CASE REPORT

Alpha-fetoprotein Secreting Neuroendocrine Carcinoma of the Liver: a Case Report and Literature Review

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Introduction

Neuroendocrine tumors (NETs) occur in organs and tissues that contain peptides and amine-producing cells with different hormonal profiles depending on the region in which they are originated [1, 2]. NETs mostly occur in the gastrointestinal and bronchopulmonary system, and they are mostly seen in rectum, jejunum/ileum, and pancreas in gastrointestinal system [3]. Hepatic neuroendocrine tumors are rarely seen, and low-grade carcinoid tumors constitute the majority of cases [4]. On the other hand, hepatic neuroendocrine carcinomas (hNECs) are high-grade tumors that are rarely observed [5].

Alpha-fetoprotein (AFP) is a glycoprotein secreted by the liver and fetal yolk sac during the gestational period [6]. Except for malign diseases such as hepatocellular carcinoma (HCC) and yolk sac tumors, AFP level increases during benign diseases such as chronic liver disease, viral hepatitis, and cirrhosis. Despite published reports showing increased AFP levels in patients with NET, most of these cases have pancreatic NET with hepatic metastases [7, 8]. AFP-secreting hNECs are available in the literature, but these tumors have generally been reported with other malignant components, such as HCC [9]. For this reason, we here presented a case with hNEC that is not associated with another malignant component that secretes AFP.

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Case Report

A 61-year-old male patient referred to our hospital with dyspeptic complaints such as epigastric pain, swelling, and indigestion. The patient had no complaints of carcinoid syndrome such as diarrhea, palpitation, and flushing. There was no abnormality in the biochemical and complete blood count tests that were performed. Ultrasonography and tomography of the abdomen revealed an indefinite limited heterogeneous hyperechogenic infiltration area filling the right lobe of the liver. No pathology was detected on all thoracic computerized tomography. A dynamic contrast-enhanced magnetic resonance (MR) imaging was performed to assess the liver mass. The tumor was entirely located on the right lobe of liver and extended to segment 4 of the left lobe ($10 \times 8 \times 7.5$ cm). It was hypo-on T1 and mild hyper-intense on T2-weighted image. Contrast-enhanced images revealed lesser enhancement of the mass compared to liver parenchyma. The tumor invaded the portal vein and dilated the bile ducts (Fig. 1). AFP level was increased by 868.3 (range = 0–9) ng/mL. Other tumor markers CEA (carcinoembryonic antigen) and CA19-9 (carbohydrate antigen 19-9) were in the normal range. In the case, which was discussed at the multidisciplinary tumor council, it was decided to perform a biopsy because of the typical HCC not found. The biopsy result was not diagnostic. In the meantime, in whole body 18-FDG-PET/CT (fluorodeoxyglucose-Positron emission tomography/computed tomography), increased FDG uptake (SUVmax = 7.9) was detected in the hypodense lesion in the right lobe of the liver and no other pathological involvement was detected. Upon the development of jaundice in the patient during this period, (indirect bilirubin = 13.2 mg/dL, direct bilirubin = 11.7 mg/dL), percutaneous bilateral drainage was performed as a result of dilatation of intrahepatic bile ducts. Right hepatectomy, portal and hepatic vein thrombectomy, and lymph node dissection were performed in the patient who had bilirubin levels decreased with percutaneous bilateral drainage. Histopathologic evaluation revealed macroscopically a mass with a maximum diameter of

Fig. 1 **a** Early phase contrast-enhanced axial image. **b** Late phase contrast-enhanced axial image. The part of the tumor extending through the hilum of liver showing more contrast enhancement (thick arrow) than other parts (thin arrow). **c** T2-weighted coronal image. The mass (asterisk) is slightly hyperintense. Bile ducts (angled arrows) are dilated due to mass effect. **d** Late phase contrast-enhanced coronal image. Tumor size and portal vein invasion (curved arrow) can be seen more prominently
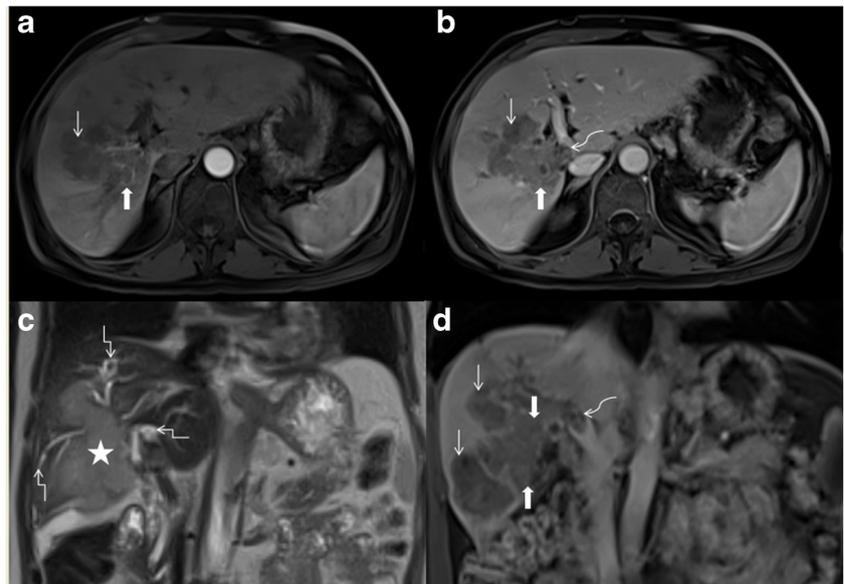
4 cm in a yellow-white color with necrotic, irregularly limited multiloculated tumor. Microscopically, a pleomorphic, hyperchromatic nucleus tumor with a solid growth pattern was observed. Twenty percent tumor necrosis and numerous atypical and typical mitoses were observed in the tumor (Fig. 2). In addition, numerous vascular tumor thrombi were noted in large vascular channels. Immune-histochemistry results were as follows: cytokeratin (CK) 7 (−), CK 19 (−), CK 20 (−), EMA (−), CD 34 (−), HepPAR (−), TTF1 (−), LCA (−), Desmin (−), Dog1 (−), CD 117 (−), s100 (−), MelanA(−), HMB 45(−), BerEP4 (−), CD99 (−), Chromogranin (−), Synaptophysin (+), CD 56 (+), PanCK (+), OSCAR CK (+), and CAM 5.2 (+). Ki-67 index was 50%, and mitosis rate was 22% (10 high-power fields
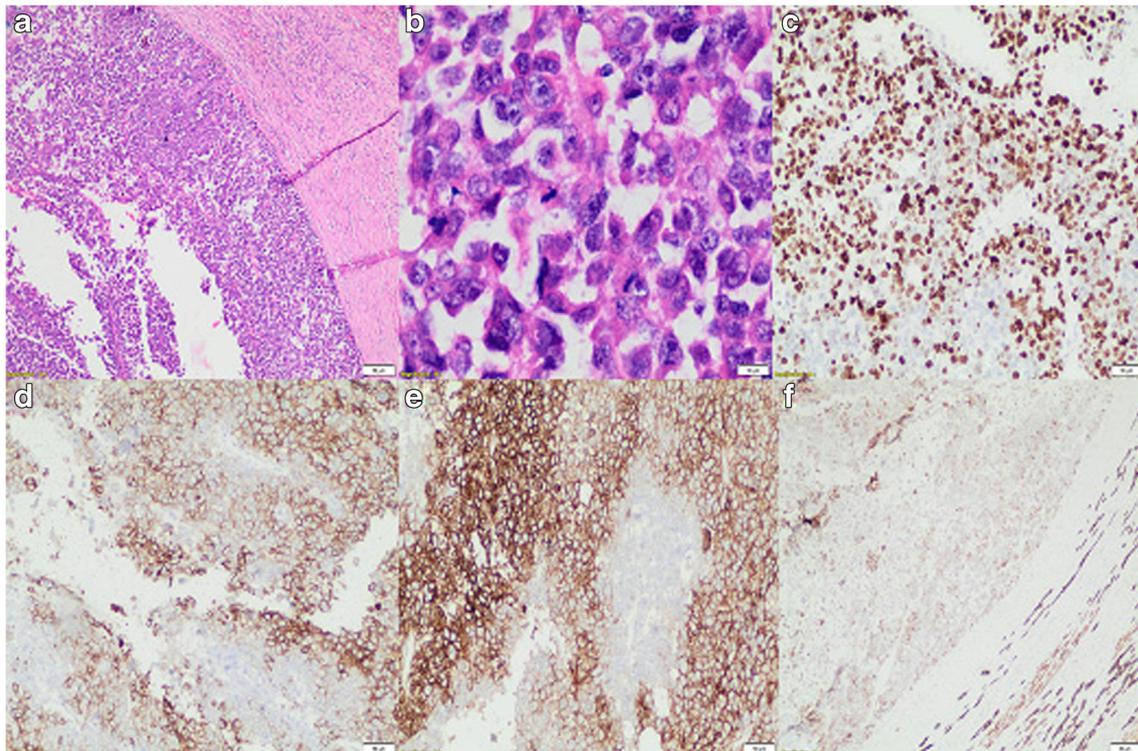
Fig. 2 **a** Liver parenchyma and tumor transit, H&E, × 10. **b** Tumor cells, hyperchromatic, atypical, mitoses, H & E, × 40. **c** In tumor cells, Ki 67% 50 (+), grade III, × 20. **d** In tumor cells, synaptophysin is 70% (++) patchy staining, × 10. **e** In tumor cells, CD56 is expressed in 70% (++), × 20. **f** PanCK patched staining, compared with liver parenchyma, × 40

(HPF)). In addition, four lymph nodes were evaluated as reactive lymphoid hyperplasia. The histopathology findings supported the diagnosis of neuroendocrine carcinoma according to the fourth edition of WHO Classification of Neuroendocrine [10]. AFP level of the patient on 29th postoperative day was normal with 8 ng/mL (range = 0–9). The etoposide/cisplatin chemotherapy regimen was initiated as adjuvant therapy to the patient with an ECOG (Eastern Cooperative Oncology Group) performance score of 0.

Discussion

According to the fourth edition of WHO Classification of Digestive System Tumors published in 2010, NET can be divided to three groups according to its grade. Low and intermediate grades are called NET grades 1 and 2, while high grades (grade 3) are called NEC. For NEC diagnosis, in every 10 HPF, > 20% mitosis (and/or > 20% Ki67 index) presence was defined. [10]. In recent years, as information about NET increase, the importance of these tumors is increasing. TNM (tumor-node-metastasis) staging was designed for pancreas, jejunum/ileum, appendix, colon, and rectum NET at the 8th edition of the TNM stage [11]. However, for hepatic NET, no such staging has yet been designed.

Primary hNEC is a very rare tumor originating from the liver. However, the vast majority of NECs in the liver are due to metastases from the primary gastrointestinal tract and lungs [5, 12, 13]. For this reason, the differential diagnosis of primary hNEC versus metastatic hepatic NEC is very important in terms of treatment options and to predict the outcome of the patient [14, 15]. In our case, in terms of primary or metastatic malignancy, both the computerized tomography and MR/PET/CT were performed, and the liver was shown as the primary focus. Octreotide scintigraphy is an adjunct technique for the diagnosis of NET and shows sensitivity up to 90% in some tumors [16]. In our case, in initial radiological imaging and biopsy results, neuroendocrine tumors were not considered and no octreotide scintigraphy was performed.

Primary hepatic NET is usually diagnosed in the late stage because it refers to non-specific clinical symptoms such as abdominal pain. In a review, 44% of the patients had the most common abdominal pain, only 16% had a carcinoid syndrome and 4% had jaundice, but this review not only examined the patients with primary NEC, but also all cases of NET [17]. Our case was referred with non-specific symptoms compatible with literature and later developed jaundice. Based on imaging, it is difficult to distinguish hNEC from other liver lesions (HCC, metastatic hepatic NEC, metastatic carcinoma, hemangioma etc.). Radiological diagnosis of primary hNEC is often found as hypervascular solid masses with/without cystic area [18]. In a study with 29 patients performed by Lie et al., primary liver NETs were reported as low intensity in T1-weighted images of MRI and hypervascularized masses with high intensity in T2-weighted images [19]. On the contrary, in our case, this primary hNEC had a hypovascular image according to liver in MRI imaging. In addition, the mass biopsy did not give a clear idea. This may be due to the lack of a standard immunohistochemical study of these tumors due to the very rare occurrence of primary liver neuroendocrine neoplasms, or because of the small size of the biopsy material.

Alpha-fetoprotein is used as a serum tumor marker for yolk sac tumors and HCC screening and monitoring. Increased levels have been reported in carcinomas of various other organs, most commonly stomach [20]. According to our primary hepatic NEC information, roughly, 70 cases have been reported in the English literature until now. When these cases were examined, Zhao et al. reported two cases with primary hNECs in which one patient had a high AFP level of 878.60 IU/mL, and the other AFP was reported in the normal range [21]. In another study, Park et al. reported 12 primary hNECs and found AFP levels in the normal range in other patients with high AFP levels of 7397 IU/mL in one patient [5]. In nine case series performed by Jia et al., an increase was reported in AFP levels for a patient. However, in this patient group, patients with liver cirrhosis and hepatitis B virus were included and all primary liver NETs were taken in this case series. Moreover, the AFP level has not been clearly indicated [22]. The AFP level over 200 IU/mL is used as a confirmatory test to differentiate HCC from other liver solid lesions in a patient with liver mass [23]. In our patient, AFP level was 868.3 ng/mL, suggesting HCC in the diagnosis period, but it was removed from the diagnosis because of not showing typical washout radiologically. Therefore, in a patient with high AFP level and liver mass, primary hNEC possibility should also be kept in mind. In addition, as in our case, serum AFP levels regressing to normal ranges after surgery may be guiding for recurrence and metastasis during following disease.

The choice of treatment for primary hNEC depends on the stage of diagnosis. Liver tumor resection or partial hepatectomy is the most effective treatment for patients with early-stage tumors [17]. TACE (transcatheter arterial chemoembolization) is the preferred treatment regimen for localized patients in further stages who are unsuitable for surgery [17]. Chemotherapy regimen etoposide/cisplatin [24] is the mostly preferred chemotherapy regimen as the genetic, pathological, and clinical features of patients with NEC in the metastatic patient group are similar to small cell lung cancer. However, there is no clear data regarding adjuvant treatment after surgery. In our patient's histopathology, the risk of micrometastasis was very high due to tumor thrombosis in numerous large vascular structures, so etoposide/cisplatin, the most effective combined chemotherapy regimen was given as adjuvant therapy for reducing the risk of recurrence.

In conclusion, primary hNEC is a very rare tumor. In a patient with a high AFP level and a primary liver mass, a

primary hNEC may be considered at a differential diagnosis. In addition, serum AFP levels may provide useful information for early recurrence and monitoring of metastasis.

Compliance with Ethical Standards

Conflict of Interest   The authors declare that they have no conflict of interest.

Informed Consent   Informed consent was obtained from all individual participants included in the study.

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