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Case Report Open Access

Clinicopathologic Characteristics and Multidisciplinary Treatment of Neuroendocrine Carcinoma of Gallbladder: Report of Three Cases with an Update

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Abstract

Primary neuroendocrine carcinoma of gallbladder (GB-NEC) is extremely rare and the clinical presentations of most patients are nonspecific. Pathological examination and immunohistochemical staining are required for the diagnosis of GB-NEC. It has a poor prognosis and often escapes detection until advanced stage. Because of rarity of GB-NEC, there is limited evidence about its clinic pathologic characteristics, treatment and prognosis. Here we reported three cases of incidental metastatic GB-NEC. Multidisciplinary treatments were adopted and they present good response and had long survival. We aimed to provide a comprehensive literature review on GB-NEC and compare it with carcinoma of gallbladder and neuroendocrine neoplasms of other origins.

Keywords: Gallbladder; Neuroendocrine carcinoma; Neuroendocrine tumors; Chemotherapy; Multidisciplinary treatment

Introduction

Neuroendocrine neoplasm (NEN) is a heterogeneous group of tumors originating from neuroendocrine cells located throughout the body, most commonly in the lung and gastrointestinal tract [1]. Data from the surveillance, epidemiology, and end results (SEER) database indicates the incidence of NENs is about 2.5–5/100,000 people [2]. NENs occur in the gallbladder are rare and only account for only 0.5% of all NETs and 2% of all gallbladder tumors [3]. Because of aggressive biological behavior and lack of specific symptoms, patients are often diagnosed at advanced stage when radical surgery is not available. Three cases we reported all underwent a multidisciplinary therapy and showed good responses.

Case Report

Case 1

A 66-year-old male complained of back pain for 1 week. Physical examination was negative. A thick-walled gallbladder with liver invasion was visualized by computed tomography (Figure 1). ECT indicated multiple bone metastases. 99mTc-somatostatin receptor scintigraphy (SRS) was positive throughout the body. Diagnostic liver biopsy was thereafter performed. Immunohistochemistry revealed strong expression of CgA, Syn, CK and CD56. Ki-67 index was 30%. Blood level of CgA was within normal limits. Considering the tumor is unresectable at this stage, chemotherapy, transarterial chemoembolization (TACE), radiotherapy of gallbladder region, somatostatin treatments were adopted based on multidisciplinary team (MDT) discussion. The chemotherapy regimen consisted of cisplatin 100 mg/m^2 given intravenously on days 1–3 and etoposide 75 mg/m^2 intravenously on days 1-3, repeated every 3 weeks. The abdominal lesions were partial response (PR) after 7 cycles of this regimen (Figure 2). The patient remained stable for 15 months after the initial chemotherapy until CT scan revealed opisthion metastasis. He underwent only one cycle of IP regimen because of intolerance of nausea and vomit caused by chemotherapy. Instead, radiotherapy of opisthion was applied to alleviate pain related to the metastasis. Abdominal CT scan revealed liver metastasis in the fifth segment (Figure 2) 10 month later. The patient underwent TACE and the liver metastasis was diminished. The patient developed rapid deterioration and jaundice 4 months after TACE. The patient died due to liver failure with overall survival (OS) of 36 month.

Case 2

A 56-year-old male complained of back pain and jaundice for 1 month. An enlarged left supraclavicular lymph node with a diameter of 2 cm was found by physical examination. Abdominal CT scan revealed a polypoid intra-luminal lesion within the gallbladder with local infiltration to the adjacent live and lymph node enlargement around the hepatic hilum and retroperitoneum (Figure 3). 99mTc-SRS depicted positive of left cervical region. Blood hormone test showed her serum CgA was 125.3 ng/ml (normal range 17~34 ng/ml). Percutaneous transhepatic cholangial drainage (PTCD) and diagnostic biopsy of left supraclavicular lymph nodes were thereafter performed (Figure 4). Immunohistochemistry was positive for CgA, Syn, CD56 and CK7. The Ki-67 index was over 80%. In January 2014, the patient underwent TACE as treatment for his liver metastases. After that, chemotherapy, radiotherapy of gallbladder region and left supraclavicular lymph nodes were adopted. The chemotherapy regimen consisted of cisplatin 40 mg/

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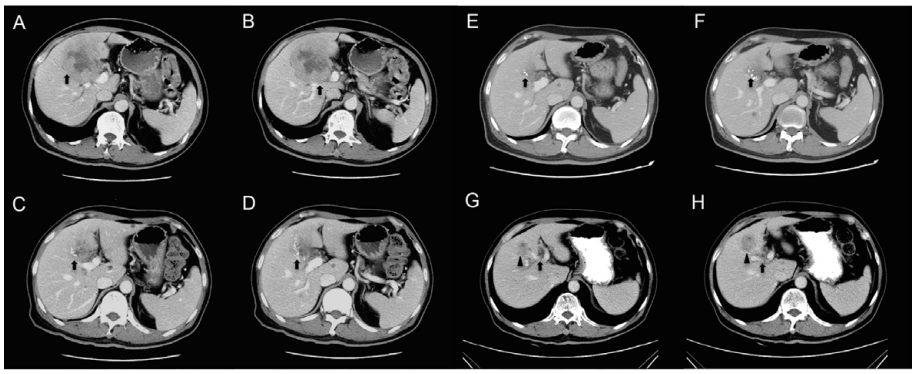

Figure 1: A, B (baseline CT scan): A thick-walled gallbladder with local infiltration to the adjacent liver (arrow); C, D (after 2 cycles of chemotherapy): gallbladder lesion diminished (arrow); E, F (after 4 cycles of chemotherapy): gallbladder lesion was stable (arrow); G, H: gallbladder lesion enlarged (arrow) and a mass in the fifth segment (arrowhead) appeared.

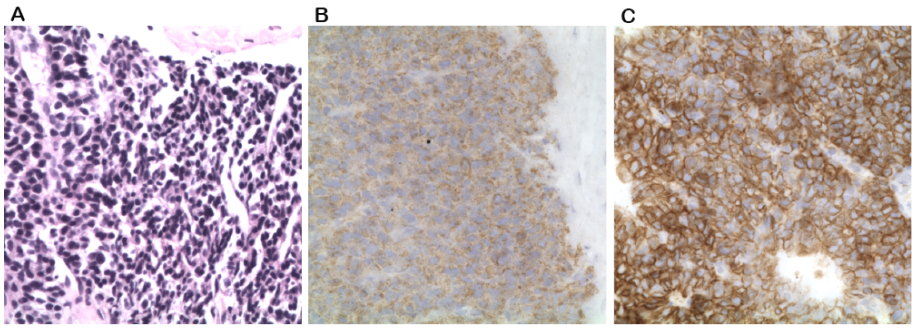

Figure 2: A, B, C, D (baseline): A polypoid intraluminal lesion (2.8 × 2.7 cm, arrow) with enlarged hepatic hilar (star) and retroperitoneal (arrowhead) lymph nodes; E, F, G, H (after 8 cycles): the mass (1.7 × 1.5 cm, arrow) and lymph nodes decreased.

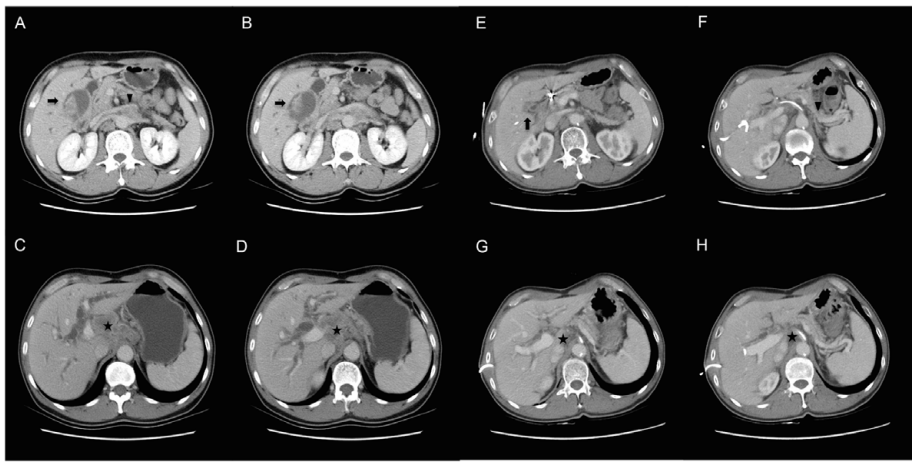

Figure 3: A, B, C, D (baseline CT scan): A thick-walled gallbladder (2.6 × 1.4 cm, arrowhead) with scattered liver metastasis (arrow); E, F, G, H (after 3 cycles): gallbladder lesion was stable (2.4 × 1.6 cm, arrowhead) with liver metastasis diminished (arrow).

m^2 and irinotecan 130 mg/m^2 intravenously on day 1, repeated every 2 weeks. The abdominal lesions were PR after 8 cycles of this regimen. After radiotherapy of gallbladder, his abdominal lesions remained stable while left supraclavicular lymph nodes increased. Thereafter he underwent 3 more cycles of IP regimen, but the lymph nodes did not shrink, rendering him to turn to radiotherapy. As of February 2015, he was alive, with stable disease and no progression or improvement in the metastatic lesions.

Case 3

A 50-year-old female presented to our hospital with a history of multiple liver masses found by ultrasound occasionally for 2 weeks. No history of jaundice, abdominal pain, or other systemic symptoms was present. Physical examination was negative. The patient underwent abdomen CT scan, which revealed several hepatic lesions and a mass in the fundus of the gallbladder lumen (Figure 5). 99mTc-SRS showed positive in

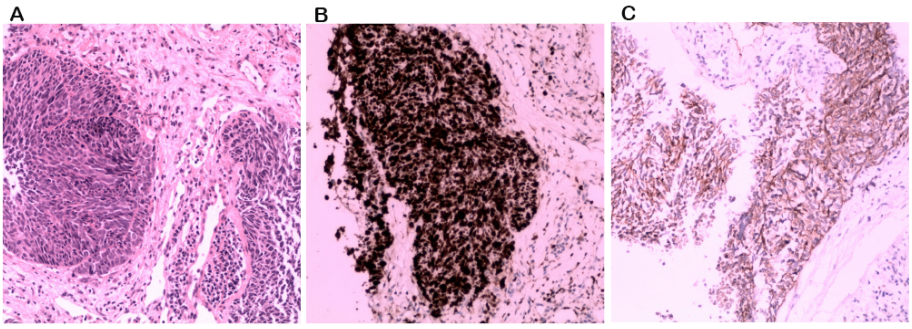

Figure 4: Pathological examination, H&E 200X; A: Case 1: A monotonous proliferation of small round cells with hyperchromatic nuclei and scanty cytoplasm; B: Case 2: Diffuse small round cells with scanty cytoplasm and round nucleus, Abundant necrosis and innumerable mitotic figures were seen; C: Case 3: Predominantly large sized, round-to-oval nuclei, proliferating in a solid and focal nesting pattern.

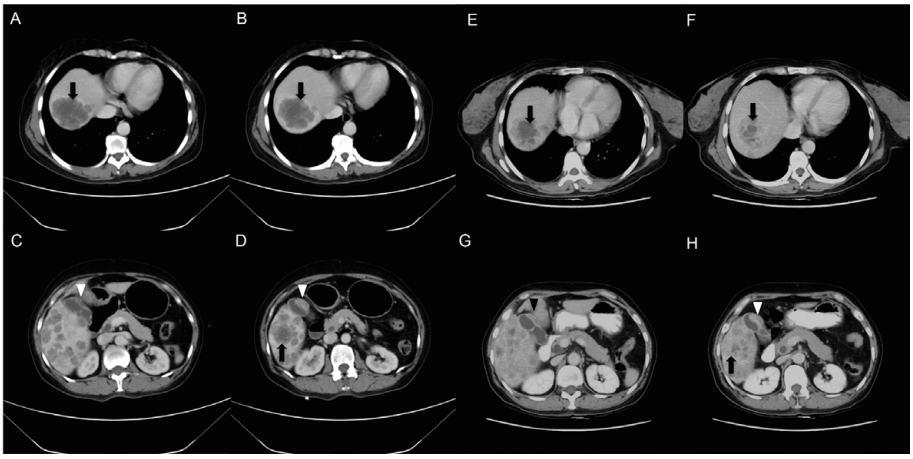

Figure 5: A: Case 1: 99mTc-SRS showed positive throughout the body; B: Case 2: 99mTc-SRS presented positive in the left cervical region; C: Case 3: 99mTc-SRS revealed positive in bilateral thyroid.

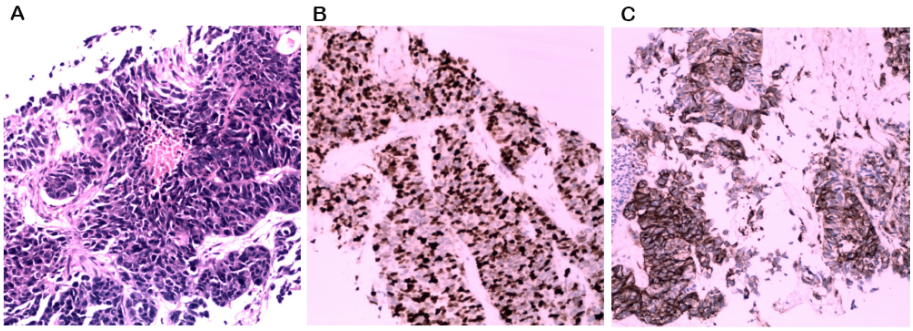

Figure 6: A: Case 1: OS 36months, PFS1 16 months, PFS2 10 months; B: Case 2: PFS 7months; C: Case 3: PFS>9 months.

the bilateral thyroid (Figure 6). While the thyroid ultrasound confirmed multiple benign hyperplastic nodules. Diagnostic biopsy of liver was performed (Figure 7). Immunohistochemistry revealed strong positivity for CgA, Syn, CD56, CK7, and CK19. The Ki-67 index was 80%. Serum CgA was 283.7 ng/ml. The patient underwent 6 cycles of chemotherapy and TACE 3 times from July 2014. The regimen consisted of cisplatin 50 mg/m^2 and irinotecan 150 mg/m^2 intravenously on day 1, repeated every 2 wk. The CT scan performed after the third cycle revealed stable disease (SD), which was confirmed after three more cycles of chemotherapy. No recurrence or metastasis was found using CT scan until February 2015.

Discussion

Symptoms

The clinical presentations of most patients are nonspecific, such as upper abdominal pain, body weight loss and jaundice, with only 1% in all cases presenting hormone-related syndromes [3]. As with other gallbladder carcinomas, NEC can readily invade the adjacent live parenchyma and later cause biliary obstruction, making it challenging to detect at early stage. GB-NEC patients are often diagnosed at advanced stage with local invasion or distal metastases, and accordingly

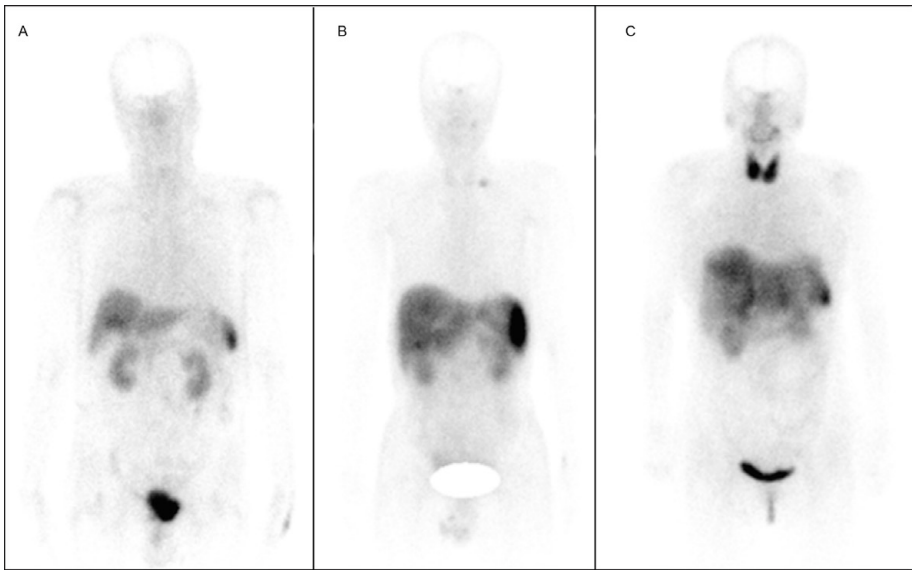

Figure 7: A. Case 1: 99mTc-SRS showed positive throughout the body. B. Case 2: 99mTc-SRS presented positive in the left cervical region. C. Case 3: 99mTc-SRS revealed positive in bilateral thyroid.

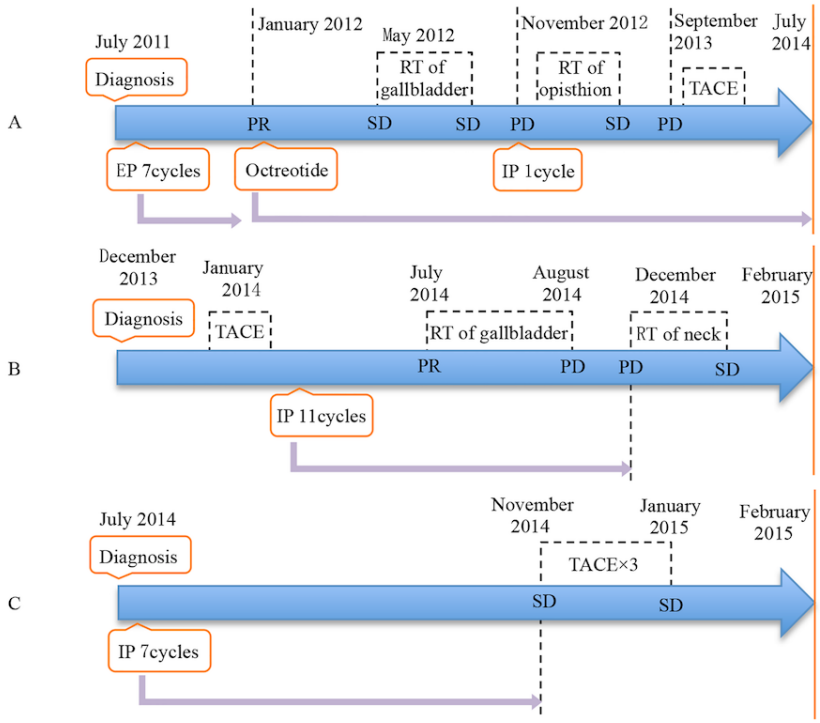

Figure 8: A. Case 1: OS 36 months, PFS1 16 months, PFS2 10 months; B. Case 2: PFS 7 months; C. Case 3: PFS>9 months.

have a poor prognosis. All of the three patients had no hormone-related symptoms, presenting back pain, supraclavicular lymph node enlargement, obstructive jaundice or even asymptomatic.

Biochemical markers

Serum CgA is currently the most useful general biomarker for the assessment of GB-NEC. Levels of circulating CgA are increased in 60% to 80% of patients with GEP-NETs [4]. An Italian multicenter observational study [5] demonstrated that higher CgA levels associated with metastatic disease, and that lower CgA levels in patients with extensive metastatic spread than in those with liver metastases only. In our study, the serum CgA of patient with multiple metastases was negative while other patients with only liver metastasis presented high CgA levels.

Diagnostic imaging modalities

Radiological findings of GB-NEC have been described as focal

or diffuse gallbladder wall thickening and an intraluminal polypoid mass with or without direct hepatic invasion, liver and lymph node metastases. These findings are non-specific and we cannot differentiate NECs from gallbladder adenocarcinomas. SRS is a sensitive modality for the identification of GB-NECs. In our study, SRS depicted multiple strong expressions in case 1 (Ki-67 30%). In case 2, the supraclavicular lymph node was positive while the original lesion was negative because of heterogeneity of GB-NEC. In case 3, nonspecific positivity in thyroid benign hyperplastic nodule denied the primary NEC of thyroid or metastasis. We deduced that SRS preferred to be positive for GB-NEC with low level of Ki-67 index. The hypothesis was confirmed by a retrospective study, which indicated that SRS was positive in 88% G3-WDNET and 50% G3-LCNEC [6]. Contrast with SRS, positron emission tomography (PET)-CT scan imaging have been used in several malignancies with high uptake of 18F-fluorodeoxyglucose but not useful for NETs except for the aggressive tumors [7]. Abgral et al. [8] demonstrated that PET-CT was more sensitive than the SRS for high Ki-67 index. Furthermore, SRS has limitation in detecting NETs<2 cm and assessing tumor size [9,10].

Treatment

Surgery remains the mainstay of treatment. However, most patients have metastatic disease and poor condition at the time of diagnosis, and cannot be approached surgically with curative intent. Cytotoxic chemotherapy remains the first-line treatment of unresectable or metastatic disease in patients with GB-NECs.

Cytotoxic chemotherapy

For patients with poorly differentiated NEC, cisplatin and etoposide (EP) are generally recommended as the primary treatment, representing one of the standard regimens for the treatment of small cell lung cancer (SCLC). Moertel et al. [11] reported an objective response rate of 67% with a chemotherapy regimen combining etoposide plus cisplatin, with median overal survival (mOS) of 19 months and progression-free survival (PFS) of 11 months. In contrast, the overall response rate (ORR) in patients with well-differentiated NET was only 7%. Since this publication, this regimen has been considered as the reference treatment for poor-differentiated NECs. A recent study demonstrated that the response rate to platinum-based chemotherapy was 31% and the median survival was 11 months in 252 GEP-NEC patients [12]. Irinotecan plus cisplatin (IP) has no significant difference in response rates compared with EP for SCLC [13]. Peking University Cancer Hospital reviewed 16 locally advanced or metastatic GEP-NEC patients treated with IP regimen. The ORR was 57.1% and the PFS was 5.5 months with mOS of 10.6 months [14]. In 2012 ASCO, a multicenter retrospective study was reported. For 206 GEP-NEC patients treated with IP/EP, the RR were 50%/27%, the PFS were 5.2/4.0 months, and mOS were 13.0/7.3 months [15]. Similar with GEP-NEC, 3 cases received platinum-based chemotherapy and achieved long survival (Figure 8).

The database of Netherlands Cancer Registry (NCR) from 2001 to 2010 demonstrated that 5 year relative survival rates (RSRs) for large cell NEC (GI-LCNEC) and small cell NEC (GI-SCNEC) were 32%/6%. Specifically, the localized were 61%/12%, the regional were 37%/17%, the metastatic were 18%/2% [16]. Histologic subtyping NEC into SCNEC and LCNEC, rather than grouping all types of high-grade neuroendocrine neoplasms together as NEC, is necessary. Okuyama et al. [17] reported one case of metastatic GB-LCNEC was reported with combination chemotherapy with cisplatin and docetaxel. The regimen, typically used for non-small cell lung carcinomas, resulted in a long-term stable condition of 22 months. Clinicopathologic characteristics of each subtype need to be more clearly defined for selection of therapy and prognosis improvement.

The 2010 WHO classification of GEP-NET implied that G3 neoplasms with Ki-67 index>20% were NECs, while several studies demonstrated that this subgroup of NENs was heterogeneous and contained both morphologically well and poorly differentiated tumors with different clinical expressions, prognosis, and sensitivity to treatment. The NORDIC study found that patients with Ki-67<55% had a lower response rate (15% vs.42%, P<0.001), but better survival than patients with Ki-67>55% (14 vs.10mo, P<0.001) [12]. The data indicated that Ki-67 index should be considered for chemotherapy treatment.

Somatostatin analogues

Somatostatin analogues are commonly used to treat symptoms associated with hormone hypersecretion in NETs; however, data on their antitumor effects is limited. Recently, studies found that somatostatin analogues can inhibit tumor cell growth directly by modulating the signal transduction of proliferation and apoptosis [18]. The PROMID study used octreotide LAR at a dose of 30 mg intramuscularly every month until tumor progression and found that the median time to progression was 15.6 months compared with 5.9 months (P<0.001) [19]. The 2013 ASCO reported CLARINET study included 204 patients with advanced, well-differentiated or moderately differentiated, nonfunctioning GEP-NETs of grade 1 or 2(Ki-67<10%). Lanreotide, as compared with placebo, was associated with significantly prolonged PFS (median>27 mo vs. median of 18.0 mo, P<0.001) [20]. In our study, for three poor-differentiated GB-NEC patients, chemotherapy was the dominant treatment. Case 1 (Ki-67 30%) received octreotide LAR after 7 cycles of EP regimen and no evidence of recurrence and metastasis was found for 10 months. For GB-NEC (WHO G3) patients with low Ki-67 index, somatostatin analogues may not only be considered as symptomatic treatment but also as antitumor agents.

Radiotherapy

Radiotherapy (RT) has not historically played a major role in the treatment of NENs. However, from the treatment of SCLCs, radiotherapy should be considered to control local recurrence or metastasis. GB-NEC mostly locates at hepatic hilar region, resulting in obstruction of biliary tracts. RT could be an optional treatment modality for achieving local control in patients with advanced GB-NECs. In our study, RT of gallbladder or abdominal cavity was adopted in 2 cases and yielded excellent local control.

Radiofrequency ablation

GB-NECs frequently metastasize to regional lymph nodes, the bones, and the liver. In addition, hepatic metastases not only lead to incapacitating symptoms but also decrease long-term survival. Surgery is the mainstay for curative intent, but in most of GB-NEC patients with hepatic metastases, when surgery cannot be employed, interventional therapy is adopted. TACE for neuroendocrine hepatic metastases have been shown to be an extremely effective treatment of symptoms related to the metastases and survival benefit [21]. As for 3 cases with liver metastasis, TACE was adopted and resulted in liver lesions decreased and symptoms relieved.

Conclusion

GB-NEC is a rare subtype of gallbladder tumor with aggressive biological behavior and poor prognosis. Most of the cases are non-hormone producing and often asymptomatic, leading it challenging

to diagnose in early stage. Pathological diagnosis and identification of clinical stage are of vital importance. Platinum-based chemotherapy and somatostatin analogues are reference treatments for unresectable or metastatic GB-NECs. Meanwhile, Ki-67 index, biological characteristics, metastasis and complications should be considered. Radiotherapy and interventional therapy are promising to control local recurrence or metastasis. In conclusion, a multidisciplinary approach including chemotherapy, radiotherapy, biological targeted therapy and interventional therapy is the primary treatment for GB-NEC. The standardization of treatment still requires further investigations.

References

1. Bosman FT, Carneiro F, Hruban RH, Theise ND (2010) WHO Classification of Tumours of the Digestive System. WHO Press 3: 978-992.
2. Oberg K, Castellano D (2011) Current knowledge on diagnosis and staging of neuroendocrine tumors. Cancer Metastasis Rev 30: 3-7.
3. Eltawil KM, Gustafsson BI, Kidd M, Modlin IM (2010) Neuroendocrine tumors of the gallbladder: an evaluation and reassessment of management strategy. J Clin Gastroenterol 44: 687-695.
4. Kiran K, Turaga LK (2011) Recent progress in the understanding, diagnosis, and treatment of gastroenteropancreatic neuroendocrine tumors. CA Cancer J Clin 61:113-132.
5. Zatelli MC, Torta M, Leon A, Ambrosio MR, Gion M, et al. (2007) Chromogranin A as a marker of neuroendocrine neoplasia: an Italian Multicenter Study. Endocr Relat Cancer 14: 473-82.
6. Vélayoudom-Céphise FL, Duvillard P, Foucan L, Hadoux J, Chougnet CN, et al. (2013) Are G3 ENETS neuroendocrine neoplasms heterogeneous. Endocrine Related Cancer 20: 649-657.
7. Adams S, Baum R, Rink T, Schumm-Dräger PM, Usadel KH, et al. (1998) Limited value of fluorine-18-fluorodeoxyglucose positron emission tomography for the imaging of neuroendocrine tumors. Eur J Nucl Med 25: 79-83.
8. Abgral R, Leboulleux S, Déandreis D, Aupérin A, Lumbroso J, et al. (2011) Performance of (18) fluorodeoxyglucose-positron emission tomography and somatostatin receptor scintigraphy for high Ki67 (≥10%) well-differentiated endocrine carcinoma staging. J Clin Endocrinol Metab 96: 665-71.
9. Maxwell JE, Sherman SK, Menda Y, Wang D, O'Dorisio TM, et al. (2014) Limitations of somatostatin scintigraphy in primary small bowel neuroendocrine tumors. J Surg Res 190: 548-53.
10. Albores-Saavedra J, Batich K, Hossain S, Henson DE, Schwartz AM (2009) Carcinoid tumors and small-cell carcinomas of the gallbladder and extrahepatic bile ducts: a comparative study based on 221 cases from the Surveillance, Epidemiology, and End Results Program. Ann Diagn Pathol 13: 378-83.
11. Moertel C, Kvols L, O'Connell M, Rubin J (1991) Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin: evidence of major therapeutic activity in the anaplastic variants of these neoplasms. Cancer 68: 227-32.
12. Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, et al. (2013) Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. Ann Oncol 24: 152-160.
13. Hanna N, Bunn Jr PA, Langer C, Einhorn L, Guthrie T Jr, et al. (2006) Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 24: 2038-43.
14. ZHLu, JLi, MLu, Zhang XT, Li J, et al. (2013) Feasibility and efficacy of combined cisplatin plus irinotecan chemotherapy for gastroenteropancreatic neuroendocrine carcinomas. Med Oncol 30: 664.
15. Yagamuchi T, Machida N, Kasuga A, Takahashi H, Sudo K, et al. (2012) Multicenter retrospective analysis of systemic chemotherapy in poorly differentiated neuroendocrine carcinoma of the digestive system. J ClinOncol 30 abstr 274.
16. Korse CM, Taal BG, van Velthuysen ML, Visser O, (2013) Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: experience of two decades of cancer registry. Eur J Cancer 49: 1975-1983.
17. Okuyama Y, Fukui A, Enoki Y, Morishita H, Yoshida N, et al. (2013) 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. Jpn J Clin Oncol 43: 571-574.
18. Grande E, Diez JJ, Pachon V, Carrato A (2010) Advances in the therapy of gastroenteropancreatic-neuroendocrine tumors (GEP-NETs). Clin Transl Oncol 12: 481-492.
19. Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, et al. (2009) Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 27: 4656-5663.
20. Martyn E, Caplin DM, Marianne Pavel MD, Jarosław B. Ćwikła MD, Alexandria T, et al. (2014) Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. N Engl J Med 371: 224-33.
21. John G, Touzios MD, James M, Rilling WS, Quebbeman EJ, et al. (2005) Neuroendocrine Hepatic Metastases Does Aggressive Management Improve Survival? Ann Surg 241: 776-785.