A Large Cell Neuroendocrine Carcinoma of the Gall Bladder: Diagnosis with 18FDG-PET/CT-guided Biliary Cytology and Treatment with Combined Chemotherapy Achieved a Long-term Stable Condition

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INTRODUCTION

Large cell neuroendocrine carcinomas (LCNEC) are aggressive malignant tumors, first described in the lungs in 1991 (1) and in the gallbladder in 2000 (2). We describe here a patient with the LCNEC of the gallbladder, who was rapidly diagnosed by 18F-fluorodeoxy glucose-positron emission tomography (18FDG-PET) and computed tomography (CT)-guided biliary cytology and effectively treated with combined chemotherapy.
CASE REPORT

A 64-year-old male without any significant previous medical history was admitted to our hospital because of abdominal fullness. Physical examination showed superficial lymphadenopathy, including the cervical, axillary and left infracavicular lymph nodes. The results of routine blood tests were normal, without marked increases in the serum concentrations of soluble IL-2 receptor (sIL-2R; 1330 U/ml) and neuron-specific enolase (NSE; 88 ng/ml). No increases in other tumor markers, including CEA, CA 19-9 and AFP, were observed. Diagnostic excisional biopsy of the left axillary lymph nodes revealed atypical cells with predominantly large-sized, round-to-oval nuclei, proliferating in a solid and focal nesting pattern in hematoxylin–eosin stained specimens (Fig. 1a). The tumor cells were positive for synaptophysin and chromogranin A (Fig. 1b) and strongly positive for Ki-67, leading to a diagnosis of poorly differentiated neuroendocrine cell carcinoma, of large cell type. Using 18FDG-PET/CT to identify the primary lesion, we observed a marked accumulation of 18FDG in the lymph nodes, a small part of the liver and the gallbladder (Fig. 2a). The abdominal CT showed a small-sized mass, 25 mm in diameter, in the gallbladder and a small low-density area in the liver (Fig. 2b). Fusion imaging with 18FDG-PET and CT showed that 18FDG had accumulated in the fundus of the gallbladder wall (Fig. 2c). To confirm the origin of this tumor, we performed fine needle aspiration of the gallbladder under CT guidance. The aspirated tumor cells were similar in appearance to the tumor cells obtained from diagnostic excisional biopsy of the lymph nodes (Fig. 3). The patient was diagnosed with a poorly differentiated LCNEC, as determined by the revised histological classification system for gastroenteropancreatic neuroendocrine tumors by the World Health Organization (4). 18FDG-PET/CT has been shown and docetaxel (60 mg/m²) every 3 weeks for four cycles, followed by intravenous carboplatin (120 mg/m²) and docetaxel (60 mg/m²) every 3 weeks for three cycles. During the treatment, Grade 3 leukopenia and neutropenia occurred in the patients. As to non-hematological toxicities, Grade 2 nausea occurred. While these toxicities were observed after cisplatin administration, all were manageable with appropriate medical treatment and postponement of administration. Then, we observed a marked decrease in superficial lymphadenopathy and the disappearance of 18FDG-PET accumulation in the lymph nodes, gallbladder and liver (Fig. 4). The serum concentration of NSE decreased markedly to 6.9 ng/ml, and the patient remained stable for 22 months. At that time, however, the tumor recurred, and the patient died of disseminated intravascular coagulation syndrome with multiple metastases of the lymph nodes, liver and bones.

DISCUSSION

Neuroendocrine cell carcinomas (NECs) of the gallbladder are relatively rare and have a poor prognosis because of their highly aggressive clinical behavior. The clinical symptoms of NECs of gallbladder consist of upper abdominal pain, discomfort, body weight loss and jaundice. However, these symptoms are non-specific. On the other hand, radiological findings of NECs of the gallbladder have been described as a mass replacing the gallbladder, focal or diffuse gallbladder wall thickening, and an intraluminal polypoid mass with or without direct hepatic invasion, liver metastasis and lymphnode metastasis (3). These findings are also non-specific and we could not differentiate NECs from common gallbladder adenocarcinomas in the absence of histopathological findings, examined by immunohistochemical expression of marker proteins such as chromogranin A, synaptophysin and NSE.

Our patient had a poorly differentiated LCNEC, as determined by the revised histological classification system for gastroenteropancreatic neuroendocrine tumors by the World Health Organization (4). 18FDG-PET/CT has been shown

Figure 1. (a) Histological appearance of tumor cells from the left axillary lymph nodes of our patient, showing predominantly large-sized, round-to-oval nuclei, proliferating in a solid and focal nesting pattern (hematoxylin and eosin staining). (b) Immunohistochemical staining showing that the tumor cells were positive for chromogranin A.
useful in confirming the origin of the lymph node metastases and in the effective clinical diagnosis of patients with these tumors. Our patient had an advanced tumor, with multiple large lymph node metastases and a gallbladder tumor only 25 mm in diameter, indicating that diagnostic cholecystectomy was not too invasive. Although echo-guided fine needle aspiration has been used to diagnose these tumors (5), we selected to utilize CT guidance, which showed

\[\text{Figure 2.} \] A coronal full length $^{18}$FDG-PET image showing a marked accumulation of radioactivity in multiple large lymph nodes, a small part of the liver and the gallbladder (arrowhead). (b) An abdominal axial CT image, showing a small-sized mass in the gallbladder (arrowhead) and a small low-density area of the liver. (c) An abdominal coronal CT image showing the wall thickness of the fundus of the gallbladder (arrowhead). (d) A coronal fused $^{18}$FDG-PET/CT image, showing that the $^{18}$FDG in the gallbladder had accumulated in an area corresponding to the wall thickness in the fundus of the gallbladder (arrowhead).

\[\text{Figure 3.} \] CT-guided aspirated bile cytology from the gallbladder, showing that tumor cells had large-sized round-to-oval nuclei, similar to the tumor cells obtained from diagnostic excisional biopsy of the lymph nodes.

\[\text{Figure 4.} \] $^{18}$FDG-PET after chemotherapy, showing the disappearance of $^{18}$FDG from the lymph nodes, gallbladder and liver.

clearly that the primary tumor site was the fundus of the gallbladder without interference by bowel gas. This non-invasive diagnostic procedure was useful and relative safe. In
Large cell neuroendocrine carcinoma of gall bladder

terms of pathological diagnosis, we could get cell cluster adequately without degeneration.

The primary treatment for NECs of the gallbladder remains surgery, but only in patients without liver involvement or distant metastases. In patients with unresectable tumors, systemic chemotherapy is the treatment of choice. In previous reports, patients with good long-term survival underwent a series of treatments, including cholecystectomy, systemic chemotherapy and radiation therapy (6). Due to the rarity of LCNEC of the gallbladder, however, only a few previous cases have been described (7–11), with most of these patients having multiple metastases or direct hepatic invasion with huge tumors at diagnosis, making them unsuitable for surgical treatment. We therefore treated our patient with a combination of cisplatin and docetaxel, using a regimen similar to that used to treat patients with non-small cell lung carcinomas, and probably large cell lung carcinomas. Taniguchi et al. (12) reported a case of adenoendocrine cell carcinoma of the gallbladder, treated with cisplatin and docetaxel after the treatment of gemcitabine monotherapy. In the case, the tumor reduction was achieved effectively. In another case, Nishimori et al. (13) reported a case of metastatic endocrine carcinoma of the pancreas, treated with cisplatin and docetaxel. The case was followed by carboplatin and docetaxel until the disease progression. In our experienced case, the combination of cisplatin and docetaxel had been effective. Since the long-term treatment with cisplatin and docetaxel may not be tolerable, we replaced cisplatin by carboplatin after four cycles of treatment. Iwasa et al. (14) showed that the first-line treatment with cisplatin and etoposide of patients with hepatobiliary and pancreatic poorly differentiated neuroendocrine carcinomas had only marginal antitumor activity and relatively severe toxicity. However, the difficulty of the differential diagnosis and the poor prognosis of NECs of the gallbladder have not changed. The standardization of diagnosis and treatment requires a prospective study with multiple institutes. While we described that a minimally invasive diagnostic procedure and immediate treatment with systemic chemotherapy resulted in stable disease for almost 2 years, further development of novel treatment is necessary to improve the prognosis of NECs of gallbladder.

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Conflict of interest statement

None declared.

References