

# Gastric Adenocarcinoma with Coexistent Hepatoid Adenocarcinoma and Neuroendocrine Carcinoma

## —A Case Report—

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Received : June 9, 2008  
Accepted : September 30, 2008

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This report represents a very rare case of a gastric adenocarcinoma that was coexistent with hepatoid adenocarcinoma and neuroendocrine carcinoma. A 77-year-old man was admitted to our hospital due to a huge ulcerofungating mass identified at the proximal body of the stomach. After a pathological diagnosis of the tumor as a poorly differentiated adenocarcinoma was made, the patient underwent a total gastrectomy with lymph node dissection. Microscopically, the tumor consisted of three morphologically distinct components—tubular adenocarcinoma, hepatoid adenocarcinoma and neuroendocrine carcinoma. The hepatoid adenocarcinoma component resembled a hepatocellular carcinoma and produced alpha-fetoprotein. The neuroendocrine carcinoma component was positive for chromogranin and synaptophysin immunostains. This is an example of the diverse morphological and immunophenotypical differentiation of gastric carcinomas.

**Key Words :** Gastric cancer; AFP; Hepatocellular carcinoma; Neuroendocrine carcinoma

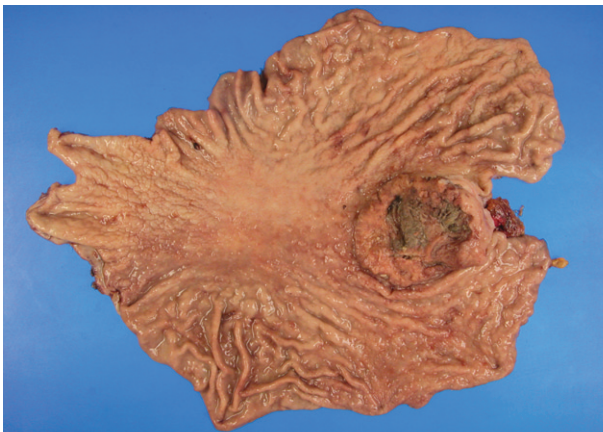
A primary gastric carcinoma is usually an adenocarcinoma based on histological classification. A hepatoid adenocarcinoma and neuroendocrine carcinoma are rare variants of gastric carcinomas<sup>1</sup>. Some hepatoid adenocarcinomas have presented with focal or extensive neuroendocrine differentiation, which were identified by a immunohistochemical analysis.<sup>2,3</sup> Cases with a coexistent choriocarcinoma or with focal choriocarcinomatous differentiation seen in the hepatoid adenocarcinoma have been reported.<sup>4,5</sup> In this study, we report a very rare case of a gastric carcinoma that presented morphologically and immunophenotypically with a distinct hepatoid adenocarcinoma, neuroendocrine carcinoma, and tubular adenocarcinoma.

## CASE REPORT

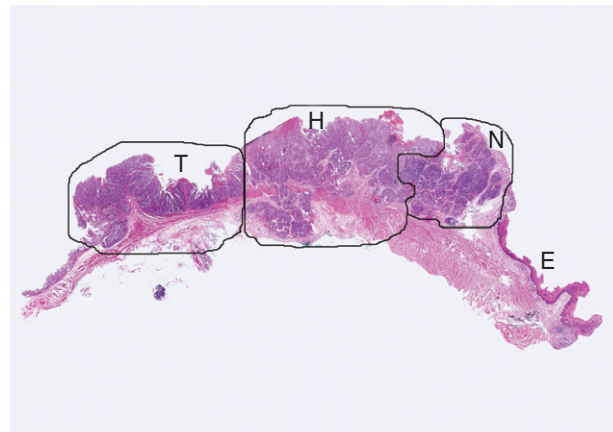
A 77-year-old man visited our hospital due to the incidental discovery of a mass on a routine health examination. The patient had no specific symptoms except for mild epigastric pain and mild weight loss prior to the examination. On a gastroduodenos-

scopic examination, a huge ulcerofungating mass was identified in the proximal body of the stomach. An endoscopic biopsy was performed and the pathological diagnosis was a poorly differentiated adenocarcinoma. The patient underwent a total gastrectomy with lymph node dissection.

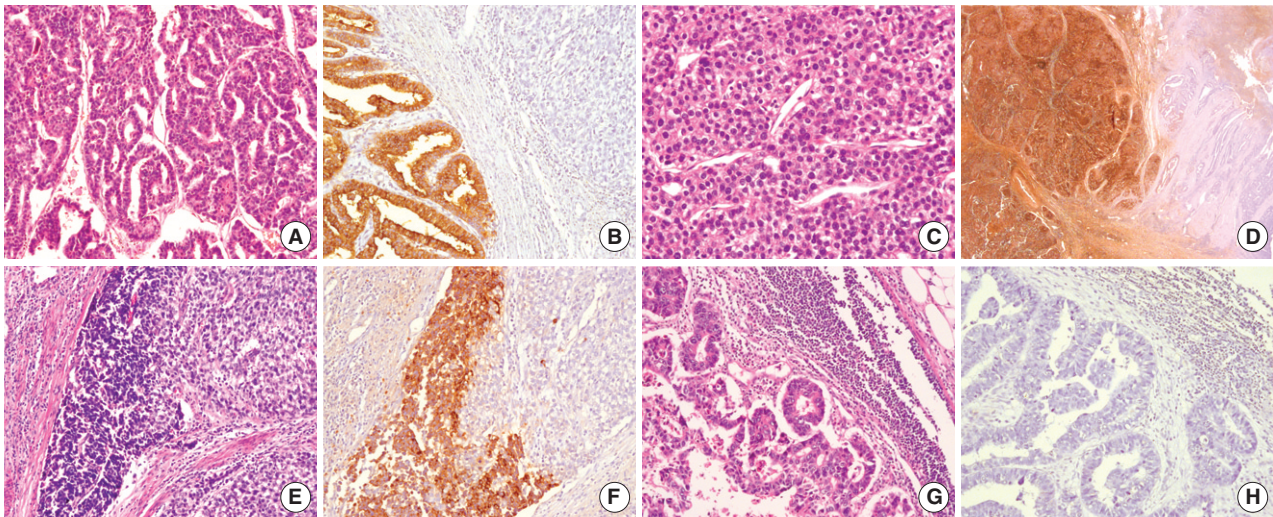
A gross examination showed a well demarcated ulcerofungating mass of 7.2 × 5.5 cm in size in the lesser curvature of the proximal body (Fig. 1). Microscopically, the tumor showed three distinct morphologic and immunophenotypic differentiation patterns—a moderately differentiated tubular adenocarcinoma, hepatoid adenocarcinoma and neuroendocrine carcinoma. The patterns comprised 40%, 45%, and 15% of the tumor volume, respectively (Fig. 2). The tubular adenocarcinomatous component showed tubulopapillary growth of cuboidal cells and was located at the distal (antral) side of the tumor mass (Fig. 3A). This area was positive for expression of the carcinoembryonic antigen (CEA) (11-7, 1:30, DAKO, Carpinteria, CA, USA) (Fig. 3B), but was negative for the expression of neuroendocrine markers such as synaptophysin (1:60, DAKO) and chromogranin (predilution, DAKO). The hepatoid adenocarcinoma areas that mimicked a



**Fig. 1.** The ulcerofungating mass is 7.2 × 5.5 cm in size and is located in the proximal body.



**Fig. 2.** Macroslide of the tumor represents three morphological components: T, tubular adenocarcinoma; H, hepatoid adenocarcinoma; N, neuroendocrine carcinoma; E, esophagus.



**Fig. 3.** (A) The cuboidal tumor cells in the tubular adenocarcinoma component show a tubulopapillary growth pattern. (B) The tumor cells are positive for CEA expression, whereas the hepatoid adenocarcinoma area (right upper corner) is negative for CEA expression. (C) The hepatoid adenocarcinoma is composed of a solid growth of polygonal cells with round, centrally located nuclei and abundant clear to eosinophilic cytoplasm. Sinusoidal vascular structures and small pseudoglandular spaces are noted. (D) The tumor cells in the hepatoid adenocarcinoma are diffusely positive for AFP (left side), while tubular adenocarcinoma component is negative for AFP (right side). Some tumor glands adjacent to the hepatoid adenocarcinoma nests are focally positive for AFP. (E) The transition from a hepatoid adenocarcinoma to a neuroendocrine carcinoma is noted at the periphery of the nests of the hepatoid adenocarcinoma. (F) Chromogranin staining highlights the transition area between hepatoid adenocarcinoma and neuroendocrine carcinoma. (G) Metastatic lymph node shows tubular adenocarcinoma component which is negative for AFP immunostain (H).

hepatocellular carcinoma were composed of a solid growth of polygonal tumor cells and occupied the central and proximal (esophageal) side of the tumor. The tumor cells had round, centrally located nuclei and abundant, clear or eosinophilic cytoplasm. Sinusoidal vascular structures and small pseudoglandular spaces were frequently seen within the tumor nests (Fig. 3C). This area was subjected to an endoscopic biopsy and preoperatively diagnosed as a poorly differentiated adenocarcinoma. The hepatoid

adenocarcinoma component was relatively well demarcated with the tubular adenocarcinoma areas. The tumor cells were diffusely positive for alpha-fetoprotein (AFP) (1:200, DAKO) expression. The expression of AFP was also noted in a focal area of tubular adenocarcinoma adjacent to the hepatoid adenocarcinoma nests. However, the majority of the tubular adenocarcinoma component was completely negative for AFP (Fig. 3D). In addition, the hepatoid adenocarcinoma was negative for expression of the CEA

and neuroendocrine markers. The transition from the hepatoid adenocarcinoma to neuroendocrine carcinoma was noted at the periphery of the nests of the hepatoid adenocarcinoma (Fig. 3E). These transition areas were highlighted by a chromogranin immunostain (Fig. 3F). The neuroendocrine carcinoma component, mainly located at the proximal side of the tumor, consisted of a solid growth of undifferentiated, small and monotonous tumor cells that were admixed with crushed, darker-staining cells. Geographic-shaped tumor necrosis was frequently noted. This area showed diffuse positivity for chromogranin and synaptophysin, as well as negativity for CEA and AFP. All three components of the tumor were diffusely stained with cytokeratin (AE1/AE3, 1:60, DAKO). Lymphatic and vascular permeation of the tumor cells were extensive and tumor thrombi within the large blood vessels were seen with hepatoid adenocarcinoma features. Metastases that originated from the tubular adenocarcinoma were identified in 3 out of 51 lymph nodes (Fig. 3G, H). The TNM classification of the tumor was T3N1M0.

The pre-operative serum AFP level was not determined and the CEA level was within normal limits. On postoperative day 7, the serum AFP level was 6,673 ng/mL. The patient did not receive systemic chemotherapy due to postoperative acute renal failure. Serum AFP and CA125 levels were increased to 68,090 ng/mL and 77.4 U/mL on postoperative day 49, respectively. On postoperative day 71, multiple hepatic masses and thrombi within portal and splenic veins were identified on an abdominal ultrasonography and computed tomography. Under suspicion of hepatic metastasis, the patient had suffered from renal failure, pseudomembranous colitis, herpes zoster and aspiration pneumonia. He died of respiratory failure on postoperative day 91.

## DISCUSSION

Since the first case of gastric carcinoma producing serum AFP was described in 1970,<sup>6</sup> many cases of AFP-producing gastric carcinomas have been reported.<sup>7-9</sup> Recently, a hepatoid adenocarcinoma has been considered as a specific entity diagnosed by histological features that resemble a hepatocellular carcinoma, regardless of AFP production.<sup>2,3,10</sup> Moreover, it should be considered separate from an AFP-producing gastric carcinoma without hepatoid features because of a prognostic difference.<sup>2</sup> Our case study contained a hepatoid adenocarcinoma with production of AFP as a part of the tumor. As most cases of hepatoid adenocarcinoma have been accompanied with a conventional adenocarcinoma, our case had a tubular adenocarcinomatous area without

AFP production in most of the tumor cells. However, a few tumor glands adjacent to the hepatoid adenocarcinoma were weakly stained for AFP. We think that this is a good example representing an immunophenotypic transition from a conventional adenocarcinoma to a hepatoid adenocarcinoma. In our case, the expression of CEA was positive in the tubular adenocarcinoma and completely negative in the hepatoid adenocarcinoma, whereas 46.7% of hepatoid adenocarcinomas with AFP production were immunoreactive for CEA as described in a study of a large series.<sup>2</sup> Nagai and colleagues<sup>2</sup> demonstrated that a small number of tumor cells were stained with neuroendocrine markers, neuron-specific enolase, chromogranin and synaptophysin, in cases of hepatoid adenocarcinomas without AFP production, as well as in cases of AFP-producing adenocarcinomas without hepatoid features. In our case, the hepatoid adenocarcinoma showed complete negativity for the expression of neuroendocrine markers. Instead, well-defined nests of small, undifferentiated tumor cells reminiscent of neuroendocrine differentiation were present as a part of the tumor. The tumor cells in this area showed diffuse and strong immunoreactivity to chromogranin and synaptophysin. The intimate spatial relationship between a neuroendocrine carcinoma and a hepatoid adenocarcinoma (presence of neuroendocrine tumor cells at the periphery of the nests of hepatoid adenocarcinoma) suggests that the neuroendocrine carcinoma was transformed from the hepatoid adenocarcinoma in this patient. A hepatoid adenocarcinoma with diffuse neuroendocrine differentiation has been described previously.<sup>3</sup> The expression of chromogranin was extensive in areas of both hepatoid and intestinal-type cell populations that were positive for AFP expression.<sup>3</sup> The previously described case is different from the present case as our case demonstrated the presence of a neuroendocrine carcinoma as a part of the tumor component, which was separated from hepatoid and tubular adenocarcinomas morphologically and immunophenotypically. Okamoto *et al.*<sup>5</sup> reported a case with coexistent neuroendocrine carcinoma, hepatoid adenocarcinoma, and tubular adenocarcinoma of the stomach, with focal choriocarcinomatous differentiation in metastatic lymph nodes. This case was very similar to ours, except for the presence of choriocarcinomatous differentiation. A case of coexistent choriocarcinoma and hepatoid adenocarcinoma has also been reported in the literature.<sup>4</sup> We believe that all of these cases are examples of diverse morphological and immunophenotypical differentiation of gastric carcinomas. The presence of morphological transition areas from a hepatoid adenocarcinoma to a neuroendocrine carcinoma, and the presence of AFP-positive cells in the tubular adenocarcinoma areas adjacent to the hepatoid adenocarcinoma suggests that the tumor

in our patient arose from a pluripotent, primitive neoplastic cell with diverse differentiation capacity.

A hepatoid adenocarcinoma has been associated with poorer patient survival than a conventional adenocarcinoma.<sup>2</sup> Our patient had developed multiple liver masses which were considered as metastasis. Although he died as a result of postoperative complication, the presence of extensive vascular invasion and distant metastasis suggests his adverse clinical outcome.

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