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CASE REPORT

Giant Cell Hepatitis in Adults

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Giant cell hepatitis is a frequent reaction of the liver to different injuries in newborns and in childhood, but rare in adults. This form of hepatitis is often accompanied by cholestasis and shows fast progression to cirrhosis. In most cases autoimmune, metabolic, toxic or viral origin can be found, but sometimes the etiology remains hidden. This paper introduces two adult giant cell hepatitis cases. Hepatitis C virus infection was the possible origin in the first case and autoimmune disease in the other one. (Pathology Oncology Research Vol 3, No 3, 215–218, 1997)

Key words: giant cell, hepatitis, adult

Introduction

Giant multinucleated hepatocytes are common and characteristic alterations in liver diseases of infancy and childhood, especially in those caused by infectious agents, intra- and extrahepatic biliary atresia, genetic and metabolic alterations.[10,11,19,26,35] The appearence of giant hepatocytes (GHC) is a non-specific tissue reaction of immature liver to different injuries, but GHC is rare in adults. Hepatitis associated with GHC in adults is called "post-infantile giant cell hepatitis" (PIGCH) or "syncytial giant cell hepatitis" (SGCH).

In the past five years, we observed PIGCH in two cases, out of approximately 1000 liver biopsy samples with acute or chronic hepatitis. The rare occurance and uncertain etiology of this form of hepatitis explain the detailed discussion.

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Abbreviations: ALAT: alanine aminotransferase; ALP: alkaline phosphatase; ANA: antinuclear antibody; AMA: antimitochondrial antibody; ASAT: aspartate aminotransferase; ELISA: enzyme-linked immunosorbent assay; GCH: giant cell hepatitis; GGT: gamma-glutamyl transpeptidase; GHC: giant hepatocyte(s); HBsAg: Hepatitis B virus surface antigen; HCs: hepatocytes; HCV: hepatitis C virus; HLA: Human Leukocyte Antigen; IgG: immunoglobulin; LSP: liver specific lipoprotein; MU: million unit; PIGCH: post-infantile giant cell hepatitis; Se Bi: serum bilirubin level; SGCH: syncytial giant cell hepatitis; SMA: anti-smooth muscle antibody; WBC: white blood cells

Case reports

Case 1

Sz. A. 60 year old female. From her clinical history: 1975, myoma uteri, total hysterectomy because of metrorrhagie, several tranfusions; 1976, chronic "non-A, non-B hepatitis"; 1992, January, weight loss, jaundice. Laboratory data are summarized in *Table 1.* (Note, that anti-HCV and autoimmune antibodies were positive.) Treatment: (Febr, 1992) i.v. vitamin K (Konakion), adrenocorticotropic hormone (3x Cortrosyn Depot), (Febr-March, 1992) ranitidine (2x1 Ulceran), antacids, (March, 1992) 3x per week 2 MU Interferon $_{2a}$ for 4 weeks. Follow up: hepatorenal syndrome, hepatic coma, exitus. *Histology* (liver biopsy; Febr, 1992): Disturbed liver architecture, pseudolobulus formation. Severe inflammatory infiltration by lymphocytes and plasma cells in the portal, periportal area and in the lobules. Large number of giant hepatocytes with 4-15 nuclei, and extended eosinophilic cytoplasm. Accumulation of intracanalicular and intracytoplasmic bile pigment *(Fig. 1).* Diagnosis: Giant cell hepatitis with incomplete septal cirrhosis. *Autopsy:* Cirrhosis micronodularis hepatis, with giant cell transformation. Nephrosis cholemica.

***Table 1.* Case 1. Laboratory data**

se bi (all)	181-495 mM/l	*se bi (direct)*	131–410 mM/l
ALAT	116-130 U/l	*anti-HCV-1,2 (Elisa)*	positive
ASAT	82-167 U/l	*HBsAg (Elisa)*	negative
GGT	10-16 U/l	*ANA, AMA, SMA*	positive
ALP	47-55 U/l	*anti-LSP IgG*	positive

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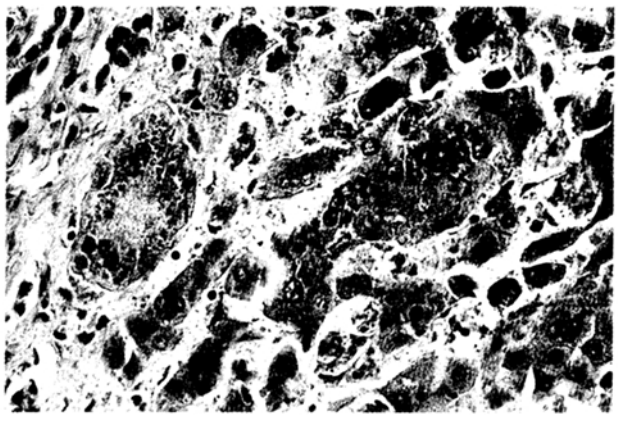

Figure 1. *Multinucleated giant hepatocytes with extended eosinophilic cytoplasm, severe cholestasis and disturbed liver architecture in an autopsy sample. (Case 1 – HE staining, x400)*

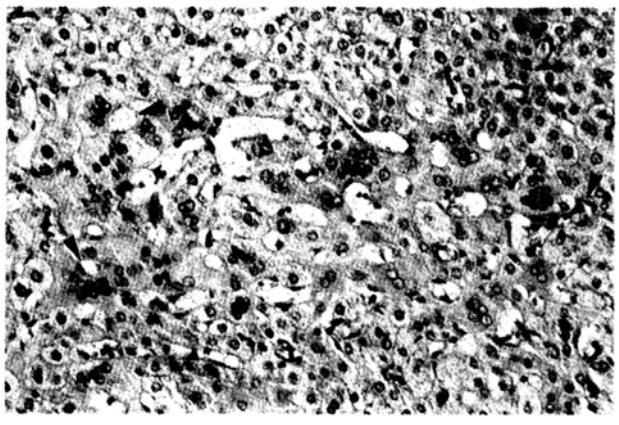

Figure 2. *Characteristic multinucleated giant hepatocytes in a midzonal area. The hepatocytes show a fusion around several hepatic sinusoids (arrowhead). (Case 2 – HE staining, x250.*

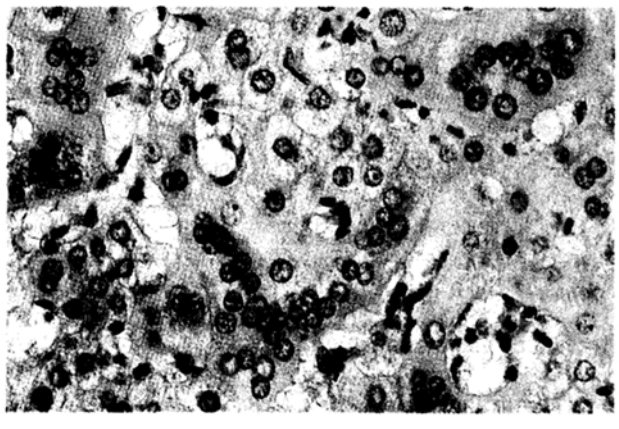

Figure 3. *Multinucleated giant hepatocytes at high magnification. (Case 2 – HE staining, x500.)*

Case 2

K.Cs. 23 year-old female. From her clinical history: 1991-92: focal leukoderma, repeated episodes of diarrhea; 1992-93: slight hepatomegaly, leukopenia after taking oral contraceptives, subfebrility of unknown origin; 1994: tonsillectomy; 1995: Jan. Polyarthritis; Febr. epigastrial pain; hepato- spleno and lymphadenomegaly. Previous medication: oral contraceptives (1992-93), ranitidine (Febr-June, 1995), isotretinoine. Recent medication (since June, 1995): silibinin (3x1 Legalon), ursodeoxycholic acid (3x1 Ursofalk), antacids. Laboratory data are summarized on *Table 2.* (Note negative viral markers and anti-nuclear antibody positivity!)

Histology: Disturbed liver architecture, without complete pseudolobulus formation. Increased amount of connective tissue, inflammatory infiltration mainly with lymphocytes. Interface hepatitis. Large number of syncytial giant hepatocytes with 4-30 nuclei. (*Figs 2, 3*). Diagnosis: chronic hepatitis with moderate/severe activity, GHC-formation, septal fibrosis.

Discussion

The formation of giant hepatocytes is a non-specific reaction of usually immature liver to different noxas with unknown pathomechanism. Some authors suggest fusion of injured hepatocytes as a way of forming giant hepatocytes,[5,13,31,32] similar to viral infections.[32] Others believe the giant cells to be the result of regeneration, plasma division without mitosis (endomitosis).[8,27,28]

Adult hepatocytes (HCs) are different from the HCs of infants in several aspects, e.g. in adults they have lower

Table 2. **Case 2. Laboratory data**

	02. 95	*04. 95*	*06. 95*	*09. 95*	*11. 95*	*01. 96*
ALAT						
(5-40 U/l)	457	92	119	247	116	68
ASAT						
(10-37 U/l)	317	87	113	190	97	97
GGT						
(7-50 U/l)	112	56	57	56	49	34
ALP						
(98-279 U/l)	446		359	515	430	284
Amylase						
(50-200 U/l)	355	402	385	518	413	
WBC						
(4-10 G/l)	2.4	2.9	3.2	3.5	3.4	3.4
ANA			pos			
HBsAg	neg		neg			
Anti-HCV	neg		neg			
se bi						
(5-25 M/l)	20		16	13	9	9

Table 3. **Etiological factors and other diseases related to PIGCH**

Autoimmune
Autoantibody positivity (ANA, AMA, ASMA)[4,16,24,25,31,33]
Autoimmune hemolytic anemia[4,21,22,24,34]
Rheumatoid arthritis[12]
Lupus erythematosus[4,6]
Colitis ulcerosa and primary sclerosing cholangitis[16]
Virus
Hepatitis A[16]
Hepatitis B[16]
non-A, non-B hepatitis[4,17]
Hepatitis C[16]
Epstein-Barr (EBV)[16]
Paramyxovirus?[24]
Chemicals
p-Aminosalicylic acid[29]
Methotrexat[3,7]
6-Mercatopurin[18]
Chlorpromazin[30]
Clometacin[23]
Amitrytylin, chlorodiazepoxide[4]
Vinylchlorid[1]
Other
Sickle cell anemia[20]
Hypereosinophilia[15]
Kugelberg-Welander syndrome[4]
Sarcoidosis[4]
Lymphoma[4]
Hypoparathyreoidism[9]
Liver transplantation[21]

regenerative capacity but a more efficient metabolic enzyme system. This could explain why the same noxa can cause giant cell formation in infants and not in adults. Giant cells might be formed in immature liver by fusion of the apical poles of HCs arranged around the dilated bile canaliculi.[13] The same effect in adult liver causes death of HCs because of weaker regenerative capacity. Giant cells are formed commonly in infancy during metabolic disorders[10,11] but do not in adults. This might be associated with the more mature enzyme system and cytoskeleton but decreased regenerative capacity.

It is known that several viruses, especially paramyxoviruses, can induce syncytial giant cells. Phillips and coworkers detected paramyxovirus-like particles by electron microscopy in the cytoplasm of giant hepatocytes in 8 syncytial giant cell hepatitis cases (2 infants, 3 children above 10 year and 3 adults).[24] Liver homogenate derived from one of the patients caused increased titer of antiparamyxoviral antibody when injected into chimpanzes.[24] Others do not accept that such are viral constituents.[14,36] Hepatitis A, B, C and Epstein-Barr virus have been also observed causing giant-cell hepatitis in adults[16] (*Table 3*). Both recurrent and de novo giant cell hepatitis have been noticed after liver transplantation,[21] where all the above mentioned viruses have been excluded.[21] Autoimmune disorders have been suggested to cause adult giant cell hepatitis.[2] In these cases, the injury of the cell membrane and the cytoskeleton could be responsible for the fusion of hepatocytes.

Several drugs and chemicals were found to cause giant cell hepatitis[1,3,7,18,23,29,30] (*Table 3*). It is important that all the above mentioned etiological factors do not cause giant cell hepatitis in the majority of cases. Therefore, other pathogenetic factors (such as specific HLA-type, genetic variations of membrane or cytoskeletal proteins, increased regenerative activity of hepatocytes etc.) could contribute to the formation of giant hepatocytes.

"Typical" clinical features of adult giant cell hepatitis were observed in Case 1: a prolonged clinical course, severe cholestasis, and progression to cirrhosis within a few months.[2] The functional capacity of the liver is maintained at the beginning of GCH, because the giant cells are metabolically active, but their life span is shorter than the normal HCs and their continuous death causes architectural disturbances.[31,32] Both HCV infection and autoimmune reactions were present in Case 1. Seventeen years after the HCV infection the activity of the hepatitis suddenly increased for unknown reasons, accompanied by a severe cholestasis. The decompensation of the parenchymal cirrhosis led to the lethal end. In Case 2, only autoimmune features appeared with no signs of viral infection. Here, the giant cell hepatitis ran a much milder clinical form, without cholestasis, but with an already altered histology. In the liver biopsy the syncytial giant cells showed a fusion around the sinusoids in the periportal or midzonal area (*Fig. 2*), induced probably by the blood-transported antibodies.

In conclusion: the etiology of the adult giant cell hepatitis is not certain, several factors may play a role in its occurrence, and the presence of hepatocyte originated giant cells are the unique criteria of the diagnosis.

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