

AFP-producing Hepatoid Adenocarcinoma in Association with Barrett's Esophagus with Multiple Liver Metastasis Responding to Paclitaxel/CDDP: A Case Report

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Abstract. *A case of alpha-fetoprotein (AFP)-producing hepatoid adenocarcinoma in association with Barrett's esophagus with multiple liver metastases, responding to chemotherapy, is reported. A 47-year-old man was admitted to our hospital with abdominal pain after subtotal esophagectomy for an esophageal adenocarcinoma in association with Barrett's esophagus, and was diagnosed as having multiple liver tumors. Most tumor markers were normal, but the serum AFP level was markedly elevated. Dynamic computed tomography and ferumoxide enhanced magnetic resonance imaging did not provide evidence of any primary hepatocellular carcinoma. Since microscopic examination of the resected tumor showed a poorly-differentiated adenocarcinoma with hepatoid features displaying AFP-immunoreactivity, the liver tumors were thus considered to be metastatic deposits. Surgery was not feasible so chemotherapeutic agents were tried, and the combination of paclitaxel (TXL) and cisplatin (CDDP) gave a partial response and good control for a period. This is the first report, to our knowledge, of effective chemotherapy for liver metastases from an AFP-producing hepatoid adenocarcinoma of the esophagus.*

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An increasing number of alpha-fetoprotein (AFP)-producing carcinomas of the gastrointestinal tract have been described in recent years (1, 2). Most are gastric adenocarcinomas (3-11), whereas esophageal tumors are relatively few (12-15). Primary hepatoid adenocarcinomas are a subtype of AFP-producing adenocarcinoma, which can be seen in a pure form or in association with ordinary adenocarcinoma in the upper gastrointestinal tract (16-18). In the esophagus they are extremely rare (19, 20). Some chemotherapeutic regimens have been tried (13, 15), but so far none have been reported as effective. A case of AFP-producing hepatoid adenocarcinoma in association with Barrett's esophagus with multiple liver metastases, which could be successfully treated with a combination of paclitaxel (TXL) and cisplatin (CDDP), is presented here.

Case Report

A 47-year-old man, with no cancer-related past or family history, was suspected as having esophageal cancer at a routine health check. Endoscopic examination revealed a lesion with a slightly depressed center surrounded by a low protrusion within a short segment of Barrett's esophagus (SSBE). On biopsy, the lesion was diagnosed as an adenocarcinoma, and subtotal esophageal resection was performed in our hospital. A histopathological diagnosis of poorly-differentiated adenocarcinoma in SSBE could then be established.

Nine months after the operation, the patient suddenly started suffering from abdominal pain and high fever and was re-admitted to our hospital. Multiple liver tumors were diagnosed by computed tomography (CT). There were no obvious physical

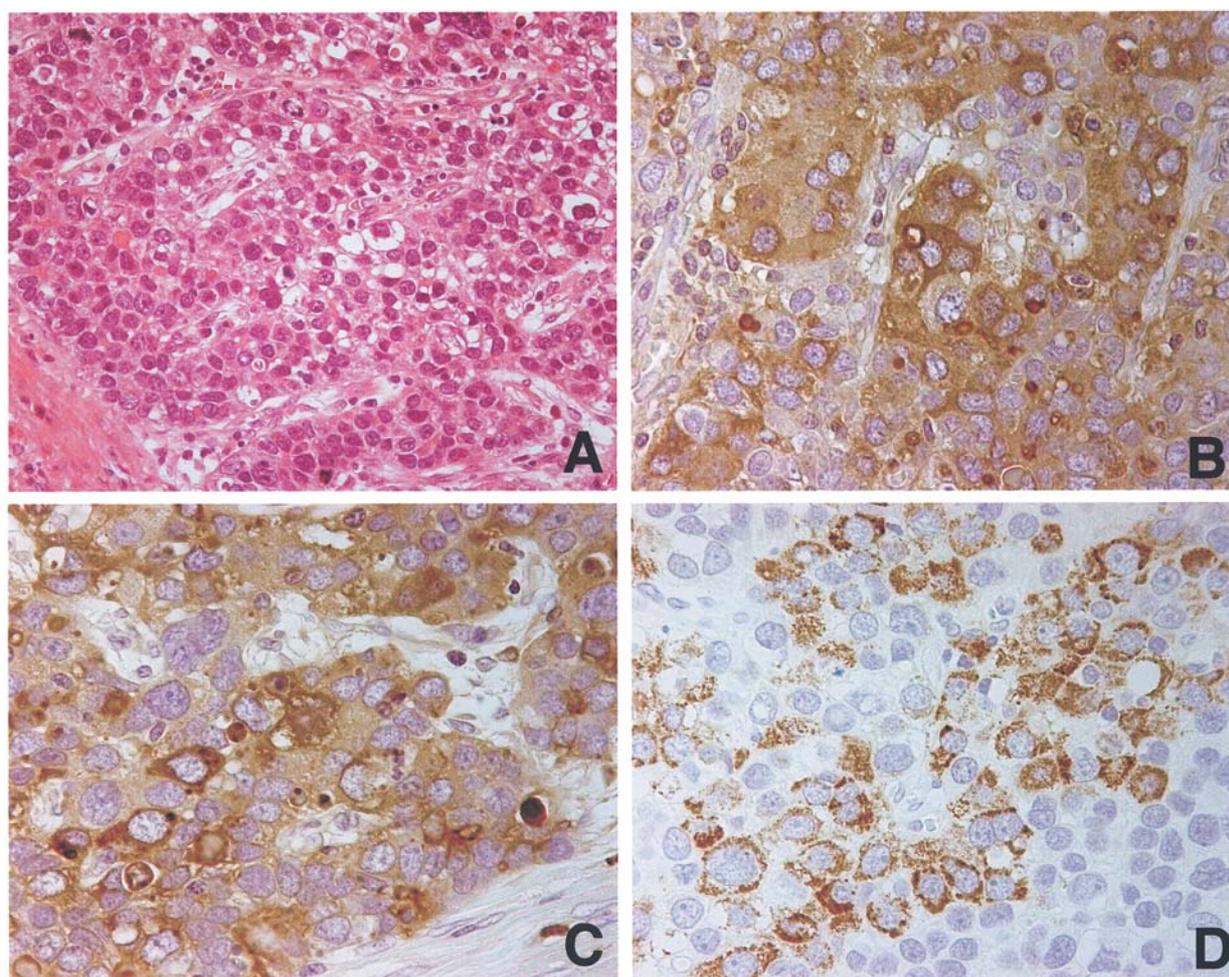


Figure 1. *Hepatoid adenocarcinoma. Neoplastic cells arranged in trabecular pattern with intervening fibrovascular stroma (A) (HE), with cytoplasmic immunoreactivity for alpha-fetoprotein (B) and alpha-1 antitrypsin (C). Immunohistochemical staining with Hep Par 1, hepatocyte-specific marker, demonstrating hepatoid differentiation (D).*

findings or abnormal laboratory data, except that serum GOT (77 IU/l) and GPT (57 IU/l) levels were slightly elevated. Serum carcinoembryonic antigen, carbohydrate antigen 19-9, and squamous cell carcinoma-related antigen levels were normal, but the AFP level was markedly elevated at 326,400 ng/ml. There was no evidence of liver cirrhosis, and both dynamic CT and ferumoxide enhanced magnetic resonance imaging (MRI) studies ruled out the possibility of a primary hepatocellular carcinoma. The slides of sections of the resected esophageal tumor were reviewed, and a diagnosis of hepatoid adenocarcinoma, rather than poorly-differentiated adenocarcinoma, was made from the trabecular arrangement of neoplastic cells with pale eosinophilic and granular cytoplasm, and intervening fine fibrovascular stroma (Figure 1A). The change in histopathological diagnosis was supported by immunohistochemical studies: the tumor cells were positive for AFP (Figure 1B) and alpha-1 antitrypsin (Figure 1C), and also

bound Hepatocyte paraffin 1 (Hep Par 1), a monoclonal antibody recognizing an antigen thought to be specific for hepatocyte mitochondria (Figure 1D). Based on these findings, the primary esophageal tumor was finally diagnosed as a hepatoid adenocarcinoma, and the multiple liver tumors were concluded to be metastatic deposits because of the high serum AFP level, although this could not be histologically confirmed.

Because the multiple liver tumors were inoperable, chemotherapy was started using the following anti-cancer drugs. At first, 1 M tegafur – 0.4 M gimestat – 1 M ostar potassium (S-1) and CDDP were administered orally and *i.v.* respectively. Although the serum AFP level decreased slightly, there was no tumor regression and the patient suffered severe adverse effects (grade 4 anorexia and grade 3 vomiting). Therefore, the chemotherapy regimen was changed to a combination of TXL and CDDP, given bi-weekly at doses of 120 mg/m² and 30 mg/m², respectively. Within two months, the

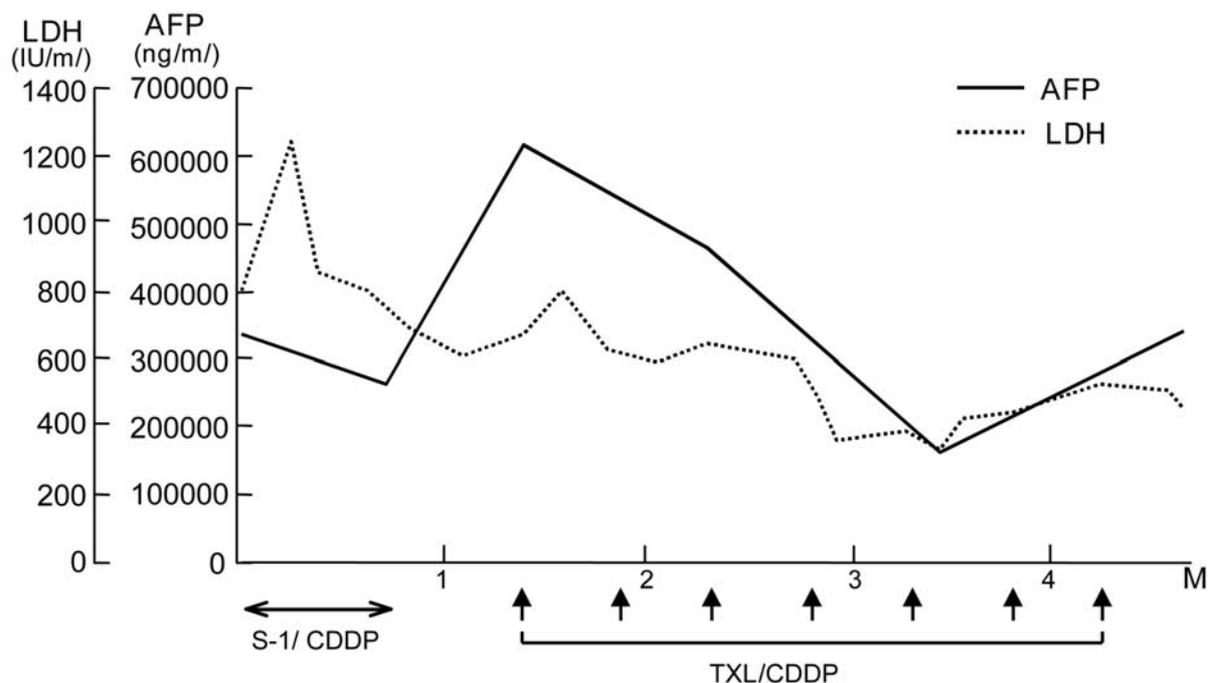


Figure 2. Changes in AFP and LDH levels during the treatment course.

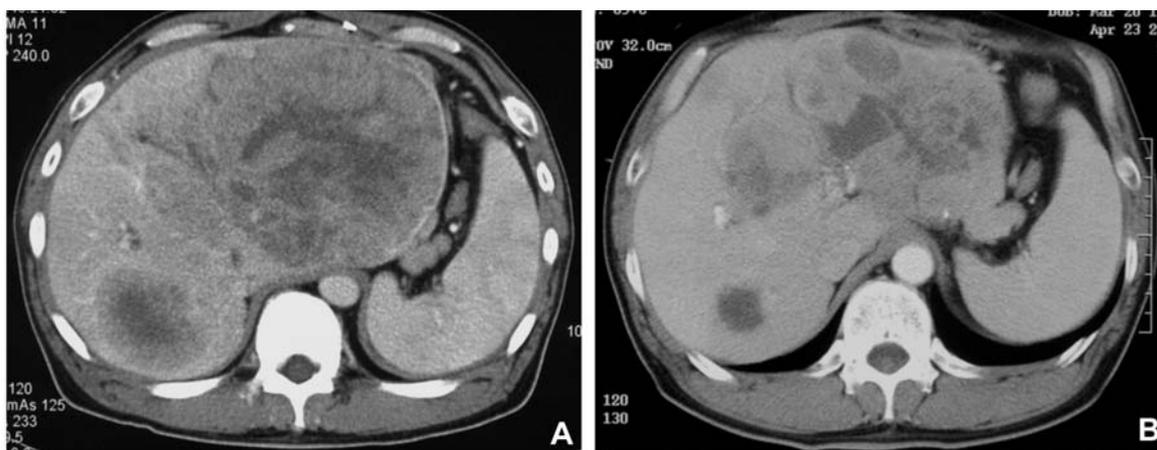


Figure 3. Computed tomograph (CT) showing multiple metastatic tumors in the liver. Before the combination chemotherapy (A). After chemotherapy, the liver tumors had significantly regressed (B).

serum AFP levels had significantly decreased from 606,800 ng/ml to 155,900 ng/ml (Figure 2). CT scan showed the liver lesions to have remarkably regressed to a level corresponding to the partial response (PR) criteria of RECIST (Figure 3). The liver tumors could be controlled for 4 months and the patient was able to continue the chemotherapy as an outpatient. However, 5 months after the diagnosis of liver metastasis, the liver tumors again rapidly enlarged and the surrounding gastrointestinal (GI) tract became involved. At 14 months after his initial operation, the patient died due to GI bleeding. Unfortunately, an autopsy was not approved.

Discussion

AFP-producing adenocarcinomas in the stomach, usually associated with advanced stage, liver metastases and a poor prognosis, are rare but well described (10, 11). To the best of our knowledge, only four cases have been reported in the esophagus (12-15). Shimakawa *et al.* described a case of an AFP-producing esophageal adenocarcinoma with a number of metastatic liver deposits, suggesting the tumor is highly metastatic to the liver, like its AFP-producing gastric counterparts.

Interestingly two out of the four cases, reported by Inoue *et al.* (14) and Shimakawa *et al.* (13) were derived from Barrett's epithelium. Our case had multiple metastatic tumors in the liver, similar to the case reported by Shimakawa *et al.* (13), and thus provides a third case of AFP-producing Barrett's esophageal adenocarcinoma. Its unique features were the hepatoid elements evident both morphologically and immunophenotypically.

Primary GI hepatoid adenocarcinoma is very rare and mostly arises from the gastric epithelium. This neoplasm has a poor prognosis, readily metastasizes to the liver and is frequently found at an advanced stage of disease. The characteristic biochemical finding is a markedly increased serum level of AFP in most cases. In the English literature, only two case reports of hepatoid adenocarcinoma of the esophagus have been reported so far (19, 20). In both cases the tumor occurred with a background of Barrett's esophagus and had metastasized to the liver, as found here. Interestingly, both had elements of choriocarcinoma and tubular adenocarcinoma.

In three of the four AFP-producing adenocarcinomas and two cases of hepatoid adenocarcinomas of the esophagus, chemotherapeutic agents were administered. In one case, multiple liver tumors and extensive lymph node tumors were treated with CDDP, 5-fluorouracil (5-FU) and leucovorin (LV) at first followed by CDDP, 5-FU and adriamycin (ADR) (13). One of the two hepatoid adenocarcinomas was treated by bleomycin. However, none of these treatments were effective. In our case, combination chemotherapy with S-1 and CDDP was tried first, but with only limited anti-tumor effects and severe adverse events were encountered. The combination of TXL and CDDP, chosen as the second regimen, was partially effective and appeared to prolong the patient's survival time. To our knowledge, this is the first report of partial response to chemotherapy in a patient with multiple liver metastases from an AFP-producing esophageal carcinoma.

In conclusion, we describe a case of AFP-producing hepatoid adenocarcinoma, occurring in Barrett's esophagus. Due to the poor prognosis in such cases, more attention should be given to histopathological diagnosis, and further information on chemosensitivity from case reports is needed. Our present report suggests that TXL and CDDP might be effective combination chemotherapy for inoperable metastatic liver tumors found with this type of tumor.

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