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Viral Hepatitis in the Autopsy Specimen*

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Summary. The livers obtained at autopsy from ten patients with viral hepatitis but without massive hepatic necrosis were studied and in two instances compared with biopsy specimens obtained from the same patients. Characteristic features were hypertrophy and hyperplasia of hepatocytes. This hepatocellular macrocytosis also involved cells exhibiting evidence of injury. The intralobular inflammatory reaction in viral hepatitis, characteristic of the biopsy specimen, was distinctly subdued in the autopsy specimen. Therefore, macrohepatocytes, although by themselves not diagnostic, should raise the suspicion of viral hepatitis in the autopsy specimen, if other features of the disease are not conspicuous.

Introduction

The histologic picture of non-fatal, acute viral hepatitis with spotty necrosis, as seen in liver biopsy specimens, is well established (Axenfeld and Brass, 1942; Mallory, 1947; Smetana, 1954; Roholm and Iversen, 1939). Less common varieties are hepatitis with collapse bridging portal and central canals (Boyer and Klatskin, 1970), and the cholestatic form in which hepatocytes are arranged in acini around bile plugs, often in the absence of conspicuous intralobular inflammation (Morrow *et al.*, 1968).

Similarly, the histologic features of fatal, massive necrotic hepatitis are well known (Lucké, 1944; Lucké and Mallory, 1946; Ritt *et al.*, 1969). By contrast, the histologic appearance of non-fatal, spotty necrotic hepatitis in the autopsy specimen is not fully established. The picture characteristically seen in biopsy specimens has hardly ever been described in autopsy specimens, despite the fact that some patients with viral hepatitis die from other causes. Therefore, the histologic features of ten patients who died with clinical, laboratory or epidemiologic evidence of acute viral hepatitis but who did not have massive hepatic necrosis were studied. In two instances the findings at autopsy were compared with those in liver biopsy specimens obtained before death.

Material and Methods

Sections of liver, usually from single blocks, taken at autopsy from ten patients who had the clinical findings of viral hepatitis were selected from the files. In two patients, a biopsy specimen (21 and 15 days prior to death) was available for comparison. These cases did not represent a consecutive series. Cases with massive hepatic necrosis or other liver diseases were excluded. All specimens had been fixed in formalin and sections were stained with hematoxylin—eosin, periodic acid—Schiff technique and aniline blue for connective tissue and were subjected to silver impregnation for reticulum fibers. Iron was demonstrated by the Prussian blue reaction. The histologic findings were graded according to a scale ranging from—to +++. The size of nuclei and cytoplasm of hepatocytes was measured with a micrometer.

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Table 1. *Clinical and gross autopsy findings*

Case	Sex	Age	Type of exposure	Time interval from exposure to jaundice	Time interval from jaundice to death	Highest bilirubin level, total/direct (mg per 100 ml)	Liver weight (g)	Cause of death	Additional significant findings
1	♀	69	(cholecystectomy)	4 months	4 weeks	29.4/20.2	1000	hepatic coma	none
2	♀	27	transfusions	3 months	5 weeks	26.0/23.0	?	hepatic coma	?
3	♂	27	transfusions	2 months	$1^1/_2$ weeks	33.9/20.0	1850	hepatic coma	acute myeloblastic leukemia
4	♂	65	transfusions	5 weeks	2 months	1.5/0.75	1830	carcinomatosis	carcinoma of lung
5	♂	49	transfusions	3 months	1 week	6.2	2000	GI hemorrhage	acute myeloblastic leukemia, miliary tuberculosis and aspergillosis
6	♀	83	transfusions	8 months	6 weeks	22.8/19.1	820	hepatic coma	none
7	♂	64	transfusions	3 months	2 weeks	75.2	1900	hepatic coma	hemolytic anemia, GI hemorrhage, cholelithiasis
8	♂	73	transfusions	5 months	4 weeks	16.4/10.4	910	hepatic coma	chronic myelocytic leukemia, GI hemorrhage
9	♂	83	transfusions	5 weeks	?	19.2/11.6	1340	hepatic coma	GI hemorrhage
10	♀	67	(B_{12} injections)	months	$2^1/_2$ weeks	34.2/17.8	880	hepatic coma	microabscesses in heart, kidneys and brain

Results

Clinical Findings

There were six males and four females (Table 1); the youngest patient was 27 years of age, the oldest 83. Eight patients had been exposed to blood transfusions five weeks to eight months prior to the onset of jaundice. The remaining two patients did not have a history of exposure to hepatitis virus. The average duration of jaundice before death was four weeks; only three patients survived for more than four weeks from the onset of jaundice. Bilirubin levels and transaminase activities were conspicuously elevated in most patients. Australia antigen had not been determined in any of the patients. In eight of the patients hepatic coma was recorded before death.

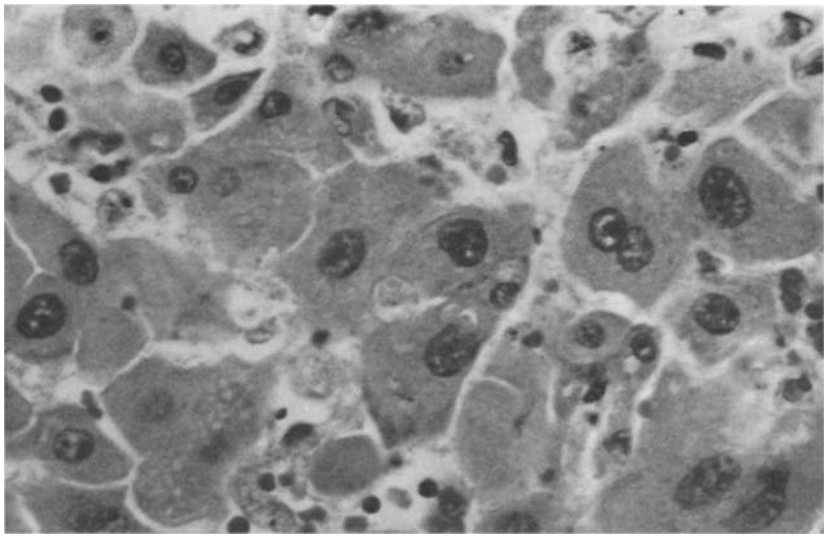

Fig. 1. Hepatocytes show enlargement of nuclei and cytoplasm. (×540, H and E)

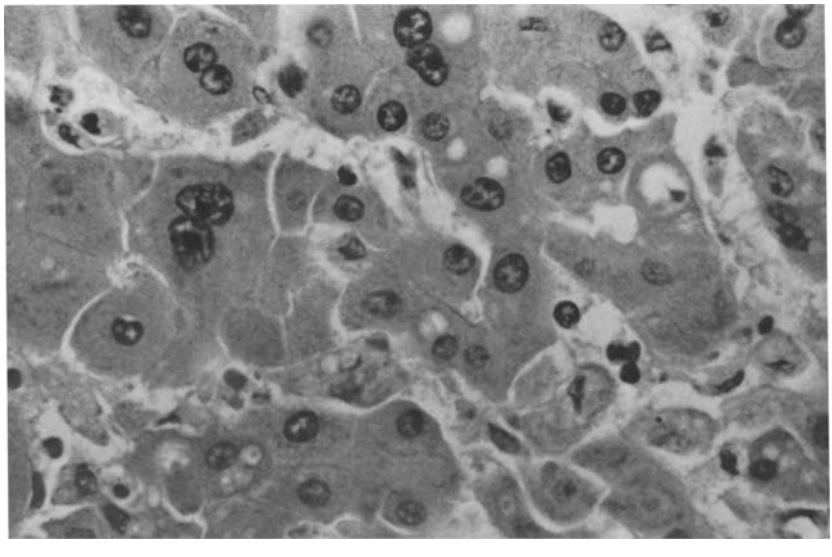

Fig. 2. Macro-hepatocytes contain small vacuoles in the cytoplasm. (×540, H and E)

Autopsy Findings

The average weight of the liver was normal (about 1400 g). The predominant histologic finding in the liver was conspicuous enlargement of the hepatocytes which varied in intensity throughout the lobule (Fig. 1). The cells measured frequently about 60 microns and exceptionally more than 100 microns in diameter. The size of normal hepatocytes in control livers was 20 microns and never exceeded 40 microns. The abundant cytoplasm was fairly homogeneous, eosinophilic and

Table 2. *Histologic*

Case[a]	Dark cells	Acidophilic bodies	Hydropic degeneration	Size of large hepatocytes (in microns)		Large cells	Bi- and multinucleated cells	Two cell thick plates
				cytoplasm	nuclei			
1 B	+++	+	++	40	15	+	−	+
A	−	−	−	70	15	++	++	+++
2 B	+++	++	+	65	15	+	+	+
A	+	−	−	50	20	++	+	+++
3 A	+	−	−	60	20	++	++	+
4 A	++	−	−	60	15	++	++	+
5 A	++	+	−	60	15	++	++	+
6 A	++	−	−	>100	20	++++	+++	+
7 A	−	−	−	80	30	+++	+++	+
8 A	+	−	−	50	15	+	+	+
9 A	−	−	−	60	15	++	++	+
10 A	+	−	−	70	15	++	+	+

[a] B = Biopsy, A = Autopsy.

almost glassy with sharply defined cell borders in some areas, while in others it exhibited irregular clumping, small vacuoles or varying amounts of basophilic granules, presumably of lysosomal origin (Fig. 2). The nuclei were enlarged, measuring 15–30 microns in diameter and had frequently several conspicuous nucleoli. The size of nuclei of normal hepatocytes was 10 microns. Some of the large nuclei were hyperchromatic or showed nuclear inclusions and chromosomal clumping. Binucleated and multinucleated cells were common. In some areas mitoses were seen. The hepatocytes were in single and sometimes in double plates. As a rule, the coherence between hepatocytes was intact, but in places the liver cell plates were broken up into single, small, rounded hepatocytes as a result of postmortal changes. Cholestasis was common as reflected in dilated canaliculi containing bile plugs and bile pigmentation of the hepatocytic cytoplasm. Loss of single hepatocytes was occasionally noted, but intralobular inflammation was not conspicuous. The described findings resulted in marked variation of neighboring liver cells in size and staining quality of both nuclei and cytoplasm. The Kupffer cells contained excess amounts of PAS positive nonglycogenic material and reacted for iron. Other alterations which are commonly found in viral hepatitis included: degenerative hepatocellular changes in the form of acidophilic shrinkage (dark cells) in most specimes, but typical acidophilic bodies and hydropic degeneration only in one specimen or not at all, endophlebitis of the hepatic vein tributaries and inflammation of the portal tracts with proliferation of bile ductules. Additional findings were centrolobular necrosis in three specimens, collapse with bridging in three, submassive necrosis in one, perilobular fibrosis in one, and mild steatosis in one.

findings in the liver

Cholestasis	Portal inflammation	Endophlebitis	Intralobular inflammation	Intralobular phagocytosis	Iron in Kupffer cells	Additional findings
−	+	++	+++	+++	−	Centrolobular necrosis
++	+	+	+	++	−	Collapse with bridging
−	+	+	++	+	−	None
++	++	+	+	+++	−	Submassive necrosis
++	++	+	++	+++	+++	Mild steatosis
−	+	+	++	+++	+	None
+	+	+	+	++	++++	Perilobular fibrosis, giant cell granulomata
+++	++	++	++	+++	+++	None
++	++	+	++	+++	+++	Centrolobular necrosis
+	+	++	+	++	−	Collapse with bridging
+++	+	+	+	++	++	Centrolobular necrosis
+++	++	++	−	++	+	Collapse with bridging

Biopsy Findings

The two biopsies differed from the autopsy specimens by an excess of inflammatory cells in the sinusoids and often between the hepatocytes consisting of lymphoid cells and mainly macrophages (Fig. 3a and b). Their presence made the alteration of the hepatocytes less conspicuous, which otherwise appeared similar to that in the autopsy specimens, including size of large liver cells (Fig. 4a and b). Acidophilic bodies, cells with dark cytoplasm and hydropic degeneration were more conspicuous. Cholestasis was not present in the biopsy specimens.

Discussion

The unusual feature in the hepatic parenchyma of the autopsy specimen of patients with viral hepatitis, but without massive hepatic necrosis, is a surprising sparsity of intralobular inflammatory reaction. The conspicuous intralobular inflammation in viral hepatitis commonly observed by liver biopsy is the reason why the lesion is designated as hepatitis, although functionally the hepatocellular alteration is more important (Popper, 1971). The relative sparsity of inflammatory infiltration in the necropsy specimen can be explained by a decreased rate of production of inflammatory cells in the dying patient (Weinbren, 1966) or by postmortal autolysis of the inflammatory cells, most of which are rich in digestive enzymes. Comparison with the biopsy specimen indicates the marked difference in the amount of intralobular inflammation. The lack of the inflammatory cells is apparently the reason why the common picture of viral hepatitis has not been described or recognized in autopsy specimens.

The absence of the intralobular inflammation in the autopsy specimen shifts the attention to the alteration of the hepatocytes in which enlargement of nuclei

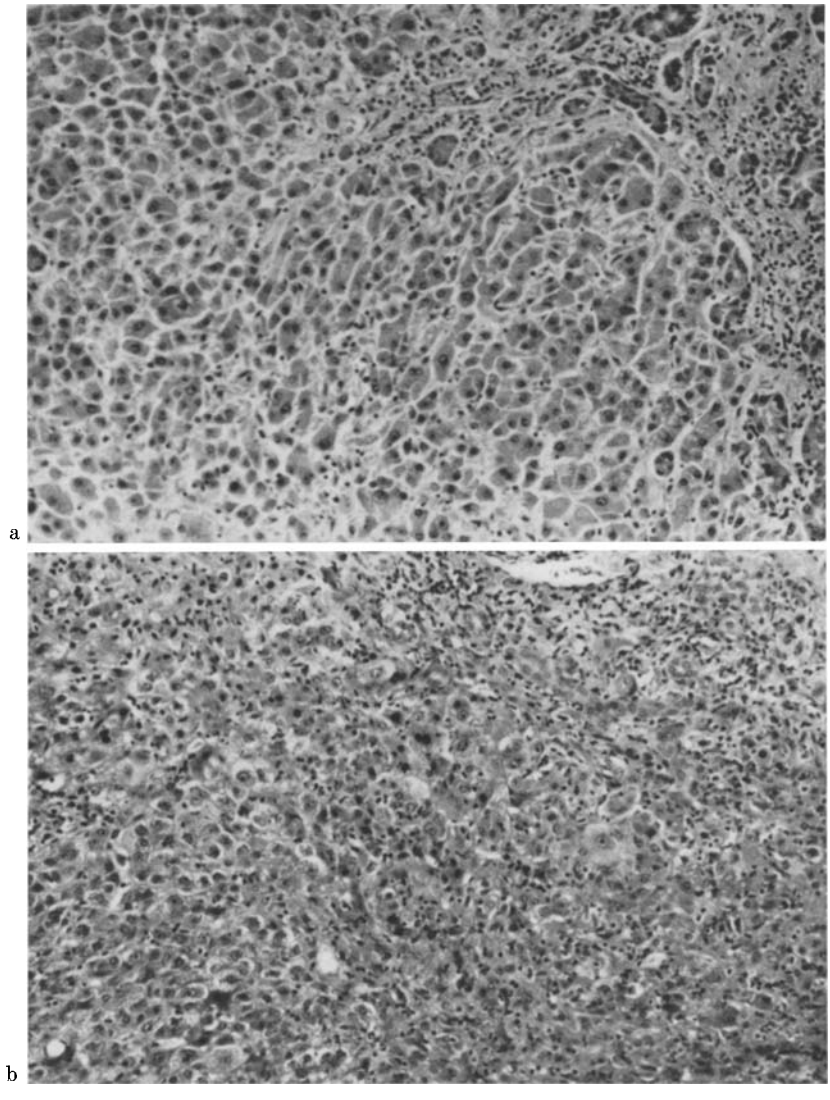

Fig. 3a and b. Comparison of the biopsy (b) and autopsy (a) specimen of case 1 shows marked difference in the amount of intralobular inflammation. (×250, H and E)

and of cytoplasm becomes a conspicuous feature, also present, but less well appreciated in the biopsy specimen. Similar changes have also been noted in autopsy specimens of massive hepatic necrosis. This reaction to injury involves hyperplasia of hepatocytes, but also hypertrophy or cell division. Mitoses have been recognized as an early feature in viral hepatitis (Bianchi *et al.*, 1971). Increased numbers of mitoses may be found, and two-cell thick plates and particularly multinucleated cells as well as large nuclei are present. These changes involve also hepatocytes showing morphologic evidence of injury as suggested

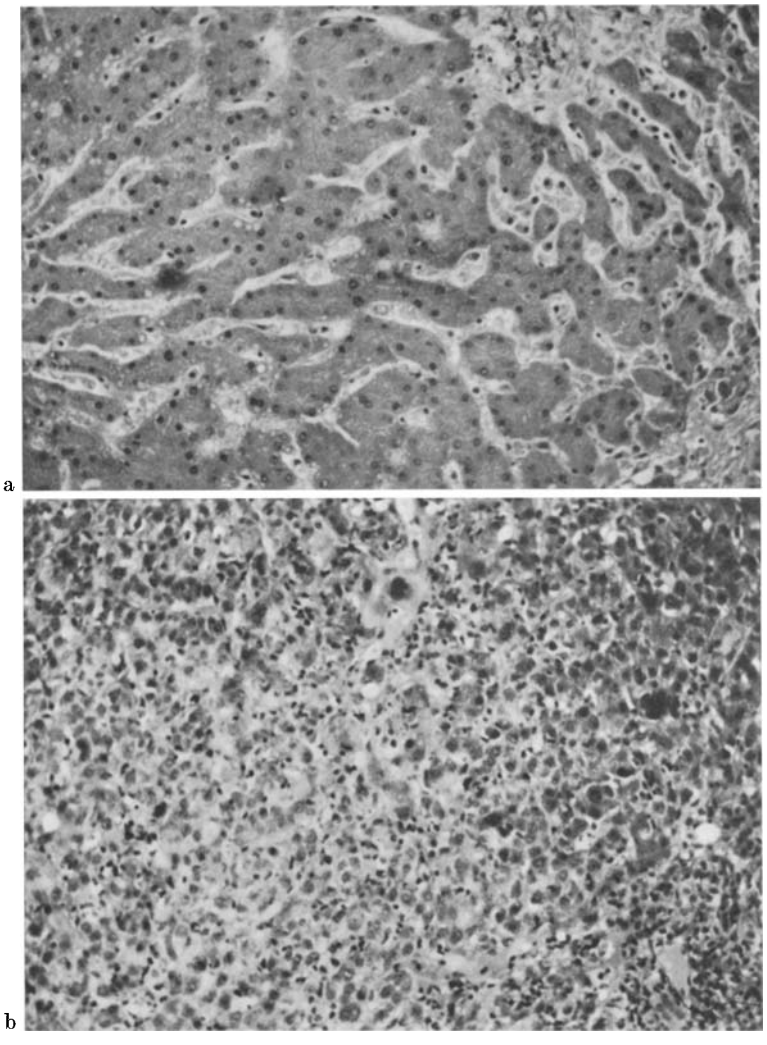

Fig. 4a and b. The autopsy (a) specimen of case 2, in contrast to the biopsy (b) specimen, shows lack of inflammation. (×250, H and E)

by irregular clumping, vacuolization and bile pigmentation of cytoplasm. This indicates that hepatocellular macrocytosis is not only a reaction of intact hepatocytes to injury of neighboring cells, but involves also damaged cells. This may represent an example of damaged cells responding to injury by division (King, 1966). The macro-hepatocytes contribute significantly to the marked variation of neighboring liver cells which is prominent in both autopsy and biopsy specimens and perhaps the most typical finding in acute viral hepatitis.

While the variation of neighboring hepatocytes in this condition is the most conspicuous feature, other alterations of viral hepatitis may be present though

they may not be characteristic enough to make the diagnosis. This includes acidophilic bodies, phagocytosis reflected in PAS positive non-glycogenic material and iron in Kupffer cells, endophlebitis of hepatic vein tributaries and portal inflammation. Collapse streaks between central and portal canals appearing as straight septa have been found repeatedly, indicating the ominous prognosis as pointed out by Boyer and Klatskin in describing subacute hepatic necrosis. In cases in which the other criteria of viral hepatitis are in the background, the described hepatocellular macrocytosis should raise the suspicion of viral hepatitis in the autopsy specimen, to be confirmed by other histological criteria.

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