Hepatoid adenocarcinoma of the stomach : report of five cases and review of the literature

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Abstract

We report on a rare hepatoid adenocarcinoma of the stomach producing alpha-fetoprotein (AFP) in five cases. Definitive features included an aggressive, invasive, and rapidly progressing neoplasm showing areas morphologically comparable to those of hepatocellular carcinomas. All patients had multiple metastases to lymph nodes and/or liver. The serum AFP level of the patients was between 83-87.900 ng/ml. Two subtotal and one palliative gastrectomy was performed. A short duration of chemotherapy was administered only in two patients. The length of survival averaged 4.7 months. Our experience together with what has been reported in literature suggest that the course of hepatoid adenocarcinoma of the stomach is more aggressive than an ordinary adenocarcinoma and that from a diagnostic point of view distinction from an adenocarcinoma may be accomplished histochemically and by measuring serum AFP levels. (Acta gastroenterol. belg., **2006**, 69, **285-292**).

Key words : ???, ???.

Introduction

Adenocarcinomas of the stomach are morphologically heterogeneous (1). A large number of tumours which could not fit into either of the two major types of gastric adenocarcinoma (namely the intestinal and diffuse types) according to Lauren's original classification (2), has been grouped as unclassified or indetermined type, such as undifferentiated (solid) carcinomas, and the mixed type (with both diffuse and intestinal/glandular components) (1,3). In this regard, the incidence of histological types of gastric adenocarcinoma reported in several series varies greatly : while the ranges of intestinal type and diffuse type are 50.0 to 57.4. 9% and 35.0-44. 9%, respectively, the rate of unclassified adenocarcinoma ranges between 2.6 and 8.7% (4,5,6). Alpha fetoprotein producing gastric cancer is a variant of unclassified adenocarcinoma (3,7,8). The neoplasm was first reported by Bourreille *et al.* in 1970 (9). Then, Ishikura *et al.* proposed the term 'hepatoid adenocarcinoma of the stomach' (10). Hepatoid adenocarcinoma is usually composed of both adenocarcinomatous and hepatocellular carcinoma-like foci ; the latter component has the full spectrum of the morphological and functional characteristics of hepatocellular carcinoma (10). Hepatoid adenocarcinoma of the stomach is uncommon ; approximately 100 cases of hepatoid gastric cancer have been published to date. The most of the cases discovered from retrospective studies of the archieves by Japanese pathologists (3). Nagai *et al.* reported 28 hepatoid tumours among their 7200 archival cases of primary stomach cancer (0.38% of all gastric tumours) (11). Therefore, it may be suggested that the low incidence of hepatoid adenocarcinoma may be due to incomplete immununohistochemical study of neoplastic tissues and the lack of studies with regard to serum AFP measurement in every patient with gastric cancer. Although histogenesis of hepatoid adenocarcinoma of the stomach is not clear yet, the presence of hepatoid areas in gastric adenocarcioma may be derivated from the primitive foregut of the embryo (7,12).

Hepatoid adenocarcinomas occur most commonly in the stomach, but, these tumors have been also reported in many different organs including esophagus(13), papilla of Vater (14), gallbladder (15,16,17), pancreas (18,19), small bowel (16), colon (20,21,22), lung (23,24), mediastinum (25), kidney (26,27), testicles (28), urinary bladder (29, 30, 31), uterus (32,33,34), ovary (35) and vagina (36). AFP-producing gastric carcinomas present an aggressive clinical course and poor prognosis due to frequent hematogenous metastasis to the liver and early involvement of the lymph nodes (11, 37,38,39).

Here, we present five cases of gastric hepatoid adenocarcinoma in which the serum AFP levels were elevated.

Case reports

Table 1 shows some clinicopathological characteristics of the cases.

Case 1

A 37-year-old woman was admitted in September 1997, with a 3-month history of epigastric pain, indigestion and weight loss (5 kg). Physical examination revealed slight tenderness in the epigastrium. Computed

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Table 1. — **Clinicapathologic manifestations of the cases**

Case	Age/Sex Male(M) Female(F)	Duration of symptoms (months)	Localisation of the tumor	Differentition of adenocancer	Serum AFP level ng/ml	Stage Surgical/ Clinical	Treatment	Survival (months)
1	37 F	3	Antrum	Poorly differentiated	3060	T1N1M0	Subtotal gastrectomy	12
2	29 M	4	Antrum	Poorly differentiated	1400	T4N2M0	Subtotal gastrectomy 1 course chemotherapy	4
3	70 M	3	Antrum	Well differentiated	1240	Multiple liver metastasis	Symptomatically	2.5
4	35 M	2	Antrum	Moderately differentiated	87900	Multiple liver metastasis	1 course chemotherapy	4
5	68 M	12	Corpus	Moderately-poorly differentiated	83	Ascites Multiple liver metastasis	Symptomatically	1

tomography of the abdomen showed mural thickening of the antrum. There was no mass in the liver. Liver function tests were normal. Serological markers for hepatitis B and C viruses were all negative. Serum AFP concentration was highly elevated at 3060 ng/ml, but the carcino-embryogenic antigen (CEA) and carbohydrate antigen 19-9 (CA-19-9) concentrations were within normal limits. Gastrointestinal endoscopy disclosed an ulcero-infiltrative carcinoma in the antrum. The microscopic appearance of the endoscopic biopsy showed two different coalescing patterns. The one part of the tumor revealed a poorly differentiated adenocarcinoma, while the other part of the tumor had morphological characteristics mimicking hepatocellular carcinoma with large polygonal cells of eosinophilic cytoplasm and a prominent nucleolus occurring as sheets, cords, and rounded nests ; some of the nests showed a trabecular pattern. A strong immunoreactivity for AFP was found in the cytoplasm of the hepatoid cells (Fig. 1). At laparotomy, the tumor was identified extending in the pyloric antrum and the lower body of the stomach. The liver was free of neoplasm in gross examination. A subtotal gastrectomy with gastrojejunostomy was performed. Microscopically, the tumor penetrated into muscle layers. Seven peri-gastric lymph nodes along the lesser and greater curvature contained metastatic tumor deposits. The histological examination of the neoplastic tissue showed similar characteristics of endoscopic biopsy. The neoplasm was composed of poorly differentiated adenocarcinoma and tumor cells were typed as “hepatoid carcinoma,” featuring large, polygonal cells with marked nuclear atypia and eosinophilic granular or clear cytoplasm and arranged in trabecular and solid nests or sheets. The carcinoma had infiltrated perineural spaces of small nerves and had extended in the lumen of venular vessels. Immunohistochemical staining revealed positive staining for AFP. The postoperative course was uneventful. Chemotherapy could not be planned due to psychiatric disorder of the patient. The patient survived 12 months.

Case 2

A 29-year-old man presented with four months history of vomiting, indigestion and weight loss (10 kg) in June 1998. He had a history of smoking 10 cigarettes per day for 15 years. He was a shoemaker in a factory since the age of fourteen ages. There was gastric cancer history in the second and third degree relatives. Admission laboratory tests were as follows : Hemoglobin : 11.2 gr /dl, alkaline phosphatase : 280 U/L AST : 40 U/l, ALT : 52 U/l. Results of other laboratory tests were all within normal limits. At endoscopy, diffusely infiltrating carcinoma was found in the pyloric region. Histopathologically, the gastric tumor showed variable histological features. Some portions of the tumor displayed a poorly glandular differentiation. In the other areas, the tumor cells tended to be arranged in a trabecular fashion or as solid nests separated by a narrow fibrous stroma. The neoplastic cells had large and abundant eosinophilic or clear cytoplasm, large vesicular nucleus and marked nucleolus. Coagulation necrosis was seen in some areas (Fig. 2). A diagnosis of hepatoid adenocarcinoma was made after immunochemical demonstration of AFP positivity in the tumor cells. Liver function tests were normal. Serological markers for hepatitis B and C viruses were all negative. The serum level of AFP was 1400 ng / ml. The serum level of CEA and CA-19-9 were normal. Abdominal C/T scan revealed a thickened antral wall and epigastric mass sized 4×4 cm. At operation, pancreas was invased. A palliative subtotal gastrectomy was performed. The results of microscopic and immunohistochemical studies of tumour tissue in the resected stomach were similar to the results of endoscopic biopsies. Chemotherapy was started which consisted of adriamycin, mitomycin C and 5-fluorouracil.

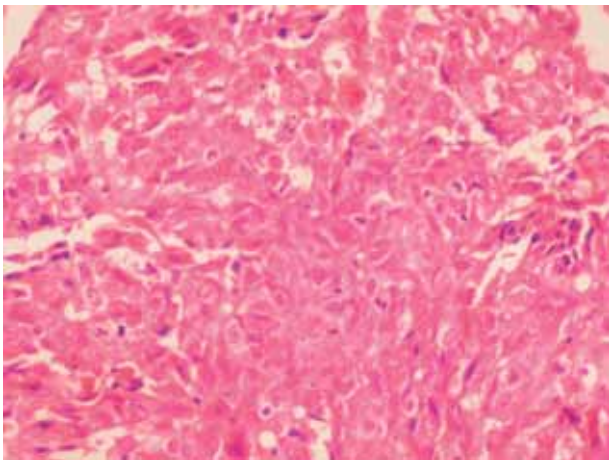

Fig. 1. — The large tumor cells have abundant eosinophilic cytoplasm, arranged in trabecular and sinusoidal pattern. In some hepatoid foci, pleomorphism of tumor cells was prominent (×400).

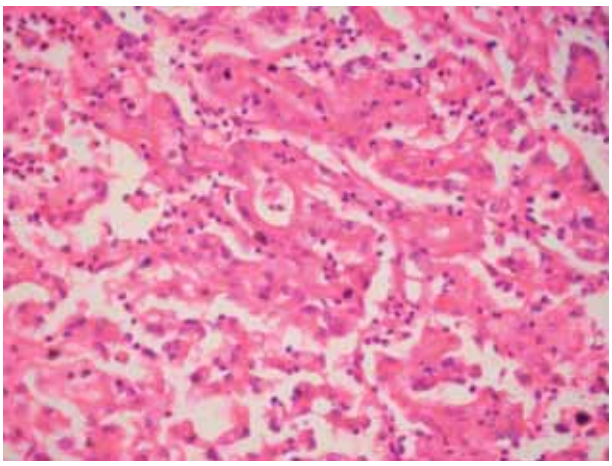

Fig. 2. — In the solid areas the tumor is composed of large poligonally-shaped cells resembling liver (×400).

After the first course of chemotherapy, clinical deterioration occurred in a short time and he was lost in four months after the presentation.

Case 3

A 70-year-old man presented with complaints of epigastric pain, vomiting and weight loss (7 kg) for 3 months in January 2000. Results of physical examination showed a large epigastric mass. Admission laboratory tests were as follows : Hemoglobin : 8.9 gr / dl, alkaline phosphatase : 344 U/L AST : 46 U/l, ALT : 62 U/l. Results of other laboratory tests were all within normal limits. Serum AFP level was high (1240 ng/ml), but the levels of CEA and CA-19-9 were normal. Serological markers for hepatitis B and C viruses were all negative. Abdominal ultrasonography and computed tomography showed, multiple solid masses sized 3-5 cm

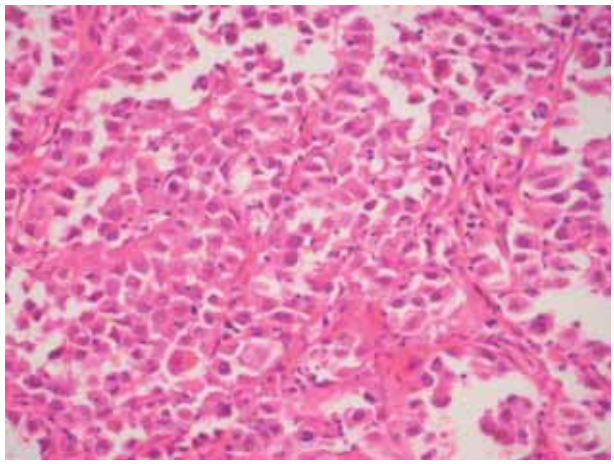

Fig. 3. — The tumor was composed of polygonal cells with large nuclei and prominent nucleoli, separated by a thin fibrous stroma, arranged in a trabecular pattern and solid nests. Tumour cells in these areas mimicked hepatocellular carcinoma cells (×400).

in the liver. The gastroscopic examination revealed polipoid masses involving the antrum. Histology of the gastric tumour revealed a typical hepatoid adenocarcinoma, predominantly resembling hepatocellular carcinoma, with some foci of well-differentiated adenocarcinoma. Tumor cells were large, and their cytoplasm was eosinophilic and granular containing polygonal, slightly pleomorhic central nuclei with prominent central nucleoli. The tumor areas were separated with fibrous stroma. There were frequent mitoses in the tumor areas. Necrosis and acute and chronic inflammatory cellular reaction were presents adjacent to the tumor areas (Fig. 3). An immunohistochemical study showed that AFP-positive cells were present in the tumor. The patient died from liver failure two and a half months after admission.

Case 4

A 35-year-old man was admitted with 2-month history of epigastric discomfort, indigestion, vomiting and weight loss (13 kg) in January 2002. The patient had smoked one pack of cigarettes per day for 17 years. He was working in an automobile sales agency. In family history, his aunt had stomach cancer. Physical examination showed bronchial rales and hepatomegaly (8 cm below to costal margins) with multiple masses. Laboratory tests results were as follows : hemoglobin 9.8 g/dl ; alkaline phosphatase 4054 U/L, AST 69 U/L, ALT 90 U/L, GGT : 325 U/L. The serum AFP level was exceptionally high (87900 ng / ml), but the serum levels of CEA and CA-19-9 were within normal limits. In the CT scan of the abdomen, multiple irregular hypodense lesions, highly suggestive of metastatic cancer were revealed in the liver, but no cirrhotic changes were observed. Serological markers for hepatitis B and C viruses were all negative. Physical and ultrasonographic

examination of the testis showed no mass. Endoscopy revealed a diffuse infiltrative tumor sized 4 cm at the greater curvature, located in the prepyloric antrum. In the microscopic examination of the endoscopic biopsies, the tumor cells were atypical large epithelial cells with large vesicular nucleus and abundant clear eosinohilic cytoplasm separated by a thin fibrous stroma, arranged in a trabecular and sinusoidal pattern, resembled moderately differentiated hepatocelluler carcinoma. There was a rarely adenoid structure. A highly mitotic activity and marked nuclear pleomorphism were observed. Immunohistochemical staining for AFP showed positivity in the hepatoid areas. An ultrasonography guided-liver biopsy test result showed a hepatocelluler carcinoma with clear cell, and AFP staining was positive. Chest radiography and thorax CT showed a reticulonoduler infiltration with diffuse lymphangitic dissemination. The patient was consulted with medical oncology, and prescribed the EAP-2 chemotherapy protocol (Etoposide, epirubicine and cisplatin). The patient died four months after the admission.

Case 5

A 68-year-old male patient was admitted with a history of 12 months of epigastric pain and weight loss (17 kg) in August 2002. He had no family history of cancer. In physical examination, hepatomegaly, ascites and left supraclavicular lymphadenopathy were found. In the CT scan of the abdomen, multiple irregular hypodense lesions, highly suggestive of metastatic cancer were revealed in the liver. Laboratory tests indicated the hemoglobin 8.4 g/dl, alkaline phosphatase 1273 U/L, AST 278 U/L, ALT 89 U/L. Among tumor markers, serum AFP, CEA and CA-19-9 levels were slightly elevated to 83 ng/ml, 43.70 ng/ml and 42.32 ng/ml, respectively. Serological markers for hepatitis B and C viruses were all negative. Endoscopy disclosed an infiltrative carcinoma located in the corpus. Gastric biopsy revealed a moderately-to-poorly differentiated adenocarcinoma. The tumor cells were atypical epithelial cells with large vesicular and hyperchromatic nucleus and abundant clear eosinophilic cytoplasm, arranged in a trabecular and sinusoidal pattern, similar to hepatocellular carcinoma. Immunohystochemical study showed AFP positivity in the tumor cells. Chemotherapy was not planned because general condition of the patient was poor. The patient died 1 month after admission.

Discussion

AFP is an oncofetal glycoprotein with a molecular mass of about 70 kDa and produced mainly in the fetal liver cells, the yolk sac cells and, to a lesser amount, in the fetal gastrointestinal epithelial cells and the kidney (40,41,42,43,44,45). After birth, AFP levels gradually decrease (45,46). In the adult life, serum AFP level increases frequently in patients with hepatocellular carcinoma, hepatoblastoma, and germ cell tumors (especially yolk sac carcinoma) (40,45,46,47,48). The synthesis of AFP, as observed in the germ cell tumors of the testes, ovaries, or of extragonadal location (sacrococcygeal, mediastinal, intracranial) can be traced back to yolk sac-entodermal-like structures based on the distribution of AFP-producing cells in the fetus (40,42,45,46). Its production is not always specific for the organs related with yolk sac and/or liver. Furthermore, AFP is produced by some other organ tumors in which gastric adenocarcinoma are one of the most common (7,11,49,50). The stomach and the liver are originated from the foregut which is suggested to be in direct continuity with yolk sac at primitive stages of development. Therefore, some gastric carcinomas may share common morphologic features and antigens with hepatocellular or yolk sac tumors (8,10,42,46,51). In the neoplastic cells, re-expression of the AFP gene, which is suppressed in normal cells after birth, concerned with hypomethylation of the 5'end of the AFP gene (45,52,53,54).

The term of hepatoid has been used to define a heterogenous neoplasms occuring in several organs. Ishikura *et al.* proposed that the neoplasms are composed of two different, but closely related areas : hepatoid and adenocarcinomatous (8,10,11,55). These neoplasms can be classified into three groups based on morphologic and functional characteristics of the tumor. Of these one, either it is a germinal tumor having focal areas of hepatoid differentiation or a somatic tumor having germinal differentiation with focal hepatoid areas. In this type, immunohistochemical staining of the hepatoid areas shows intense AFP positivity, focal alpha-1 antitripsin (A1AT) positivity and polyclonal carcinoembryogenic antigen (pCEA) negativity. The second one of these neoplasms is an adenocarcinoma having morphologic characteristics of hepatoid differentiation presented with polygonal cells arranged in solid nests or sheets separated by sinusoids or bile secretion and /or bile canalucili formation. Immunhistochemical study of this type reveals patchy staining for AFP, always stain for A1AT and albumin (ALB), and not always stain for pCEA. The third type of these neoplasms is a fetal gastrointestinal tumor producing AFP without any morphological feature of hepatocellular differentiation. Immunohistochemical study of this type shows AFP positivity and beta human chorionic gonadothropin (B-HCG) positivity and frequently contains CEA-positive cells (16,31,56). Aizawa *et al.* proposed another subtype characterized by a poorly differentiated medullary adenocarcinoma producing AFP (56). Ooi *et al.* reported a case of poorly differentiated medullary adenocarcinoma of the stomach producing gastrointestinal tract rather than hepatic or yolc sac type of AFP (57). On the other hand, cases of hepatoid adenocarcinomas with negative AFP staining coined as 'non-AFP producing hepatocellular carcinoma' have also been reported (11,56,58). To differentiate between hepatoid adenocarcinoma and non-hepatoid adenocarcinoma of the stomach, the measurement of AFP carbohydrate chain is also useful.

The serum AFP has a liver-type binding pattern with the lectin concanavalin A (Con-A) in the patients with hepatoid adenocarcinoma (45,56). However, it was reported that this was not significant, because such a liver-type binding pattern was shown in only 20% of AFP-producing tumors. Therefore, hepatoid adenocarcinoma should be diagnosed on the basis of histopathologic characteristics because the neoplasm has a poor prognosis even if the tumor is non-AFP producing carcinoma (11,17,56).

The incidence of AFP-producing gastric cancer has been reported to represent 3% of all gastric cancers (59, 60). AFP-producing gastric cancer is very aggressive and its prognosis is very poor compared with that of the common types of adenocarcinoma (16,50,61). More than 90% of the patients succumb to death within five years. The production of AFP is not only factor for the bad prognosis of the neoplasm (3). Lymphatic and venous invasion of the gastric wall and high rates of liver metastasis, of both synchronous and metachronous types are frequent in the hepatoid adenocarcinomas. After radical surgery, the poor outcome of the disease continues because of early liver metastasis produced by extensive vascular invasion and blood-borne metastasis (7,37,44, 59,66). Neoplastic cells grossly proliferate within veins which are detected as tumor thrombi. However, the ability to survive and to proliferate in veins of neoplastic cells is observed usually in only a few types of carcinoma such as hepatocellular and renal cell carcinomas (11,37,38).

The aggressive behavior of AFP-producing gastric carcinoma may also be related with a rich neovascularization in the neoplastic stroma. With regard to angiogenesis, the expression of vascular endothelial growth factor (VEGF) and the significant microvessel density had been shown in the AFP-producing gastric carcinoma (67). The high malignant potential of AFP-producing gastric cancers had also been explained by the weak apoptotic index and the high proliferating activity compared with that of AFP-negative gastric cancers (67). Another possibility for the invasiveness of hepatoid adenocarcinoma is that the neoplasm frequently produces A1AT, alpha-1 anti-chymotrypsin (ACT) and AFP. A1AT and ACT have immunosupressive and protease-inhibitory properties that increase invasiveness. Furthermore, AFP has an inhibitory effect on autologous lymphocyte transformation (11,68-70).

The cellular and molecular factors responsible for the aggressive course of AFP-producing gastric carcinomas have not been clarified. But, a high frequency of c-Met protein expression and high proliferative status was reported in AFP-producing gastric cancer in comparison to that of non-AFP producing carcinomas. On the other hand, the expression of VEGF-C (an VEGF isoform) was more frequently observed in AFP-producing gastric cancer than in stage-matched AFP-negative gastric cancer (62,71).

The majority of coexistent tubular adenocarcinomas with hepatoid adenocarcinoma were reported to be as the intestinal type. It has been suggested that phenotypic shift from the gastric to the intestinal type occurs during tumor progression. Then, it has been claimed that phenotypic shift from the intestinal type to hepatoid adenocarcinomas may occur (72). Transdifferentiation of adenocarcinoma cells into hepatoma-like cells has been reported to play a role in the pathogenesis of hepatoid adenocarcinomas. The production of bile, AFP, ALB, A1AT, transferrin, and detection of ALB mRNA expression in hepatoid adenocarcinoma tissues support the view that neoplastic cells acquire hepatic phenotype (10, 27,33,48,73,74). The phenotypic shift from tubular adenocarcinoma to hepatoid adenocarcinoma has been suggested to increase the metastatic ability of the neoplasm. LOH at18q21, in which some tumour suppressor genes are located, was detected more frequently in hepatoid adenocarcinomatous components than tubular adenocarcinomatous components. In an another study reported by Fujii *et al.*, 19 cases of AFP-producing hepatoid gastric adenocarcinomas and an average 4.6 chromosomal arms of nine chromosomal arms were found to be deleted (65). LOH was most frequently detected on 17p, 13q, 3p, 9p, 11q, 18q and 8p in the study (65). The uniform LOH patterns also suggest that a monoclonal origin is present mixed hepatoid and tubular adenocarcinomas of the stomach (65,66,75). Moreover, p53 mutations commonly observed in human neoplasms including gastric cancers have been explained by a monoclonal origin between histologically different neoplasms within the tumor (65,66,75).

Microscopically, hepatoid adenocarcinoma of the stomach is characterized by both of a prominent hepatoid component and an adenocarcinomatous component (10,50). Hepatoid component resembles to hepatocellular carcinoma evidenced by a solid pattern with formation masses, nests and trabecula of large polygonal cells with abundant eosinophilic cytoplasm separated by a fine fibrous stroma. On the other hand, adenocarcinomatous component of the neoplasm may be well, moderately or poorly differentiated and arranged in tubulopapillary pattern. Bile production and/or bile canaliculi formation is occasionally revealed. In the hepatoid component of the neoplasm as in hepatocellular carcinoma, PAS-positive, diastase-resistant intra and extracellular hyaline globules are common (8,10,11,76-78).

Hepatoid adenocarcinomas and HCC also share similar immunohystochemical characteristics. The neoplastic cells of the hepatoid component frequently produces AFP, A1AT, alpha-1 anthychymotrypsin, low molecular weight cytokeratin (LMWCK), anti-epithelial membrane antigen (EMA), ALB, pre-albumin, factor XIIIa, ferritin, neuroendocrine markers such as chromogranin 1-3, and monoclonal Hep Par 1 antibody, monoclonal carcino-embryonic antigen (CEA), and pCEA. AFP staining is identified either diffusely or focally in the neoplastic cells. CEA staining is vigorous in the adenocarcinomatous component and focally in the hepatoid component of the neoplasm. The neoplasm is

immunoreactive for CK8 and CK19 and negative for CK7. Positivity for CK18 and CK20 is observed in the some cases. The hepatocyte paraffin 1 (Hep Par 1), a monoclonal antibody which reacts with most hepatic cells in paraffin-embedded tissues and albumin gene mRNA by means of in situ hybridization (ISH), is also used for investigation of the hepatic tissue origin. Central coagulation necrosis is seen frequently in many areas of the tumor nodules. Intravascular proliferation of hepatoid is prominent, and tumor trombi is sometimes observed (3,11,12,31,50,74,76,79-81).

Symptoms to support diagnosis of hepatoid adenocarcinoma are not specific. The most common symptoms are epigastric pain, weight loss, general fatigue related with anemia. Inagawa *et al.* reported a summary of clinical features of 85 patients with hepatoid adenocarcinoma of the stomach described in the literature. In general, the average age of the patients was 53.5 (44-87) and male : female ratio was 58 :25 (82). The average age of our patients was 42.8 (29-70) and male : female ratio was 3 :1. Viral markers of hepatitis B and C were uniformly negative in our patients. No special features of cirrhosis or fibrosis of the liver was detected by ultrasonography and CT scan of the abdomen. In our cases as well as in the most of 85 patients reported in the literature, the tumor was localized in the antrum (82). The average serum AFP level was reported to be 51130 ng/ml in 85 cases in the literature (82). The average serum AFP level of our patients was 18737 ng/ml (range 83-87900 ng/ml). Furthermore, like the cases in the literature the tumors were in advanced stage, and metastasis to the liver and/or lymph nodes were only observed in a couple of our cases (82).

In summary, hepatoid adenocarcinoma is a highly aggressive neoplasm that can be confused with hepatocellular carcinoma. The antrum is a common site. The neoplasm usually produces large amounts of AFP. Liver metastasis is the first clinical manifestation of the neoplasm in some cases. Venous involvement by neoplastic cells is frequent. The histologic diagnosis can be based on the identification of both a hepatoid pattern and areas with typical adenocarcinoma features. Tumor cells in the hepatoid areas contain multiple serum proteins sush as AFP, A1AT, alpha-1 antichymotrypsin, albumin, and transferrin. The cells in the adenocarcinomatous areas may show some of the former proteins, and CEA is often demonstrated.

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