Histological and Immunohistochemical Findings in Two Subtypes of Hepatitis B Related Acute Liver Failure

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BACKGROUND

Acute liver failure (ALF) occurs when rapid-onset, severe liver cell damage results in coagulopathy and encephalopathy. Multiple etiologies yield a remarkably similar syndrome including acetaminophen overdose, drug-induced liver injury, and Hepatitis B Virus (HBV) infection. ALF in the setting of HBV occurs in 1% of **primary acute** HBV infections (AHBV-ALF), but can also evolve during chronic HBV infection (CHBV-ALF), particularly in **reactivation**, when patients receive immunosuppressive or cancer chemotherapy.

OBJECTIVE

To determine if **primary acute** HBV infection and **reactivation** of HBV can be distinguished by HBV immunohistochemical bio-markers in liver: HBV core antigen (HBcAg) & HBV surface antigen (HBsAg)

METHODS

We examined biopsies from 21 HBV-ALF patients from the Acute Liver Failure Study Group (ALFSG) immunostained using dye-labeled antibodies for HBV core antigen (HBcAg) and HBV surface antigen (HBsAg). We also reviewed hematoxylin & eosin (H&E) staining for overall morphology (degree of necrosis, presence of plasma cells) and reviewed clinical history to stratify each case as either AHBV-ALF (**primary** infection, N=11) or CHBV-ALF (**reactivation**, N=10). For H&E, we assessed frequency of plasma cells, percent tissue necrosis, and degree of collapse.

RESULTS

Overview of Results

Eleven biopsies had <25% viable hepatocytes, making further analysis of staining patterns unsuccessful. The remaining acute HBV cases had very little, if any, HBsAg staining and variable levels of nuclear HBcAg staining. In contrast, one reactivation CHBV-ALF case had intense staining for both HBsAg and HBcAg, probably related to the presence of immunosuppression.

Summary of Key Results

- The number of viable hepatocytes were <25% in 3 out of 11 AHBV-ALF cases and 8 out of 10 CHBV-ALF cases, thus leaving 8 acute cases and 2 chronic cases available for analysis
- For the HBcAg staining, in the cells that stained, the AHBV-ALF group had less intense staining and a more focal distribution of stained cells, with most of that staining localized to the nucleus, while one of the CHBV-ALF group had more intense staining, a more diffuse distribution of stained cells, and mostly cytoplasmic staining
- For the HBsAg staining, in the cells that stained, the AHBV-ALF group had less intense staining and a more focal distribution of stained cells, with most of that staining in the cytoplasm, while one of the CHBV-ALF group had very intense staining, which was diffuse and located in the nucleus and cytoplasm, while the other was weakly focal and located in the cytoplasm
- All samples except for one acute case stained positive for the presence of plasma cells, although there was no readily apparent difference in number, distribution, or localization between the acute and chronic groups
- There were no unique features on H&E noted between the acute and chronic groups

Figure 1. Chronic (Immunosuppressed) HBsAg Stain

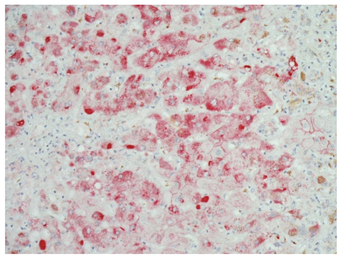


Figure 2. Chronic (Immunosuppressed) HBcAg Stain

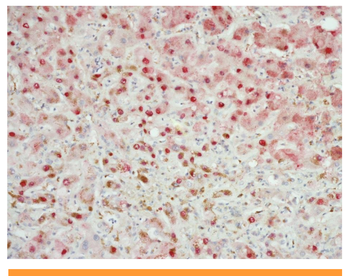


Figure 3. Chronic (Immunosuppressed) H&E Stain

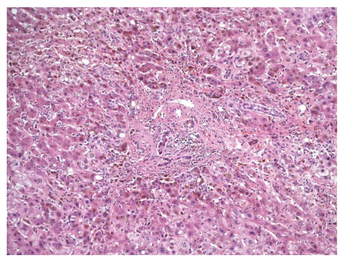


Figure 4. Acute HBsAg Stain

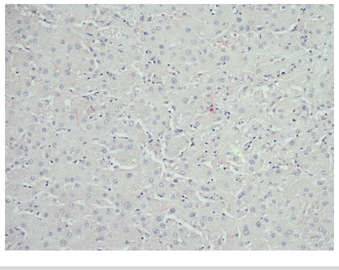


Figure 5. Acute HBcAg Stain

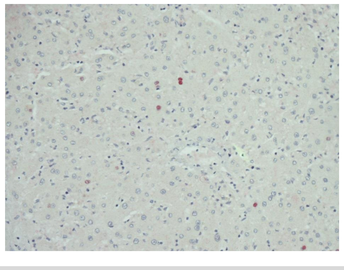


Figure 6. Acute H&E Stain

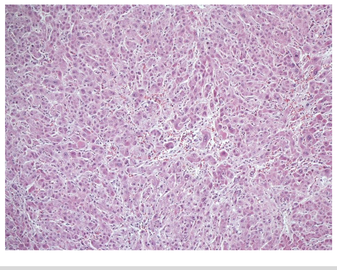
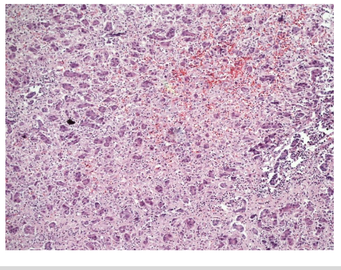


Figure 7. Acute H&E, Demonstrating Scant Viable Hepatocytes

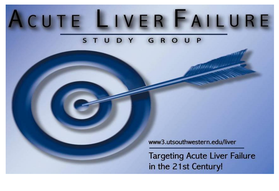


Notes About Figures (Pictures taken at 200x magnification)

Figure 1: There is very intense, yet diffuse, staining of the cytoplasm and some minor, diffuse staining of the cellular membrane.
Figure 2: There is very intense, yet diffuse, staining of both the nucleus and cytoplasm.
Figure 3: These is a relative preservation of normal hepatocellular architecture in about half to three-quarters of the tissue.
Figure 4: There is very little staining, although any staining that does exist is mainly focally located in the cytoplasm.
Figure 5: There is very little staining and any staining that does exist is mainly focally located in the nucleus.
Figure 6: There is >75% preservation of the normal hepatocellular architecture.
Figure 7: This is an example of a sample where there is extensive hepatocyte necrosis, with only <25% viable hepatocytes, which led to exclusion from further consideration in the study.

SUMMARY AND CONCLUSIONS

- Immunohistochemical staining of liver biopsies/explants revealed scant viable hepatocytes in more than half, limiting assessment of location of viral products within cells.
- Immunosuppression leads to much higher levels of HBV proteins within hepatocytes, evidenced by florid staining for both HBcAg and HBsAg, suggesting that the virus may be directly cytotoxic in this setting.
- In general, when assessment was possible, AHBV-ALF demonstrated little to no HBsAg and variable amounts of HBcAg staining.
- These two forms of acute liver failure due to hepatitis B have remarkably different pathogenetic phenotypes and the different injury patterns likely account for the different staining patterns.
- A limitation of our study was the small sample size. We hope to access additional biopsy samples and expand the sample pool in the future.



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