Virchows Arch. A Path. Anat. and Histol. 363, 303–309 (1974)

Chronic Septal Hepatitis*

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Received April 20, 1974

Summary. A type of chronic hepatitis designated as chronic septal hepatitis was distinguished morphologically from chronic aggressive and chronic persistent hepatitis: 18 cases were separated from chronic aggressive hepatitis by the absence of destruction and inflammatory infiltration of the limiting plate and from chronic persistent hepatitis by the presence of connective tissue septa. Clinically, many patients were asymptomatic despite hepatomegaly and elevated serum transaminase activities while immune markers were usually absent from the serum. Chronic septal hepatitis was often seen after corticosteroid therapy of chronic aggressive hepatitis, but it also occurred de novo. Transition to cirrhosis was not observed during follow-up for 5 years to 2 months except in one case with high serum gamma-globulin. Until a classification based on etiology becomes available chronic septal hepatitis might be separated from other types of chronic hepatitis.

On the basis of histological criteria, chronic hepatitis has been divided into two types (De Groote *et al.*, 1968): (1) chronic persistent hepatitis characterized by chronic inflammatory infiltration of portal tracts with little or no piecemeal necrosis or fibrosis; (2) chronic aggressive hepatitis, characterized by chronic portal inflammation with destruction of the limiting plate and formation of fibrous septa. A subgroup showing necrosis or collapse bridging central canals and portal tracts (Boyer and Klatskin, 1970) or multilobular collapse (Baggenstoss *et al.*, 1972) has the greatest tendency of transition into cirrhosis. While reviewing over 200 biopsy specimens from patients with chronic hepatitis, we noticed a group of cases which differed from these two types. These cases showed chronic portal inflammation without destruction of the limiting plate and therefore could not be classified as chronic aggressive hepatitis. There was, however, formation of fibrous septa which is not a feature of chronic persistent hepatitis. These cases were designated as "chronic septal hepatitis". This communication describes the histological features of this type of chronic hepatitis and presents the clinical and laboratory data and follow-up information of these patients. In addition, a morphologic classification of chronic hepatitis (Popper and Schaffner, 1971) is presented in an attempt to place chronic septal hepatitis into proper context.

Material and Methods

The 18 cases described here were part of an ongoing study of chronic hepatitis. In 5 patients one liver biopsy specimen was available for review, in 10 patients 2 and in 3 patients 3 speci-

* This work was supported by Grant AM 03846 from the National Institute of Health.

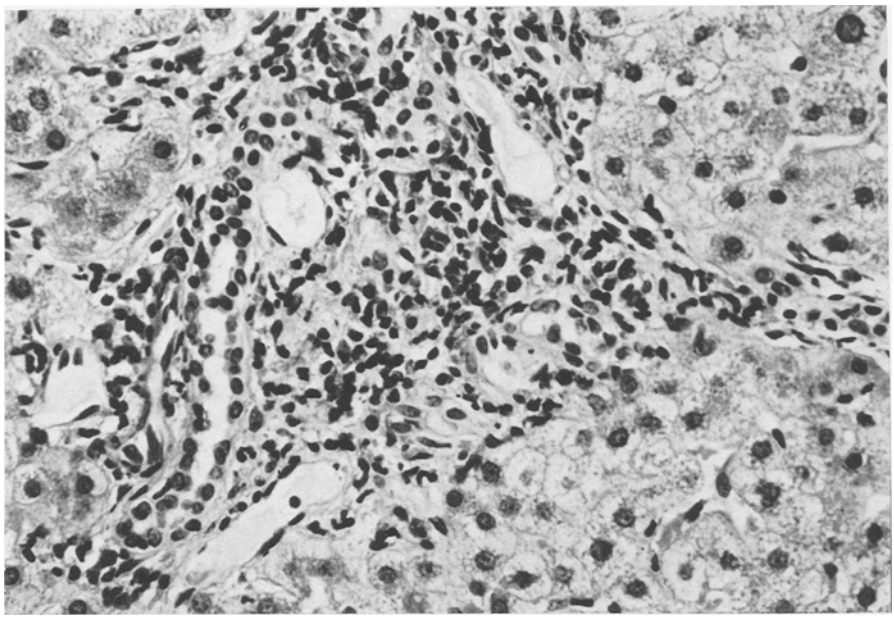

Fig. 1. The portal tract is enlarged and infiltrated predominantly by lymphocytes. There is little piecemeal necrosis and the lobular parenchyma is intact. (× 250, hematoxylin and eosin)

mens. Needle biopsy specimens were fixed in 10 per cent buffered formalin. Paraffin sections were stained with hematoxylin and eosin and with chromotrope aniline blue for connective tissue. All patients were followed by one of us. Additional clinical data were obtained from the patients' hospital charts. The following laboratory tests were performed on all patients' sera: bilirubin, alkaline phosphatase activity, albumin, globulin, transaminase activities, mitochondrial and smooth muscle antibodies and antinuclear factor as determined by the indirect fluorescent antibody technique (not performed on one patient) and hepatitis B antigen (HB Ag) by radioimmunoassay and immunoelectroosmophoresis. The patients were followed for 2 months to 5 years. The histological findings and the clinical and laboratory data were compiled independently and then correlated with each other.

Results

Eighteen liver biopsy specimens showed a combination of histological features which are not seen in chronic persistent or chronic aggressive hepatitis. These were chronic portal inflammation without erosion of the limiting plate, but with formation of fibrous septa. The portal tracts were moderately enlarged and infiltrated predominantly by lymphocytes, mixed with plasma cells and macrophages (Fig. 1). The inflammatory cells did not extend into the adjacent liver parenchyma and the limiting plate was intact. There was little bile ductular proliferation and no ductal destruction. Fibrous septa of varying length extended from the portal tracts into the parenchyma, but only rarely reached the central veins or adjacent portal tracts. The septa were usually straight and thin (Fig. 2) and often contained a bile ductule (Fig. 3), but only few inflammatory cells.

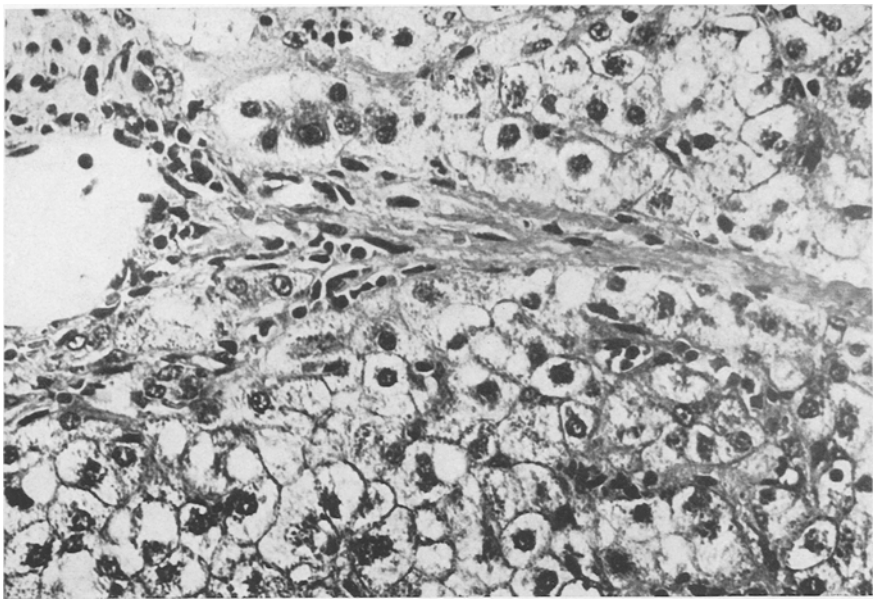

Fig. 2. A thin straight septum extends from the portal tract into the lobular parenchyma. There is little inflammatory infiltration. (× 250, chromotrope aniline blue)

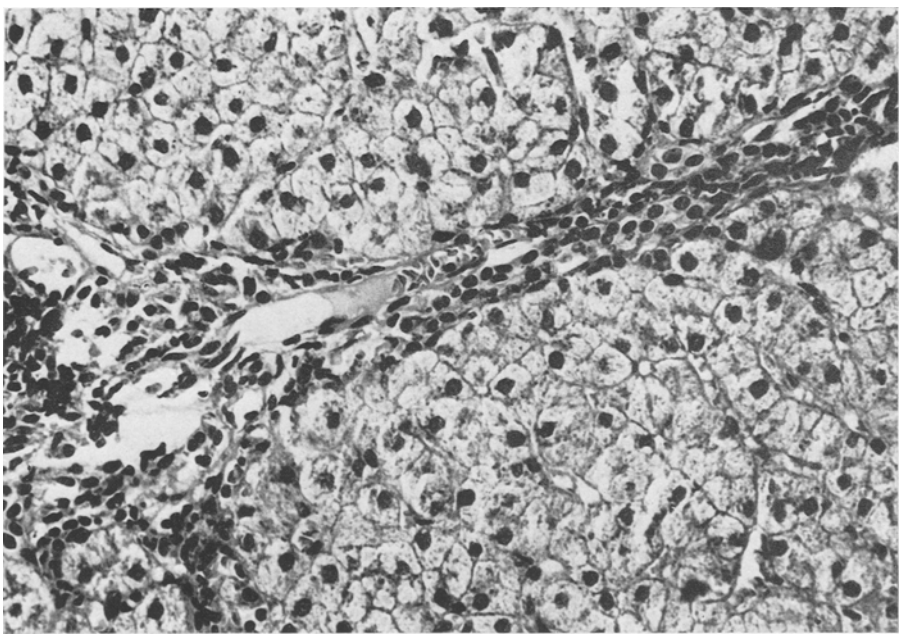

Fig. 3. This septum contains a bile ductule. Inflammatory infiltration is mild. (× 250, hematoxylin and eosin)

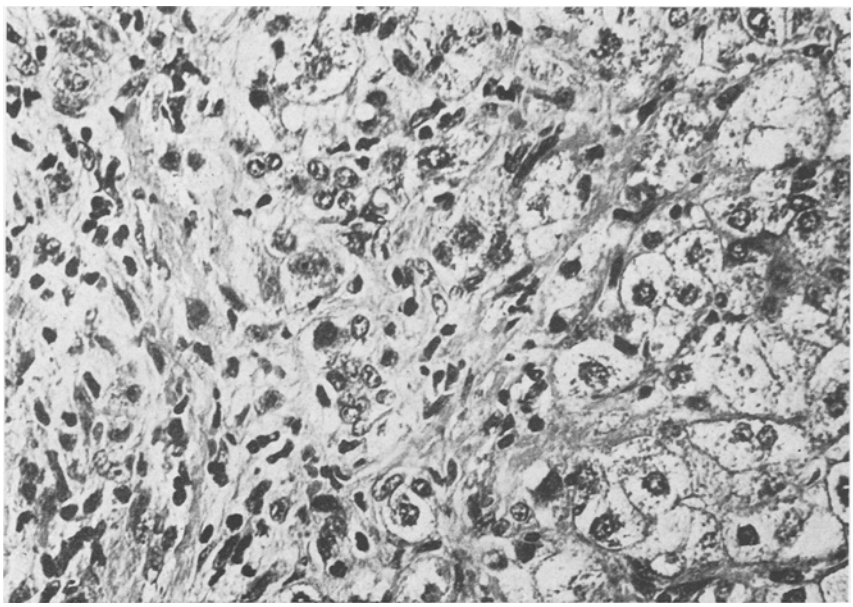

Fig. 4. Irregular fibrous bands extend from the portal tract into the lobular parenchyma and surround hepatocytes. (× 250, chromotrope aniline blue)

Exceptionally, the septa were curved. Irregular perihepatocellular fibrosis resulting in step-like septa with trapping and acinus or rosette formation of hepatocytes was seen in two specimens (Fig. 4). The hepatic parenchyma showed occasional necrosis of single hepatocytes with focal accumulation of inflammatory cells and mild activation of the sinusoidal lining cells. There was no evidence of diffuse hepatocellular damage, of cholestasis, of acidophilic bodies or of increased regeneratory activity.

Nine patients showed chronic aggressive hepatitis on biopsy specimens obtained one to $2^1/_2$ years earlier, 3 of them with confluent necrosis bridging central canals and portal tracts. Three patients showed no significant change of chronic septal hepatitis on specimens 4 months to 2 years apart, however one patient revealed chronic aggressive hepatitis with transition to cirrhosis 11 months after a biopsy had disclosed chronic septal hepatitis. This patient had elevated serum gamma-globulin (2.66 g per 100 ml) initially and strongly positive mitochondrial antibodies. Finally, one patient showed metastatic adenocarcinoma on a liver biopsy specimen 5 months after the diagnosis of chronic septal hepatitis had been made.

Clinically (Table 1), 8 patients were symptomatic when the diagnosis of chronic septal hepatitis was made, however, the vast majority of patients had hepatomegaly and/or elevated serum alkaline phosphatase activities (up to 300 mU/ml; normal up to 85 mU/ml) and/or transaminase activities (up to 200 mU/ml; normal up to 40 mU/ml). Serum gamma-globulin was elevated above 2.5 g per 100 ml in one patient who subsequently developed chronic aggressive

Table 1. Clinical and laboratory data of 18 patients with chronic septal hepatitis

Case number	Age	Sex	Symptoms	Hepato-megaly	Serum activities of Alkaline phospha-tase	Trans-aminases	Tissue anti-bodies[c]	HB Ag	Cortico-steroid therapy
1	49	F	—	−	↑	N[a]	ANA++	−	+
2	18	M	fever, abdominal pain	+	N	↑	—	−	−
3	60	F	fatigue	+	N	↑	—	−	−
4	56	M	—	−	N	↑	—	−	−
5	25	F	—	−	N	↑	—	−	+
6	19	F	arthralgias	+	↑	↑	—	−	+
7	66	M	—	+	↑	↑	—	−	−
8	36	F	—	−	↑	↑	ASM+	−	+
9	32	M	fever, colitis	+	↑	↑	—	−	+
10	58	M	colitis	−	↑	↑	—	−	+
11	21	F	—	−	N	N	—	−	+
12	48	F	abdominal pain	+	↑	↑	AMA++	−	+
13	22	F	—	−	N	N	—	−	+
14	55	M	abdominal pain	+	N	N	—	−	+
15	35	M	fever, arthral-gias, skin rash	+	N	↑	—	+	+
16	8	M	abdominal pain arthralgias	+	↑	↑	—	−	+
17	77	M	—	+	N	↑	ND[b]	−	+
18	27	M	—	−	N	↑	—	+	+

[a] N = normal.
[b] ND = not done.
[c] Antinuclear (ANA), smooth muscle (ASM) or mitochondrial (AMA) antibodies.

hepatitis with transition to cirrhosis. Serum antibodies to mitochondria, smooth muscle or nuclei and HB Ag were infrequent. Fourteen patients were on corticosteroid therapy. All are asymptomatic five years to two months after establishing the diagnosis except for one patient who has a metastatic carcinoma of unknown origin, one with progressive systemic sclerosis and one with recurrent fever.

Discussion

The cases presented here were separated by morphologic criteria from the other types of chronic hepatitis (De Groote *et al.*, 1968). They represent a histologically distinct group because of the presence of septa accompanied by portal inflammation without destruction or inflammatory infiltration of the limiting plate (piecemeal necrosis) and without significant inflammatory activity in the lobular parenchyma. The septa formation suggests that the inflammatory process had extended previously beyond the boundary of the portal tracts and therefore represents a morphologic component not present in chronic peristent hepatitis. This is supported by the chronic aggressive hepatitis documented on previous biopsies in 9 patients. The name "post hepatitic scarring" is not proposed because the persistence of inflammatory changes in the portal tracts may not be con-

Table 2. Morphologic classification of chronic hepatitis

Morphologic term	Present term	Lobular parenchyma	Portal tracts	Transition into cirrhosis
Portal[a]	Persistent	Minor spotty necrosis Kupffer cell activation	Chronic inflammation	Rare[b]
Periportal	Aggressive	Destruction of limiting plate Periportal inflammation Fibrous septa	Chronic inflammation	Sometimes
Lobular	Subacute hepatic necrosis	1. Diffuse hepatitis 2. Bridging necrosis 3. Multilobular necrosis	Chronic inflammation	Frequent
Septal	?	Fibrous septa	Chronic inflammation	Rare[b]

[a] Sometimes it may be difficult to separate chronic portal hepatitis from non-specific portal inflammation or from residual changes or recurrent and protracted forms of acute viral hepatitis (Bianchi *et al.*, 1971).
[b] Patients with hypergammaglobulinemia may develop cirrhosis (Popper *et al.*, 1973).

sistent with this term. The name "chronic septal hepatitis" permits recognition of both features, inflammation and fibrous septa, and is also helpful as a supplement to the morphologic classification of chronic hepatitis (Table 2). Fibrous septa may result from active fibroplasia around damaged hepatocytes which are often arranged in acini or rosettes. These septa are irregular and step-like, whereas septa around bile ductules are straight or slightly curved. In contrast to such active septa, passive septa may develop after collapse. They are straight if they follow confluent necrosis bridging central canals and portal tracts or they represent broad fibrotic areas if they follow multilobular necrosis. There is, however, reason to believe that secondary fibroplasia may take place after collapse (Kent *et al.*, 1959).

The morphologic distinction of a group of cases calls for a description of the clinical features of the patients which might characterize the group as an identifiable entity. Only few patients with chronic septal hepatitis are symptomatic with non-specific complaints, however, the majority has hepatomegaly and elevated serum transaminase activities. Immune markers such as antibodies to mitochondria, smooth muscle or nuclei and HB Ag are infrequently detected in the serum. Many patients have been treated with corticosteroids, often for chronic aggressive hepatitis. This suggests that chronic septal hepatitis may be a regressing form of chronic aggressive hepatitis, particularly if the inflammatory response is suppressed by corticosteroid therapy, but it may also occur de ovo without iatrogenic immunosuppression. The prognosis appears to be good if the serum gamma-globulin level is normal since only one patient in this series developed cirrhosis so far. Chronic hepatitis may be caused by a variety of etiologic factors some of which are known and then included in the diagnostic term, such as chronic alcoholism or metabolic disorders. Frequently, however, the etiology and pathogenesis of chronic hepatitis are not clearly established, e.g.

in chronic hepatitis following suspected viral hepatitis or in drug hepatitis. Until the etiology of the different types of chronic hepatitis is firmly established, classification will have to be based on clinical manifestations including prognosis or on morphologic criteria. The latter can be applied more objectively since a liver biopsy is usually available.

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