Virchows Arch (1998) 432:85–87

CASE REPORT

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α-Fetoprotein-producing gastric carcinoma presenting focal hepatoid differentiation in metastatic lymph nodes

Received: 7 November 1996 / Accepted: 20 May 1997

Abstract Hepatoid adenocarcinoma (HA) is a rare variant of adenocarcinoma of the stomach, which is clinically characterized by increased level of serum α-fetoprotein(AFP) and poor prognosis. Microscopic findings include both adenocarcinomatous and hepatoid elements. A case of gastric adenocarcinoma with focal hepatoid differentiation confined within the metastatic lymph nodes occurred in a 55-year-old woman, who developed an advanced gastric carcinoma composed entirely of a typical papillo-tubular adenocarcinoma. Metastatic tumors were present in 8 of 13 perigastric lymph nodes, and 3 of these showed medullary and trabecular tumour growth reminiscent of hepatocellular carcinoma with immunohistochemical positivity for AFP. Preoperative serum AFP was 630 ng/ml and dropped to 76 ng/ml 2 weeks after the operation. Microscopic and immunohistochemical studies on the entire primary tumour tissue failed to demonstrate a focus of hepatoid or an AFP-positive area. This suggests that elevation of serum AFP may be reflected by focal hepatoid differentiation only in the metastatic lymph nodes, requiring extensive evaluation of the metastatic tumour in regional lymph nodes in the case of AFP-producing gastric carcinoma.

Key words Hepatoid adenocarcinoma · AFP-producing gastric carcinoma · Stomach · Alpha-fetoprotein · Metastasis

Introduction

Since Boureille et al. [1] first reported a case of stomach cancer with elevated serum AFP, such AFP-producing gastric carcinomas have been reported worldwide [2–9], but especially in Japan. In 1985, Ishikura et al. [4] proposed the term hepatoid adenocarcinoma of the stomach, which was defined as a variant of gastric carcinoma in which both adenocarcinomatous and hepatoid areas are confirmed microscopically. Cumulative series [5–8] have shown that hepatoid adenocarcinomas of the stomach has a strong tendency to lymphatic and venous invasion and liver metastasis, and even early gastric cancers are known to have a poor prognosis [7]. Microscopically, hepatoid adenocarcinoma of the stomach is diagnosed by demonstration of hepatoid areas, which are histologically similar to hepatocellular carcinoma of any subtype. However, the diagnosis is often missed without awareness that hepatoid areas are usually found in the deeper parts of the tumours and/or in metastatic lymph nodes. In this report we describe a case of gastric adenocarcinoma in which the serum AFP was elevated and hepatoid areas were found only in metastatic spread to perigastric lymph nodes.

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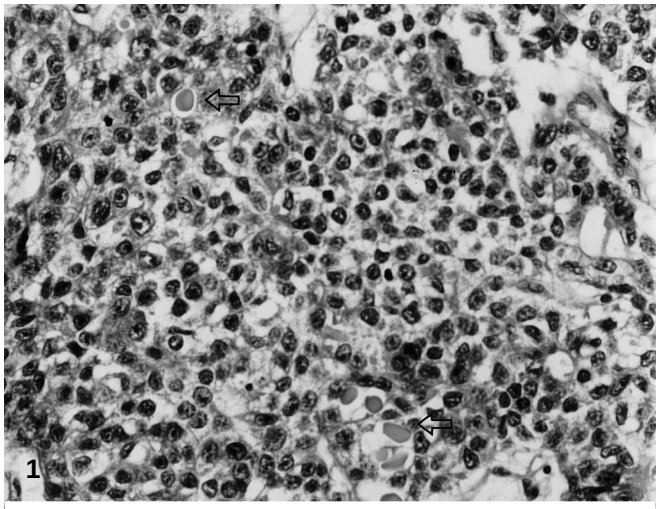
Clinical history

A 55-year-old woman was admitted to Seoul National University Hospital with a 2-year history of epigastric discomfort and indigestion. Endoscopic examination of the stomach disclosed an ulceroinfiltrative gastric cancer in the high body. Preoperative serological examination revealed elevated AFP (630 ng/ml). Liver function test was otherwise normal and the serological markers for hepatitis B and C viruses were all negative. Abdominal sonographic examination and computed tomography failed to show any mass in the liver. Radical total gastrectomy was performed and 2 weeks after the operation the serum AFP level fell to 76 ng/ml. The postoperative course was uneventful, and the patient remains alive 7 months after operation.

Materials and methods

All of the tumour tissue was sampled from the formalin-fixed subtotal gastrectomy specimen. Histological slides from paraffin-embedded blocks were stained with HE. Immunohistochemical stainings were done on formalin-fixed, paraffin-embedded tissues using the avidin–biotin peroxidase technique. The primary antibodies consisted of anti-AFP (Dakopatts, Denmark) and anti-β-HCG (Dakopatts, Denmark).



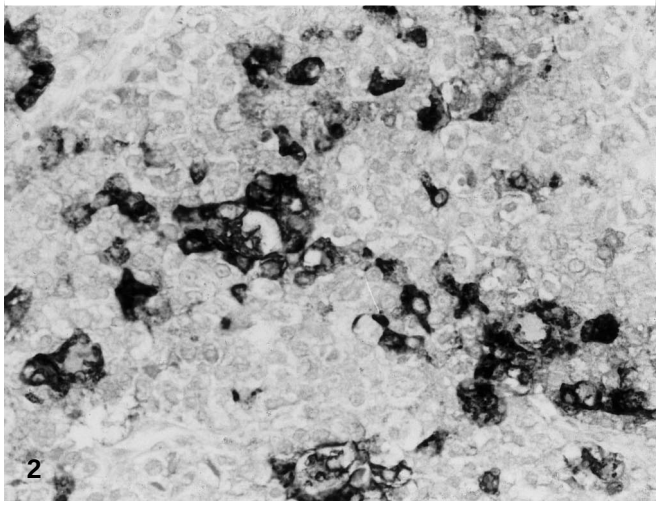


Fig. 1 Photomicrograph of metastatic lymph node, demonstrating tumour cells with abundant cytoplasms and centrally located nuclei. Tumour cells are arranged in a solid pattern. Hyaline globules are found in extracytoplasmic spaces (*arrow*). HE, ×200

Fig. 2 Immunohistochemical staining. Metastatic tumour in the perigastric lymph node shows patchy, strongly positive reaction for α-fetoprotein. Immunoperoxidase, ×200

Pathological findings

The resected stomach contained a 4×4-cm ulceroinfiltrative tumour in the high body along the lesser curvature. The adjacent mucosal folds showed distinct convergence toward the tumour. The serosal surface was smooth and glistening and free of adhesion to adjacent organs. Perigastric lymph nodes along the lesser curvature were enlarged.

Microscopically, the primary tumour was composed purely of adenocarcinoma and tumour cells were well to moderately differentiated and arranged in a tubulo-papillary pattern. The tumour penetrated the muscle coat and invaded the subserosal layer. Multiple venous and lymphatic tumour emboli were seen in the submucosal and muscle layers. The majority of tumour emboli appeared as solid cell nests without a glandular configuration. However, there was no focus suggestive of hepatoid differentiation in the entire primary tumor. Eight of 13 perigastric lymph nodes along the lesser curvature (regional lymph node 3) contained metastatic tumour deposits, and 3 of these showed hepatoid areas in which tumour cells were arranged in a solid pattern (Fig. 1). These nodes with hepatoid areas were located within 3 cm of the edge of the primary tumour. Tumour cells were large, and their cytoplasm was eosinophilic and granular, containing polygonal, slightly pleomorphic central nuclei. However, there was no evidence of bile production. Extra- and intracytoplasmic hyaline globules were scattered in these areas. Immunohistochemical staining revealed positivity for AFP (Fig. 2) and negativity for beta-human chorionic gonadotrophin (β-HCG). The primary tumour in the stomach was negative for both AFP and β-HCG.

Discussion

AFP is a useful tumour marker for hepatocellular carcinoma and yolk sac tumour. However, its production is not always a specific finding in tumours of the organs of yolk sac derivatives or liver, and AFP is produced by neoplastic cells in gastric cancer [1–9], gallbladder carcinoma [10, 11], pancreatic carcinoma [12, 13], lung cancer [14, 15] and renal cell carcinoma [16]. In utero, the liver and yolk sac and also the gastrointestinal tract and kidney all produce AFP [17]. In tumour cells, re-expression of the AFP gene, which is suppressed in normal cells after birth, is related to hypomethylation of the 5′ end of the AFP gene [18, 19].

AFP is a glycoprotein and has variants according to its affinity for lectin, such as concanavalin A or lens culinalis agglutinin A [20, 21]. Yolk sac-type AFP has a low affinity and hepatic type AFP, a high affinity for concanavalin A [20]. Lectin affinity of AFP produced by gastric carcinomas varied and AFP of Ishikura et al. cases showed lectin affinity similar to hepatic type AFP [5]. In Ooi et al. series, four cases had lectin affinity similar to yolk sac-type AFP and one case had lectin affinity similar to hepatic type AFP [22]. Although Ishikura et al. cases showed foci histologically similar to hepatocellular carcinoma, Ooi et al. cases did not demonstrate histological features of either hepatoid or embryonal differentiation. On the basis of the histological findings, AFP-producing gastric carcinomas has been classified into three subtypes: the hepatoid, yolk sac, and enteroblastic types [23]. It seems that gastric carcinoma can produce AFP through differentiation of its progenitor tumour cells into hepatocelluar, embryonal, or enteroblastic lines. Recently, Aizawa et al. [6] added another subtype, poorly differentiated medullary type. Ooi et al. cases were also of the poorly differentiated medullary type, and these authors reported that the AFP produced by their patients was of the gastrointestinal tract type, rather than hepatic or yolk sac type [9].

Since about 30% of hepatocellular carcinomas do not produce AFP [24] and there are AFP-negative hepatoid adenocarcinomas such as those reported by Nagai et al. [8], hepatoid adenocarcinoma cannot be the same as the hepatoid type of AFP-producing gastric carcinoma. It includes both the hepatoid type of AFP-producing gastric

carcinoma and the AFP-negative adenocarcinoma with hepatoid differentiation. Nagai et al. [8] also emphasized that hepatoid adenocarcinoma, as defined by its characteristic histological features, has a poor prognosis whether or not the tumour produces AFP, and that hepatoid adenocarcinoma should therefore be distinguished from AFP-producing carcinoma with hepatoid features.

Microscopically, diagnosis of HA requires the presence of both adenocarcinomatous and hepatoid areas in the primary tumour of the stomach [4]. However, the present case may be an extreme example of the hepatoid area's not being obvious in the primary tumour whilst evident in metastatic foci. In our previous study of 14 cases of HA of the stomach [9], hepatoid areas tended to occur in deeper parts of the primary tumours and to be found in metastatic lymph nodes. In those cases, metastatic lymph nodes showed hepatoid and/or adenocarcinomatous areas. We examined the entire primary tumour tissue from the stomach in this case, which consisted exclusively of well-differentiated adenocarcinoma and gave negative immunostaining to AFP in all the sections examined. Elevation of serum AFP seemed to be entirely reflected in the hepatoid areas in metastatic lymph nodes that were also positive for AFP in immunohistochemical staining. The poor prognosis of HA is not surprising, as it is reflected in a high incidence of venous and lymphatic invasion as well as metastasis to perigastric lymph nodes.

The appearance of hepatoid areas in metastaic lymph nodes in the present case is not clearly understood. One possible explanation is that a small hepatoid area might have been missed in the primary tumour of the stomach. This is not very likely, because meticulous microscopic examination of the entire primary tumour tissue failed to demonstrate any focus of hepatoid differentiation, and it all gave negative immunoreactivity to AFP. Another possibility is that HA may occur through development of new subclone from the primary adenocarcinoma during tumour progression, which apparently acquires the ability to invade more deeply and to metastasize, as well as to undergo hepatocellular transdifferentiation.

Unless pathologists are aware of the possibility, expression of AFP-producing gastric carcinoma in the broad sense could be an additional exit for this subtype. Among subtypes of AFP-producing gastric carcinoma, the hepatoid type is alleged to be the most malignant. Thus, it is essential to examine the metastatic lesion meticulously to search for a hepatoid area in the metastatic foci. Similar examples are also found in the dedifferentiated sarcomas in which metastatic foci often show a totally undifferentiated pattern while the primary lesion is composed of differentiated tumour.

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