

Hepatoid adenocarcinoma of the stomach : case report and short notes on immunohistochemical markers

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Abstract

Hepatoid adenocarcinoma of the stomach is a rare type of gastric carcinoma with an extremely poor prognosis. We describe a 72-year-old man who underwent esophagogastroduodenoscopy which revealed 50 mm exulcerated lesion with a central necrosis on the lesser curvature and the posterior wall of the body of the stomach. Gastric biopsy revealed a poorly differentiated (anaplastic) adenocarcinoma. The serum level of alpha-fetoprotein (AFP) was (3220 ng/mL). After diagnosis of AFP-producing gastric adenocarcinoma, total gastrectomy, with splenectomy, was performed. The tumor showed immunohistochemical positivity for AFP and Hep Par 1. According to these histopathological and immunohistochemical findings, the tumor was diagnosed as hepatoid adenocarcinoma. At 24 months postoperatively the patient is still alive without metastatic disease on repeated abdominal CTs. Because of the poor prognosis for this histological type of tumor, accurate diagnosis of hepatoid adenocarcinoma is important, and long-term follow-up is required. (*Acta gastroenterol. belg.*, 2009, 72, 253-256).

Key words : gastric cancer, hepatoid adenocarcinoma, alpha-fetoprotein-producing cancer, hepatocyte-paraffin-1 positive cancer.

Introduction

The prognosis of patients with gastric cancer is related to the histological type of tumor and tumor extent, and includes both nodal involvement and direct tumor extension beyond the gastric wall. Tumor grade also provides some prognostic information. Several classification systems have been proposed to aid the description of gastric cancer. The two most commonly used are the Lauren and the World Health Organization (WHO) systems. The WHO system assigns grades to adenocarcinoma based on the degree of the resemblance to metaplastic intestinal tissue. It categorizes histology into 5 subtypes : adenocarcinoma (intestinal or diffuse), papillary, tubular, mucinous and signet-ring cell. Unfortunately all these systems are somewhat non-specific because there are subgroups of gastric adenocarcinomas whose 'behavior' is biologically different.

Thus, hepatoid adenocarcinomas (HAC) are defined to be primary extrahepatic tumors characterized by the histological structures of hepatoid differentiation resembling hepatocellular carcinomas (HCC) and also by production of alpha-fetoprotein (AFP). In 1970, Bourreille et al. reported the first case of gastric cancer producing serum AFP (1). In 1985 Ishikura *et al.* defined the hepatoid variant of gastric carcinoma, as a tumor microscopically composed of both adenocarcinomatous and hepa-

toid components (2). Adenocarcinomas with hepatoid differentiation have been reported at a variety of sites including the ovary (3), lung (4), gallbladder (5), esophagus (6), duodenum (7), pancreas (8), uterus (9, 10), and urinary bladder (11) ; among these, the stomach is the most common site involved. HAC in the stomach is felt to be related to HCC because the stomach and liver are both embryologically derived from the primitive foregut of the embryo (2). HAC is easy to diagnose if hepatoid areas are clearly distinguishable within the gastric tumor. However, in anaplastic variants or cases with massive liver metastases, it may be difficult (12). In these cases the gross findings in the stomach coupled with the very high serum AFP levels are distinctive. The histological features of AFP-producing gastric carcinomas have been described by several investigators (13, 14). Now it is known that HAC of the stomach is a distinct entity composed of polygonal cells arranged in a solid or trabecular manner that resembles hepatocellular carcinoma despite the production of AFP (15). AFP-producing gastric cancer is histologically classified into three subtypes : HAC, the yolk sac type, and the intestinal type. The similarity with hepatocytes does not only refer to morphology but also includes bile production, protein and mRNA synthesis of AFP, albumin, and transferrin, and PIVKA-II. Therefore it can be speculated that tumors originating in mucosal epithelium acquire the phenotype in the process of development. This suggests that tumor cells acquire a phenotype similar to that of hepatocytes, i.e., the ability to produce AFP, during the process of dedifferentiation (14).

In 1993, Wennerberg *et al.* reported the development of a new monoclonal antibody named hepatocyte paraffin 1 (Hep Par 1), which reacts with paraffin-embedded normal and neoplastic liver tissue (16). Subsequent studies confirmed Hep Par 1 as a relatively specific marker for HCC and hepatoblastomas, though 30-45% gastric adenocarcinomas were also positive for Hep Par 1 (17, 18). This means that adenocarcinomas with hepatoid fea-

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Submission date :

Acceptance date :

tures must be considered in the differential diagnosis of Hep Par 1-positive lesions. Therefore, immunostaining with Hep Par 1 and AFP increases diagnostic sensitivity and specificity.

We report a rare case of the hepatoid variant of gastric adenocarcinoma. The clinical characteristics of our patient are evaluated and diagnostic and treatment strategies are discussed.

Case report

A 71-year-old man underwent total gastrectomy after gastric biopsy which revealed poorly differentiated (anaplastic) adenocarcinoma. The serum level of AFP was elevated (3220 ng/mL), but the levels of carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) were within normal limits. The surgically resected specimen showed an elevated tumor, 5 cm in maximal diameter, with central ulceration and surface

erosion, involving the body, from the lesser curvature to the posterior-wall. Thus it was classified as macroscopic *c Type 3*, according to the general rules of the Japanese Gastric Cancer Association (JGCA) (19). Light microscopic examination revealed that tumor invasion was throughout the gastric wall in some areas. The tumor showed two types of histology. The major part, composed of large polygonal cells with abundant eosinophilic cytoplasm with vesicular nuclei and visible nucleoli, arranged in a trabecular pattern, resembled moderately differentiated HCC (Fig. 1). An area of common-type adenocarcinoma was seen in the smaller part of the tumor (Fig. 2). Immunohistochemistry showed that the HCC-like cells were diffusely positive for AFP (Fig. 3) and Hep Par 1 (Fig. 4). Based on these pathologic and immunohistochemical findings, the tumor was diagnosed as HAC of the stomach. Out of the 17 histologically examined lymph nodes from the resected specimen, cancer metastases were found in three. The tumor

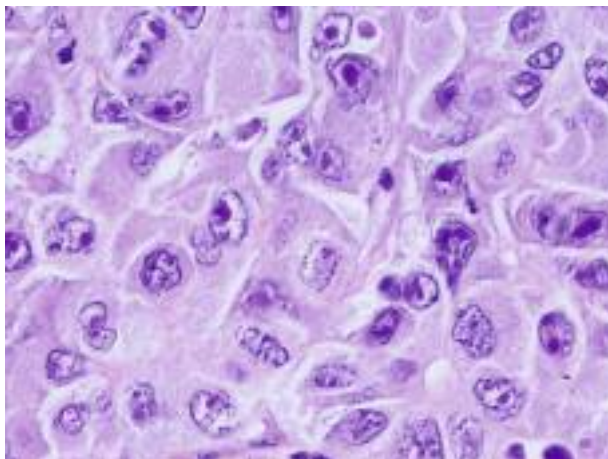


Fig. 1. — Larger magnification of the tumor microscopy reveals polygonal cells with vacuolar nuclei and prominent nucleoli (H&E stain, ×400).

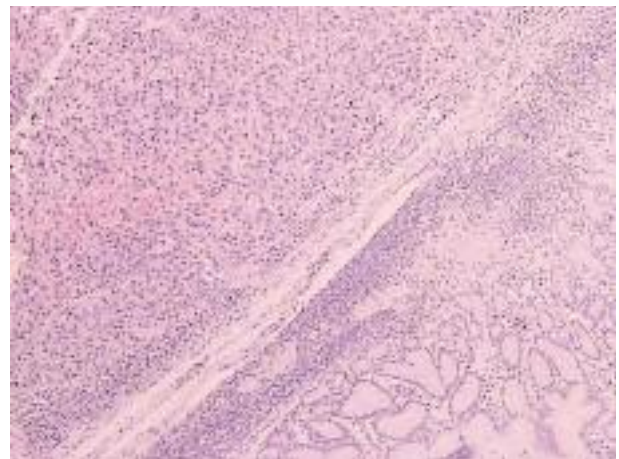


Fig. 2. — The major part of the tumor (upper part of the photomicrograph) was composed of cords of polygonal cells and resembled moderately differentiated hepatocellular carcinoma (H&E stain, ×40).

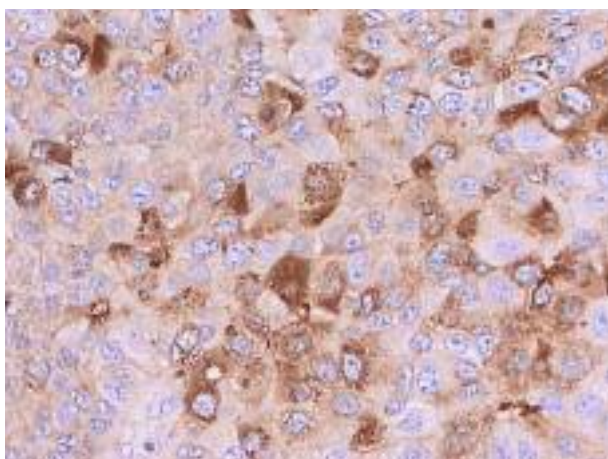


Fig. 3. — Immunohistochemical staining for alpha-fetoprotein (AFP) shows diffuse positivity in the hepatoid areas (×200).

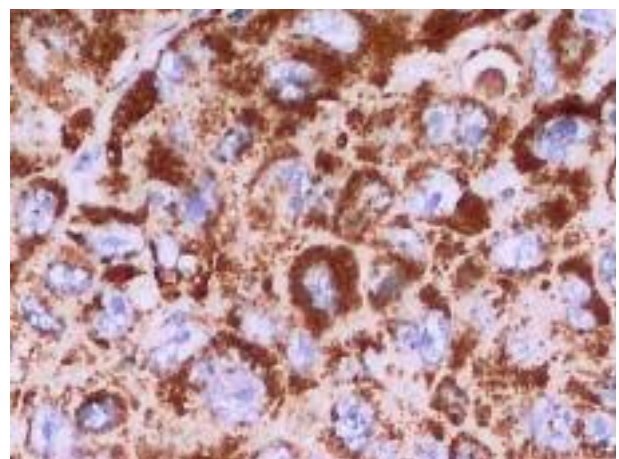


Fig. 4. — Immunohistochemical staining with monoclonal antibody for hepatocyte paraffin 1 (Hep Par 1 stain, ×400).

was diagnosed as *Stage IIIA* (T3, N1, M0) according to the American Joint Committee on Cancer (AJCC) and also *Stage IIIA* (T3, ly2, N1, H0, M0) according to the JGCA (19). The patient was checked every six months through measurements of AFP and abdominal MSCT. After 2 years, the patient is still without local recurrence or distant metastasis.

Discussion

HACs are defined to be primary extrahepatic tumors resembling HCC and producing AFP (usually in the thousands ng/L) (2, 14). AFP, a known tumor marker for hepatocellular carcinoma and extragonadal germ cell tumors, has been found to be a sensitive serum marker in other extrahepatic hepatoid type tumors (20). AT motif binding factor-1 (ATBF1) was identified as a modulator of AFP production by hepatocellular carcinoma, and the decreased expression of the protein was also reported in AFP-producing gastric cancer. ATBF1 regulated AFP expression and inhibited transcription in hepatoid variant (21).

AFP producing gastric cancer accounts for 1.3-15% of all gastric cancers (22-28). AFP can be detected immunohistochemically in the cytoplasm of hepatoid adenocarcinoma cell-like hepatocellular carcinoma cell. The stomach is the most common site of HAC (29-32). In respect of the growth pattern, poorly differentiated adenocarcinoma of the solid type, small cell neuroendocrine cell carcinoma or parietal cell carcinoma may be listed as a differential diagnosis for HAC. Former tumors never contain any cells positive for AFP, while HAC contain neither argyrophil granules nor cells positive for phosphotungstic acid hematoxylin. Every effort must be made to identify and to report such cases for accurate estimation of incidence and prevalence of this distinct and rare entity. Immunohistochemical staining with Hep Par 1, AFP and set of cytokeratins (CK) must always be performed, especially when clinically and pathologically the origin of the primary tumor cannot be determined. Lee *et al.* showed that 44.2% of gastric carcinomas expressed Hep Par 1, but they did not make the distinction between classic adenocarcinoma and HAC histopathologically or with other immunohistochemical markers (33). The study of Lugli *et al.* was the systematic investigation of the epidemiology of Hep Par 1 expression in 3,940 tissue samples and showed that Hep Par 1 is a specific marker for HCC (73%), although several non-hepatic tumors occasionally show some Hep Par 1 positivity. Positivity for gastric adenocarcinoma was 4.1% (34). Others showed higher specificity for hepatocellular (93%) and gastric (70%) carcinomas, but also it was not specified if these gastric carcinomas were hepatoid variants or just gastric adenocarcinomas as a single entity (35). Immunostaining for CK7, CK8, CK18, CK19, CK20, AFP, p-CEA, and Hep Par 1 revealed that hepatoid areas of both primary and metastatic HAC have a specific immunoprofile. Also, positivity of virtually all

HACs for AFP, CK8, CK18, and the membranous, canalicular staining for p-CEA underline its hepatoid nature. On the other hand, positive staining for CK19 and CK20 and frequent negativity for Hep Par 1 in both primary tumors and their metastases were distinctive features of HAC. Furthermore, HAC differs from hepatocellular cholangiocarcinoma, being negative for CK7 (36).

HAC often metastasizes to the liver, frequently shows at an advanced stage of disease and because of that, is recognized as a tumor with an extremely poor prognosis with a 5-year survival rate of less than 10% (14, 24, 37, 38). The reasons for the poor prognosis are not clearly understood. One possibility is that HAC produces alpha-1 antitrypsin (AAT) and/or alpha-1 antichymotrypsin (ACT) as well as AFP. AAT and ACT have immunosuppressive and protease-inhibitory properties that enhance invasiveness (39, 40). AFP also has a suppressive effect on lymphocyte transformation (41). In addition, AFP-producing gastric cancer has high proliferative activity, weak apoptosis, and rich neovascularization (42). Pronounced vascular infiltration is caused by higher expression of vascular endothelial growth factor (VEGF) with angiogenic or lymphangiogenic function (43). Even if metastases are not present preoperatively, liver metastases can occur within a year after surgery, thus, close observation and long-term follow-up is required (29). Furthermore, these tumors are known to be resistant to chemotherapy (44). However, several patients in whom chemotherapy was effective have been reported (45, 46). Therefore, even if hepatoid gastric adenocarcinoma is diagnosed, curative resection (if indicated) and further chemotherapy are recommended.

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