

SEATO MEDICAL RESEARCH STUDY ON HEPATITIS

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GENERAL INFORMATION: Studies 1 and 2 on viral hepatitis and leptospirosis are final reports and cover in considerable detail the pathology found in the liver biopsies in each disease. The study on Viral Hepatitis in US Troops in Thailand will be completed in several more months

Kupffer cells — The Kupffer cells show hypertrophy and the number is increasing in most of the cases. Mitotic figures of Kupffer cells are frequently observed. Focal necrosis of the Kupffer cells is present. Some of the Kupffer cells display marked acidophilia and hyaline changes of the cytoplasm and when they are dislodged into the sinusoids may resemble acidophilic cells very closely. In certain cases, the Kupffer cells may proliferate, forming small clusters which simulate a granuloma.

Sinusoids — In forty-one cases, sinusoids of the liver lobules contain an increasing number of lymphoid and mononuclear cells. In three cases, the cells are neutrophils.

Acidophilic cells — Round bodies which are slightly smaller than the liver cells are seen in the sinusoids in thirty-three cases. These bodies contain one nucleus and the cytoplasm is deeply acidophilic and hyaline. The twenty-one cases, the texture of these bodies is homogenous; in another ten cases they appear vacuolated or foamy. Both liver cells and Kupffer cells probably give rise to these bodies.

Portal area - In forty-six cases the portal area shows mild to moderate infiltration. The cells are mostly lymphoid cells, plasma cells and macrophages. A small number of granulocytes are present in ten cases. In addition, in fifty-two cases there is concomitant proliferation of perilobular ductules. In twenty-one cases formation of small septa projecting from the portal area into the lobules is noted. In four of these cases, some of the septa link together resulting in nodule formation of the liver lobules.

Bile stasis - Spotty stasis of bile is noted in seventeen cases while a moderate degree of bile stasis is noted in another nine cases. This is seen in the form of bile plugs in the cytoplasm of the liver cells or in the lumen of bile canaliculi or rarely in the lumen of ductules but never in the lumen of bile ducts. There is no bile lake nor bile granuloma. In some instances the liver cells may rearrange to form small glands enclosing the droplets.

Ductules - Proliferation of ductules is noted in fifty-two cases. They are mostly perilobular ductules but occasionally, intralobular ductules may be affected. The septa which project from the portal areas in most instances contain ductules.

Lipochrome pigment - An increased amount of yellowish lipochrome pigment in the liver cells and Kupffer cells is invariably present. In the liver cells the lipochrome pigment appears as brown, granular pigment in the pericanalicular location. In Kupffer cells it appears as yellowish, partly homogenous partly granular pigment. Sometimes it is seen in individual Kupffer cells but more often this lipochrome containing macrophage would appear in clusters in the sinusoids as well as in the connective tissue of the portal areas. The pigment is iron negative, PAS positive and partially acid fast. In some of the Kupffer cells there may be a hazy bluish staining around the lipochrome pigment in sections for iron.

Hemosiderin - In two cases, a small amount of hemosiderin granules is present in the liver cells in the periportal area. In twelve cases, mild to moderate degree of hemosiderin is present in the Kupffer cells. Most of these cells contain no lipochrome pigment as previously mentioned.

Histological Changes in Relationship to Duration of Disease - The morphological expression in these biopsies can be classified into 5 types:-

1. Active hepatitis. There is progressive necrosis of liver and Kupffer cells and inflammatory reaction in the lobules and portal areas. Acidophilic cells are frequently observed. There is no cholestasis. Lipochrome pigment in the liver cells and Kupffer cells is present in increasing amount.

2. Active hepatitis with cholestasis. The pathological changes are in general similar to type 1 but a mild degree of cholestasis is present.

3. Active hepatitis with partial glandular transformation. Features of active hepatitis with cholestasis are present. In addition, some of the liver cells exhibit glandular transformation around the vicinity of bile.

4. Healing hepatitis. Necrosis of the liver cells and Kupffer cells is inconspicuous. Prominent findings are the increase in amount of lipochrome pigment in Kupffer cells and in macrophage in the portal areas. In most instances, increased peribiliary lipochrome granules in the liver cells is also noted. The inflammatory reaction in the lobules may be subsiding, but in the portal areas, an increase in number of cells is always present.

5. Healing hepatitis with prominent scar formations. The findings are somewhat similar to type 4 but there is marked enlargement of portal areas, which appear to be stellate in shape with thin septa projecting. The septa consist mostly of proliferating ductules and connective tissue. In some cases, the septa from one portal area link up with septa from other portal tracts, encompassing a portion of liver lobule. Whether the scar formation noted in these cases would persist or would disappear can not be stated from this study.

Table II shows the various types of morphologic response in patients biopsied at different times after onset of disease.

Follow up Information - In the group biopsied within seven days of illness, follow-up on liver functions was available in six cases. Four of these were found to have liver functions within normal limits at two, three and four months, respectively on their first follow up. Two showed slightly elevated GPT, and slight hyperbilirunemia, one at one month and the other at four and one half month after the liver biopsies were done. No further follow up information was available.

In the group biopsied between 7-14 days after onset, follow ups were available in eight cases. Four cases were found normal when they were examined at nine, seven, five and one half and one month after liver biopsies were done. In three cases, examined at ten, one and one half and one month, there was slight hyperbilirubinemia but other tests were normal. In one other case, the bilirubin was found to be 4.4 mg% and SGOT 43, SGPT 47 units, four months after the biopsy.

In the group biopsied between 14-21 days after onset of disease, one was found to be normal 4 months after the biopsy. One had total bilirubin level of 1.2 mg%, GOT level of 102 units, and GPT of 72 units, two and one half month after the biopsy. Another case had a total bilirubin level of 2.6 mg% but the transaminase was within normal limits.

In the group between 21-28 days, one case had a normal liver function at 2 months, three had slight hyperbilirubinemia at 2, 2½ months respectively while transaminase level was normal.

In the group biopsied after 28 days of disease, one had normal functions at 5 months and the other had GPT value of 101 units at 9 months after the biopsy.

Hepatitis in Abnormal Hemoglobin Gene Carrier-Electrophoresis of hemoglobin was performed in forty-four of these cases and five were found to be heterozygous gene carrier for hemoglobin E (AE). The morphologic expression in these cases shows no discernable differences from other cases with hemoglobin A. The amount of hemosiderin in the Kupffer cells varies from nine to about the same amount present in other cases of viral hepatitis. The number of cases is too small, and no cases of homozygous gene carrier (EE) or Thalassemia hemoglobin E carrier is encountered, thus no conclusion regarding host response to hepatitis varius in homozygous or Thalassemia gene carrier can be made.

G6PD Deficiency and Hepatitis - Screening test for G6PD in erythrocytes was done in thirty-nine cases of this series and three were found to be deficient for this enzyme. The pathological changes in the liver biopsies of these three cases are not different from other cases of hepatitis.

SUMMARY AND CONCLUSION: The histopathologic characteristics of viral hepatitis encountered in this series are in general, somewhat similar to what have been described elsewhere with few minor exceptions. Cholestasis appears to be encountered in liver biopsies with active hepatitic processes in at least one fourth of the cases, and may be found also in cases during healing. The degree of cholestasis is not severe and usually is not associated with any abnormalities of the liver cells or ductules. In three cases, some degree of glandular transformation of the liver cells is noted in association with cholestasis. Whether this represents another form of hepatitis caused by different strains of hepatitic agents, or whether this due to an unusual type of host response of undefined nature can only be speculated. A follow up biopsy in one of this case of glandular transformation of liver cells performed two weeks after the first biopsy revealed that the process was healing. There was little evidence of bile stasis in the second biopsy and the liver cells were arranged in single cell plate. Glandular transformation was not observed.

In more than half of the cases the activity of the pathological processes reaches its height within 2 weeks after the onset. Healing probably occurs at different rate since evidences of healing are present in biopsies obtained within the first 7 days of disease. In nine cases, periportal scar appears rather prominent but there is no indication that the lesion will progress into cirrhosis.