liver responds to the systemic stress from the tumour, sometimes resulting in cellular adaptations like dysplasia. Table 2

Table 1.Distribution of Cases

Disease	No. of Cases
Hepatitis	2
Hepatocellular carcinoma	2
Lymphoma	2

Table 2.Age and Gender Distribution

carcinoma Type	Age		Mean %	
Hepatocellular carcinoma	37	78	5750	
Adenocarcinoma	49	65	5700	
Lymphoma	66	35	5050	
Hepatitis	61	55	5800	
Gender	Hepatocellular carcinoma	Adenocarcinoma	Lymphoma	Hepatitis
Male	1	1	2	1
Female	1	1		1

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Table 3.Large Cell Dysplasia in Liver Disease

Liver Diseases	Adenocarcinoma (n = 2)	Hepatitis (n = 2)	Hepatocellular Carcinoma (n = 2)	Lymphoma (n = 2)
	800	229	427	902
	708	315	792	820
Mean%	75.4	27.2	60.9	86.1

A total of 1000 cells were counted in each case and the percentage of LCD is shown in Table 3.

A higher percentage of LCD observed in patients with lymphoma (86.1%) indicated towards dysplastic changes in the liver due to indirect effects such as inflammation, immune dysregulation, or hepatotoxicity from treatments like chemotherapy or radiation.

The high percentage observed in the case of adenocarcinoma (75.4%) is also significant which may be due to indirect effects, such as chemotherapy-related liver damage, metastasis-induced inflammation, cytokine release, oxidative stress and malnutrition.

The LCD percentage observed in HCC and hepatitis were 60.9% and 27.2%, respectively.

Discussion

LCD, also known as large cell change or large cell dysplasia, refers to a condition in which hepatocytes (liver cells) undergo abnormal enlargement and display atypical features, such as irregularly shaped nuclei, increased nuclear size, and abnormal chromatin patterns, the leading cause to it is a combination of sustained liver injury, chronic inflammation, oxidative stress, and genetic instability.[3]It is a sign of hepatocyte response to persistent damage and is particularly relevant as a precursor lesion in chronic liver diseases, especially in cases of cirrhosis and hepatitis.[1] It is generally thought of as a premalignant cytologic change of hepatocytes that has been linked to cirrhosis, hepatocellular carcinoma (HCC), and chronic liver disease related to hepatitis B virus.[4]

As per our study, we found that the largest percentage of LCD was seen in lymphoma cases. To the best of our knowledge, no such association has yet been reported in world literature. However, these were known cases of lymphoma and were treated by chemotherapy. The liver biopsy was taken to detect liver involvement during follow-up. Since liver biopsies are not taken before the start of lymphoma chemotherapy, it is difficult to know whether the LCD occurred during the course of the disease or if it was already there when lymphoma started. Hence whether it was the cause or the effect of lymphoma is difficult to conclude.However, it could also be reactive changes in the liver cells rather than a precursor to malignancy. It has also been reported that liver cells undergo dysplasia as a response to chronic stress rather than as a step toward transformation into HCC.[5]

The percentage of LCD in cases of adenocarcinoma was also high (mean: 75.4%).

Large cell liver dysplasia in the context of adenocarcinoma may arise from indirect effects, such as chemotherapy-related liver damage, metastasis-induced inflammation, cytokine release, oxidative stress and malnutrition due to cancer cachexia caused by advanced adenocarcinoma, these mechanisms do not directly cause hepatocellular carcinoma but they create a stressed liver environment that can predispose cells to dysplastic changes.[6] However, an extensive search in world literature failed to show any paper with such a finding.

The percentage of LCD in hepatitis (27.2%) and HCC (60.9%) was highly significant in our study. The causes of large cell liver dysplasia, or large cell change, in hepatitis are reported widely.[1]However, whether it's a premalignant change induced by viral hepatitis, which leads to malignant transformation, is controversial. Some authors have reported it to be multifactorial and related to the prolonged stress and damage that chronic hepatitis inflicts on liver cells. In the context of chronic hepatitis B or C infection, the liver is subject to ongoing inflammation, immune response, and cellular turnover, which can lead to large cell change as a precursor to liver dysplasia and may lead to hepatocellular carcinoma (HCC).[1]

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