Hepatoid Adenocarcinoma of the Stomach: A Case Report

Midenin Hepatoid Adenokarsinomu: Olgu Sunumu

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This study was presented at the 5th National Hepatology Congress, 05-07 June 2005, Istanbul

Abstract
Hepatoid adenocarcinoma is a rare variant of adenocarcinoma of the stomach with a very poor prognosis. Hepatoid adenocarcinoma is characterized by a distinct morphology and immunohistochemistry, clinically characterized by the increased level of serum alpha fetoprotein. Microscopic findings include both adenocarcinomatous and hepatoid elements. The diagnosis of hepatoid adenocarcinoma of stomach is not dependent on whether alpha fetoprotein is produced; actually, histological features are important for diagnosis.

Keywords: **Adenoma, Liver Cell; alpha-Fetoproteins; Neoplasm Metastasis; Stomach Neoplasms.**

Özet
Hepatoid adenokarsinom, midenin kötü prognozlu nadir bir adenokarsinom formudur. Hepatoid adenokarsinom farklı morfoloji ve immunohistokimya, klinik olarak artmış serum alfa fetoprotein düzeyleri ile karakterizedir. Mikroskobik bulgular hem adenokarsinom hem de hepatoid elementleri içerir. Midenin hepatoid adenokarsinom tanısı alfa fetoprotein üretip üretmediğine bağlı değildir; gerçekte, tanı için histolojik özellikler önemlidir.

Anahtar Kelimeler: **Adenom, Karaciğer Hücresi; alfa–Fetoprotein; Mide kanseri; Tümör Yayılımı**

Submitted : January 24, 2008
Revised : July 25, 2008
Accepted : August 06, 2008

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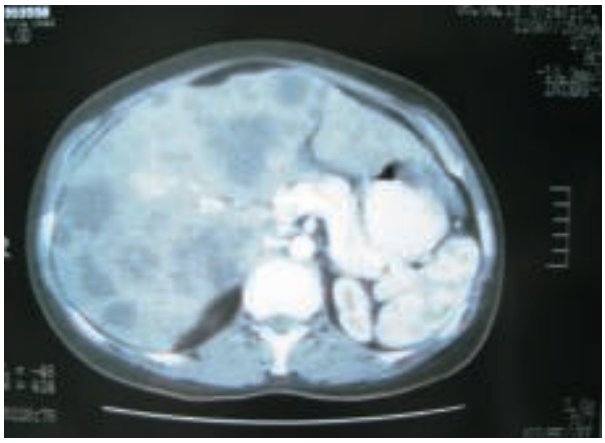
Introduction

Alpha fetoprotein (AFP) is an oncofetal protein and found normally in larger amounts during fetal development. It is synthesized in fetal liver, yolk sac and gastrointestinal tract. Synthesis usually stops at birth, and hence its presence in the serum after 1 year of age is associated with pathological conditions. AFP is correspondingly increased in about 80% of patients with hepatomas, 60% of patients with nonseminomous germ cell cancers and occasionally in patients with other cancers. Elevated levels may also be explained by nonmalignant liver diseases (e.g., hepatitis, cirrhosis and necrosis) (1, 2).

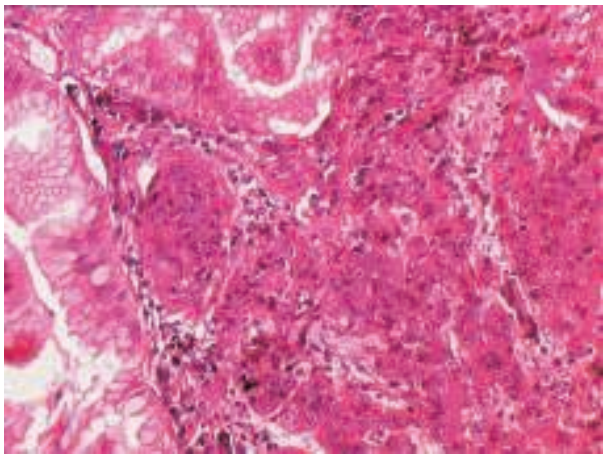
AFP-producing gastric tumors was first described by Bourreille in 1970. Since that time, other cases have been described and the incidence was reported to be 1.3%-15% of all gastric carcinomas (3). Ishikura et al (4, 5) proposed the term "hepatoid adenocarcinoma of the stomach" for primary gastric cancer with the histological features of hepatocytic differentiation and the production of large of amounts of AFP. We aimed to present this very rare and interesting case.

Case Report

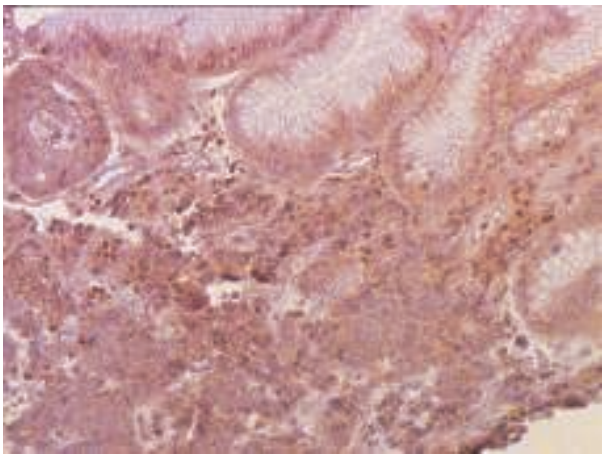
A 40-year-old Turkish woman, complaining of fatigue, loss of weight and abdominal pain, was admitted to our hospital. On physical examination, anemic conjunctiva and hepatomegaly was detected. Laboratory data showed anemia (hemoglobin 10.5 g/dl), low proteinemia (total protein 5.4 mg/dl) and slight liver dysfunction (aspartate aminotrasferase 114 IU/l and alanine aminotrasferase 61 IU/l). The serum level of AFP was elaveted (5000 ng/ml) but the levels of carbohydrate antigen 19-9 (CA19-9) and carcino-embryonic antigen (CEA) were within normal limits. Hepatitis B surface antigen and antibody, and hepatitis C antibody, were all negative. Endoscopic examination revealed an elevated tumor, extending from the antrum to the body of stomach. Gastric biopsy was also performed during endoscopic examination. Abdominal computed tomography (CT) and ultrasonography showed thickening antrum wall of stomach and multiple solid lesions in liver, highly suggestive of metastasis from gastric tumor (Picture 1). On the other hand, cirrhotic change was not observed. Microscopically tumor cells were well to moderately differentiated and arranged in a tubulo-papillary pattern. Tumor areas were characterized by cords of polygonal cells with an oval nucleus and prominent nucleoli, separated by a fine network of sinusoids. In these areas, the immunohistochemical profile was similar to that observed in hepatocellular carcinomas, in that the tumor cells were positive with AFP (Picture 2 and 3). There was a canalicular type of reactivity with polyclonal anti-CEA (pCEA) antibody. On the basis of these pathological and immunohistochemical findings, the tumor was diagnosed as hepatoid adenocarcinoma of the stomach. After diagnosis, she was treated orally with anticancer drugs tegafur-uracil with leucovorin and i.v. cisplatin. In spite of intensive chemothrerapy, the patient succumbed to her disease three months after diagnosis.



Picture 1. Image of the abdominal computed tomography showing multiple solid lesions in the liver.



Picture 2. Photomicrograph demonstrating tumor cells with abundant cytoplasm and centrally located nuclei. Tumor cells are arranged in a tubulo- papillary pattern.



Picture 3. Immunohistochemical staining. Tumor cell show patchy, strongly positive reaction for alfa-fetoprotein. Immunoperoxidase x200.

Discussion

AFP is an oncofetal glycoprotein that is produced by fetal liver yolk sac and gastrointestinal tract. Embryologically, the liver arises as a ventral outgrowth of the distal end of the fetal foregut. Due to the embryological proximity, it has been claimed that emergence of AFP producing hepatoid foci, or enteroblastic foci in gastric cancer, result from the dedifferentiation of the tumor cells to these progenitor cell types (2).

Hepatoid differentiation in neoplastic tumors occurs not only in primary hepatic carcinoma but also in other malignant disorders, particularly carcinomas. The stomach is the most common site of these tumors. AFP-producing neoplastic tumors have been reported in various organs; for instance, lung, pancreas, colon, bladder and ovary (3, 6).

Hepatoid adenocarcinomas are described to be primary extra-hepatic tumors resembling hepatocellular carcinomas and excessive production of AFP. There are two histological types of AFP-producing gastric carcinoma: A well differentiated papillary or tubular type with clear cytoplasm and a medullary type that is characterized by polygonal cells arranged in solid nests or sheets, with scattered large pleomorphic or multinucleated giant cells, which are indicative of fetal enteroblastic differentiation. These two types may sometimes coexist in a single tumor. To differentiate hepatoid adenocarcinoma from nonhepatoid adenocarcinoma of the stomach, AFP isoform measurement is also useful but the diagnosis of hepatoid adenocarcinoma of stomach is not dependent on whether AFP is produced, actually, histological features are important for diagnosis (2, 3, 7).

Primary gastric hepatoid adenocarcinomas are well known to have a poor prognosis because of frequent liver and/or lymph node metastases (7-9). The reasons for poor prognosis are not clearly understood. The poor prognosis of the tumors may be attributed to extensive venous involvements by tumor cells and production of AFP, presence of antitrypsin/alpha-1 antichymotrypsin which has immunosuppressive and protease-inhibitory properties which enhance invasiveness. The other reasons for poor prognosis are that hepatoid adenocarcinoma has high proliferative activity, weak apopitosis and a rich neovascularization (3, 5, 9).

Fluorouracil (5-FU) is the main drug for the treatment of metastatic gastric cancer. In addition to 5-FU, cisplatin, leucovorin, doxorubicin, mitomycin and methotrexate are also combined to the regimens. Shimada et al (10) reported a patient achieving complete remission of metastatic liver tumors using irinotecan plus low dose cisplatin. Hirao et al (11) reported a patient who successfully treated with irinotecan and mitomycin after first line treatment failure. Nevertheless, a standardized and effective treatment has not been established yet.

As a conclusion, we want to underline this rare tumor with poor prognosis, different histological pattern and increased serum AFP levels.

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