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Pathology of Subacute Hepatic Failure

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Introduction

Subacute hepatic failure (SAHF), a clinical syndrome carrying a poor prognosis both in terms of mortality and morbidity, appears to be more frequent in some of the Asian countries, including India, than in the West. The etiopathogenesis and pathology of this condition is ill understood.

The pathologic features of SAHF described here are based mostly on light microscopy of needle biopsy specimens (percutaneous or peritoneoscopic) of liver obtained in life or postmortem from 42 patients seen in the Gastroenterology Department of the All-India Institute of Medical Sciences, New Delhi between January 1985 and June 1992. In seven of these cases, transmission electron microscopic examination was also carried out, primarily to evaluate the ultrastructural characteristics of certain hepatocytic alterations observed on light microscopy.

Clinical and light microscopic findings

All patients were categorized as having SAHF on clinical criteria as follows: 'Jaundice persisting or progressively deepening for more than 4 weeks and moderate to marked ascites with or without hepatic coma of variable grades'. The age of these patients ranged from 20 to 69 yr (mean 42.5); there were 31 men and 11 women. During a period varying between 4 to 50 weeks, 23 died and the remaining 19 were alive when last seen. The male-to-female ratio was 3.6 in the fatal group and 2.2 in the survivors, suggesting a preponderance of males in the fatal group. Approximately 70% of patients who died were biopsied within 12 weeks of illness, most such biopsies being post-mortem, whereas within this period only about a third (32%) of the survivors were biopsied. Some of the biopsies from survivors showed changes of recovery and healing.

The liver biopsies revealed different types and grades of hepatocellular injury and mesenchymal reaction. By far the commonest injury was bridging necrosis (Fig 1) which was observed in 36 (86%) of 42 cases, almost universally (22 of 23 cases – 96%) in the fatal group but also in the majority (14 of 19 – 74%) of those

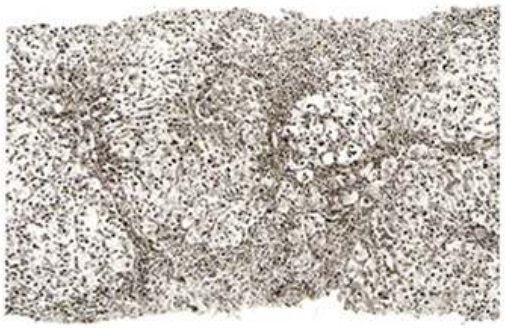

Fig 1: Extensive and generally wide bridging necrosis markedly distorting the normal hepatic architecture and giving a remarkable resemblance to the picture of cirrhosis. The hepatocytes in the parenchymal islands show swelling and cytoplasmic clearing. This patient survived the disease. [H & E X 90].

alive (Table 2). This lesion represents necrosis of columns of hepatic lobular parenchyma consisting of one or more liver cell plates connecting vascular territories. Such necrotic bridges can run between portal vein radicals (PP), between portal vein radicals and hepatic (central) vein tributaries (CP) or between central vein tributaries (CC). The bridges can also occur as combinations of the three types (Table 3); they can be narrow or wide, few or extensive, and show linear collapse of framework without elastic fiber formation.

In all cases who died the bridging necrosis was extensive and generally wide (Table 2) such that the

Table 1: SAHF: Bridging necrosis in liver biopsy vs outcome

Outcome	n	Bridging necrosis		
		Absent	Present	Type
Alive	19	5	14	Thin 9, wide 5
Dead	23	1	22	Wide & mostly extensive
All	42	6	36	

*Thin fibrous bands - 3

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normal lobular architecture was significantly distorted, frequently with resemblance to parenchymal nodulation of cirrhosis in the hematoxylin-eosin (HE) stain (Fig 1). Even in preparations stained using stains for reticulin and collagen fibers, the similarity to the microscopic appearance of cirrhosis was strong because of the collapse and partial condensation of the fiber framework of the necrotic parenchyma. Careful examination of HE stained material revealed loose edematous tissue of necrotic zones with extravasation of blood, occasional remains of dead hepatocytes and attempted pseudoductular proliferation (Fig 2). Orcein staining for elastic tissue provided considerable help in distinguishing recent bridging necrosis from fibrous septa of cirrhosis. Unlike in cirrhosis, the collapsed framework in SAHF contains very little or no elastic fibres. An additional advantage of the Orcein stain in this situation dealing with subacute hepatopathy is its ability to detect hepatitis B surface antigen. In surviving patients, bridging necrosis was thin in more than half (9 of 14, 64%) and wide in about a third (5 of 14, 36%). In 3 of the 19 survivors the thin bridges had already healed, composed of fibrous tissue only while in a further two the hepatic histology was that of acute hepatitis without any bridges (Table 2). Segmental areas of panlobular necrosis affecting all hepatocytes of complete and some contiguous lobules was additionally present in 9 of 23 (39%) patients who died and in only 3 of 19 (16%) who survived. Spotty and focal necrosis of individual (apoptosis) and small groups of a common finding in acute non-fatal hepatitis was seen in all cases.

The hepatocytes showed a variety of alterations, some typical of acute hepatitis like hydropic change, ballooning or apoptosis but others somewhat unique and unusual for a disease with significant hepatocellular failure. In several places the liver cells instead of being hydropic were smaller than normal cells with compact basophilic or more than normally eosinophilic cytoplasm with some double cell plate arrangement. This change referred to as 'non-reactive' for want of a more appropriate term was almost universal in patients who died (22 of 23, 96%) (Table 3) along with absence of hepatocytic swelling (Fig 2 & 3). Only one of these patients subjects showed hydropic change. On the contrary, 16 of 19 survivors showed diffuse hydropic change of hepatocytes (Fig 1) and in only one non-reactive change was seen. Thus, this non-reactive change appears to be directly related to mortality in SAHF (Table 3). In a few cases scattered small focal areas of hepatocytic loss with cell debris collections were noticed. Lipid accumulation was generally conspicuous by its absence except in occasional cases where small focal areas of mild lipid accumulation were seen, possibly as a terminal event. In two fatal cases, Mallory hyaline was encountered in some hepatocytes. Mitosis was not encountered and only indirect evidence of regeneration was seen in the form of focal areas of double cell plates. Active pseudoductular proliferation in some cases represented abortive hepatocytic regeneration.

Another interesting morphologic abnormality, next in frequency and uniqueness to the non-reactive change, was marked ductular cholestasis at the interface of hepatic lobules and portal tracts. Cholestasis at one or more sites was seen in 34 cases, including 21 of 23 who died and 13 of 19 were alive (Table 4). Cholestasis was considered cellular when it was either intracytoplasmic or canalicular, since canaliculi are adjacent parts of specialized cell membranes. Ductules (canals of Hering) are composed of transitional hepatocytes between more mature liver cells in the inner aspect (hepatic venular side) of the lobule and bile ducts in the portal tract. Ductular cholestasis either alone or along with cellular cholestasis was much more common in fatal cases (19 of 21, 98%) than in survivors (8 of 19, 42%; Table 4).

Ductular cholestasis alone was very rare, encountered in only one patient in each group, whereas cellular bile stasis without ductular involvement was seen in 5 of 13 fatal and 2 of 21 surviving patients. Bile stasis in ductules at the lobule-portal tract interface was most severe in SAHF that terminated fatally, morphologically

Table 2: SAHF: Topography of bridging necrosis vs outcome

Outcome	n	Bridging necrosis*				
		PP	CP	PP-CP	CP-CC	PP-CP-CC
Alive	14	1	1	2	1	9
Dead	22	3	-	10	-	9
All	36	4	1	12	1	18

*PP = Portal-to-portal; CP = Central-to-portal; CC = Central-to-central

Table 3: SAHF: Hepatocyte morphology vs outcome

Outcome	n	Hepatocyte morphology		
		Hydropic change	Non-reactive change	Normal
Alive	19	16	1	2
Dead	23	1	22	-
All	42	17	23	2

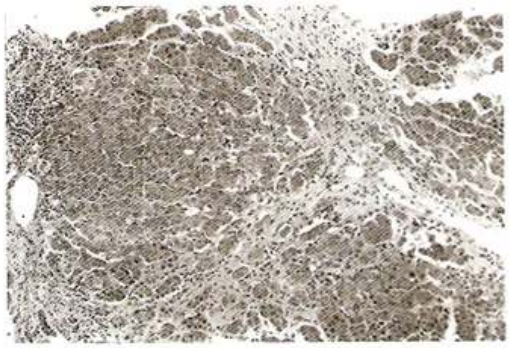

Fig 2: 'Non-reactive' change of hepatocytes which are somewhat smaller than normal and completely lacking in cytoplasmic clearing. The necrotic bridges are composed of loose tissue with extravasated red cells. This patient succumbed to the disease [H & E X 130].

manifesting as rounded, tubular or irregularly shaped lakes with mild to moderate inspissation (Fig 3). To unsuspecting an observer this picture may mimic an obstructive cholangiopathy particularly because of the presence of significant number of neutrophils in the inflammatory exudate and the non-reactive hepatocytes appearing not too different from normal liver cells. Two findings however help to distinguish this lesion from severe extra-hepatic obstruction: i) bile ducts appear normal in number and structure, and ii) there is no significant comparable cholestasis in the lobular canaliculi.

Moderately severe mesenchymal reaction was evident in most biopsies. The inflammatory response comprised of lymphocytes and histiocytes together with significant numbers of neutrophils and few plasma cells. Eosinophils were only occasionally encountered. Kupffer cell hyperplasia varied from mild to moderate degree and in some cases contained lipofuscin pigment. The latter was commonly observed in survivors, who had histologic suggestion of recovery. Early fibroblastic proliferation was apparent in areas of necrosis with the start of neovascularization and confluence of collapsed hepatic sinusoids. The portal tracts even when not involved in the bridging process, were enlarged, moderately edematous and frequently showed inflammatory cell collections and pseudoductular proliferation.

Electron microscopy

In seven SAHF patients, four with vacuolation of hepatocytes and three with non-reactive change, ultrastructural examination was carried out. The patient with vacuolated hepatocytes had non-rosetted dispersed glycogen similar to that as in the toxin-primed rats while in those cases with non-reactive change, glycogen was conspicuously reduced or absent.

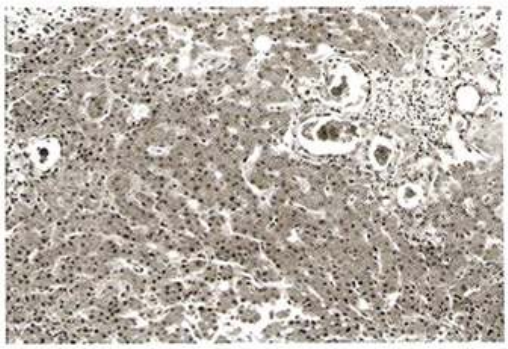

Fig 3: Marked ductular cholestasis at the lobule - portal tract interface, bridging necrosis and lack of hepatocytic swelling and clearing with 'non-reactive' change in a patient who died of the disease. [H & E X 120].

Discussion

While a consistent feature in the hepatic histology of our cases of SAHF has been the presence of different grades and extent of bridging necrosis, the most striking abnormality encountered is the 'non-reactive change' in hepatocytes. With any hepatocytic injury leading to significant and often fatal hepatocellular failure, one expects to see extensive necrosis and loss or retrogressive changes of hepatocytes. The swelling and ballooning of liver cells observed in various acute hepatopathies in humans and experimental animals has been generally attributed to retrogressive hydropic change of cellular injury capable of progressing to irreversible change of necrosis. However, most of our SAHF cases in whom the liver cells were not swollen and revealed the non-reactive change of near normal appearance, died. On the other hand, in patients who remained alive most liver biopsies showed the swelling of hepatocytes characteristic of acute hepatitis. Thus, if lack of swelling is associated with high mortality, does it conversely mean that the hepatocytic swelling in the subjects who survived represents a benefi-

Table 4: SAHF: Hepatic cholestasis vs outcome

Outcome	n	Cholestasis			
		None	Cellular only*	Ductular only	Cellular* and ductular
Alive	19	6	5	1	7
Dead	23	2	2	1	18
All	42	8	7	2	25

*Intracytoplasmic and/or canalicular

cial and protective adaptation? Some support for this hypothesis was obtained from some of the experimental studies in rats carried out by two of us (NCN and SDG). Animals primed by a small dose of hepatotoxin like carbon tetrachloride, aflatoxin B1, or acetylfluorine developed hepatocytic swelling akin to what is seen in human acute hepatitis. Interestingly, these animals became completely resistant to a large dose of the same toxin that proved highly hepatotoxic and lethal to non-primed animals. Detailed examination of the post-priming hepatocyte swelling showed an abundance of non-rosetted dispersed glycogen. One of the earliest and sensitive indicators of liver cell damage is rapid loss of glycogen. Thus the glycogen-rich swollen cells generated by toxin priming were not injured cells but ones adapted for protection against larger insults.

We therefore conclude that for some in a proportion of SAHF patients, unknown reason, adaptive transformation of hepatocyte for protection asgainst injury does not occur, resulting in the non-reactive change. Lack of this protective adaptation along with extensive bridging necrosis, accompanied by significant hemodynamic alterations and defective or abortive parenchymal regeneration, may contribute to death. In fulminant acute hepatitis, hepatocellular failure results from extensive loss of functional parenchyma due to panlobular necrosis. In SAHF, on the other hand, panlobular necrosis is only focal but the available hepatocytic population lacks adaptative response to injury seen in non-fatal acute hepatitis. Thus, a combination of necrosis, bridging and focal panlobular, and the inability of surviving cells to withstand insult results in death, albeit at a relatively slower speed than in acute fulminant disease.