Int J Clin Exp Pathol 2012;5(8):845-851
www.ijcep.com/ISSN:1936-2625/IJCEP1208024

Case Report

Intramucosal stomach adenocarcinoma metastasizing as a large intraabdominal mass with focal choriocarcinomatous differentiation

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Received August 27, 2012; Accepted September 11, 2012; Epub October 1, 2012; Published October 15, 2012

Abstract: We report a case of gastric intramucosal adenocarcinoma giving rise to a large metastatic intraabdominal mass with focal choriocarcinomatous differentiation. The main histological picture of the surgically resected abdominal tumor was well differentiated adenocarcinoma with focal choriocarcinomatous differentiation. Serum hCGβ level showed 710mIU/dl postoperatively, and the gastric lesion featured small foci of well differentiated adenocarcinoma in adenoma with no choriocarcinomatous differentiation. The origin of the abdominal tumor was the main point of question. HNF4α is a transcription factor of embryonic liver differentiation, whose distribution is restricted to hepatocytes and certain neoplastic tissue including gastric adenocarcinoma. Hep Par 1 is originally developed for the discrimination of hepatocellular carcinoma, but a part of gastric adenocarcinoma also shows positive staining. Immunostaining with panel of antibodies for CK7, CK20, HNF4α, and Hep-Par1 showed pattern of gastric adenocarcinoma, and a diagnosis of a very rare intramucosal gastric adenocarcinoma metastatic to the abdominal cavity was established. Diagnostic utility of the panels of above antibodies for discrimination of the tumor origin was confirmed, and the relation between the metastatic ability of the gastric adenocarcinoma and its choriocarcinomatous differentiation is discussed.

Keywords: Stomach, choriocarcinoma, Hep-par 1, HNF4α, intramucosal carcinoma

Introduction

Choriocarcinoma is a highly malignant, widely metastatic trophoblastic tumor which usually occurs in the uterus but also may be found in the male testis. Almost all remaining choriocarcinomas arise in midline locations such as the mediastinum, retroperitoneum, and pineal gland. Only rarely has the neoplasm been reported in the gastrointestinal tract, and in the documented cases, the stomach is the most common site of origin [1]. Gastric choriocarcinomas occur in adults from 30 to 80 years old, but most commonly in elderly males (2 to 1) compared as adenocarcinomas. Histologically, they feature typical mixtures of cytotrophoblastic and syncytiotrophoblastic elements, with syncytial cells containing human chorionic gonadtropin (hCG). They may appear homogeneous, but more usually present adenocarcinomatous components [1, 2]. Rarely choriocarcinomatous elements may appear only in metastatic sites [1].

HNF4α belongs to the nuclear steroid-hormone-receptor superfamily of transcription factors, and is a central regulator of hepatocyte differentiation and function of embryonic cells [3]. Its production is limited to several normal and neoplastic tissues [4, 5]. By immunohistochemistry, gastric adenocarcinomas show positive reactions, but human trophoblastic tissue generally shows no staining [5].

Hepatocyte paraffin 1 is a monoclonal antibody developed specifically to react with hepatic tis-

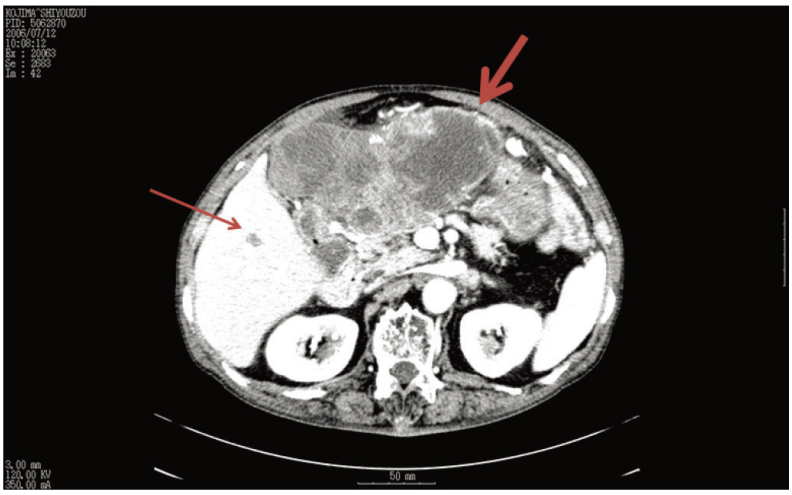

Figure 1. Abdominal CT scan. The large arrow indicates an abdominal tumor. The small arrow shows liver metastasis.

sue, but some cases of adenocarcinoma of various organs show positive reaction in routine formalin-fixed paraffin embedded tissue [6-9]. A few cases of gastric adenocarcinoma which show positive reaction to Hep Par1 are reported [6, 8, 9].

We experienced a case with the large abdominal mass consisting of a well differentiated adenocarcinoma with focal choriocarcinomatous components. Although the patient had small foci of gastric intramucosal well differentiated adenocarcinoma without choriocarcinomatous components, submucosal invasion was not apparent, and the origin of the abdominal and liver tumors was unknown. We studied the origin of abdominal tumor using immunohistochemistry for HNF4α, HepPar1, CK7, and CK20, and verified the gastric origin of this tumor. This is a very rare case of metastatic gastric intramucosal adenocarcinoma with choriocarcinomatous differentiation.

Case report

The patient is a 73 year-old male with no particular past medical history. He felt difficulty in urination and defecation from June 2006, and had abdominal distention and abdominal pain. A large intraabdominal mass and multiple liver tumors were found by abdominal CT scan and he was admitted to the hospital in July. At admission, No peculiar abnormal laboratory data were seen by routine laboratory tests. No obvious pulmonary lesions were evident by a chest CT scan. The abdominal tumor was observed as a high density mass on T2 contrasting CT scan, pushing aside the transverse colon. No obvious feeder arteries were apparent. No connection with the pancreatic duct and bile duct was found but continuity with the stomach was suspected (**Figure 1**). The liver showed multiple nodules with diameters a few millimeters. Tumor cytology of ascites pointed to an adenocarcinoma. At this time, two bulging lesions of the stomach (anterior walls of the pylorus and the angulus) were discovered by gastrointestinal series (**Figure 2**). From four regions of the stomach (anterior wall of fundus, anterior wall of pylorus, anterior wall of angulus, and large curvature of body), gastric endoscopic biopsies were taken, and severely atypical epithelium focally enough for well differentiated adenocarcinoma was found in the pyloric and angulus walls. From the above results, gastric adenocarcinoma with metastasis to the abdominal cavity and liver was suspected.

Laparotomy, partial pancreatectomy with splenectomy, partial hepatectomy, and gastrectomy was performed. In the surgically resected material of the abdominal tumor, the main histological feature was well differentiated adenocarcinoma, but focal choriocarcinomatous elements were found. Postoperatively, serologic test demonstrated a high hCGβ level of 710mIU/dl (EIA method). The testis, pituitary gland, mediastinum showed no abnormalities by radiologic imaging. No gynecomastia was seen.

He was discharged at September, and chemotherapy was performed, but the postoperative course was dismal and the patient died in Jury 2007. An autopsy was not performed. The origin of the abdominal tumor was the point of discussion.

Table. Immunohistochemical properties of the patient's tumors

Antibody	Source	Dilution	Antigen retrieval	Abdominal tumor		Gastric tumor
				Adenocarci	Choriocarci	
CK7	DAKO	×100	1	+	+	+
CK20	DAKO	×50	2	-	-	-
Cdx2	Novocastra	×50	3	-	-	-
HNF4α	Perceus Proteomicus	×100	2	+	-	+
Hep Par1	DAKO	×50	4	+	-	+
EMA	DAKO	×200	None	+	-	+
HCG	DAKO	×3000	None	-	+	-
AFP	DAKO	×1000	None	-	-	-

1: 0.05%protease PBS room temperature 10min; 2: 10mM citrate pH6.0 pressure cooker 5min; 3: 10% TRS pressure cooker. 5min; 4: pH9 100°ERS 20min.

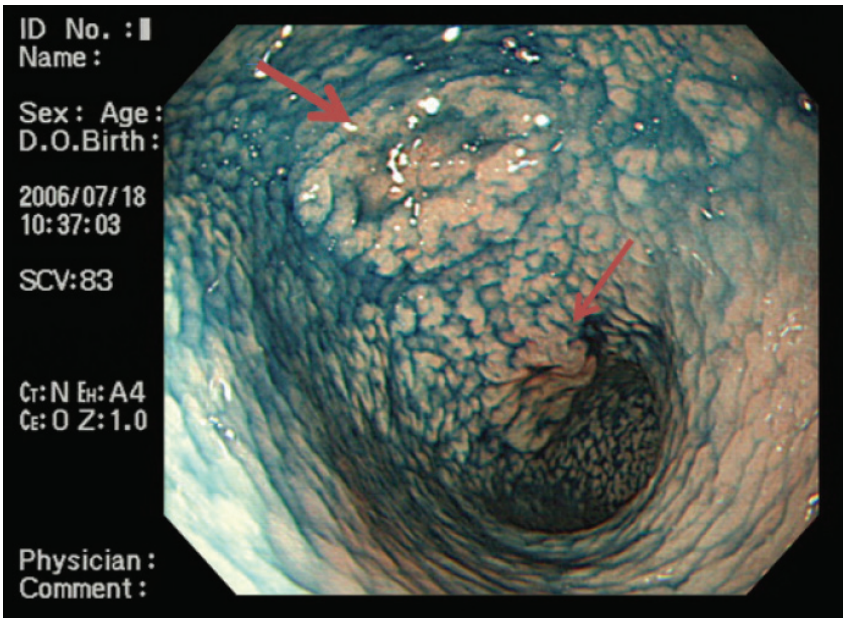

Figure 2. Endoscopic view of the gastric tumors. Two bulging lesions are seen in the antrum (arrows).

Materials and methods

Pathological specimens were taken from the resected stomach, abdominal tumor, and liver tumors, processed for embedding in paraffin, sectioned and stained with ordinary hematoxylin-eosin stain. The entire resected stomach was cut into 28 pieces in oblong card feature and examined precisely by microscopy. Some selected slices were stained by PAS+alcian blue stain. In representative sections of gastric adenocarcinoma, gastric non-neoplastic mucosa, abdominal tumor, and liver tumors, immunohistochemical staining was performed using the antibodies listed in the **Table** with the ABC method using an automated immunostainer (Kyowa medicus, Tokyo).

Pathological findings

The main abdominal tumor was attached to the anterior wall of gastric cardia, but direct invasion of the stomach, liver, pancreas, and superior mesenteric vein was not apparent by naked-eye observation. The abdominal tumor measured 20cm × 20cm × 20cm, and was a soft reddish mass with prominent necrosis and hemorrhage. On microscopy, its main component was well differentiated adenocarcinoma, but large areas of choriocarcinomatous differentiation was also noted. These contained many multinucleated syncytiotrophoblastic cells with deep staining eosinophilic to amphophilic cytoplasm as well as many mononucleated cytotrophoblasts. Bizarre large nuclei were also abundant. In the adenocarcinomatous regions, papillary growth of small atypical cells with gland formation was apparent. There were many blood vessels in choriocarcinomatous region associated with large areas of necrosis. There was transition between regions showing ordinary adenocarcinoma and choriocarcinoma (**Figure 3a** and **3b**). No elements recognizable as definite teratoma found in any sections. By PAS+alcian blue stain, abundant PAS positive cells were seen in the

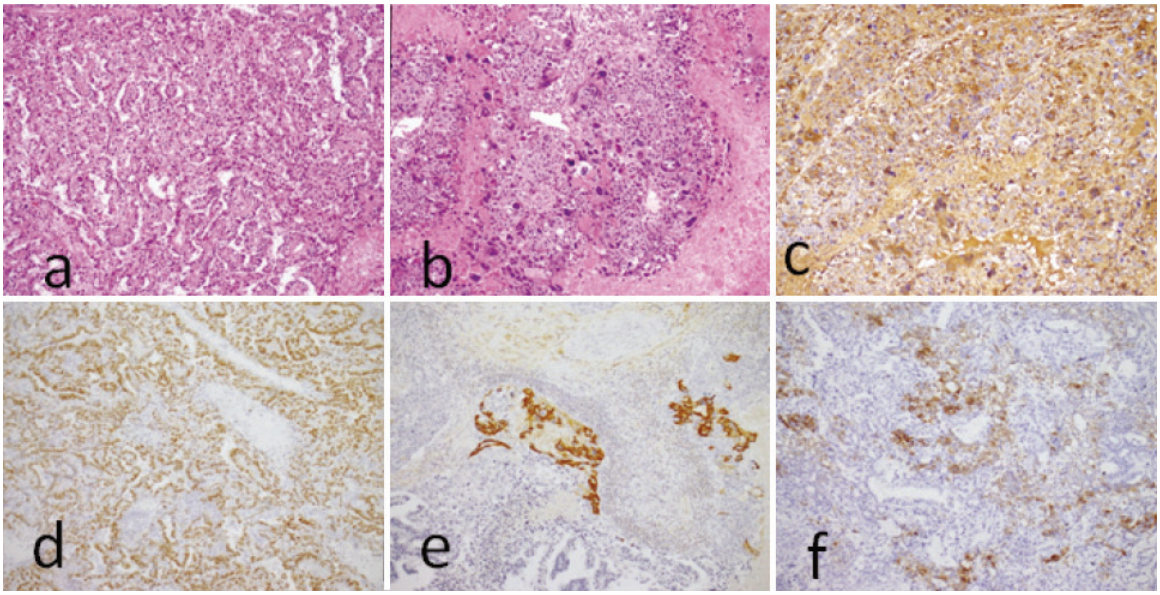

Figure 3. A. Microscopic view of the abdominal tumor. Adenocarcinomatous region. (HE, original magnification ×100); B. Microscopic view of the abdominal tumor. Choriocarcinomatous region. (HE, original magnification ×100); C. hCG immunostaining of the abdominal tumor. (hCG, original magnification ×100); D. HNF4α immunostaining of the abdominal tumor. (HNFα original magnification ×100); E. CK7 immunostaining of the abdominal tumor. (CK7, original magnification ×100); F. Hep Par 1 immunostaining of the abdominal tumor. (Hep Par 1, original magnification ×100).

adenocarcinomatous regions, but were scarce in the choriocarcinomatous regions.

The gastric tumors were both located in the anterior wall of angulus and pylorus, measured 1 cm×1 cm each, and showed features of well differentiated adenocarcinoma in adenomas (**Figure 4a**). No submucosal invasion was seen. Twelve lymph nodes were examined, but no metastasis was found. Thus, the lesions were diagnosed as early intramucosal well differentiated adenocarcinomas arising from adenoma of the stomach. The remaining gastric mucosa exhibited marked atrophic gastritis with intestinal metaplasia. Helicobacter organisms were not found. The liver tumors were of well differentiated adenocarcinoma type without choriocarcinomatous differentiation.

The results of immunostaining were summarized in **Table**. hCGβwas positive in syncytiotrophoblastic and cytotrophoblastic cells of the abdominal tumor (**Figure 3c**), but adenocarcinomatous region was negative . The adenocarcinomas in the stomach and the liver also did not stain. AFP showed no positive reaction in either the abdominal tumor or the gastric adenocarcinoma.

HNF4α was stained positive in the nuclei of the abdominal tumor (adenocarcinomatous foci), liver tumors, and gastric intramucosal adenocarcinoma (**Figure 3d** and **4b**), but not in the regions showing choriocarcinomatous differentiation. The intestinal metaplastic epithelium of non-neoplastic gastric mucosa also showed positive nuclear expression.

Both abdominal tumor and gastric adenocarcinomas showed staining pattern of CK7 positive, CK20 negative, and Hep Par1 positive (**Figure 3e** and **3f**, **4c** and **4d**). EMA showed focal staining to abdominal tumor and gastric adenocarcinoma. Cdx2 did not stained in both the abdominal tumor and gastric adenocarcinomas.

From these results, a diagnosis of gastric intramucosal well differentiated adenocarcinoma metastatic to the abdominal cavity and the liver was made.

Discussion

Many case reports of choriocarcinoma primary in the stomach have been published. Most authors have emphasized the theory of “retrodifferentiation” to explain how tumors contain-

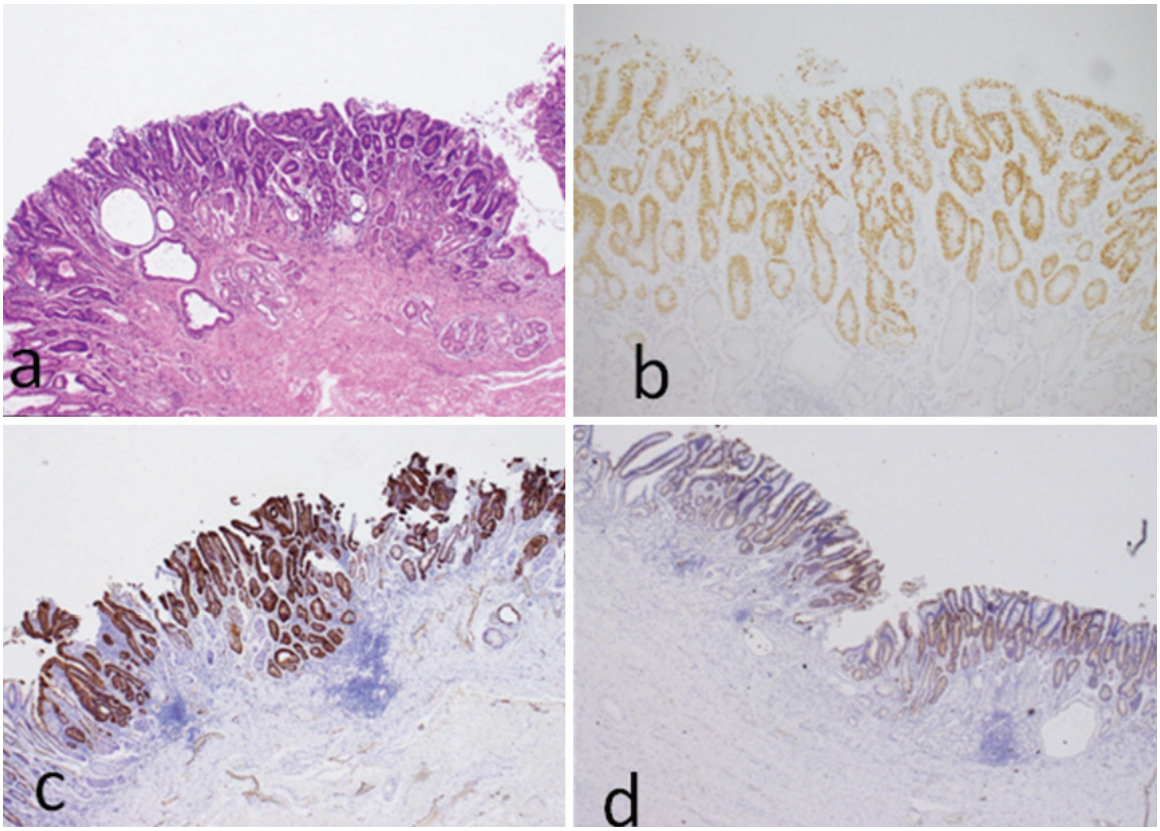

Figure 4. A. Microscopic view of the gastric tumor. (HE original magnification ×40); B. HNF4α immunostaining of the gastric tumor. (HNF4α, original magnification ×100); C. CK7 immunostaining of the gastric tumor. (CK7, original magnification ×40); D. Hep Par 1 immunostaining of the gastric tumor. (Hep Par 1, original magnification ×40).

ing trophoblasts can occur in the stomach [1]. This theory which was first proposed by Pick in 1926 (cited in 1) is now accepted the most authentic evaluation [1, 2]. All cells contain the entire genetic material for the whole organism, so if the certain surrounding environment does exist, cancers can differentiate in unusual directions including the formation of malignant trophoblasts. This hypothesis is based on the observation that many cases of primary gastric choriocarcinoma are found in coexistence with an ordinary adenocarcinoma, a transition from adenocarcinoma to choriocarcinoma being demonstrated in some cases.

In our abdominal tumor, choriocarcinomatous differentiation is evident, and several primary origins other than the stomach were conceivable.

HNF4α is a transcriptional protein involved in hepatic differentiation of embryonic tissue [3]. HNF4α antigen expression is restricted to certain tissues [4, 5]. For example, small intestine and colorectal mucosa show expression, but breast, prostate, and ovarian tissues do not [5]. Normal gastric mucosa lacks the antigen, but gastric adenocarcinoma and intestinal metaplastic mucosa are generally positive [5]. In an earlier study by Tanakas [5], all 14 cases of ordinary gastric adenocarcinoma showed positive reactions for HNF4α antibody. In our case, HNF4α showed positive staining in the abdominal tumor mainly in adenocarcinomatous regions, and also the gastric intramucosal adenocarcinoma.

Hep Par 1 is antibody originally developed for the discrimination of hepatocellular carcinoma, but a few gastric adenocarcinomas (signet ring cell type and intestinal type) show positive reaction to Hep Par1 [6-10]. In our case, both abdominal tumor and gastric adenocarcinoma showed positive staining for Hep Par 1.

No abnormality was found by pre- and postoperative laboratory testing in the patient's testis. But, there is the possibility of regression of a testicular germ cell tumor (so-called burned-out tumor), i.e. many cases of extragenital germ cell tumors has their disappearing primary tumors in testis [11]. But in general, HNFα, shows no positive reaction to gonadal tissue [5], and Hep Par 1 also shows no positive reaction to testicular germ cell tumor [6]. So, a testicular origin is unlikely in this case.

The differential diagnosis of cholangiocarcinoma is necessary. The ordinary cholangiocarcinoma shows immunohistochemical staining pattern of Hep Par 1 negative, CK7 positive, and CK20 positive [10, 12]. Our case showed Hep Par 1 positive, CK7 positive, and CK20 negative staining pattern. Further, as yet, there is no case report of cholangiocarcinoma with choriocarcinomatous differentiation.

Thus, the abdominal tumor of our case was strongly suspected as being derived from the gastric adenocarcinoma.

Intramucosal gastric cancer usually has excellent prognoses, but rare metastatic intramucosal gastric cancers have been described. Song et al. [13] found 2.0%(40cases) of their 1981 intramucosal cancers in Korea to show lymph node metastasis, and suggested a diffuse type histology and deep invasion into muscularis mucosa as important predictive factors. Listrom and Fenoglio-Preiser [14] have reported that gastric lymphatics normally begin as a plexus of vessels immediately superficial to, within, and below the muscularis mucosa, and the upper two-thirds of the gastric lamina propria is normally lack lymph vessels. But, blood vessels yet could be found in the high levels of the normal mucosa. [15] With gastric choriocarcinoma, there is a tendency for the choriocarcinomatous component to metastasize via blood vessels, while the adenocarcinomatous component follows the lymphatics [1]. Our tumor showed no metastasis to regional lymph nodes, and there were metastatic lesions in the abdominal cavity and the liver. This fact also suggests hematogenous spread of the gastric adenocarcinoma.

There is ever-growing evidence that neoplastic transformation in vivo and in vitro is frequently preceded and/or accompanied by biochemical, morphological, and behavioral transitions characteristic of a cell undergoing retrodifferentiation [16]. Owing to the above discussed retrodifferention theory, in the gastric choriocarcinoma, morphological retrodifferentiation will be accompanied by functional retrodifferentation, i.e. restoration of gene expression for hCG production which has been suppressed under non-cancerous conditions. The gastric tumor of our case may had a tendency to choriocarcinomatous retrodifferentiation, and this fact may have a relation to the metastatic ability of this tumor.

This case might have some contribution to the pathogenesis of gastric choriocarcinoma, and the diagnostic utility of HNF4α and Hep Par 1 for gastrointestinal adenocarcinoma is verified.

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