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Complete Clinical Response of a Patient with Advanced Alpha-fetoprotein Producing Gastric Cancer Treated with Chemotherapy and Trastuzumab

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Abstract

Gastric cancer is the 7th leading cause of cancer death in Taiwan, and is the fourth most common cancer worldwide. Alpha-fetoprotein producing gastric cancer is a subtype of gastric cancer which has more aggressive behavior and has been considered as having unfavorable prognosis. Since the case of alpha-fetoprotein producing gastric cancer was first reported, many cases have been reported, mostly in Japan and China, and rarely in Taiwan. No standard therapy is currently available. However, radical surgery and chemoradiation therapy might positively impact clinical outcomes. Since FDA approved targeted therapies for advanced gastric cancer, reports improving prognosis using targeted therapies for advanced gastric cancer producing alpha-fetoprotein have appeared in the literature.

We described a case of advanced alpha-fetoprotein producing gastric cancer which was treated with chemotherapy and targeted therapy, resulting in complete clinical response of liver metastasis and the primary tumor in the stomach.

Keywords: Alpha-fetoprotein; Gastric cancer; Capecitabin; Oxaliplatin; Trastuzumab; Targeted therapy; Liver metastasis

Abbreviations

AFP: Alpha-fetoprotein; AFP-GC: Alpha-fetoprotein Producing Gastric Cancer; HCC: Hepatocellular Carcinoma. IHC: Immunohistochemical Staining. AST: Aspartate Aminotranferase; ALT: Alanin Aminotransferase; HCV: Hepatitis C virus; CEA: Carcinoembryonic Antigen

Introduction

Elevated serum levels of AFP were initially used for screening and monitoring hepatocellular carcinoma (HCC) [1]. Later, high serum levels of AFP was found in many other malignant neoplasm including the primary site in the lung, ovary, stomach and the germ cell tumor such as yolk sac tumor in the testis and the mediastinum [2-6]; of which, the gastric cancer is the most common [7]. Since the first case of AFP producing gastric cancer (AFP-GC) was reported [7], many cases have been reported all over the world, mostly in Japan and China, with the incidence ranging from 1.5 to 3%. Huang and Tsung [8] reported he first case of AFP-GC in Taiwan. Later, more cases were reported [9,10]. AFP-GC is a subtype of gastric cancer, which has more aggressive behavior, and has been considered as having unfavorable long term survival rate due in part to the higher propensity of liver metastasis and lymphovascular invasion as compared with non-alpha-fetoprotein producing gastric cancer. Since FDA approved targeted therapies for advanced gastric cancer, reports improving prognosis using targeted therapies for advanced gastric cancer producing alpha-fetoprotein have appeared in the literature. The present study describes a case of advanced alpha-fetoprotein producing gastric cancer which was treated with chemotherapy and targeted therapy, resulting in complete clinical response of liver metastasis and the primary tumor in the stomach.

Case Presentation

A 54-year old man consulted Tsai Clinic with a chief complaint of epigastric pain for several weeks, and body loss of 7kg in 3 months. His laboratory data revealed slight anemia with hemoglobin of 11.1g/dl, and hematocrit of 34%. His liver function tests showed slight elevation of serum levels of AST (93IU/L) and ALT (47IU/L), with a markedly elevated level of serum alkaline phosphatase (>1200IU/L). Testing for hepatitis B surface antigen and HCV were negative. Serum level of CEA was 108ng/ml, and serum level of alpha-fetoprotein was 16,390ng/ml. Upper gastrointestinal endoscopy revealed a Borrmann type II-like tumor which was found at the cardia portion of the stomach (Figure 1). Biopsy was done, and microscopic examination showed poorly differentiated adenocarcinoma (Figure 2). Because of highly elevated serum level of alpha-fetoprotein, the diagnosis of AFP-GC was rendered. Computer tomography (CT) demonstrated multiple space occupying lesions (Figure 3). Her2 evaluation was performed initially using immunohistochemical staining with the results considered as equivocal (2+), and was referred for fluorescent in situ hybridization (FISH) which was interpreted as positive. The patient was referred to National Yang-Ming University Hospital for treatment. He was treated following modified Xelox regimen; oxaliplatin 85mg/m^2 and capecitabin 500mg, bid, 14 days a cycle for12 cycles; trastuzumab was given intravenously every two weeks, 6mg/kg as loading dose, decreased to 4mg/kg. The therapy started from March 5, 2016, completed on September 30, 2016, but continued to

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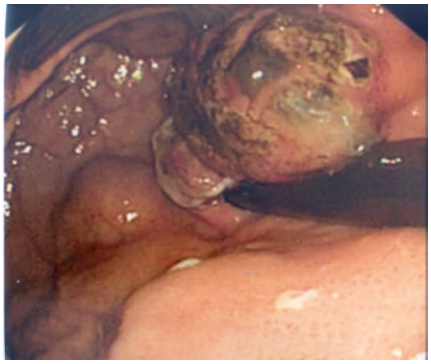

Figure 1: Gastroscopic examination revealed a polypoid lesion in the cardia portion of the stomach.

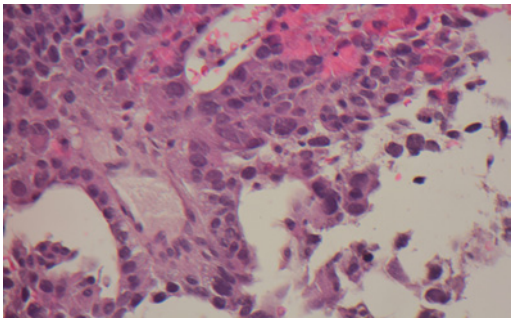

Figure 2: Gastric biopsy specimen showed poorly differentiated adenocarcinoma (H&E.x400).

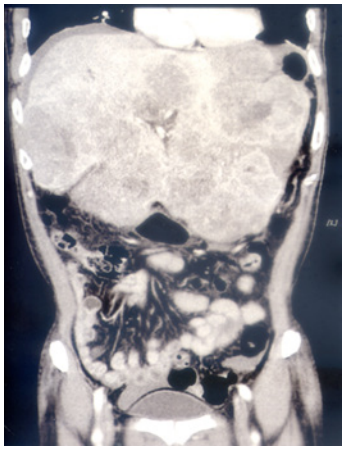

Figure 3: Computed tomography (CT) revealed multiple liver metastasis.

be on capecitabin as maintenance dose. The patient experienced only grade 2 peripheral neuropathy, and doing very well when he was seen at his follow-up on July 1, 2017. CT scan showed complete resolution of liver metastasis (Figure 4). All tumor markers returned to normal levels (Table 1). Follow-up gastroscopic examination was performed on March 1, 2017, and failed to demonstrate tumor at the previous site (Figure 5).

Discussion

Our patient had negative testing for hepatitis B and C. It was unlikely that he had HCC metastasized to the stomach. Dynamic

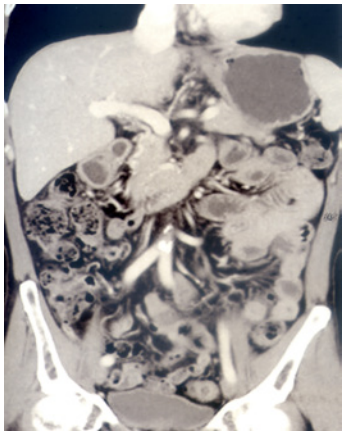

Figure 4: Computed tomography 4 months after therapy revealed complete resolution of liver metastasis.

Table 1: Serum levels of tumor markers.

Date	Serum level of CEA (ng/ml)	Serum level of AFP (ng/ml)
03/08/2016	107.98	16,390
04/28/2016	55.2	455
06/21/2016	4.0	3.7
07/12/2016	2.6	3.3
08/16/2016	1.8	2.8
12/12/2016	1.9	3.4

CEA: Carcinoembryonic Antigen; AFP: Alpha-fetoprotein.

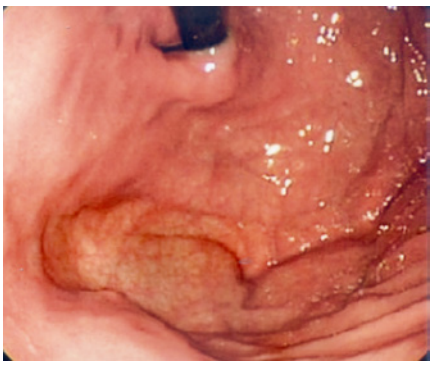

Figure 5: Followup gastroscopy examination showed a normal mucosa at the previous tumor site.

computer tomography also confirmed that the lesions in the liver were from metastasis. Furthermore, his gastric biopsy specimen showed poorly differentiated adenocarcinoma with markedly elevated serum level of AFP supporting the diagnosis of AFP-GC. Negative immunohistochemistry staining on his gastric biopsy specimen did not negate the diagnosis of AFP-GC. In the literature, the immunoreactivity for AFP was negative in some reported cases [11]. The reason could be related to its sensitivity. In our patient, the serum level of AFP was 16,398ng/ml, sensitivity should not have been the issue. Another explanation could be due to the limited sampling [12]. A recent study by Kinjio et al. [13] suggested that the gastric carcinoma started on the mucosa, which differentiated into enteroblastic type and hepatoid type. During the process of tumor invasion and proliferation, the tumor cells acquired the AFP

production ability. Therefore, the tumor cells from the surface could be negative for the AFP reactivity.

No standard therapy is currently available. However, radical surgery and chemoradiation therapy might positively impact clinical outcomes [14]. AFP-GC with liver metastasis has a particularly dismal prognosis, regardless of whether it is synchronous or metachronus. FDA approved targeted therapies for advanced gastric cancer and cancer arising from gastroesophgageal junction on October 20, 2010, and established a new paradigm using trastuzumab in combination with chemotherapy in patients with advanced gastric cancer overexpressing HER2. Subsequently, reports on improving prognosis of prolonged survival of AFP-GCs patients treated with trastuzumab followed [15-17]. The case reported by Ogasawara et al, was a 65-year-old man with advanced AFP-GC treated with chemotherapy with trastuzumab resulting in marked reduction of the tumor size in the liver as well as in the stomach. The patient was still alive 35 months after initial therapy. The case reported by Wang et al. was a 49-year-old Chinese male with locally advanced AFP-GC. He was treated with chemotherapy and trastuzumab containing regimen as neoadjuvant therapy. Subsequently, he received total gastrectomy with extended D2 lymph node dissections showing pathological complete response.

Trastuzumab (Herceptin) is a monoclonal antibody of a very specific immune system protein, which targets the HER2 protein, causes cell cycle arrest at G1, and exhibits antitumor activity in HER2 ovrexpressed gastric cancer cells [18]. Additionally, trastuzumab can enhance cytotoxic effect s of chemotherapy in gastric cancer xenograft overexpressing HER2 [19]. Therefore, assessment of HER2 status is now mandatory for selecting patients' eligibility for this treatment [20].

Conclusion

We report the first case of clinical complete response after chemotherapy in combination with trastuzumab in an advanced APF-GC overexpressing HER2. We consider this rare case to be of significant value with respect to the treatment of AFP-GC with multiple liver metastases. Our therapeutic modality is safe, and is worth further investigation.

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