Alpha-fetoprotein-producing hepatoid gastric adenocarcinoma in a child presenting with spontaneous gastric perforation

Suna Emir[1], Neslihan Karakurt[1], Esra Karakuş[2], Emrah Şenel[3], Ceyda Kırsaçlıoğlu[4], Hacı Ahmet Demir[1], Diclehan Orhan[5]

Divisions of [1]Pediatric Hematology and Oncology, [4]Pediatric Gastroenterology, [2]Department of Pathology, and [3]Department of Pediatric Surgery, SB Ankara Children's Hematology Oncology Training and Research Hospital, and [5]Division of Pediatric Pathology, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey. E-mail: neslihankarakurt@gmail.com

SUMMARY: Emir S, Karakurt N, Karakuş E, Şenel E, Kırsaçlıoğlu C, Demir HA, Orhan D. Alpha-fetoprotein-producing hepatoid gastric adenocarcinoma in a child presenting with spontaneous gastric perforation. Turk J Pediatr 2014; 56: 88-91.

Gastric adenocarcinoma is a rare entity in the pediatric population. Gastric hepatoid adenocarcinoma with elevated serum alpha-fetoprotein (AFP) is seen extremely rarely in children.

A 12-year-old boy was admitted to the hospital with complaint of abdominal pain. X-ray revealed free air density below the diaphragm. Emergent laparotomy showed perforated stomach. Four weeks after the operation, he was re-admitted with severe gastrointestinal obstruction symptoms. He underwent an explorative laparotomy, which revealed intestinal edema and diffuse small solid nodules covering the peritoneum. Serum AFP level was mildly elevated. Endoscopic evaluation of the upper gastrointestinal tract was performed, and a gastric mass was detected. All pathological findings were compatible with gastric carcinoma showing hepatoid differentiation.

We report an unusual case of AFP-producing hepatoid gastric adenocarcinoma presenting with gastric perforation. This is, to the best of our knowledge, the first reported case of AFP- producing hepatoid gastric adenocarcinoma presenting with gastric perforation in a child.

Key words: alpha-fetoprotein-producing gastric carcinoma, children, hepatoid adenocarcinoma, gastric perforation.

Gastric cancer is rarely seen in children[1]. Children suffering from gastric cancer often present with dysphagia, abdominal pain, distension, mass, hematemesis, melena, and/or hematochezia[2]. Gastric perforation is an uncommon presentation of gastric cancer[3]. Gastric hepatoid adenocarcinoma (GHAC) with elevated serum alpha-fetoprotein (AFP) level is a rare type of gastric cancer that is more frequent in older patients[4]. It usually presents in advanced stage with liver metastasis and has a poor prognosis. Here, we describe a 12-year-old boy with a diagnosis of AFP-producing GHAC. To the best of our knowledge, this is the first reported case in children.

Case Report

A 12-year-old boy was admitted to the emergency department with severe abdominal pain. He had no relevant medical history, except for epigastric pain, anorexia, fatigue for two weeks, and weight loss of 4 kg in one month. There was no family history for cancer. The physical examination showed generalized abdominal tenderness. Since plain abdominal X-ray revealed free air density below the diaphragm, an emergent laparotomy was performed, and perforation of the stomach was observed. No other pathological finding was reported by the operating surgeon. After surgical repair of the perforation, he was discharged in a week uneventfully. Four weeks' postoperatively, he was re-admitted to the emergency department with severe gastrointestinal obstruction symptoms. The physical examination revealed tenderness and

distension of the abdomen, but there were no other positive findings. He underwent a second explorative laparotomy, which revealed intestinal edema and small solid nodules measuring up to 5 mm covering the peritoneum, mesentery and omentum. Multiple biopsies of these nodular lesions from intestinal serosal surfaces and the peritoneum were performed during surgery. The pathology of the multiple biopsies was reported as malignant, and an oncology consultation was requested. Abdominal computed tomography (CT) showed mild ascites and thickening in the prepyloric area of the stomach. Thorax CT did not show any sign of lung infiltration, but bilateral pleural effusion was noticed. Since the clinical, laboratory, and pathological findings, except for mildly elevated serum AFP (207 mg/dl, normal: 0-7 mg/dl), were not enough to make a definitive diagnosis, an esophagogastroduodenoscopy was performed 10 days after the second operation. A gastric mass of 4 cm in the prepyloric area was observed (Fig. 1). Histopathological examination of intestinal serosal surfaces and the peritoneum revealed poorly differentiated carcinoma in the intestinal wall and serosal adipose tissue. The tumor cells were arranged mainly in small and large nests, and smaller areas of glandular formations were also observed. Tumor cells had large, round, vesicular nuclei, a coarse chromatin pattern, and occasionally clear cytoplasm and hyperchromatic nuclei. Areas of necrosis, karyorrhectic debris and apoptotic bodies were also observed. Mitotic activity was found to be 6 per 10 high power fields. The neoplastic cells showed cytoplasmic positivity for cytokeratin AE1/AE3 and membranous positivity for CD99, and were focally positive for AFP. Ki-67 index was determined as 90%. Peritoneal fluid examination also revealed tumor cells. Biopsy material taken endoscopically from the gastric mass revealed tumoral lesions located in the mucosa and submucosa with expansive development and the same pathologic features. Tumor cells were large, had hyperchromatic nuclei, prominent nucleolus, and eosinophilic cytoplasm. Immunohistochemically, the tumor cells were positive for cytokeratin 7 and showed focal positivity for AFP (Figs. 2, 3). Periodic acid-Schiff-positive globules were observed. Some cells were cytoplasmically mucin-positive. These findings are compatible with gastric carcinoma showing hepatoid differentiation. *Helicobacter pylori* was negative. Lesions on the peritoneum and intestinal serosal surfaces were defined as metastases of the gastric adenocarcinoma.

After the second operation, abdominal distension and tenderness progressed. The patient's general condition worsened. Since the tumor was surgically unresectable, the patient was treated with a combined chemotherapy consisting of paclitaxel (200 mg/m^2 on day 1), cisplatin (15 mg/m^2, on days 1-5), and 5-fluorouracil (FU, 750 mg/m^2 on days 1-5). After two cycles of this regimen, tumoral shrinkage was not achieved and the patient lost weight despite total parenteral nutrition. He received four cycles of cisplatin (100 mg/m^2 on day 1), adriamycin (30 mg/m^2 on day 1), 5-FU (500 mg/m^2 on days 1-5) and docetaxel (50 mg/m^2 on day 1), cisplatin (100 mg/m^2 on day 1), irinotecan (20 mg/m^2 on days 1-5) alternately. No recovery was observed in abdominal ultrasound and CT. Due to severe abdominal pain, he received palliative radiotherapy (180 cGy) to the tumor region. Because of progressive disease, a combined regimen of bevacizumab (7.5 mg/kg on day 1), irinotecan (150 mg/m^2 on day 2, docetaxel (60 mg/m^2 on day 2), and oxaliplatin (85 mg/m^2 on day 3) was initiated as a salvage therapy. After one course of this regimen, the patient died with progressive disease, eight months after the initial diagnosis.

Discussion

Gastric adenocarcinoma is a rare entity in the pediatric population. A recent study reported that it constitutes 1.2% of all pediatric malignancies[5]. Fewer than 30 cases have been documented[2-5]. The latest study was performed by Subbiah et al.[5]. They reported that in a period of 18 years, five pediatric patients were diagnosed as gastric adenocarcinoma in one particular cancer center, which was 0.08% of all cancer patients[5]. Based on location, gastric tumors may present with symptoms of dysphagia, abdominal pain, distension, hematemesis, melena, and/or abdominal mass. Our patient presented with abdominal pain and gastric perforation. Spontaneous gastric perforation due to malignancy is an uncommon complication in children. Mahar et al.[6] reviewed perforated gastric cancer reports, which included 127 patients. They reported

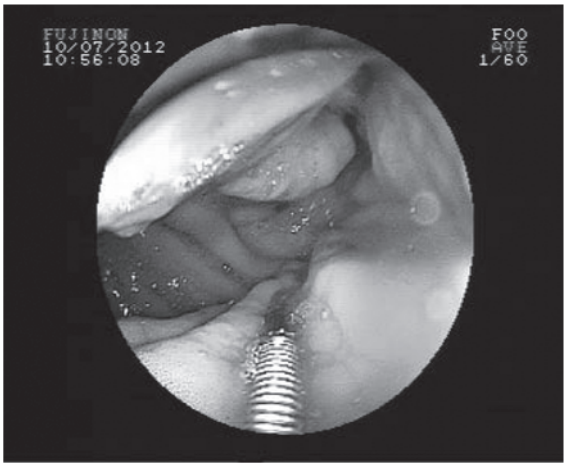

Fig. 1. Endoscopic appearance of the hepatoid gastric carcinoma.

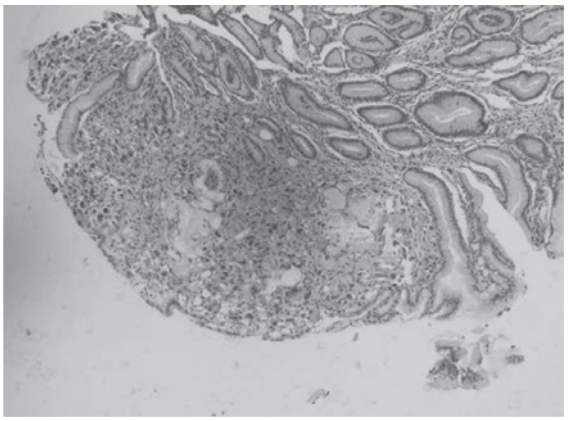

Fig. 2. Gastric biopsy: Gastric adenocarcinoma with hepatoid features, composed mainly of solid and focal glandular formations. Hematoxylin and eosin (HE) stain × 100.

that less than 3% of gastric cancers presented with gastric perforation, and the median age ranged from 61-72 years. Patients with gastric perforation in the setting of malignancy present with symptoms that are not indistinguishable from those of benign peptic ulcer disease. To our knowledge, there has been no gastric cancer patient presenting with gastric perforation in the pediatric population. Our patient had epigastric pain of only two weeks and had no history of peptic ulcer disease, and his other symptoms, which were loss of weight, anorexia and fatigue, started in a short period of time. All these findings were atypical for peptic ulcer disease. Soon after the surgery, we performed an endoscopy, in which a mass was observed in the stomach. In our opinion, in atypical clinical presentation of gastric perforation in children, endoscopy should be performed as soon as possible after surgical repair.

Hepatoid adenocarcinoma (HAC) is a rare extrahepatic tumor resembling the histological appearance of hepatocellular carcinoma, and it mostly expresses AFP. It usually originates from the stomach. Similar to the other previously published HAC cases, the most striking feature in our case is the "hepatoid" appearance of the tumor tissue.

The abnormal elevation in AFP in the serum of children is usually peculiar to yolk sac tumor or hepatoblastoma. In addition, some reports showed that AFP can also be produced by gastrointestinal tract organs, rectal carcinoma, gallbladder carcinoma, lung carcinoma, and bladder cancer in adults[7]. Our patient did not have any sign of chronic liver disease or inflammatory bowel disease, which can also cause elevated serum AFP levels. Since the tumor specimen was positive for AFP, we believe that the mildly elevated serum AFP level was due to the tumor.

The first case of AFP-producing gastric cancer was reported by Ishikura et al.[8]. In a recent study from China, it was reported that among the 4,426 patients with gastric cancers evaluated, 104 of all cases (2.3%) were diagnosed as AFP-producing gastric cancer. In that study, preoperative serum AFP levels ranged from 10 to 3,000 mg/L, and the median value was 41 mg/L[7]. Our patient also had a mildly elevated serum AFP level (207 mg/L). Liu et al.[7] reported that there was

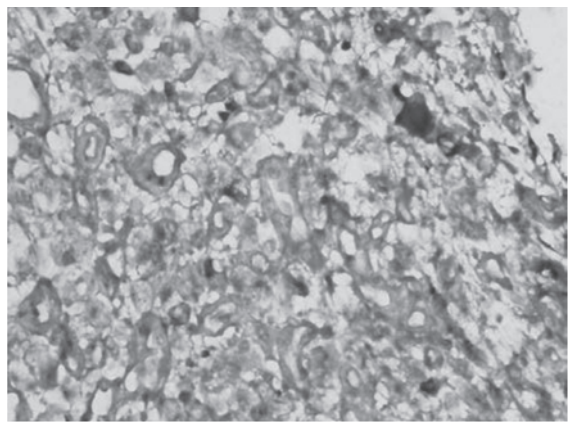

Fig. 3. Immunohistochemical staining for alpha-fetoprotein (AFP) shows diffuse positivity in the hepatoid areas. Immunoperoxidase x 400.

a significantly higher incidence of vascular invasion, lymph node metastasis and liver metastasis in the AFP–positive group than in the negative group. Fifty percent of patients have liver metastasis. In another study, Chang et al.[9] also reported that there was a higher frequency of venous invasion, lymph node metastasis, liver metastasis, and advanced stage in the AFP-positive group than in the negative group. These observations indicated that AFP-producing gastric cancer has a poorer prognosis than common gastric cancer. Our patient did not have liver metastasis. He had advanced stage disease due to peritoneal carcinomatosis. In the literature, it has been reported that liver metastasis can occur late after the first diagnosis[10,11]. Patients should be followed up for liver metastasis in short periods of time.

The case described in this paper is the youngest patient in the literature. Occurrence of AFP-producing GHAC in a child has not been described in the English literature before. Because of the rarity of gastric adenocarcinoma in children, the treatment approach is usually based upon the treatment modalities used in adult patients. There is no standard treatment modality. Surgery, neoadjuvant and/or adjuvant chemotherapy and radiotherapy are used for different patients. Combination chemotherapy regimens containing cisplatin and 5-FU are the most widely used regimens for first-line therapy of gastric adenocarcinoma[12]. With a median survival time of 7–10 months, metastatic gastric adenocarcinoma is an aggressive malignancy in adults, and the two-year survival is approximately 10–15% with conventional chemotherapy[13]. Our patient did not respond to several chemotherapy regimens. He had peritoneal carcinomatosis at the initial diagnosis and died due to progressive disease.

In conclusion, the diagnosis of gastric carcinoma is usually difficult since initial symptoms are often mild and indefinite. Ultrasonography and CT studies may be non-diagnostic and falsely negative. In children who present with symptoms of peptic ulcer disease, early gastrointestinal system endoscopy with biopsy can prevent delay in the cancer diagnosis. Our case is very interesting in many aspects. Most importantly, this is the first reported case in a child of AFP-producing hepatoid gastric adenocarcinoma presenting with gastric perforation.

REFERENCES

1. Harting MT, Blakely ML, Herzog CE, et al. Treatment issues in pediatric gastric adenocarcinoma. J Pediatr Surg 2004; 39: e8–e10.
2. Ladd AP, Grosfeld JL. Gastrointestinal tumors in children and adolescents. Semin Pediatr Surg 2006; 15: 37-47.
3. Roviello F, Rossi S, Marrelli D, et al. Perforated gastric carcinoma: a report of 10 cases and review of the literature. World J Surg Oncol 2006; 4: 19.
4. Vlachostergios PJ, Voutsadakis IA, Barbanis S, Karasavvidou F, Papandreou CN. AFP-producing hepatoid adenocarcinoma of the stomach: a case report. Cases J 2009; 2: 9296.
5. Subbiah V, Varadhachary G, Herzog CE, Huh WW. Gastric adenocarcinoma in children and adolescents. Pediatr Blood Cancer 2011; 57: 524-527.
6. Mahar AL, Brar SS, Coburn NG, Law C, Helyer LK. Surgical management of gastric perforation in the setting of gastric cancer. Gastric Cancer 2012; 15 (Suppl): S146-152.
7. Liu X, Cheng Y, Sheng W, et al. Clinicopathologic features and prognostic factors in alpha-fetoprotein-producing gastric cancers: analysis of 104 cases. J Surg Oncol 2010; 102: 249-255.
8. Ishikura H, Fukasawa Y, Ogasawara K, et al. An AFP-producing gastric carcinoma with features of hepatic differentiation. A case report. Cancer 1985; 56: 840-848.
9. Chang YC, Nagasue N, Abe S, et al. Comparison between the clinicopathologic features of AFP-positive and AFP-negative gastric cancers. Am J Gastroenterol 1992; 87: 321-325.
10. Shibata Y, Sato K, Kodama M, Nanjyo H. Alpha-fetoprotein-producing early gastric cancer of the remnant stomach: report of a case. Surg Today 2007; 37: 995-999.
11. Chang YC, Nagasue N, Abe S, et al. Alpha fetoprotein producing early gastric cancer with liver metastasis: report of three cases. Gut 1991; 32: 542-545.
12. Price TJ, Shapiro JD, Segelov E, et al. Management of advanced gastric cancer. Expert Rev Gastroenterol Hepatol 2012; 6: 199-208.
13. Shah MA, Ramanathan RK, Ilson DH, et al. Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol 2006; 24: 5201–5206.