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Original Research Article

Histomorphological Spectrum and Clinicopathological Correlation of HBV Positive Liver Disease

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Abstract:

Background: The Hepatitis B virus (HBV) infection constitutes a significant global health issue, affecting almost two billion individuals globally, with around 350 million enduring chronic illness. Chronic viral hepatitis (CVH) is clinically characterized by sustained liver inflammation for a minimum of six months, accompanied by a recognizable hepatotropic viral infection, corroborated by clinical manifestations and/or biochemical irregularities. The clinical range of HBV infection is extensive. During the acute phase, it varies from subclinical or anicteric hepatitis to icteric, and infrequently, fulminant hepatitis. During the chronic phase, patients may either remain asymptomatic carriers or advance to chronic hepatitis, cirrhosis, and hepatocellular cancer. Notwithstanding progress in non-invasive diagnostics, liver biopsy continues to be the definitive standard for the confirmed diagnosis of chronic liver disease, as well as for precise staging, grading, and the exclusion of concurrent hepatic pathology.

Aim: To assess the histological spectrum of chronic hepatitis B via liver biopsy and to link biopsy results with clinical and biochemical markers.

Methods: This retrospective study analyzed 127 HBV positive liver biopsies from June 2017 to September 2019. Liver biopsies were performed to assess the severity of liver inflammation and f ibrosis, which were graded using the scoring system.

Results: The clinical symptoms and liver pathology were discovered to have substantial nonlinear correlations. Increased likelihood of mild to severe inflammation were substantially connected with older age. Patients with stage III and IV and the presence of HBe antigen and anti-HBe antibodies were shown to be significantly correlated [P-value < 0.05]. Ultrasonography indicated no significant abnormalities in most cases, although radiographic evaluation revealed altered liver echotexture in 25% of patients. A large portion, however, showed elevated HBV DNA levels; 35% had viral loads greater than 20,000 IU/mL, and 18% had viral loads greater than 1 million IU/mL, satisfying the threshold for initiating antiviral treatment.

Conclusions: In order to identify CHB patients who are more likely to experience moderate to severe inflammation and substantial fibrosis, routine monitoring of clinical markers such as ALT, AST, and GGT levels is essential. Our findings emphasize the usefulness of combining age and important biochemical markers into non-invasive diagnostic algorithms for the early detection and management of liver pathology.

Keywords: Hepatitis B Virus; HAI Score; HBeAg; Anti HBe Antibody; Fibrosis, inflammation; fibrosis.

Introduction

As a primary cause of cirrhosis, hepatocellular carcinoma (HCC), and chronic liver disease, hepatitis B virus (HBV) infection continues to be a significant global public health concern, especially in developing nations [1]. The clinical course of HBV infection is highly varied, ranging from inactive carrier status to progressive chronic hepatitis with fibrosis, cirrhosis, and malignant transformation [2]. This heterogeneity reflects the intricate relationship between viral replication, host immune response, and environmental variables [3].

When evaluating HBV-associated liver disease, liver biopsies remain essential, especially when determining the degree of fibrosis and disease activity [4]. Histomorphological examination not only aids in diagnosis but also gives prognostic information and guides therapy decisions [5]. Portal and periportal inflammation, interface hepatitis, lobular necroinflammation, hepatocellular ballooning, ground-glass hepatocytes, and different degrees of fibrosis are typical histological characteristics of HBV infection [6].

Despite breakthroughs in non-invasive markers, clinicopathological correlation using liver histology remains the gold standard for determining disease severity [7]. The objective of this study is to examine the histomorphological spectrum of liver disease caused by HBV and to establish a correlation between histological results and biochemical and clinical markers.

Materials and Methods

This is a retrospective analysis of 127 HBV positive liver biopsies amongst the total biopsies received in Department of pathology, KEMH over a period of three years. (June 2017 to September 2019)

Sample Collection

- Investigations including liver function test, INR, HBV markers (HBsAg, HBeAg), HBV DNA levels, fibroscan, USG abdomen and upper GI endoscopy were collected.
- Slides stained with H& E stain
- Special stains [Masson trichrome, reticulin, orcein, PAD & Prussian blue]
- Histomorphological features including
- Normal architecture preserved/distorted,
- Portal inflammation, interface hepatitis, lobular inflammation, confluent necrosis,
- Portal fibrosis, cirrhosis,
- Ground glass hepatocytes, steatosis%, steatohepatitis
- Iron overload, granulomatous inflammation, presence of plasma cells was noted.
- Grading and staging of liver biopsy were done by using the Ishak modified histological activity index (HAI) grading system and the Ishak modified histological staging system.
- NASH clinical reaserch network (NASH – CRN) scoring comprising of NAFLD activity score (NAS) and fibrosis stage used for assessing steatohepatitis associated with HBV induced chronic hepatitis.
- Grading of iron deposition on prussian blue staining using searle modification of scheuer system (based on magnification of resolution, representing an acinar overview).

Inclusion Criteria: All liver biopsies of adult patients with HBV positive status (HBsAg>6 months) on serology.

Exclusion Criteria: Pediatric liver biopsy

Results

Of the total 127 liver core biopsies studied, gender distribution was most commonly seen in male = 90 (71%) and female =37 (29%) with male to female ratio 2.4:1

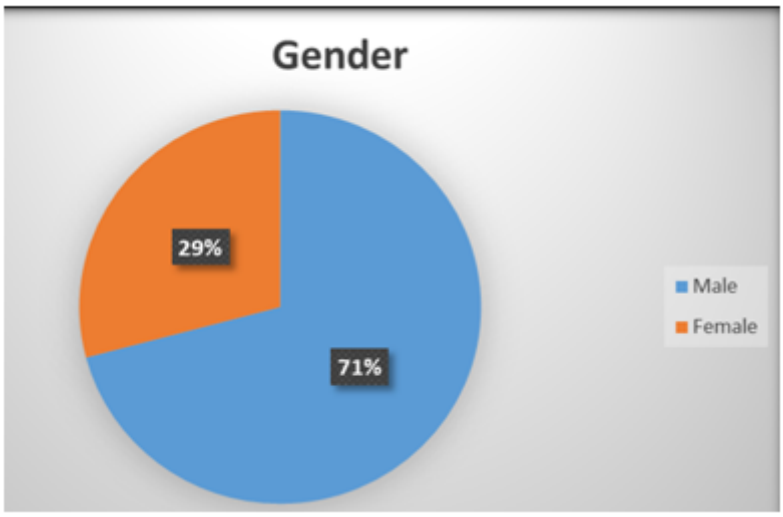

Figure 1: represents gender distribution

There are 39 (31%) maximum cases seen in 5th decade followed by 30 cases (24%) 4th decade. only 6 (5%) and 8(6%) cases were seen below 20 years and above 60 years.

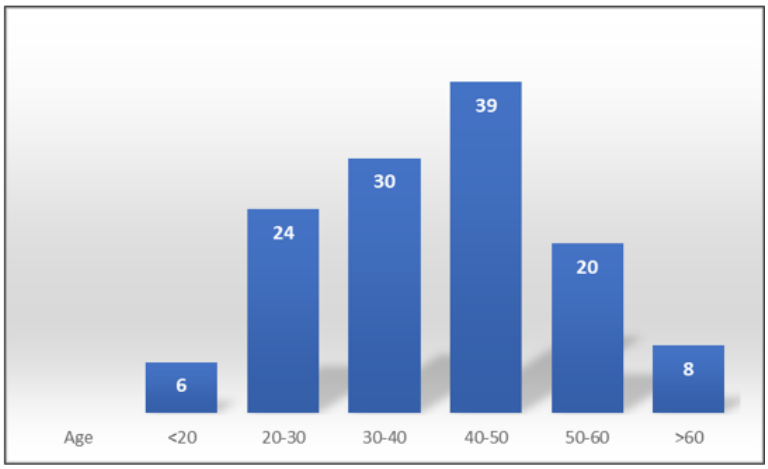

Figure 2: represents age and decade distribution

OT/PT was mild to moderately raised in 94 (74%) cases and ALP mildly raised in 15 (12%) cases. Rest other test including total/ direct bilirubin, total protein/albumin and INR were within normal limits in all cases.

Table 1: Represents the normal and elevated levels of biochemical tests

Test N=127	Normal		Elevated	
	Number	Percentage (%)	Number	Percentage (%)
1.ALP	112	88%	15	12%
2. OT/PT	33	26%	94	74%
3.T/D Bil	127	100%	0	0%
4.TP/Alb	127	100%	0	0%
5. INR	127	100%	0	0%

Of the 127 cases 86 (68%) cases show normal echotexture on USG abdomen, whereas 7 (6%) cases show fatty liver, 32 (25%) cases show altered/coarse echotexture which was correlated well with abnormal fibroscan and 2 (1%) cases show liver SOL.

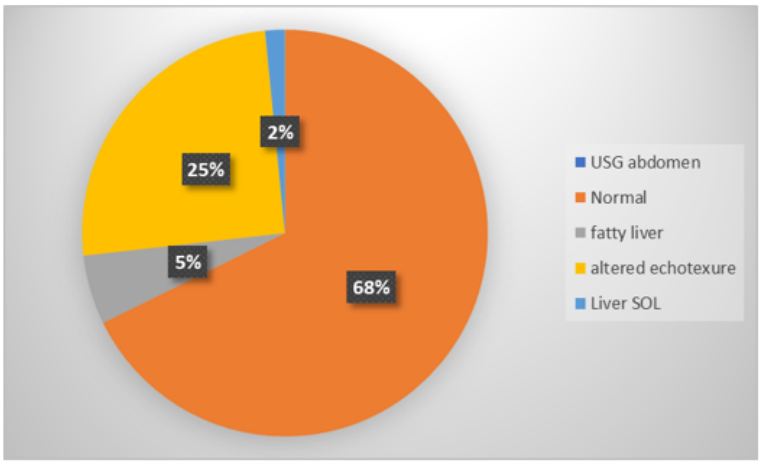

Figure 3: The pie chart represents the distribution of USG, fatty liver, altered echotexture, and liver SOL.

Of the 127 cases,

HBV- DNA (n=127)

HBeAg positive = 22 (17%)

HBeAg negative = 105 (83%).

Table 2: Number of HBV DNA and its number in percentage

HBV DNA (IU/ml)	Number (%)
<2000	29 (23%)
>2000	30 (24%)
#>20000	44 (35%)
#>1 million	24 (18%)

34 cases (27%) showed normal liver biopsy, 83 cases (65%) showed features of chronic hepatitis and 10 cases (8%) with fibrosis/ cirrhosis.

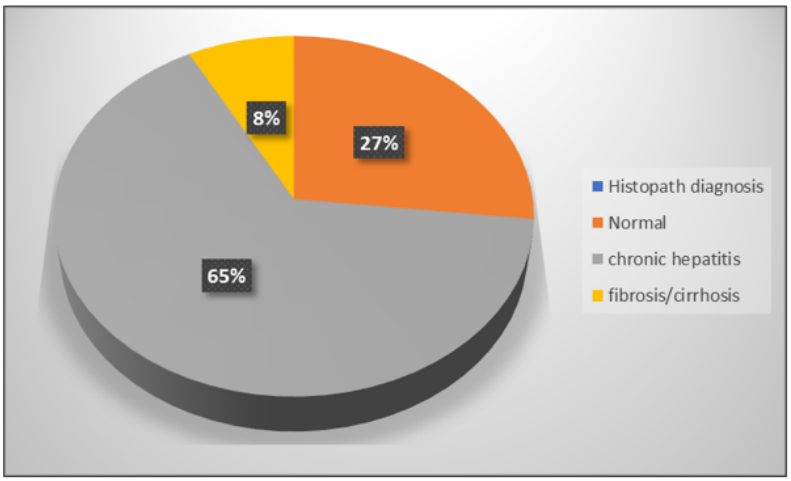

Figure 4: The pie chart represents the distribution of histopathological diagnosis, chronic hepatitis, fibrosis and normal.

The 81 (64%) cases show no fibrosis and 11 (9%) cases show stage 5 (advanced fibrosis) and only 2 (1%) case show (stage 6 cirrhosis) among all.

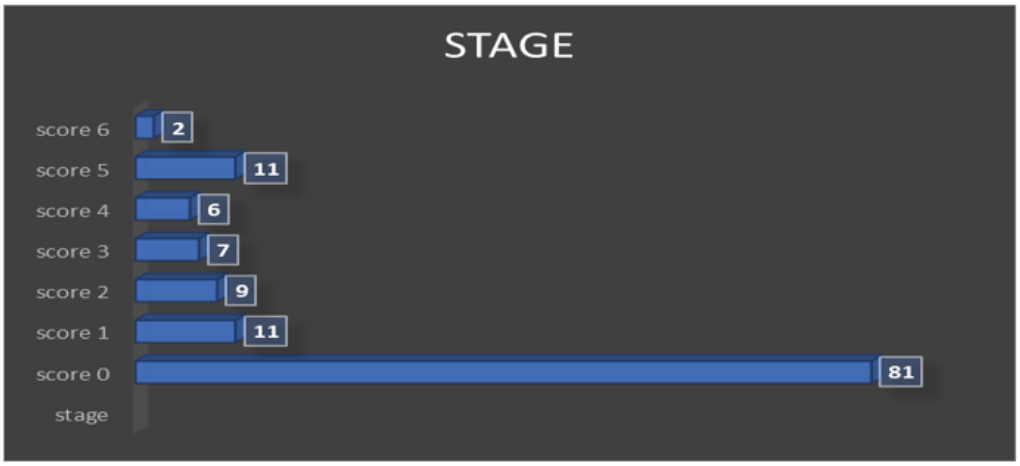

Figure 5: Represents the score and advanced stages of fibrosis

Amongst the four phases of the disease, majority of cases in our study falls under immune active HBeAg negative phase and inactive chronic HBV i.e. HBV carrier phase.

Table 3: Represents the active HBeAg, Anti HBs with HBV DNA and interpretation

HBsAg	HBeAg	Anti HBs	Anti HBe	HBV DNA	Interpretation %
Positive 127	Positive 22	negative	negative	(>1000000) 15	Immune tolerant phase 12%
Positive 127	Positive 22	Negative	Negative	(>20000) 07	Immune active HBeAg positive 5%
Positive 127	Negative 105	Negative	positive	(>2000) 28	Immune active HBeAg negative 22%
Positive 127	Negative 105	Negative	Positive	(<2000) 29	Inactive chronic HBV 23%

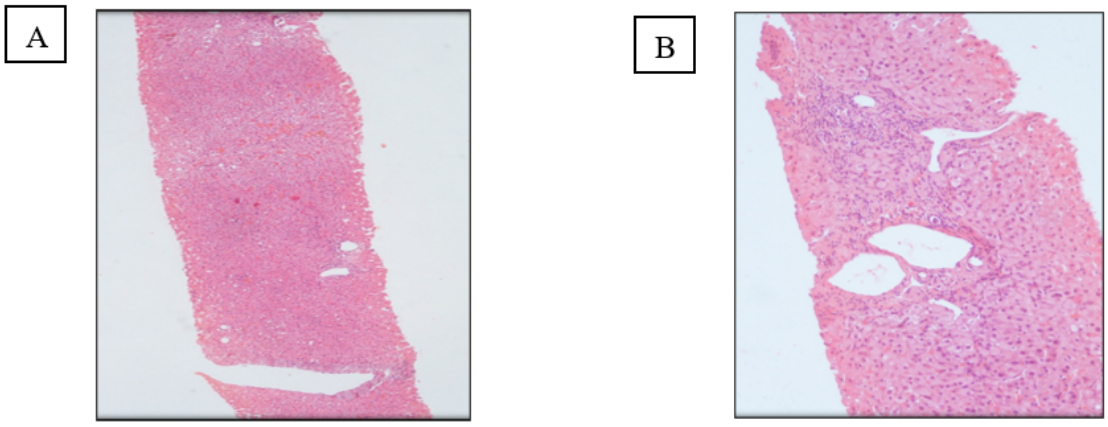

Figure 6: Histopathological images of liver biopsy. A) Liver core biopsy with normal histology (HE 40 x). B) HBV carrier with prominent GG hepatocytes (HE 100x)

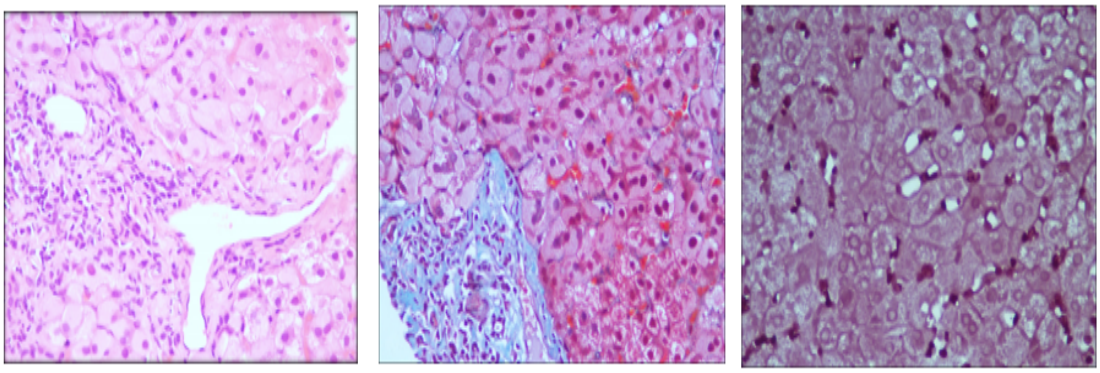

Figure 7: Histopathological images of GG hepatocytes on HE, MT & orcein stain at 400x.

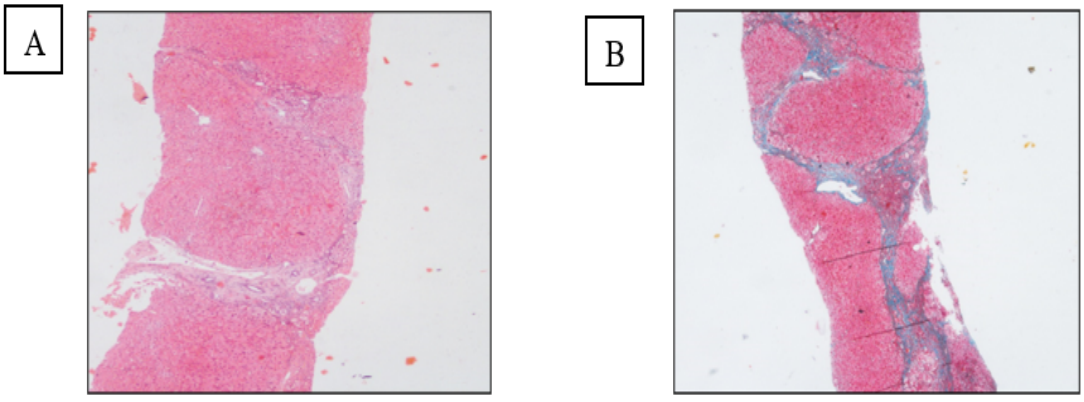

Figure 8: Histopathological images of A) liver biopsy with cirrhosis (HE 100x). B) Bridging septa and complete nodule highlighted on MT (40 x).

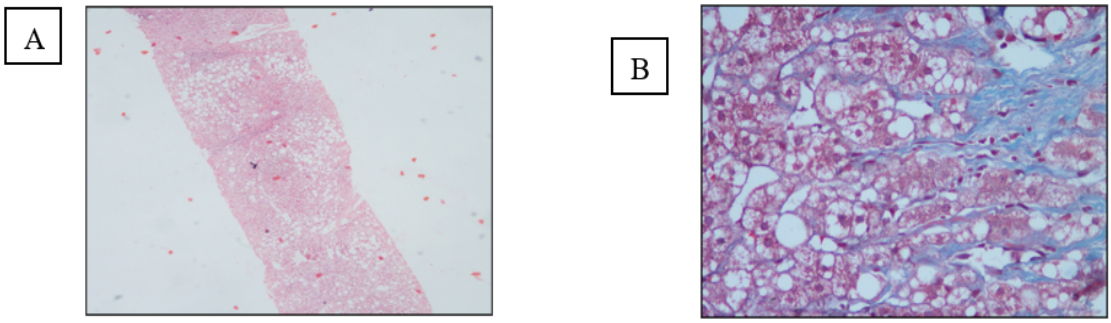

Figure 9: Histopathological images of A) liver core biopsy with features of steatohepatitis (HE 100x). B) Steatohepatitis with pericellular fibrosis (MT 400x).

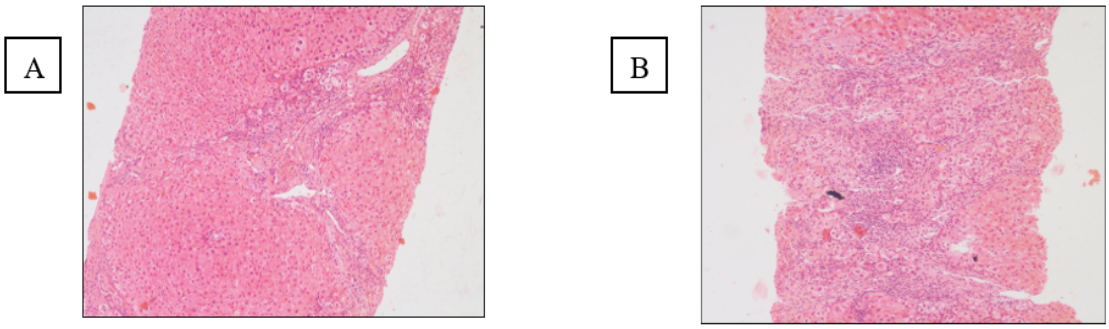

Figure 10: Histopathological images A) bridging septa and nodule formation with hepatocytes rosette (HE 100x). B) Dense portal inflammation with severe IH, hepatocyte rosette in case of HBV with AIH (HE 100x) inset shows plasma cells.

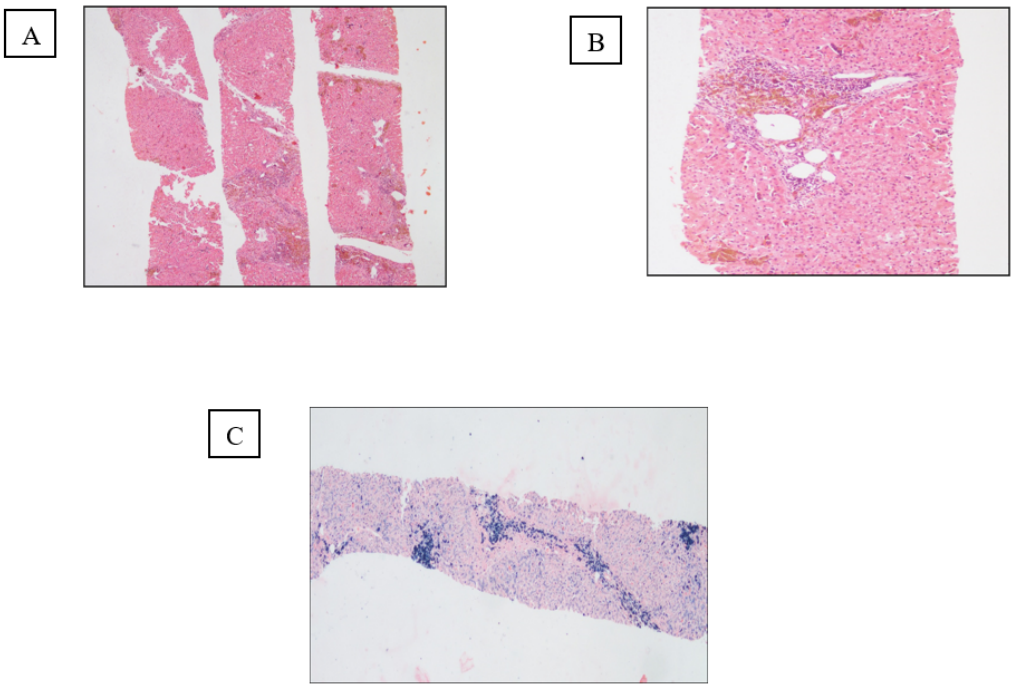

Figure 11: Histopathological images A) multiple liver biopsy cores showing portal tract inflammation with iron overload in known case of HBV and B thal major (HE 40x). B) bridging septa with iron overload (HE 10x). C) liver biopsy with grade 4 iron overload (Prussian blue 40x).

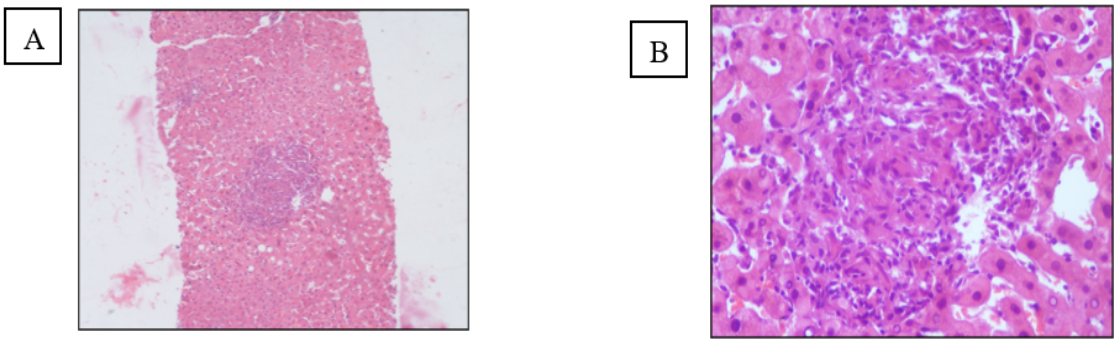

Figure 12: Histopathological images A) liver biopsy showing granulomatous inflammation (HE100x). B) epithelioid granuloma with Langhan's giant cell (HE 400x).

Discussion

Chronic hepatitis B virus (HBV) infection remains a huge worldwide health burden, particularly in developing countries, where a substantial number of infected individuals remain asymptomatic for protracted periods [8]. Liver biopsy continues to serve a vital role in detecting disease activity, fibrosis, and related pathological alterations, especially in individuals with contradictory clinical, biochemical, or virological findings [9]. The present work investigated the histomorphological spectrum of HBV-positive liver samples and connected these findings with clinical, biochemical, serological, radiographic, and elastographic characteristics.

With a male-to-female ratio of 2.4:1, a pronounced male preponderance (71%) was noted in this study, which is in line with previously published epidemiological data indicating higher HBV prevalence and disease progression in males [10]. This gender gap has been attributed to behavioral, immunological, and hormonal reasons. The bulk of patients belonged to the fifth decade of life, followed by the fourth decade, showing that HBV-related liver disease often becomes clinically or incidentally evident throughout middle age, when cumulative viral harm emerges as histological alterations [11].

Despite proven biochemical, virological, or histological abnormalities, a significant number of individuals were clinically asymptomatic, and the majority of cases were discovered inadvertently [12]. This emphasizes how sneaky chronic HBV infection is and how crucial regular screening and monitoring are, especially in endemic areas. Similar findings have been documented in past research, when a sizable portion of patients with chronic hepatitis B did not exhibit obvious clinical signs despite continuing liver damage [13].

Biochemical measures showed mild to moderate increase of transaminases and OT/PT in approximately three-fourths of patients, suggesting persistent hepatocellular damage. However, bilirubin levels, serum proteins, albumin, and INR were within normal ranges in all patients, indicating sustained synthetic liver function in the majority [14]. These results support the established inability of liver function tests to reliably assess the degree of histological disease, especially during the early or dormant stages of chronic hepatitis B. Thus, reliance simply on biochemical markers may underestimate underlying liver damage.

In 25% of patients, radiological assessment showed changed liver echotexture; nevertheless, ultrasonography revealed no substantial abnormalities in the majority of cases. This lends more credence to the idea that early or moderate hepatic fibrosis may be difficult to detect with standard imaging. On the other hand, 21% of cases had increased liver stiffness (>8 kPa) according to the FibroScan assessment, which correlated favourably with coarse echotexture on ultrasonography and histological evidence of fibrosis. This concordance underlines the utility of non-invasive elastography as an adjuvant to liver biopsy, particularly for fibrosis assessment and longitudinal surveillance.

Serological and virological profiling indicated HBeAg positive in 17% of cases, demonstrating a decreased proportion of patients in the immune-active replicative phase. A sizable portion, however, had increased HBV DNA levels; 35% had viral loads greater than 20,000 IU/mL, and 18% had viral loads greater than 1 million IU/mL, satisfying the requirements for starting antiviral medication. This highlights how crucial it is to quantify viral loads when making treatment decisions, even for patients with mild biochemical abnormalities or few symptoms.

Histopathological investigation indicated a wide spectrum of liver abnormalities, ranging from normal architecture to severe fibrosis and cirrhosis. While 27% of samples were histologically normal, the majority (65%) revealed signs of chronic hepatitis, characterized by portal inflammation and different degrees of interface activity. This result shows that even if there are few clinical symptoms, a significant percentage of HBV-positive people have active histology illness. In 8% of cases, fibrosis

and cirrhosis were seen, indicating severe disease and highlighting how persistent HBV infection progresses if treatment is not received.

The appearance of ground-glass hepatocytes in 46% of cases constitutes a traditional histological marker of chronic HBV infection, related to intracellular build-up of hepatitis B surface antigen. This aspect underlines the diagnostic utility of liver biopsy in confirming HBV-related disease, particularly in instances with equivocal serological or clinical results.

A number of coincidental pathological abnormalities were found in addition to HBV-related alterations. Steatohepatitis (9%) and hepatic steatosis (17%) were very prevalent, indicating the growing co-occurrence of chronic viral hepatitis and metabolic-associated fatty liver disease. Because metabolic variables may hasten the advancement of fibrosis and negatively impact treatment outcomes, this overlap has significant therapeutic consequences. The finding of granulomatous inflammation in a small proportion increases the likelihood of concomitant infectious or immune-mediated etiologies, warranting additional clinical correlation [15].

Interestingly, 4% of cases had autoimmune-like characteristics, including interface hepatitis and plasma cell-rich inflammation. These results underline the significance of thorough clinicopathological correlation to prevent misdiagnosis and improper immunosuppressive medication, as well as the diagnostic difficulties presented by overlapping autoimmune and viral hepatitis patterns. A tiny percentage of biopsies show iron excess, which could be a sign of metabolic dysregulation or secondary hemosiderosis and further exacerbate liver damage.

Overall, this investigation demonstrates the diverse clinicopathological range of HBV-positive liver disease, highlighting the possibility of substantial histological damage even in asymptomatic people with laboratory parameters that are almost normal. The findings underline the continued significance of liver biopsy as a diagnostic and prognostic tool, particularly in resource-limited settings and in instances with equivocal non-invasive tests.

Limitations and Future Directions

This study's cross-sectional design and lack of long-term follow-up data to evaluate therapy response and disease progression are among its drawbacks. Understanding of HBV-related liver pathology would be significantly improved by future research that includes longitudinal outcomes and treatment response correlations.

Conclusion

The current study concludes by highlighting the significance of integrated clinicopathological examination in HBV-positive patients in order to precisely determine disease activity, direct treatment choices, and stop the development of severe liver disease. The histomorphological spectrum of HBV-positive liver disease is broad, spanning from severe cirrhosis and hepatocellular carcinoma to an inactive carrier state. Histological evaluation provides excellent insights into disease activity and fibrosis stage, which correlate significantly with clinical and biochemical indicators, particularly serum transaminase levels and viral load.

In situations where non-invasive markers are unsatisfactory, liver biopsy is still an essential tool for the thorough assessment of HBV infection. It may be possible to stop the advancement of end-stage liver disease and hepatocellular carcinoma by identifying patients with severe necroinflammation and fibrosis early on.

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