

Effective treatment of gallbladder neuroendocrine carcinoma with nivolumab

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May 13, 2023

Key clinical message

Gallbladder (GB) neuroendocrine carcinoma (NEC) is rare and has poor prognosis. Furthermore, there is no consensus on treatment of GB-NEC.

Here, we report a case of GB-NEC for which nivolumab was effective.

Key word: Gallbladder NEC, immune checkpoint inhibitors, EUS-FNA

Introduction

Neuroendocrine neoplasms (NEN) often occur in the pancreas (P-NEN) and gastrointestinal tract (GINEN) [1]. Gallbladder (GB) NEN is rare and accounts for only 0.5% of all NEN and 2% of all gallbladder tumors [2]. Furthermore, patients with GB-NEC have poor prognosis [3]. Currently, there are no diagnostic imaging findings for GB-NEC. For NEC, a platinum-based regimen is commonly used, but there is only one report suggesting effectiveness of nivolumab [4]. Here, we report a case involving successful treatment of GB-NEC with nivolumab.

Case history/examination

An 89-year-old Japanese man presented to our department with gallbladder cancer. He had been suffering from left upper lobe (S1+2) lung cancer (papillary adenocarcinoma, pT3N2M0, pStage IIIB). Left upper lobectomy with regional lymphadenectomy. Left mediastinal lymphadenectomy had been performed three years prior, but was followed by mediastinal lymph node metastases and an intrapulmonary metastasis in the right lobe two years before. The patient received chemoradiotherapy which stabilized the metastases. Follow-up PET-CT revealed that¹⁸F-fluorodeoxyglucose (FDG) had accumulated in the fundus of the gallbladder (Standard Uptake Value (SUV) max:4.2) and the hepatoduodenal lymph nodes (SUVmax:3.2) as well as in mediastinum lymph nodes (right carina lymph node SUVmax:11.0, para-aorta lymph node SUVmax:6.1). A tumor in the gallbladder and those in the hepatoduodenal lymph nodes had diameters of 15 mm and 12 mm, respectively. No significant change was observed in lung tumor size (Figure 1). The patient's medical comorbidities included left internal carotid artery stenosis, early colorectal cancer, early bladder cancer, hypertension, and hyperuricemia Physical examinations of the thorax and abdomen showed almost normal findings. He did not have any disability or any signs of cognitive dysfunction.

Differential diagnosis, investigation and treatment

As a result of the examination, the patient was diagnosed with primary GB cancer and metastasis of right lower lobe (S6) lung cancer (adenocarcinoma, cT1N2 M0, cStage IIIA). Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of lymph nodes in the hepatoduodenal ligament revealed small-cell-type neu-

roendocrine carcinomas (SCNEC) which indicated primary GB cancer with lymph node metastasis, rather than metastases of the lung adenocarcinoma.

Prognosis of GB carcinoma with lymph node metastasis and SCNEC is quite poor [5, 6]. The patient, an octogenarian, had performance status of 0 (CTC Version 2.0) , but he had various critical comorbid diseases such as recurrence of lung cancer. Therefore, we first recommended chemotherapy instead of definitive surgery. However, the standard platinum-based regimen of SCNEC proved intolerable because of his general status. Although there are few studies suggesting that nivolumab is effective against neuroendocrine carcinoma and GB cancers [4, 7], Nivolumab monotherapy (240 mg, every two weeks) was initiated. At that time, neuron-specific enolase (NSE) was significant (35.7 ng/mL).

Outcome and follow-up

After 10 courses of nivolumab, a CT scan showed that the GB tumor had shrunk without remarkable lymphadenopathy in the hepatoduodenal ligament, but with limited lymphadenopathy adjacent to the abdominal aorta (Figure 2). A tumor marker, NSE, turned negative (12.9 ng/mL) (Figure 3). Even though prognosis of GB carcinoma with lymph node metastases is quite poor (median OS: 13.5 months) [8], radical resection of the tumor can prolong survival in cases in which metastases disappear after chemotherapy. Therefore, we decided to operate for the following reasons: 1. We could remove the tumor completely with lymphadenectomy next to the abdominal aorta. 2. If the tumor increased during further nivolumab monotherapy, we would have been unable to achieve complete resection by surgery.

Furthermore, surgery seemed likely to be tolerated by the patient because he was almost healthy and because the surgery did not require major hepatectomy or bile duct resection. We meticulously explained the foregoing to the patient and his family and obtained consent for surgery. Then, an extended cholecystectomy and lymphadenectomy around hepatoduodenal ligament and sampling of lymph nodes proximal to the abdominal aorta were performed. After surgery, no major adverse events were observed, except delayed gastric emptying, Clavien dindo grade II, and acute gastric mucosal lesions, Clavien dindo grade IIIa. Histopathologically, the atrophied gallbladder had a tumor in its fundus (15x8x10 mm). (Figure 4). Upon microscopic examination, NEC and adenocarcinoma (in situ) components were mixed (Figure 5). Most components of the tumor were NEC, and adenocarcinoma in situ (AIS) was present at both ends of the NEC. Histologically, there was no metastasis in the hepatoduodenal ligament, but there was metastasis beside the abdominal aorta. PD-L1 28-8 IHC showed that the PD-L1 expression rate was less than 10% (Figure 5). Histological evaluation of the chemotherapeutic effect was Grade 0, no change (6th Ed. of General Rules for Clinical and Pathological Studies of Cancer of the Biliary Tract). One month after the surgery, adjuvant nivolumab monotherapy was initiated. Three months have elapsed since the surgery, and no recurrent lesion has been observed.

Discussion

Primary GB-neuroendocrine tumors (NET) account for 0.5% of all NET and 2.1% of all GB cancers[9]. The most common primary tumor sites are the gastrointestinal and respiratory tracts [2] ,and GB-NEC is very rare. Although there is no comprehensive epidemiological information on gallbladder NEC, there is a report that the median age of patients is 58.4 years (range 26-75), with an M:F ratio of 7:8. Median overall patient survival is 26 months for those without lymph node metastasis and 10.4 months for patients with it [10].

Cisplatin and Etoposide (EP therapy) or Cisplatin and Irinotecan (IP therapy) is widely recommended for NEC, but the response rate and median overall survival (OS) are unfavorable (EP: response rate, 12%; median OS 6.9 months , IP: response rate, 39%; median OS 10.1 months) [11].

In the present case, considering the patient's age and medical history, we started nivolumab monotherapy. As a result of image examination, though the paraaortic lymph node swelled, the GB tumor clearly shrank and swelling of hepatic duct lymph node disappeared. A tumor marker against NEC, NSE turned negative.

These findings suggest that nivolumab can be effective against GB-NEC. Nevertheless, PD-L1 28-8 immunohistochemistry (IHC) was positive in less than 10% of cancer cells. This suggests the following two possibilities: 1. PD-L1 positive cells were killed by nivolumab, leaving only colonies of negative cells. 2.

Nivolumab activates T cells, which kill PD-L1 negative cells. Drug sensitivity of cancer cells varies from cell to cell because each cancer cell has a different genetic background. Therefore, although ICIs are very effective for cancer cells with high PD-L1, ICIs may also be effective against subgroups with low or undetectable PD-L1. Actually, it has been reported that in lung cancer, ICIs respond even when the expression rate of PD-L1 is extremely low [12]. Recent studies suggest that PD-L1 inhibitors themselves may activate tumor-reactive T cells and enhance anti-tumor immunity [13]. Further studies on the correlation between the PD-L1 expression rate and the ICI response rate in gallbladder cancer are awaited.

EUS-FNA is quite useful because its sensitivity to GB cancer is 96% [14]. In this case, we detected NEC using the EUS-FNA technique for lymph nodes in the hepatoduodenal ligament. However, in cases in which primary tumors have both NET and non-neuroendocrine components, so-called mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN), EUS-FNA may not be able to detect all of them. NEC is highly malignant and readily metastasizes to other tissues. Therefore, even if an NEC component is detected by biopsy of metastatic lymph nodes, the primary tumor may contain non-neuroendocrine components such as adenocarcinoma.

It is necessary to choose an effective chemotherapy regimen for all tumor components. Multiple EUS-FNA enables collection of multiple samples, which can facilitate correct diagnosis and selection of an appropriate chemotherapy regimen, but dissemination and bile leakage are problematic [15]. Furthermore, NEC is located deep within an area of vascular or perineural invasion [16]. As a result, most MiNEN are diagnosed from surgical specimens [17]. Therefore, it is important to diagnose using serum tumor markers, imaging tests, or EUS-FNA. Ultimately, it may be useful to collect samples surgically.

In conclusion, EUS-FNA is useful for diagnosis of GB-NEC. However, because the primary tumor may be MiNEN rather than NEC, it is better to perform a biopsy when selecting a chemotherapy regimen. Nivolumab may enhance the immune function of T cells by some means other than inhibition of PD-1, and it may be effective against GB-cancer involving NEC despite the low expression of PD-L1.

Ethics approval and consent to participate

N/A

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest and that there are no relevant financial disclosures to report.

Funding

None

Author contributions

KH performed all clinical interventions and critically revised the final manuscript.

SK made substantial contributions to conception, design, data acquisition, and interpretation of the study and was involved in initial drafting of the manuscript.

Other authors were involved in revision of the final manuscript.

All authors reviewed the final manuscript, approved the final version, and agree to be accountable for all aspects of the work.

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Figure Legends

Figure 1.

PET-CT revealed FDG accumulated in the fundus of the gallbladder (SUV max:4.2) (dotted arrow) and hepatoduodenal lymph nodes (SUVmax:3.2) (solid arrow) as well as lymph nodes of the mediastinum.

Figure 2.

CT images (a) before chemotherapy and (b, c) after ten courses of Nivolumab. After Nivolumab, the tumor had clearly shrunk (b, arrow), but limited lymphadenopathy proximal to the abdominal aorta emerged (c, arrow).

Figure 3.

NSE turned negative after ten courses of Nivolumab.

Figure 4.

There was a mass (15 x 8 x 10 mm) on the lower side of the gallbladder, which was atrophied, with a thickened wall overall.

Figure 5.

NEC (solid arrow) and adenocarcinoma (in situ) components (dotted arrow) were mixed (a). In the NEC component, the N/C ratio was increased, and abnormal mitosis was observed (b). Furthermore, glandular duct structure disappeared, and solid growth of NEC was observed (b). PD-L1 expression is rarely seen (c).

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