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Pure alphafetoprotein producing neuroendocrine carcinoma of the stomach: A case report

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ABSTRACT

Alpha-fetoprotein-producing gastric carcinoma (AFP-GC) is a rare malignant tumor, and has been regarded as a distinct category because of its particularly aggressive biological behavior and poor patient prognosis. In the literature, AFP-GC was never reported in neuroendocrine carcinoma of the stomach. In this article, we described a 60-year old man who sought medical attention because of epigastric pain and poor appetite. His laboratory data were within normal limits except for elevated serum level of alpha-fetoprotein. He was found to have an ulcer on gastroscopic examination which led to the final diagnosis of AFP producing neuroendocrine carcinoma of the stomach. He underwent a radical gastrectomy followed by chemotherapy using leucovorin and 5-fluorouracil.His disease was brought under remission for only six months before radiological recurrence occurred. His recurrent disease was treated with irinotican plus cisplatin without a significant response. His prognosis looked grave. We reported the first case of AFP producing gastric neuroendocrine carcinoma to share our experience.

Keywords: gastric cancer. Alpha-fetoprotein. Neuroendocrine carcinoma. Chemotherapy. Immunohistochemical stainings. Radiological recurrence.

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The first case of alpha-fetoprotein producing gastric cancer (AFP-GC) was reported by Bourreille et al, in 1970[1]. Subsequently, many cases have been reported all over the world, mainly in Asia. The reported incidence of AFP-GC was 2.3% in China[2], and 1.5 to 3% in Japan[3]. AFP-GC has been considered as having unfavorable long-term survival rate due in part to the higher incidence of liver metastasis and lymphovascular invasion. Kinjo et al,[4] classified AFP-GC into four types: 1. hepatoid (HPT); 2. enteroblastic (ENT); 3.common (COM) adenocarcinoma type; 4. Yolk sac tumor type (YST). To the best of our knowledge, AFP-GC has never been reported in pure neuroendocrine carcinoma of the stomach. Herein, we report the first case of pure alpha-fetoprotein producing gastric neuroendocrine carcinoma.

Case presentation

A 60-year old man sought medical attention because of epigastric pain and poor appetite for several weeks. His laboratory data were within normal limits except for elevated serum level of alpha-fetoprotein to 85 ng/ml. Tests for hepatitis B surface antigen and HCV were negative. Upper gastrointestinal endoscopy revealed a 2 cm ulcerative lesion at the high body (Fig 1A). Biopsy was performed, and the pathological diagnosis of neuroendocrine tumor, grade 3, was rendered. Computer tomography (CT) demonstrated thickening of the gastric wall with lymphadenopathy. No apparent tumor mass was found (Fig 1B). He underwent a total gastrectomy on January 23, 2019.

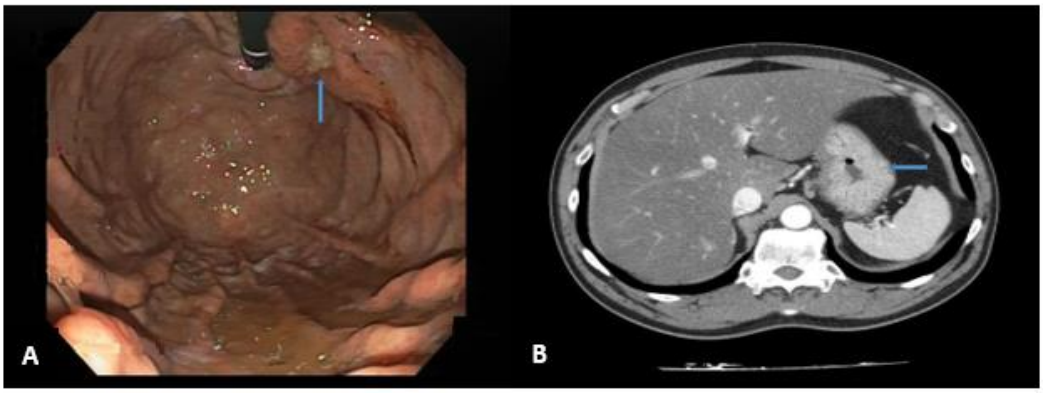

Fig 1. A. Gastroscopic examination revealed a tumor at the cardia portion of the stomach. B. Computer tomography revealed thickening of the gastric wall with perigastric lymphadenopathy.

Histopathological findings:

The specimen consisted of a stomach which was opened by the surgeon. There was an ulcerated tumor, measuring 3.5x2.5 cm, at the cardia portion (Fig 2A). Histologic sections of the tumor showed a solid growth pattern (Fig 2B). The tumor cells have

round and hyperchromatic nuclei with coarse chromatin and prominent nucleoli. The mitotic rate was nearly 30 per high power fields. Tumor

invaded through the muscular layer, with 12 lymph nodes showing metastasis among 21 examined. Lymphovascular invasion as well as perineural invasion was found. Neuroendocrine carcinoma (NEC) was considered. The pathological staging was pT3N3a, and the clinical staging was IIIA. After the surgery, the AFP came down to 19.7 ng/ml. Immunohistochemical stainings were performed to confirm the diagnosis.

Immunohistochemical staining:

For staining, we used an automated stainer (Dako) according to the vendor's protocol. Appropriate controls were used for each antibody. The staining results were interpreted according to the extent of positive cells as follows; <1%, negative; 1% to 30%, focal; > 30% diffuse. The results of immunohistochemical stainings were as follows; Synaptophysin diffuse expression;CD56 diffuse expression; Chromogranin A diffuse expression; Alpha- fetoprotein diffuse expression; Glytican 3 diffuse expression; Ki67 exhibiting 40% nuclear reactivity; (Fig 3A,3B,3C,3D,3E,3F);TTF 1, negative, Her 2/neu negative; CD45 negative. The above immunohistochemical phenotypes plus high mitotic activity and high Ki67 confirmed the diagnosis of alpha-fetoprotein producing neuroendocrine carcinoma (NEC), large cell type [7].

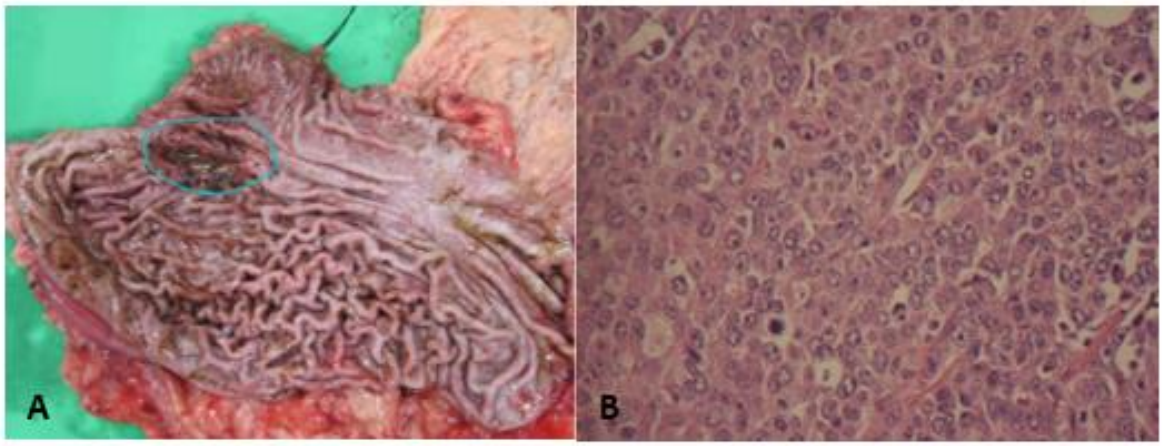

Fig 2. A. The resected specimen of the stomach reveals a tumor at the cardia, 3.5x2.5 cm. B. Histologic features of the tumor shows a solid pattern. The tumor cells are round and hyperchromatic with eosinophilic and granular cytoplasm. (H & E stain, x400).

Therapy

After the diagnosis was established, the patient started to receive chemotherapy.

However, owing to lack of the standard therapy, the patient was treated with FOLFOX regimen which is composed of leucovorin and 5-Fluorouracil. The first cycle started on February 27, 2019, and the 12th cycle ended on August 26, 2019. The patient suffered from minor manageable side effects during the course of therapy. His serum level of AFP was within the normal limits after therapy.

Unfortunately, she was found to have radiological recurrence on February 27, 2020.

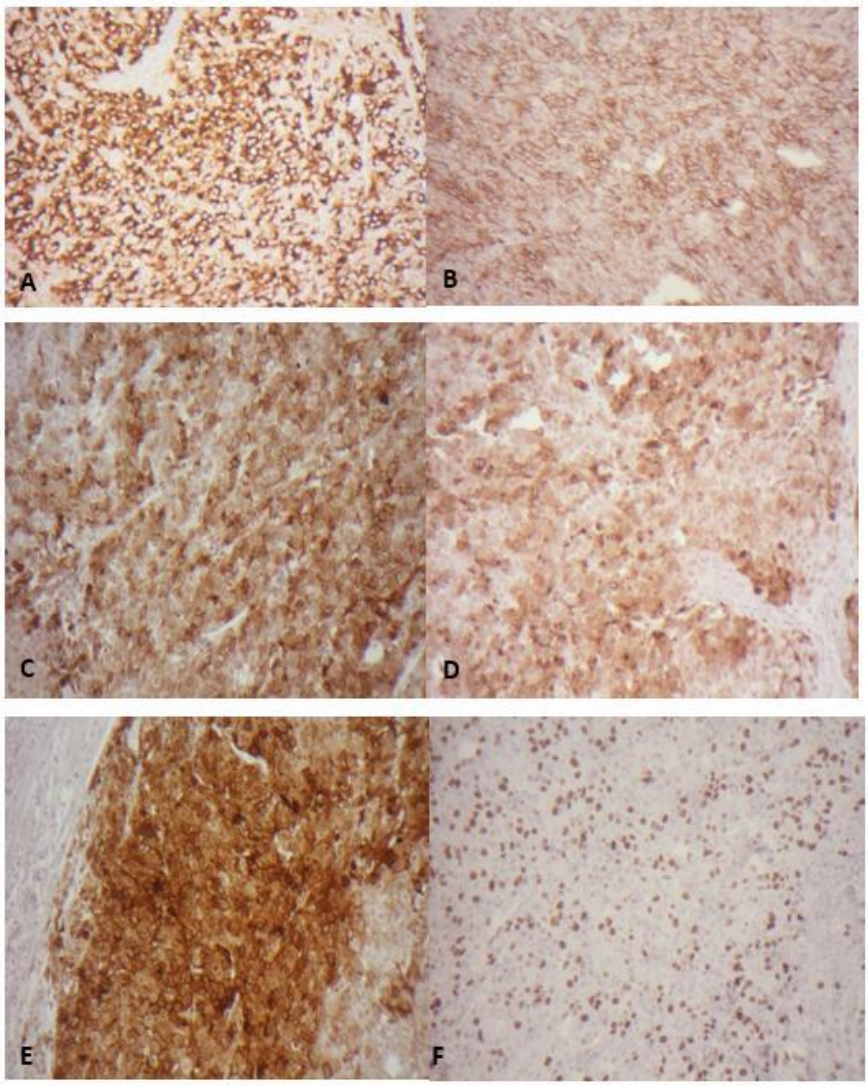

Figure 3. Immunohistochemical findings. A. Diffuse synaptophysin expression in cytoplasm. X400. B. Membranous expression of CD56.X400. C. Diffuse chromogranin expression in cytoplasm.x400.D. Diffuse AFP expression in cytoplasm. X400. E. Diffuse glytican-3 expression in cytoplasm. X400. F. Focal Ki 67 expression in nucleus, 40%. X400.

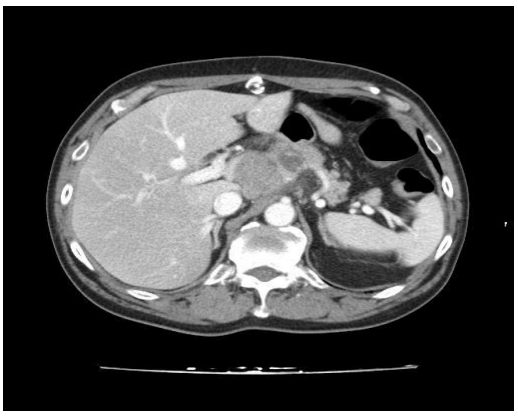

Fig 4. Computer tomography showing enlarged celiac lymph nodes 6 months after the first chemotherapy.

His CT displayed a group of the celiac enlarged lymph nodes (Fig 4) with highly elevated AFP to 8729 ng/ml. He immediately received the second chemotherapy using Irinotecan plus Cisplatin. During the second course of chemotherapy, he suffered more serious side effects, such as nausea, vomiting, pancytopenia, diarrhea, and weight loss, necessitating hospital admission several times. At this writing, he just completed the 8th cycles of chemotherapy without any significant response. His serum level of alpha-fetoprotein was 4960 ng/ml. His prognosis looked grave.

Discussion

In our case, the growth pattern, morphology plus immunohistochemical studies met the current diagnostic criteria of NEC, as defined by the WHO classification [5].

In order to rule out the possible gastric composite tumor[6], five paraffin tissue blocks were examined, and no hepatoid carcinoma, common adenocarcinoma or other components were found.

NEC of the stomach is a rare but highly malignant tumor and prone to liver metastasis like AFP-GC. In a study by Ishida et al,[7] among 7886 surgically resected gastric cancer, 40 cases (0.5%) were pure NEC of large cell type. None of NEC in this study was associated with alpha-fetoprotein production. In our case, it was unusual that liver metastasis has not occurred t, albeit lymphovascular invasion was prominent.

The focal or diffuse expression of TTF-1 was observed in 19 cases (37%) in the study by Ishida et al,[7]. In our case, there was no TTF-1 expression. In 2010, FDA approved Herceptin to treat Her2/neu-positive metastatic gastric cancer in combination with chemotherapy[8,9]. We encountered a patient with AFP-GC with extensive liver metastasis. His Her2/neu was strongly positive, he received Herceptin in combination with chemotherapy using oxaliplatin plus capecitabine, and has been disease free for four years[10]. In the current case, his Her2/neu was negative, therefore, he was not the candidate for Herceptin therapy.

Conclusion

We report the first case of AFP gastric neuroendocrine cancer. There were no specific symptoms for this tumor. Immunohstochemical stainings of the gastroscopic biopsy led to an accurate diagnosis. There is no standard treatment to follow. We treated this patient with radical surgery, combined with chemotherapy using leucovorin and 5-fluoruracil. His disease was under remission for only six months, and did not respond to the second chemotherapy. Apparently, we need more reports and more research on this topic.

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