Hepatocellular Carcinoma associated Hemolytic Uremic Syndrome unrelated to Chemotherapy

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A 67-year-old man, diagnosed as hepatocellular carcinoma by percutaneous needle aspiration biopsy of liver mass, presented microangiopathic hemolytic anemia, thrombocytopenia and renal failure from the early phase of the illness. We could establish the diagnosis of cancer-associated hemolytic uremic syndrome which was unrelated to chemotherapy clinically. This is a rare case reported in adult hepatoma patients.

Key Words : Hepatocellular carcinoma, Hemolytic uremic syndrome.

INTRODUCTION

Hemolytic uremic syndrome (HUS) is a rare disorder which was first described by Gasser et al.(1955) as a disease mainly of infancy and early childhood and characterized by microangiopathic hemolytic anemia(MAHA), thrombocytopenia and acute renal failure.

HUS was first described in children but HUS has also been reported in adults (Byrnes et al., 1986) and HUS in adults is usually associated with infection, pregnancy(Segonds et al., 1979), malignancy or use of particular drugs(Byrnes et al., 1986; Magley et al., 1992).

In case of cancer-associated HUS, most cases have been reported in association with anticancer chemotherapy but cancer-associated HUS can occur de novo in some malignancies such as prostate(Van-Merwe et al., 1987 ; Multinovie et al., 1982 ; Eugene et al., 1987) stomach(Ortega-Marcos et al., 1985) and lung cancers(Avvento et al., 1988). Re-

cently we encountered a case of hepatocellular carcinoma(HCC) associated HUS in an adult which was not related to chemotherapy.

CASE REPORT

A 67-year-old man was admitted because of fever and right upper abdominal pain. The abdominal pain was continuous and dull in nature and had developed 3 weeks previously. Five months before admission, a routine medical examination including complete blood count, renal function test and abdominal ultrasonography was done, and no specific abnormality was detected. Three weeks prior to admission, fever and right upper abdominal pain developed and the pain became severe. So he visited another hospital and he was treated under the impression of pyogenic liver abscess and sepsis with ceftazidime, amikacin and metronidazole but his condition didn't improve. He was referred to our hospital for further evaluation.

He had no previous history of viral or alcoholic hepatitis or chronic liver disease. Physical examination revealed icteric skin and sclera and a distended abdomen with shifting dullness. The liver was tenderly palpated with 5cm-width at the midclavicular line below the right costal margin.

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Fig. 1. Peripheral blood smear shows normocytic normochromic red cells with some schistocytes and helmet cells(WrightX1000).

Fig. 2. Bone marrow aspiration smear reveals moderately hypercellular marrow with erythroid hyperplasia and an adequate number of megakaryocytes(WrightX400).

Fig. 3. Hepatocellular carcinoma. On CT, an ill-defined low density mass is identified in the anterior segment of the right lobe. The liver is enlarged With hypertrophy of the caudate lobe. See the linear low density area (arrow) along the posterior branch of the right portal vein and the round area (arrow-head) around the main portal vein, suggesting periportal edema associated with tumor.

Laboratory studies disclosed the following values : hemoglobin, 5.6g/dl ; leukocytes, 27.0×10^9 /L

(neutrophil 89%, lymphocyte 7%) ; platelets, 6×10^9 /L ; reticulocyte count, 4.3% ; plasma

hemoglobin, 60.1mg/dl(normal<5mg/dl) ; LDH 2732IU/L(normal 297-537IU/L) ; erythrocyte sedimentation rate, 21mm/hr(normal<10mm/hr) ; blood urea nitrogen, 143mg/dl ; creatinine, 6.6mg/dl ; prothrombin time, 21.3 sec (1.93 INR ; control, 12.4sec) ; activated PTT, 41.5sec (control, 29 sec) ; fibrinogen, 371mg/dl (normal 200-400mg/dl).

On peripheral blood smear, red blood cells looked normocytic and normochromic. Many schistocytes and helmet cells were noted (Fig. 1). Bone marrow examination revealed erythroid hyperplasia, adequate number of megakaryocytes and reactive plasmacytosis (Fig. 2). FDP, D-dimer and antiglobulin tests were negative.

Liver function test showed the following values : serum aspartate transaminase (AST), 50IU/L (nor-

mal<40IU/L) ; serum alanine transaminase (ALT), 11IU/L(normal<40IU/L) ; alkaline phosphatase, 146IU/L(normal 66-220IU/L) ; total bilirubin 28.8mg/dl(normal 0.2-1.2mg/dl) ; direct bilirubin 13.8mg/dl(normal 0-0.5mg/dl) ; α -fetoprotein<3ng/ml by radioimmunoassay (normal<20ng/ml).

HBs Ag was negative and anti-HBs was positive.

Both ultrasonography and abdominal CT showed hepatomegaly and a 13X8X10 cm sized low density mass in the right lobe of the liver(Fig. 3). Additional ill-defined smaller lesions were found in both lobes. No bacteria or fungus grew in the blood and liver aspirates. Percutaneous needle aspiration from the main mass of the liver showed poorly differentiated hepatocellular carcinoma (Fig. 4).

From hospital day 4 the patient's general condition was deteriorated rapidly so he was transferred to the intensive care unit and managed empirically with plasmapheresis and hemodialysis under the diagnosis of HCC-associated HUS.

Antiplatelet agents and corticosteroid were also tried but all in vain.

On the 10th hospital day, the patient became comatous and systolic blood pressure dropped down below 60mmHg in spite of infusion of inotropic agent. He died from circulatory collapse.

DISCUSSION

Cancer-associated HUS is characterized by MAHA, thrombocytopenia and renal dysfunction in cancer patients. Exclusion of sepsis and disseminated intravascular coagulation(DIC) is necessary to diagnose cancer-associated HUS because hemolytic anemia, thrombocytopenia, and renal failure can also develop in sepsis or DIC(Williams et al., 1991; Brenner et al., 1991). Our case also had some similarities with sepsis, and actually had been first treated under the impression of pyogenic liver abscess. But we could rule out sepsis and DIC by the early association of hemolysis and renal failure, negative culture results of blood and liver aspirate, and normal FDP and D-dimer tests. Another condition, which should be differentiated from cancer-associated HUS, is thrombotic microangiopathy associated with some vascular tumors(Donald et al., 1971 ; Inceman et al., 1969). This condition could be excluded by the absence of consumptive coagulopathy and the early appearance of severe renal dysfunction in our case.

Avvento et al.(1988) and Milford et al.(1993)

Fig. 4. Fine needle aspiration cytology discloses cellular smear composed of cell nests in a trabecular pattern or singly scattered neoplastic cells. Tumor cells are polygonal with abundant eosinophilic granular cytoplasm. Nuclei are round or lobulated, centrally placed, and have a prominent nucleolus. Green bile pigments are noted in the cytoplasm of tumor cells(arrows) (Hematoxylin & Eosin, X400).

categorized cancer-associated HUS into two groups. One is the group in which HUS occurs after receiving anticancer chemotherapy, and in the other group HUS occurs de novo, not associated with anticancer chemotherapy. Cancer-associated HUS unrelated to anticancer chemotherapy have been reported in patients with prostatic carcinoma (Van-Merwe et al., 1987; Multinovie et al., 1982; Eugene et al., 1987), gastric adenocarcinoma (Ortega-Marcos et al., 1985) and small cell lung cancer (Avvento et al., 1988).

Although the full spectrum and pathophysiology of cancer-associated HUS is not known, there are several possible explanations for the development of MAHA in cancer-associated HUS. Lohrman et al. (1973) and Antman et al. (1979) suggested that MAHA is secondary to trauma of erythrocytes circulating through microvessels with fibrin strands. The tumor produces procoagulant materials and subsequent DIC in microvessels. Erythrocytes transversing the web of fibrin are destroyed. Another explanation is the fragmentation of erythrocytes by contact with tumor emboli especially in the lung (Lohrmann et al., 1973; Antman et al., 1979).

In our patient the pathogenetic mechanism of MAHA is not clear but we think that the former mechanism is more probable than the latter because there was no evidence of lung metastasis or pulmonary embolism.

Cancer-associated HUS has been empirically treated by plasmapheresis, hemodialysis, corticosteroids, antiplatelet drugs and staphylococcal protein A immunopheresis (SPA) with diverse outcomes. The prognosis of cancer-associated HUS is usually poor in spite of aggressive therapy. According to Lesene et al. (1989), the favorable prognostic factors in cancer-associated HUS are cancer status at syndrome presentation and treatment with corticosteroids and SPA. Cantrell (1985) and Schieppati (1992) reported that severe renal involvement at the onset implied poor prognosis. Refractoriness to treatment in our patient was thought to be due to rapid progression of hepatoma and severe renal dysfunction.

In 1993, Milford et al. (1993) reported a case of HUS associated with HCC in a 7-year-old boy. This case had many clinical similarities with our case, in that initial presentation of hepatocellular carcinoma was severe MAHA, thrombocytopenia, azotemia and HUS were unrelated to anticancer chemotherapy, refractory to treatment and rapidly progressed to death.

These two cases of HCC associated with HUS suggest that there might exist a subset of hepatoma of unique biological behavior which rapidly progresses to a fatal outcome regardless of treatment and may be complicated by HUS. More clinical observations are needed to clarify this aspect.

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