Giant Cell Transformation of the Liver in Chronic Hepatitis with Confluent Lobular Collapse (Report of A Case)

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Abstract: We present a case of diffuse giant cell transformation of the liver in an adult male patient with known chronic active hepatitis who recently developed confluent lobular collapse. The patient was a 41-year-old man with known chronic liver disease under close follow-up for 5 years, who was recently given 400 packs of unknown herb medicine for newly developed duodenal ulcer. Subsequently slow progressive abnormalities of liver function test developed. Hepatic needle biopsy showed considerably compromised lobular architectures by the features of chronic active hepatitis with superimposed multifocal lobular collapse and diffuse replacement of hepatocytes by multinucleated giant cells. Many giant cells showed intracytoplasmic accumulation of protein-bound copper pigments and canalicular cholestasis. A cytoplasmic mosaic pattern of stainability was partly related to the amount of glycoprotein in the liver. Chronic active hepatitis with multifocal lobular collapse seems to be another causative form of giant cell transformation of hepatocytes in adulthood, and this phenomenon is assumed to reflect reparative process of immature hepatocytes following lobular collapse.

Key words: Giant cell transformation, Chronic active hepatitis, Confluent lobular collapse, Liver, Adulthood

INTRODUCTION

Giant cell transformation of the liver is a characteristic feature of neonatal hepatitis involving the near-total population of hepatocytes, but is also a morphological reflection in cases of congenital biliary atresia and several toxic injuries in the neonates and infants as well (Craig and Landing 1952; Schaffner and Popper 1963). However, such giant cell reaction in adults seems a rare reparative process of hepatocytes to a variety of parenchymal injury and is found occasionally, though spotty in distribution, in cases of acute viral hepatitis or other hepatic process including drug-induced hepatitis (Montgomery and Rueba 1976). Furthermore, diffuse giant cell transformation in the adult is a quite unusual manifestation, and even its association with chronic active hepatitis seems extremely rare (Schmidt and Cueni 1972; Richey et al. 1977). We present a case of diffuse giant cell transformation of hepatocytes in adult with chronic active hepatitis modified by confluent lobular collapse.

CASE

A forty one-year-old man with 5 year history of chronic liver disease was admitted to Seoul National University Hospital (SNUH) on April 12, 1983. He was first seen 5 years before admission (May, 1978) at SNUH because of fatigue, right upper quadrant pain and dark urine which appeared one

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year before the visit. Physical examination at that
time was significant for a palpable soft liver 3 cm
below the right lower costal margin. No other hepatic
stigmata were found. Serum protein was 7.3
gm%, albumin 4.8 gm%, alkaline phosphatase 5.2
King-Armstrong unit, SGOT 215 IU/l, SGPT above
126 IU/l, and total bilirubin 0.31 mg%. Serum
HBSAg was negative, and no urinary abnormality
was detected. The initial clinical diagnosis was per-
sistent viral hepatitis and he was under the regular
follow-up observation with administration of hepa-
totics. In March, 1980, he was seen at the Out-
patient Clinic with mild jaundice and turbid urine.
Liver edge was palpable. SGOT was 85 unit, SGPT
169 unit, and alkaline phosphatase 8.5 King-
Armstrong unit. Serum HBSAg was negative, and
urinalysis was normal.

He remained relatively well thereafter until five
months before admission, when a dull hunger pain
developed in the perigastrium. Gastric endoscopic
examination showed an active duodenal ulcer, and
the patient was treated with antacid until one
month before admission. During the period he had
a history of frequent attacks of upper respiratory in-
fecion and epistaxis, and more than 400 packs of
herb medicine containing Yak-suk and other un-
known substances were administered. One day be-
fore admission physical examination showed the
patient to have a firm hepatic edge 5 cm below the
right margin. The spleen was not palpable. There
was no history of nausea, vomiting, melena or
blood transfusion.

On admission physical examination revealed a
temperature of 36.9°C, a pulse 100 and respira-
tions 22. The blood pressure was 100/70 mmHg.
Jaundice and spider angiomas were observed. The
abdomen was flat, and liver was palpable 5 cm be-
low the right costal margin with a firm and blunt
edge. Urinalysis was normal. Hemoglobin was 13.7
gm% and white cell count 7900/mm³ with a nor-
dmal differential count. The prothrombin time was
12 seconds and partial thromboplastin time 31
seconds. Urea nitrogen was 10 mg%, bilirubin 2.4
mg%, phosphorus 3.5 mg% and protein 7.1
gm%(the albumin 3.5 gm% and the globulin 3.6
gm%). SGOT was 240 IU, SGPT 132 IU, LDH 300
IU and alpha-fetoprotein 15 units. HBSAg was
negative but anti–HBS and anti–HBC were positive.

A radionucleide liver scan showed diffuse hepatic
enlargement and irregularly decreased uptake in
the left lobe. A peritoneoscopic examination
showed an uneven surface of the liver with a sharp
edge and firm consistency, a hypertrophic left lobe
and mild splenomegaly. A needle biopsy of the liver
was performed. During admission the levels of
SGOT/SGPT fluctuated, ranging from 316/144 to
363/185 IU/l and alkaline phosphatase was 270
IU/l (nl:30–115 IU/l). He was discharged April 12,
1983. One month after discharge he was seen at the
Outpatient clinic. Serum albumin was 2.5
gm%, bilirubin 5.5 mg%, SGOT/SGPT 250/120 IU/
l, alkaline phosphatase was 265 U. On September
7, 1983, SGOT returned down to 100 IU, SGPT 87,
and bilirubin 0.55 mg%.

PATHOLOGIC FINDINGS

Microscopically, the hepatic lobular architecture
was disrupted by confluent lobular collapse alter-
nating with islands of regenerating hepatocytes
(Fig. 1) Portal spaces were irregularly expanded
with heavy small round cell infiltration together with
close approximation of portal structures by col-
lapsed lobules and profound condensation of the
reticular framework.(Fig. 2) The remained lobular
unit disclosed the unevenly distorted limiting
plates by active piecemeal necrosis aside from
scattered portal to central type of bridging necrosis.
The modified hepatic lobules were largely made of
pleomorphic, bizarre and multinucleated hepato-
cytes measuring up to 80 μ in the greatest di-
ameter, and each cell contained many nuclei rang-
ing from 5 to 22. The cytoplasm varied in stainabil-
ity but were generally eosinophilic and granular,
often containing hemosiderin and protein-bound
copper pigments by orcein staining.(Fig. 3–6) Each
of those multinucleated hepatocytes exhibited a
mosaic pattern of cytoplasmic stainability by
peripheral homogeneous eosinophilia and central
granularity corresponding to the amount of gly-
cogen and mitochondria.(Fig. 3) Nuclei were small,
round and contained a single prominent nucleolus,
and mitoses were rarely found.(Fig. 4) There were
scattered areas of hepatocytes to form acini or
rossette with occasional central canalicular bile
plugging. Each of giant cells was surrounded by a
well formed reticulin fibers and sinusoidal struc-
tures.(Fig. 5) Mononuclear hepatocytes were only
demonstrable in one area of less severe paren-
chymal loss.

DISCUSSION

The pathogenesis of giant cell transformation has
been the subject of much controversy, and various
etiological agents and factors have been listed, but
experimental back-up for its full understanding has remained inconclusive (Capembell and Gilbert 1967). Among the various infectious diseases, hepatitis B virus (HBV) infection may be a cause for such transformation but the establishment of giant cell transformation by HBV infection is extremely rare regardless of its chronicity, and even so, the pattern of giant cell response is only spotty in distribution. Schmidt and Cueni (1972) described 7 cases of giant cell hepatitis-like pattern in cases of acute viral hepatitis with submassive necrosis near the central veins as well as at the margins of the necrotic zones and septa.

In this case the serologic marker studies for HBV infection suggest an episode of HBV infection in the past. Since this patient's lesion lasted more than 5 years it might be regarded as a chronic viral hepatitis. Negative serum HBsAg but positive anti-HBs and anti-HBc at the time of study do not exclude chronic HB viral hepatitis; in fact, serum HBsAg is positive in only 73% of HB related chronic hepatitis in Korea (Kim et al, 1984), and 11.4% of chronic active hepatitis were only positive for anti-HBs and anti-HBc.

The most striking feature in this case is the complication of confluent lobular collapse or submassive hepatic necrosis in the regenerative phase, in which the role of herb medication should be considered. Herb medicine-induced hepatic injury is one of the most serious iatrogenic problems in Korea, often causing acute hepatic failure or massive hepatic necrosis by mechanisms of both cytotoxicity and hypersensitivity. Unfortunately the pharmacology of herbs prescribed by herb doctors remains unknown, and their modes of pharmacological action have been undetermined. In our institute we have found submassive hepatic necrosis in 10 out of 88 herb medicine-induced hepatitis (Kim et al. 1982).

The cytologic changes of giant cells are basically identical to those in neonatal hepatitis, biliary atresia, and other infectious or metabolic disorders, indicating that the lesion is nonspecific in its reaction to the hepatic injury (Elsner 1973). It is of interest, however, to note that multinucleated giant hepatocytes appear more often in human neonates than in adults, and similarly it is easier to create this reaction in the fetal or neonatal animal model than in the adult animal. Thus, this reaction seems to occur ontogenetically in younger cells in both human beings and animal model. In contrast to the spotty regenerative process and rapid turnover to mature hepatocytes during the usual evolutional process of HB viral hepatitis, submassive necrosis triggered by herb medication might result in multifocal regeneration of young hepatocytes which are easily transformed into giant cells. The reported cases of giant cell transformation in regard with HBV infection are mostly associated with submassive hepatic necrosis during the acute phase of viral hepatitis (Klemperer and Killian 1926; Schmidt and Cueni 1972).

Ultrastructural observation of giant cells suggests that they represent a regenerative process as they contain normal cytoplasmic organelles and abundant endoplasmic reticulum. Moreover, the absence of cell membrane remnants in the cytoplasm of multinucleated hepatocytes makes it improbable that they result from the union of several fused cells (Elsner 1973). The mозaic staining pattern of transformed giant cells is not a rare alteration of hepatic cytoplasm. It often manifests with polymerization of intracytoplasmic glycogen by delayed fixation or aberration of mitochondrial population; such an even stainability of giant cell suggests a different glycogenic density during the transformation. Increased protein-bound protein granules in the giant cells may reflect a feature of persisting cholestasis. Thus, our case may represent the clinico-pathologic consequences of a patient who started with zero-converted acute HB viral hepatitis with subsequent development of chronic hepatitis and superimposed submassive hepatic necrosis following herb medication. During this process newly regenerating immature hepatocytes became vulnerable to the same etiology for confluent necrosis, resulting in diffuse giant cell transformation. It seems unlikely that in our case giant cell transformation was caused by acute viral hepatitis with submassive necrosis, because in most giant cell hepatitis the lesions progress into cirrhotic phase or normalize within one year. It is crucial to study additional such cases to elucidate the natural history of giant cell transformation.

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응혈성 소염 암괴(의과사)를 동반한 만성 활동성 간염에 있어서의 간격세포 전환증

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성인형 미만성 간격세포 전환증은 극히 예외적인 형태학적 병변으로 간주되며 그 발생 기전을 이해하기 위해서 증례의 추적을 요구하고 있다. 또한 이러한 증례는 세계분열란 극히 드물며, 국내 문헌에는 전혀 보고되어 있지 않다. 저자들은 최근 다발성 고혈압사 예후를 동반한 성인 만성간염 증례에서 미만성 간격세포 전환증을 경험하였기에 그 발생 기전을 중심으로 검토하였다. 환자는 41세 남자로서 지난 5년간 만성 간질환의 병력을 가지고 추적 관찰되어 왔던 바, 병발된 소화성 계양에 대한 치료목적을 겸하여 복용한 네이오스의 항기독성 질환으로 자연적으로 악화되는 간기능 검사상의 변형을 바탕으로 간자세조영을 시행하였다. 간 조직은 만성 활동성 간염의 기본 조직상을 바탕으로 다발성 소엽괴사(의과사)를 동반한 조직상을 보였고, 간질 간세포도 미만성으로 다발성 간세포를 동반하여 있었다. 또한 다수의 간세포의 세포질내에는 단백질 혹은 독소의 축적과 아울러 모세혈관내 단백신체가 관찰되었고, 세포질의 모자막의 해식성은 당하로 및 사립 세포와 관련되어 해석하였다. 성인에 있어서의 간격세포 전환증의 발생기전을 미술 간행체의 수복성 재생기전과 관련 고안하였다.
LEGEND FOR FIGURES

Fig. 1. Photomicrograph of a needle biopsied hepatic tissue. Lobular disarray is quite profound and parenchmal injury is widespread. Bridging necrosis (arrow) is multifocal. (H&E, X40)

Fig. 2. Islands of regenerating multinucleated hepatocytes are separated by areas of lobular collapse and heavy portal inflammation. Piecemeal necrosis is clearly seen. (H&E, X100)

Fig. 3. The hepatocytes are large and multinucleated with a mosaic pattern of cytoplasmic stainability. Nucleoli are rather prominent. (H&E, X200)

Fig. 4. Multinucleated hepatocytes surrounded by sinusoidal structures. Number of nuclei ranges from two to nine per cell. (H&E, X400)

Fig. 5. Individual multinucleated hepatocytes are intervened with a well-formed reticulin framework. (Reticulin stain, X400)

Fig. 6. Two multinucleated giant cells. Note abundant, coarsely granular protein-bound copper pigments. (Orcein stain, X400)