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Case Report

Alpha-Fetoprotein-producing Neuroendocrine Carcinoma of the Pancreas with Multiple Liver Metastasis: A Case Report

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Abstract

Alpha-fetoprotein (AFP) is a well-known tumor marker for hepatocellular carcinoma (HCC). However, Grade 3 AFP-producing neuroendocrine tumor (NET) is a rare and aggressive cancer. We report the case of a 68-year-old female admitted for multiple liver tumors and an elevated AFP level discovered during a routine health examination. A computed tomography (CT) scan showed a pancreatic body–tail tumor with multiple liver tumors. Microscopy revealed that the tumor tissue was composed of trabecular growth of tumor cells containing abundant cytoplasm. The tumor cells were positive for chromogranin A, INSM1, synaptophysin, and CK19. These histopathological findings supported the diagnosis of an AFP-producing G3 pancreatic NET (pNET). Her serum AFP level decreased by approximately 70% after three courses of chemotherapy, including etoposide and cisplatin. After 3 months of treatment, a CT scan showed progression of bone metastasis, and the patient died 13 months after diagnosis. This case highlights that serum AFP may be a useful tumor marker for monitoring the treatment response in patients with metastatic pNETs.

Keywords: Alpha-fetoprotein, case report, liver metastasis, neuroendocrine tumor, pancreas

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous malignancy that arise from various organs containing neuroendocrine tissue, with most occurring in the gastrointestinal tract.[1] NETs can be categorized as functional and nonfunctional depending on symptoms associated with tumor-releasing peptides, such as carcinoid syndrome. High-grade NETs exhibit high mitotic activity and an aggressive clinical course, and therefore, pancreatic high-grade NETs generally have a worse prognosis than low-grade well-differentiated NETs. Nonfunctional pancreatic NETs (pNETs) account for two-thirds of all pNETs and often present with no specific symptoms. As a result, they are frequently diagnosed at an advanced stage.

Alpha-fetoprotein (AFP) is a well-known tumor marker for hepatocellular carcinoma (HCC) and yolk sac tumors.

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AFP is typically used to detect HCC in patients with chronic hepatitis B and C[2] and to monitor the treatment response. An elevated serum AFP level can also occur when gastrointestinal tract cancer metastasizes to the liver. A few case reports have reported an elevated serum AFP level in NET patients.[3-7] However, mixed HCC-neuroendocrine carcinoma (NEC) or NEC with hepatoid differentiation can also present in this manner.[8,9] Here, we report a case of an AFP-producing Grade 3 NET of the pancreas with liver metastasis.

Case Report

Clinical course

A 68-year-old female presented to the emergency department at Chang Gung Memorial Hospital, Linkou Branch in May 2024 due to an elevated alkaline phosphatase level and multiple liver tumors noted on abdominal echography during a routine health examination. Six months earlier, she suffered from abdominal fullness and constipation. In addition, she complained of decreased appetite and body weight loss of 4 kg in 1 year. She did not smoke or drink alcohol. A physical examination on admission revealed a palpable liver edge 5 cm below the costal margin. There was no family history of gastrointestinal cancer.

Laboratory studies showed a hemoglobin concentration of 11.0 g/dL, white blood cell (WBC) count of 6,600/μL, and platelet count of 378,000/μL. Elevated levels of serum tumor markers including serum AFP (585.7 ng/ml; normal: 0–9 ng/ml) and serum carbohydrate antigen 19-9 (CA19-9) (175.0 U/mL; normal: 0–37 U/ml) were also noted. The levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 125 (CA-125) were in the normal range, and there was no serologic evidence of hepatitis B or C.

After admission to our hospital, a series of investigation were performed, including abdominal computed tomography (CT) [Figure 1], esophagogastroduodenoscopy (EGD), and colonofiberscopy (CFS). Abdominal CT showed a pancreatic body–tail tumor measuring 8.2 cm × 5.5 cm, with multiple liver tumors (two largest target lesions: S8 10.6 cm × 6.6 cm and S7 5.7 cm × 4.8 cm) and a right ischium bone metastasis. EGD and CFS showed no obvious tumors in the esophagus, stomach, duodenum, or colon. A liver core biopsy was then performed based on the imaging findings.

Histopathological findings

Pathological assessment of the biopsy specimen revealed three cores of yellowish, fragmented, and soft liver tissue, measuring 1.1 cm to 1.7 cm in length. Light microscopy revealed liver tissue with trabecular growth of tumor cells containing abundant cytoplasm and dilated sinusoids in fibrous stroma [Figure 2]. Mitotic figures numbered 6 per 10 high-power fields. The differential diagnosis included NET and HCC. Immunohistochemistry showed that the tumor cells were positive for chromogranin A, INSM1, synaptophysin, and CK19, with scattered positive staining for AFP and negative for hep-par1 and glypican 3 [Figure 3]. The Ki-67 labeling index was around 60%. These histopathology findings supported the diagnosis of an AFP-producing NET, Grade 3.

Follow-up

The patient was treated with five courses of chemotherapy and immunotherapy that included etoposide, cisplatin, and durvalumab. The serum AFP level decreased to 181.2 ng/ml after 2 months of treatment, but then increased to 312.6 ng/ml 1 month later. Follow-up CT after treatment demonstrated several newly-developed osteoblastic foci in the right pubic bone. Due to progressive disease, she was treated with a second-line chemotherapy regimen of 5-FU, leucovorin, and irinotecan. Her clinical condition gradually worsened, and she needed parenteral nutrition support. Her serum AFP level gradually increased to 688.1 ng/ml after 5 months of treatment, and she eventually died from cancer progression 13 months after the initial diagnosis [Figure 4].

Discussion

AFP serves as a tumor marker for the diagnosis and monitoring treatment response of patients with HCC.[10] In Taiwan, about one in eight people are HBV or HCV carriers, which contributes to a high prevalence of HCC. In our case, we performed CT and ultrasound-guided liver tumor biopsy to distinguish between liver HCC and pancreatic cancer with liver metastasis.

pNET is a rare disease, with an incidence of approximately 1 per 100,000 people. Most cases are sporadic, but some are associated with hereditary syndromes such as multiple endocrine neoplasia type 1, Von Hippel–Lindau, and neurofibromatosis type 1.[11] Around one-third of pNETs are nonfunctional. These patients may present with nonspecific

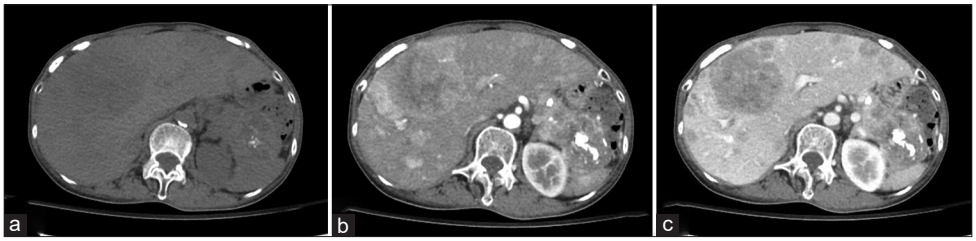

Figure 1: Radiologic findings of a pancreatic alpha-fetoprotein-producing neuroendocrine carcinoma with liver metastasis. (a) Precontrast computed tomography (CT) image. (b) Contrast-enhanced arterial phase of the CT scan. (c) Contrast-enhanced venous phase. CT scan showed an 8.2 cm × 5.5 cm pancreatic tail tumor with calcification and multiple liver metastases. CT: Computed tomography

symptoms, including jaundice, pancreatitis, bloating, abdominal pain, or intestinal obstruction.[12] Imaging examinations such as ultrasonography, CT, magnetic resonance imaging, and endoscopic ultrasonography are useful for localizing tumors.[13] Tissue biopsy is essential for a definitive pathological diagnosis.

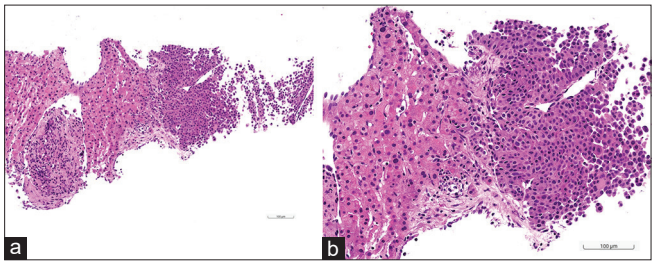

Figure 2: Histopathological findings. Junction area of normal liver tissue and neuroendocrine tumor. (a) Hematoxylin and eosin stain, ×100. (b) ×200

According to the WHO Classification of Endocrine Organs (2017)[14] and Digestive System (2019)[15] criteria, a Grade 3 NET is defined as a tumor with neuroendocrine morphology (in nests, cords, or trabeculae), high mitotic figures (Ki-67 >20%), and uniform neuroendocrine immunoreactivity. In the present case, immunohistochemistry showed positive staining for chromogranin A, INSM1, and synaptophysin, which was consistent with an NET. Some case reports have shown that NETs can have focal AFP positive staining.[3-7] Hep-par1 and

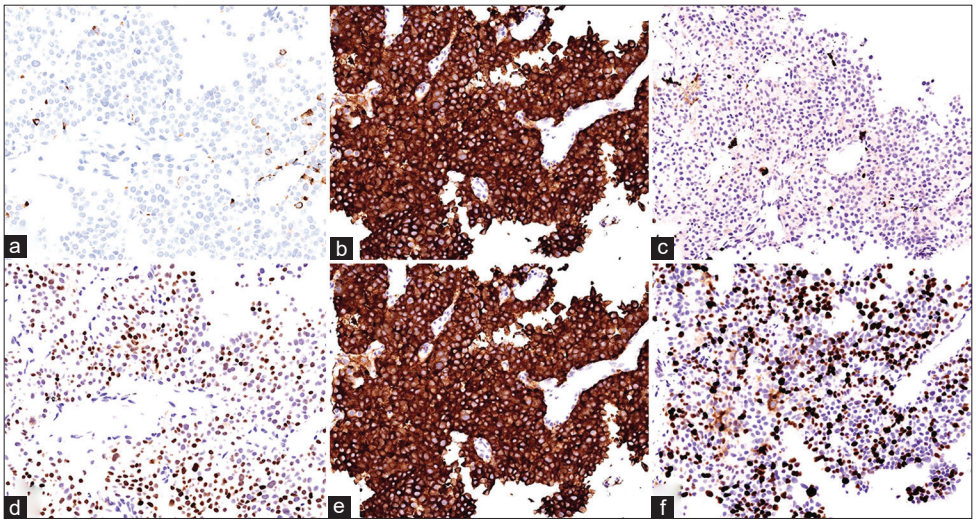

Figure 3: Immunohistochemical staining of the tumor. (a) Scattered positively for alpha-fetoprotein (AFP). (b) Positive staining for chromogranin A. (c) Negative for hep-par1. (d) Positive staining for INSM1. (e) Positive staining for synaptophysin. (f) Ki67 staining. AFP: α-Fetoprotein

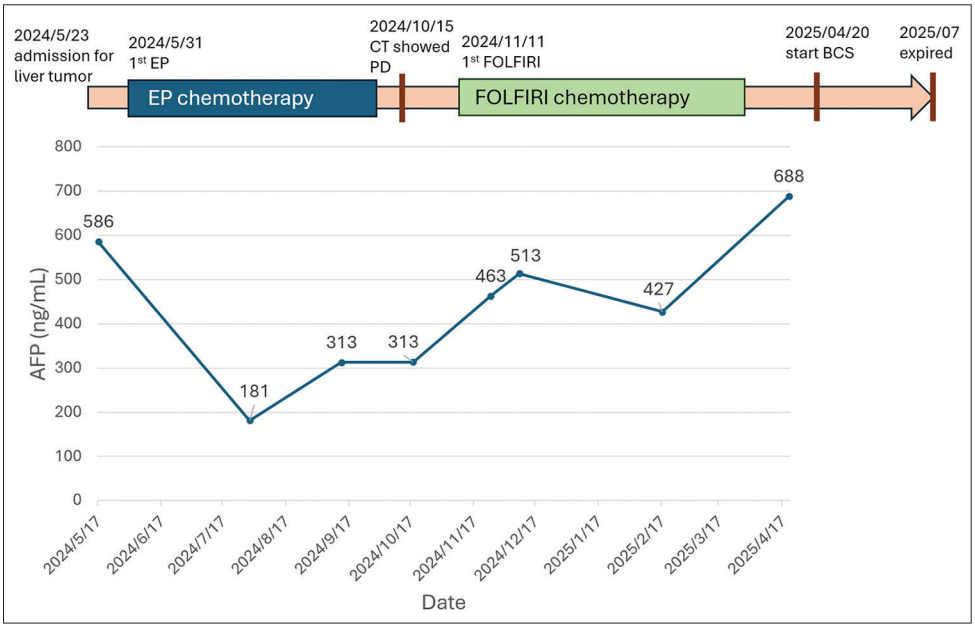

Figure 4: Serum alpha-fetoprotein (AFP) changes and timeline of treatment of the patient. AFP: α-Fetoprotein, BCS: Best supportive care, CT: Computed tomography, EP: Etoposide + cisplatin

glypican 3 were negative in this case, supporting our exclusion of HCC or mixed HCC-NEC.[16]

Metastatic high-grade NETs or carcinomas are generally considered to have a poor prognosis. Notably, elevated AFP is a poor prognosis factor for NETs.[17] Curative intent resection is not recommended for pNETs with liver metastasis.[12] Platinum-based chemotherapy such as cisplatin/carboplatin + etoposide or cisplatin + irinotecan is considered the most effective treatment for high-grade NETs or metastatic NEC.[18] A clinical trial reported progression-free survival of around 6 months and overall survival of around 12 months, and a previous study showed that AFP can be used for monitoring pNET recurrence after surgery.[3] In the present case, serum AFP level was used to monitor treatment response, which was consistent with the CT findings of progressive disease when the AFP level rebounded after 3 months of etoposide + cisplatin chemotherapy.

This case of an AFP-producing G3 pNET with liver metastasis highlights that AFP level can be used to monitor the treatment response and detect disease progression in patients receiving chemotherapy.

Declaration of patient consent

This study was performed in accordance with and conforming to the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Author contributions

Conception: JSW, TCC, KYY, WCC; Acquisition of data: JSW, TCC; Drafting of the manuscript: JSW, TCC, KYY, WCC. All authors have read and agreed to the final version of the manuscript.

Data availability statement

All data generated or analyzed during this study are included in this published article.

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Nil.

Conflicts of interest

Dr. Wen-Chi Chou, an editorial board member at *Journal of Cancer Research and Practice*, had no role in the peer review process of or decision to publish this article. All authors declared no conflicts of interest in writing this paper.

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