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Spontaneous Regression of Hepatocellular Carcinoma -A Case Report-

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Spontaneous regression of cancer is a rare phenomenon seldom described in patients with hepatocellular carcinoma. A 54-year-old Korean woman suffered from cytologically-proved advanced hepatocellular carcinoma, for which she received no treatment. Papanicolaou's smears revealed high cellularity. Many clusters of polygonal cells showed long, thick anastomosing cords covered by flattened endothelial cells. The polygonal cells showed small hepatocytoid appearance, characterized by increased nuclear/cytoplasmic ratio. She remained in good clinical condition and, at 4 years of follow-up, the hepatocellular carcinoma could not be visualized radiologically. To date, only 14 case reports of apparently spontaneous regression of hepatocellular carcinoma have been published in the English literature. The mechanisms underlying this intriguing phenomenon remain unknown.

Key Words : *Hepatocellular carcinoma; Spontaneous regression*

INTRODUCTION

Hepatocellular carcinoma (HCC) is a malignant tumor frequently occurring in Koreans. It is well known that the prognosis of HCC is extremely poor. Most patients die within 3-6 months after diagnosis from gastrointestinal hemorrhage, progressive cachexia or liver failure[1]. Spontaneous regression of HCC is a rare phenomenon and has, to our knowledge, been described in very few patients[2-8]. The underlying mechanism of this regression is unclear. We report here a case of fine needle aspiration biopsy (FNAB)-proved HCC, with spontaneous regression demonstrated by imaging study.

CASE

A 54-year-old female was admitted because of burning pain in her right upper abdomen for 5 days, which tended to increase when she coughed or took a deep breath. Her past medical history had relevance to liver cirrhosis associated with hepatitis B virus. There was no known history of excessive alcohol intake, blood transfusion, exposure to hepatotoxic chemicals, family history of liver disease or oral contraceptive intake. She did not smoke. On physical examination, the right upper abdomen was tender and irregular hepatomegaly was noted 4 cm below the costal margin. Laboratory studies disclosed leukocytes $7 \times 10^3/\mu L$, hemoglobin 8.9 g/dL, Hct 25.1%, platelet $123 \times 10^3/\mu L$, total bilirubin 0.5 mg/dL, serum aspartate transaminase (AST) 55 IU/L, serum alanine transaminase (ALT) 44 IU/L, α-fetoprotein (αFP) 3-4 ng/mL, CA19-9 17 U/mL and CEA 6.1 ng/mL. Hepatitis B surface antigen was positive. Both abdominal ultrasonography and computed tomography showed a well-circumscribed space-occupying lesion in the right lobe, measuring 7 cm in the largest diameter (Figure 1).

Computed tomography-guided FNAB was performed at the mass. Papanicolaou's smears revealed high cellularity (Figure 2). Many clusters of polygonal cells showed long, thick anastomosing cords covered by

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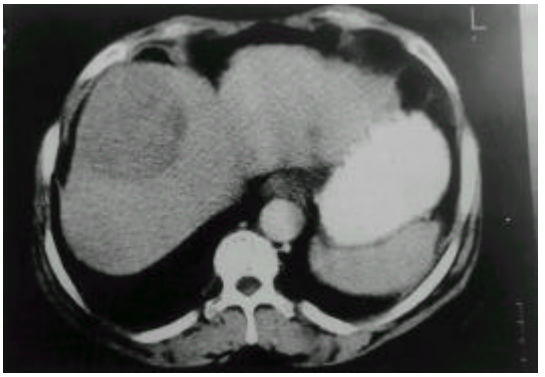

Figure 1. Abdominal computed tomography shows a well-circumscribed space-occupying lesion in the right lobe, measuring 7 cm in the largest diameter.

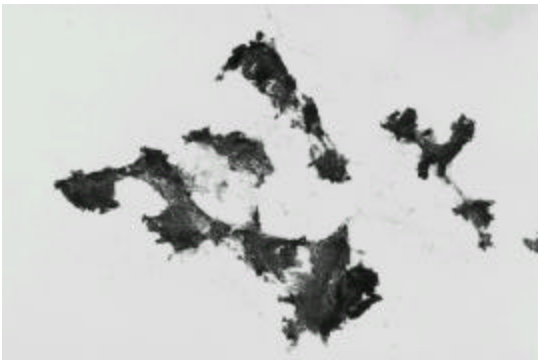

Figure 2. Papanicolaou's smears reveal high cellularity.

flattened endothelial cells (Figure 3). The polygonal cells showed small hepatocytoid appearance, characterized by increased nuclear/cytoplasmic ratio (Figure 3, inlet), and the cytologic diagnosis was a well differentiated hepatocellular carcinoma.

She refused further therapy and was discharged. Thereafter, she did not take any medical treatment or folk remedy. But she remained in good physical health during 4 years when she was admitted again because of nausea, vomiting and diffuse dull abdominal pain. On physical examination, her right hypochondrium was slightly tender, but no palpable mass was found. The laboratory findings were as follows: AST/ALT 53/31 IU/L, total bilirubin 1.9 mg/dL, αFP 5.3 ng/mL and CEA 4.4 ng/mL. Both abdominal ultrasonography and computed tomography showed no definite evidence of spaceoccupying lesion in the right hepatic lobe where the tumor was located, but only a vague wedge-

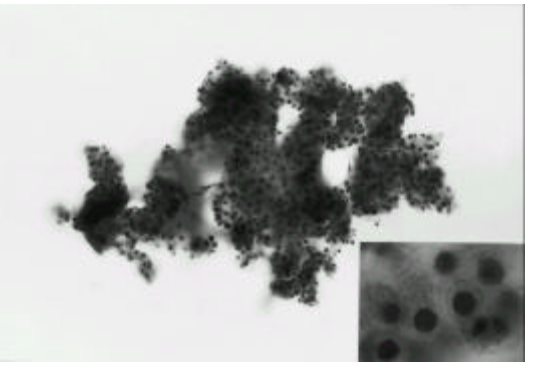

Figure 3. Many clusters of polygonal cells show long, thick anastomosing cords covered by flattened endothelial cells. The polygonal cells show small hepatocytoid appearance, characterized by increased nuclear/cytoplasmic ratio (inlet).

shaped area with low density was noted at the hepatic dome. The liver showed fine nodularity on the surface (Figure 4). No fine needle aspiration biopsy or needle biopsy was performed.

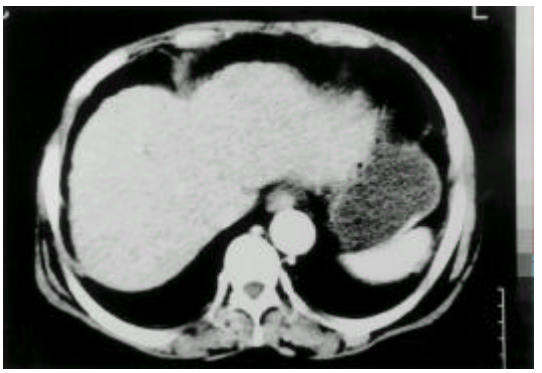

Figure 4. Abdominal computed tomography shows no definite evidence of space-occupying lesion in the right hepatic lobe where the tumor was located, and the liver shows fine nodularity on the surface.

DISCUSSION

Diagnosis of HCC in this case was based on suggestive imaging studies combined with FNAB. The cytologic findings of this case are high cellularity, trabecular pattern showing long, thick anastomosing cords

composed of small hepatocytoid cells characterized by increased nuclear/cytoplasmic ratio. FNAB is an increasingly popular means to evaluate liver mass and the accuracy of diagnosing HCC by liver FNAB has been reported to vary between 73% and 95%, with a mean of approximately 85%[9]. The most important cytologic criteria for the diagnosis of HCC are a markedly cellular smear, increased nuclear/cytoplasmic ratio, trabecular pattern, hepatocytoid appearance of tumor cells, endothelial lining, presence of bile, giant cells, intranuclear cytoplasmic inclusions and prominent nucleoli[10,11]. Well-differentiated HCCs are sometimes detectable mainly by the reduction in cytoplasmic size[12]. It is sometimes difficult to differentiate well differentiated HCC from hepactic adenoma and nonneoplastic liver by FNAB. Because the increased nuclear/cytoplasmic ratio and more thickened layer of cells arranged in a trabecular pattern are not observed in hepactic adenoma and nonneoplastic liver[10,11], we excluded the possibility of hepatic adenoma and nonneoplastic liver.

Spontaneous regression of cancer is estimated to occur once in 60,000-100,000 cancer patients[13]. With respect to HCC, only 14 cases have, to our knowledge, been published in the English literature to date[2-8]. Most patients were older men of either Asian or Caucasian origin. Five patients had serological evidence of viral hepatitis and one patient was a heavy drinker. Seven patients had histological evidence of liver cirrhosis. The size of the HCC ranged from 2.5 to 13 cm. In eight cases, tumor regression was histologically confirmed.

Biological explanations proposed for apparently spontaneous regression of cancer can be broadly categorized into hormonal influences, withdrawal of environmental factors required for tumor growth, selective deprivation of oxygen and nutrients, use of unconventional medicine and ill-defined immunological mechanisms altering host resistance[13]. Johnson *et al.*[4] reported a female patient with spontaneous partial regression of HCC after discontinuation of anabolic steroid. In this patient, spontaneous regression could be attributed to a fall in testosterone concentration and a decrease in peripheral conversion to estradiol. The development of HCC appears to be stimulated by estrogens or an increasing estrogen/ testosterone ratio. Imaoka *et al.*[5] reported a male patient with spontaneous regression of HCC, resulting from infarction due to arterial thrombus. HCC is a rapidly growing tumor and, therefore, highly dependent on its vasculature. This vasculature originates for the most part in the hepatic artery and tumor ischemia may acutely develop due to occlusion of a feeding artery. The two patients described by Lam *et al.*[3] and Chien *et al.*[7] had been taking herbal medicine, and they subsequently treated 20 and 25 patients with HCC with the same combination of herbs, respectively. Because tumor regression could not be detected in any of the patients treated, they concluded that it is unlikely that the herbal preparation had an effect on HCC. A fast-growing HCC in a poorly vascularized cirrhotic liver may become ischemic and necrotic on a more chronic basis. What factors, then, could have been involved in the regression of HCC in this patient? A follow-up biopsy or laparotomy was, unfortunately, not performed, but cirrhotic changes observed on imaging study could have caused ischemia, contributing to the spontaneous regression of the tumor.

In our opinion, well-documented cases of so-called spontaneous regression of cancer should continue to be brought to attention. Even though an individual history can not provide a complete explanation of the underlying mechanisms, accumulation of such data will contribute to further understanding of this rare phenomenon.

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