Case Report

Neuroendocrine liver metastasis in gastric mixed adenoneuroendocrine carcinoma with trilineage cell differentiation: a case report

Wenjin Zhang1, Weihua Xiao2, Haifen Ma2, Mingfei Sun2, Hongtan Chen1, Shusen Zheng1

1Division of Hepatobiliary Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University, School of Medicine, 79 Qingchun Road, Hangzhou 310003, China; 2Division of Pathology, Beilun People’s Hospital, 1288 Lushan East Road, Ningbo 315800, China

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Abstract: Mixed adenoneuroendocrine carcinoma (MANEC) is a rare disease, which mostly occurs in the gastrointestinal tract and pancreas. Here we report a case of gastric MANEC with tri-lineage differentiation in which only the neuroendocrine component had metastasized to the liver. Liver and gastric masses were detected by abdominal computed tomography, and the preoperative relationship between liver and gastric masses was unknown. The histopathological analysis after operation confirmed the gastric mass to be MANEC, whereas the liver mass was actually the metastatic neuroendocrine component of the gastric MANEC. In the pathologic diagnosis, tri-lineage differentiation, including tubular adenocarcinoma, neuroendocrine carcinoma and squamous cell carcinoma was observed in the gastric MANEC tissues. The mitotic and Ki-67 labeling indexes of the resected tumor tissue were high, and thus, the tumor was classified as a grade G3 neuroendocrine carcinoma, which has a poor prognosis. Multiple low-density masses were found in the right lobe of the liver 2.5 months after operation.

Keywords: Mixed adenoneuroendocrine carcinoma, gastroenteropancreatic neuroendocrine tumor, differentiation, immunohistochemistry

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are uncommon lesions and are usually derived from neuroendocrine cells distributed mainly in the mucosa and submucosa of the gastrointestinal tract and pancreas. Advances in diagnostic techniques, such as computed tomography (CT), magnetic resonance imaging, ultrasonography, endoscopy, and serological hormone tests, have led to an increase in the documented incidence of GEP-NETs. Epidemiology data from the European Neuroendocrine Tumor Society indicated that the incidence of GEP-NETs is about 1 per 100 000 population for pancreatic tumors and 1.95-2.5 per 100 000 for gastrointestinal tumors [1, 2]. The 2010 World Health Organization (WHO) guidelines classify GEP-NETs into three categories based on the histopathological evaluation of mitotic and Ki67 labeling indexes: (i) well-differentiated NETs including grade G1 and G2-NETs; (ii) poorly differentiated (small or large cell type) neuroendocrine carcinoma (NEC); and (iii) mixed adenoneuroendocrine carcinoma (MANEC) [3]. The incidence of MANEC, one of the rarest types of GEP-NETs, has not yet been epidemiologically analyzed. Here we report a case of gastric MANEC with liver metastasis resembling a large single hepatocellular carcinoma under abdominal CT. After radical resection, tri-lineage differentiation including tubular adenocarcinoma, neuroendocrine carcinoma and squamous cell carcinoma was observed in the pathological diagnosis of the gastric MANEC tissue. The liver mass was actually the metastatic neuroendocrine component of the gastric MANEC.

Case presentation

A 68-year-old man complaining of dull epigastric and right upper quadrant abdominal pain...
for 3 months was found to have a mass in the left lobe of the liver on ultrasound examination. The patient was admitted to our hospital for further treatment. He had undergone a 5 kg weight loss within the last 3 months. No significant positive signs were found on physical examination. Past medical history showed that he had suffered from chronic gastric ulcer and chronic hepatitis B for 5 years.

All serum tumor markers including alpha-fetoprotein, carcinoembryonic antigen, and carbohydrate antigen 19-9 were normal. Serum hepatitis B core antibody was positive, whereas hepatitis B surface antigen and hepatitis B e antigen were negative. The serum hepatitis B virus DNA level was below 5 × 10³ copies/ml. Liver function was normal.

Upon arrival, the patient was treated with gastric intubation because of vomiting and underwent further abdominal enhanced CT examination. The CT scan showed a mass, 12 cm in diameter, located in the left lobe of the liver (Figure 1A). The enhancement degree of the liver mass increased significantly in the arterial phase and decreased markedly in the venous phase (Figure 1A). A mass with mucosa enhancement was observed in the antrum of the stomach during the arterial phase (Figure 1B). Swelling lymph nodes were also observed above the antrum of the stomach (Figure 1C). Gastroscopy revealed a 3 cm diameter, ulcerating malignant-looking mass in the antrum of the stomach (Figure 1D). The preoperative relationship between the liver and gastric masses was uncertain. Therefore, left hepatectomy and distal gastrectomy were performed.

**Pathological findings**

The ulcerating mass in the antrum of stomach involved the gastric serous coat. Hematoxylin
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Figure 2. Specimen removed from the gastric mass shows MANEC. A: Representative section of the gastric tumor shows MANEC. Hematoxylin and eosin stain showing the close juxtaposition of the adenocarcinoma and neuroendocrine carcinoma components. ×200. B: The neuroendocrine carcinoma component expresses synaptophysin, whereas the gland-forming adenocarcinoma component does not. ×200. C: The neuroendocrine carcinoma component expresses chromogranin A, whereas the gland-forming adenocarcinoma component does not. ×200. D: Representative section showing the mitotic activity of the neuroendocrine carcinoma component. ×400. E: Representative section showing the Ki-67 staining of the neuroendocrine carcinoma component. ×200. F: Representative section showing the intracellular bridges in the trabecular region (arrow). ×400. G: Representative section showing CK5 expression in a small area of the trabecular region. H: Representative section showing the expression of p63, a basal/progenitor marker, in a small area of the trabecular region.

and eosin (HE) staining of the ulcerating mass showed two regions with distinct morphological features, which were closely juxtaposed. Cells in the upper right area were arranged in a gland-forming pattern, whereas cells in the lower left area were arranged in solid/trabecular and nodular patterns (Figure 2A). Synaptophysin and chromogranin A staining were positive in the solid/trabecular and nodular regions but negative in the gland-forming region (Figure 2B, 2C). Based on the histological features, the pathological diagnosis of the gastric mass was MANEC. The mitotic index was 50 mitoses per 10 high-power fields (HPFs), and the Ki-67 labeling index was 70% (Figure 2D, 2E). In addition, intracellular bridges a future of squamous differentiation were observed in small areas in the solid/trabecular region (Figure 2F). Positive cytokeratin CK5 staining further confirmed squamous differentiation (Figure 2G). Local positivity of p63 protein, a basal/progenitor marker, was also noted in a small area of the trabecular region (Figure 2H). The liver mass was coated with intact pseudocapsule, and the section was solid without necrotic foci. Immunohistochemical staining showed that the mass was negative for hepatocyte antigen and positive for caudal type homeobox 2 (CDX2), which strongly suggested its gastrointestinal origin (Figure 3A, 3B). In addition, almost all of the tumor cells in the histological section of the liver mass were positive for chromogranin A and synaptophysin (Figure 3C, 3D). Together, these observations indicated that the liver mass was the metastatic neuroendocrine component of the gastric MANEC.
Follow-up

The patient had recovered 2 weeks after operation and his body weight increased by 3 kg. The patient refused chemotherapy and was followed up as an outpatient in our hospital. No recurrence was detected on enhanced CT scan 1 month after operation. However, 2.5 months

Figure 3. Specimen removed from the liver mass shows metastasis from gastric MANEC. A. Tumor cells in the liver mass were negative for hepatocyte antigen, whereas normal hepatocytes were positive for hepatocyte antigen (arrow). ×200. B. Tumor cells in the liver mass were positive for CDX2. ×200. C. Almost all of the tumor cells in the liver mass were positive for chromogranin A. ×200. D. Almost all of the tumor cells in the liver mass were positive for synaptophysin. ×200.

Figure 4. Enhanced abdominal CT after operation. A. Enhanced abdominal CT showing no signs of recurrence 1 month after operation. B. Multiple low-density masses are found in the liver 2.5 months after operation.
after operation, multiple low-density masses were found in the right lobe of the liver on abdominal enhanced CT scan (Figure 4A, 4B).

Discussion

NETs exhibiting both exocrine and neuroendocrine differentiation were known as mixed exocrine-endocrine carcinoma according to the 2000 WHO classification; however, such tumors have been renamed as MANEC according to the 2010 WHO classification [3]. According to the 2010 WHO grading system, MANECs of the digestive tract characterized by a mitotic count of >20 per 2 mm² (10 HPFs, 40× magnification) and >20% Ki-67 labeling index are categorized as G3 [3]. The Ki-67 labeling index is calculated as the percentage of Ki-67-positive cells in areas consisting of 500 - 2000 cells with the highest density of Ki-67-positive cells [3-5]. In our reported case, the mitotic index was 50 mitoses per 10 HPFs and the Ki-67 labeling index was 70%.

Histologically, MANEC is characterized by the coexistence of gland-forming epithelial cells and neuroendocrine cells, with both components being malignant and accounting for more than 30% of the tumor [3]. In our case, HE and immunohistochemical staining of the gastric mass showed the close juxtaposition of the NEC and adenocarcinoma. Synaptophysin and chromogranin A were positive in the tumor nests arranged in a solid/trabecular pattern but not in the gland-forming epithelia component.

Immunohistochemical staining of the liver mass showed negative hepatocyte antigen and positive CDX2 expression, which indicated the gastrointestinal origin of the mass [6, 7]. Furthermore, immunohistochemical staining for neuroendocrine markers showed that almost all of the cells in the liver mass tissue section were positive for synaptophysin and chromogranin A. Based on these results, we concluded that the liver mass was the metastatic outcome of the gastric MANEC.

The MANEC displayed a tri-lineage differentiation pattern in the gastric mass tissue section. In addition to NEC and adenocarcinoma, squamous cell carcinoma differentiation was also observed in the solid/trabecular region. Intercellular bridges, a morphological feature of squamous cell carcinoma, were evident in the HE stain of the solid/trabecular region. CK5 positivity further confirmed squamous cell differentiation in the solid/trabecular region. Other cases have reported the coexistence of squamous cell carcinomas and NECs in the esophagus, duodenum and stomach [8-10].

MANECs have given rise to the concept of “histogenetic tumor typing”. Molecular-level analysis has suggested that MANECs might arise independently from two different precursor cells in a synchronous fashion or arise from a multipotent stem cell. Furlan et al. [11] analyzed five MANECs with a focus on polymorphic microsatellite markers and observed a close genetic relationship between the two distinct histological components of the MANECs. This finding supports the hypothesis that a monoclonal mechanism of tumorigenesis is the most frequent genetic event in MANECs. In our reported case, local positivity of p63, a basal/progenitor marker, was found in the NEC component of MANEC (Figure 2H). This could partially explain the existence of squamous cell carcinoma in the MANEC.

Gastric NECs present as large, solitary and ulcerated masses arising in any part of the stomach and are frequently associated with lymphatic and vascular invasion and distant metastases. The prognosis of NECs is closely related to tumor size, invasion and metastasis state and differentiation degree [12, 13]. Poorly differentiated NECs accompanied with adenocarcinoma, such as MANEC, indicates a worse prognosis [14]. The 5-year overall survival rate of MANEC remains unknown.

In our case, the MANEC presented as a large (3 cm in diameter) ulcerating mass with gastric serous coat involvement in the antrum, swelling lymph nodes at the pyloric region and a large solitary metastatic liver mass. Together, these factors suggested a poor prognosis for our patient. Two and a half months after operation, multiple low-density masses were found in the right lobe of the liver but no signs of recurrence were found in the gastrointestinal region.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Shusen Zheng, Division of Hepatobiliary Pancreatic Surgery, The
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First Affiliated Hospital, Zhejiang University, School of Medicine, 79 Qingchun Road, Hangzhou 310003, China. E-mail: drzwj2002@163.com

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