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Giant Cell Transformation of the Liver in Chronic Hepatitis with Confluent Lobular Collapse (Report of A Case)[1]

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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 mozaic pattern of stainability was partly related to the amount of glycogen 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 collape.

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 hepatitic process including drug-induced hepatitis (Montgomery and Ruebner 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-Amstrong 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 persistent viral hepatitis and he was under the regular follow-up observation with administration of hepatotonics. In March, 1980, he was seen at the Outpatient 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 antiacid until one month before admission. During the period he had a history of frequent attacks of upper respiratory infection and epistaxis, and more than 400 packs of herb medicine containing Yak-suk and other unknown substances were administered. One day before 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 respirations 22. The blood pressure was 100/70 mmHg. Jaundice and spider angiomas were observed. The abdomen was flat, and liver was palpable 5 cm below the right costal margin with a firm and blunt edge. Urinalysis was normal. Hemoglobin was 13.7 gm% and white cell count 7900/mm^3 with a normal 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 alternating 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 collapsed lobules and profound condensation of the reticular framework.(Fig. 2) The remained lobular unit disclosed the unevently 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 hepatocytes measuring up to 80 μ in the greatest diameter, and each cell contained many nuclei ranging from 5 to 22. The cytoplasm vaired in stainability 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 mozaic pattern of cytoplasmic stainability by peripheral homogeneous eosinophilia and central granularity corresponding to the amount of glycogen 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 rosette with occasional central canalicular bile plugging. Each of giant cells was surrounded by a well formed reticulin fibers and sinusoidal structures.(Fig. 5) Mononuclear hepatocytes were only demonstrable in one area of less severe parenchymal 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 (Capmbell 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 hepatitits. 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 hypersenstivity. Unfortunately the pharmacology of herbs prescribed by herb doctors remains unknown, and their modes of pharmacological action have been undetermined. In our institution 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 multfocal 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 remmants in the cytoplasm of multinucleated hepatocytes makes it improbable that they result from the union of several fused cells (Elsner 1973). The mozaic 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 ueven 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 sero-converted acute HB-viral hepatitis with subsequent development of chronic hepatitis and supeirmposed submassive hepatic necrosis following herb medication. During this process newly regeneratring immature hepatocytes became vulnerable to the same etiology for confluent necorsis, 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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=국문초록=

융합성 소엽 압괴(교괴사)를 동반한 만성 활동성 간염에 있어서의 간거대세포 전환증

서울대학교 의과대학 병리학교실*, 내과학교실** 및 간연구소

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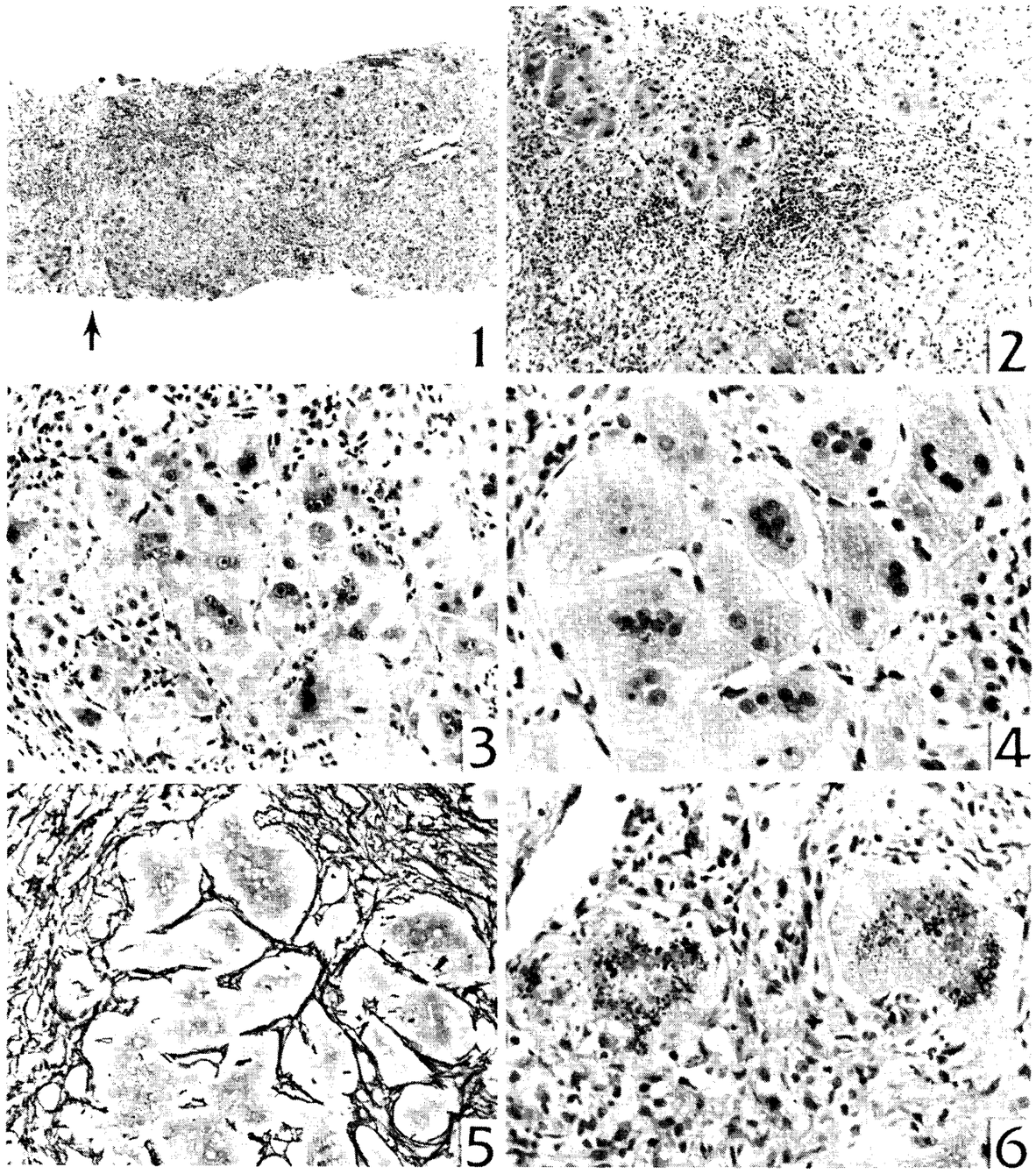
성인형 미만성 거대세포 전환은 극히 예외적인 형태학적 병변으로 간주되며 그 발생 기전을 이해하기 위해서 증례의 축적을 요구하고 있다. 또한 이러한 증례는 세계문헌상 극히 드물며, 국내문헌에는 전혀 보고되어 있지 않다. 저자들은 최근 다발생 교괴사를 동반한 성인 만성간염 증례에서 미만성 간거대세포 전환증을 경험하였기에 그 발생 기전을 중심으로 검토하였다. 환자는 41세 남자로서 지난 5년간 만성 간질환의 병력을 가지고 추적 관찰되어 왔던 바, 병발된 소화성 궤양에 대한 치료목적을 겸하여 복용한 내용미상의 한약과 관련하여 지속적으로 악화되는 간기능 검사소견을 바탕으로 간침생검을 시행하였다. 간 조직은 만성 활동성 간염의 기본 조직상을 바탕으로 다발성 소엽괴사(교괴사)를 동반한 조직상을 보였고, 잔존 간세포는 미만성으로 다핵성 거대간세포로 대치되어 있었다. 또한 다수의 거대세포의 세포질내에는 단백결합형 동색소의 축적과 아울러 모세담관내 담즙울체가 관찰되었고, 세포질의 모자익양 염색성은 당원량 및 사립체수와 관련지어 해석하였다. 성인에 있어서의 거대세포 전환증의 발생기전을 미숙 간세포의 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 collapese and heavy portal inflammation. Piecemeal necrosis is clearly seen. (H&E, X100)

Fig. 3. The hepatcytes 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)