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SHORT COMMUNICATION

Neuroendocrine carcinomas of the gallbladder: Lessons learnt from cases at opposite ends of the spectrum

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Summary

Neuroendocrine tumors are the rarest tumors of gallbladder. The most aggressive variant is neuroendocrine carcinoma which represents about 0.5% of all gallbladder carcinomas and 0.2% of all neuroendocrine tumors. It seems possible that survival rates can be improved by utilizing wide surgical resection combined with chemotherapy. We report on two cases of extreme presentation, including age, extend of disease and treatment modalities.

Key words: *gallbladder, neuroendocrine tumors, resection, treatment*

Introduction

Primary neuroendocrine neoplasms of the gallbladder (GB-NENs) represent an extremely rare entity that accounts for only 0.5% of all NENs and 2% of all gallbladder tumors [1]. To date, the largest series have been reported in the Surveillance, Epidemiology and End Results (SEER) registry with 278 cases of GB-NEN diagnosed from 1973 to 2005 [2]. According to the existing literature, age at presentation ranges from 26 to 79 years, showing a slight female predominance [1].

Gallbladder neuroendocrine carcinomas (GB-NECs) are poorly differentiated GB-NENs showing a highly malignant potential, whereas carcinoid tumor is the well-differentiated counterpart that usually has a better prognosis [3]. The symptomatology of GB-NECs is usually nonspecific and their diagnosis is most often made incidentally during pathologic examination of the gallbladder after surgery for cholelithiasis or other biliary pathology [2,4].

Given the paucity of cases in the literature, the knowledge on clinicopathological characteristics and prognosis of GB-NECs remains scarce. Herein, we report on two cases of GB-NECs, both occurring in young aged patients, but with totally different presentations; one found incidentally and the other presenting as a metastatic liver mass.

Case 1

A 29-year-old man presented with epigastric pain and nausea for 48 hrs. Physical examination revealed epigastric tenderness without rebound or guarding. His past medical history was noncontributory. Computed tomography (CT) of the abdomen and pelvis demonstrated a dilated gallbladder with partially visible internal sludge and stones, dilation of the common duct measuring 1 cm and liver with mild intrahepatic biliary ductal dilatation. No other masses or lymphadenopathy were noted. Mesenteric stranding adjacent to the

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distal pancreas was noted along with fluid layering along the left lateral conus fascia. MRI/MRCP performed demonstrated numerous surrounding T2 hypointense gallstones within the gallbladder and the neck measuring 0.4 cm in size, extrahepatic common bile duct dilatation up to 0.8 cm and inflammatory stranding about the pancreas along the body and tail consistent with pancreatitis. Serum lipase levels were >2000. A diagnosis of gallstone pancreatitis was established.

The patient underwent ERCP with stone removal and laparoscopic cholecystectomy was further recommended. The operation was uncomplicated and the postoperative course uneventful. Pathology from the gallbladder specimen revealed a large cell neuroendocrine carcinoma grade 1, with the tumor cells being strongly positive for synaptophysin and chromogranin, weakly positive for CDX2, focally positive for CK7, and negative for CK20 and TTF-1. Immunohistochemistry revealed strong immunoreactivity for pan-cytokeratin. Lymphovascular invasion was present on original H&E stained section, but not present on CD31 immunostained section. The mitotic count was 1/2 mm^2. The Ki-67 index was 2.6%. The cystic duct margin was negative for tumor. The tumor was less than 0.5 mm from the inked outer surface of the specimen. The cystic duct margin was free of disease but focal lymphovascular infiltration was present. There was no family history of neuroendocrine tumor. Multidisciplinary Oncology Meeting recommended radical cholecystectomy. Two weeks later, he underwent open resection of liver segments 4 and 5 and hilar lympadenectomy. There was no evidence of disease either in the liver parenchyma or lymph nodes. The patient recovered uneventfully. With this pathology, the medical oncology team did not recommend any further therapy but suggested close follow-up with CT scan every 3 months for the first year and then with an increase in interval after that time. A follow-up CT scan performed 2 months thereafter revealed no evidence of metastatic disease within the chest, abdomen or pelvis (Figure 1).

Case 2

A 36-year-old female with history of hypertension (on treatment for the last 4 years) and morbid obesity presented for further evaluation and management of multiple hepatic masses in the setting of elevated HCG levels. Her symptoms started 4 months prior when she developed for a few days abdominal pain in the epigastrium that self-resolved without any interventions; this was presumed to be secondary to cholelithiasis. She had been amenorrheic for the past 2 months, and prior to this did

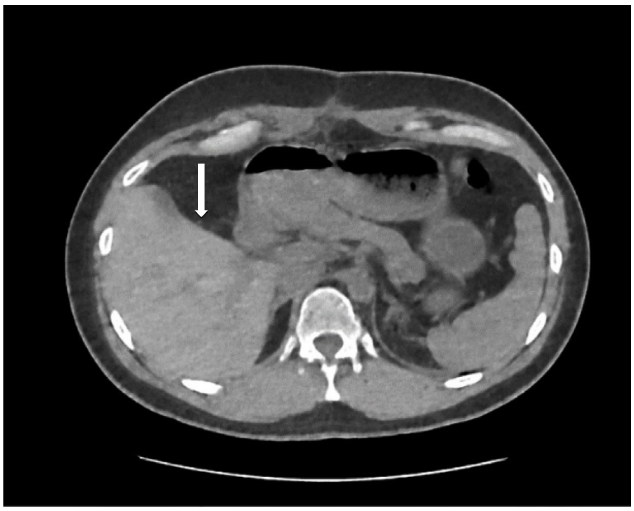

Figure 1. CT of the abdomen/pelvis with i.v contrast after radical cholecystectomy. White arrow indicates the postresectional liver surface.

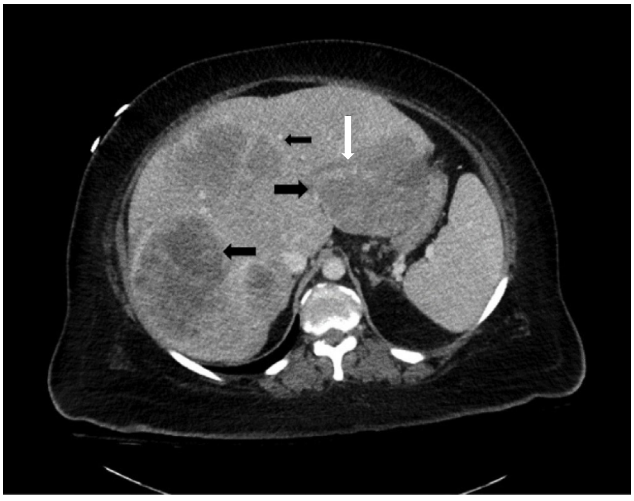

Figure 2. CT scan of the abdomen/pelvis with iv contrast showing multiple liver masses with intraparenchymal hemorrhage. White arrow indicates areas of active contrast extravasation and black arrows indicate the liver masses.

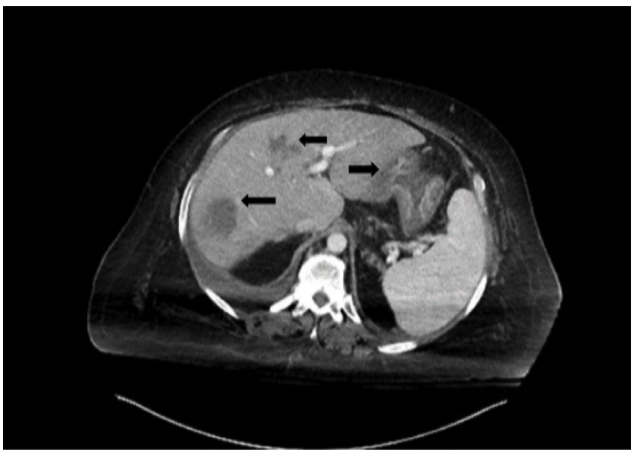

Figure 3. CT of the abdomen/pelvis with iv contrast demonstrating liver mass decrease after embolization. Black arrows indicate the significantly decreased liver masses.

have a history of irregular menstruation. During the second episode of epigastric pain, the patient was evaluated by her primary physician. During the workup, which included x-ray of the abdomen, a urine pregnancy test was positive. A MRI of her abdomen performed showed "six large liver masses, the largest of which measured 11x8.7 cm in the lateral segment of the left hepatic lobe, non-typical for hemangioma", as well as findings of cholelithiasis without cholecystitis. A pelvic ultrasound was performed as well which was notable for a difficult to visualize uterus/ovaries, endometrial stripe thickness of 10-11 mm, no adnexal masses or free fluid and no clear gestational sac or tubal gestation.

CT revealed choledocholithiasis with several large liver masses with intratumoral haemorrhage, initially thought to represent adenomas (Figure 2). She underwent ERCP with sphincterotomy, stent placement, and removal of stones from bile duct and embolization of her liver masses to reduce the risk of hemorrhage. One month later, another CT revealed a reduction in size of her embolized masses in the right liver, but no response to the embolized lesions in the left lobe (Figure 3). One month later, she developed recurrent right upper quadrant abdominal pain possibly due to cholecystitis. A hepatobiliary iminodiacetic acid (HIDA) demonstrated non-filling of the gallbladder consistent with cystic duct obstruction. MRI/MRCP done at this time demonstrated further enlargement of the hepatic masses, raising the possibility of malignancy rather than adenoma. Given these findings, the decision was made to proceed with cholecystectomy and biopsy of the liver lesions.

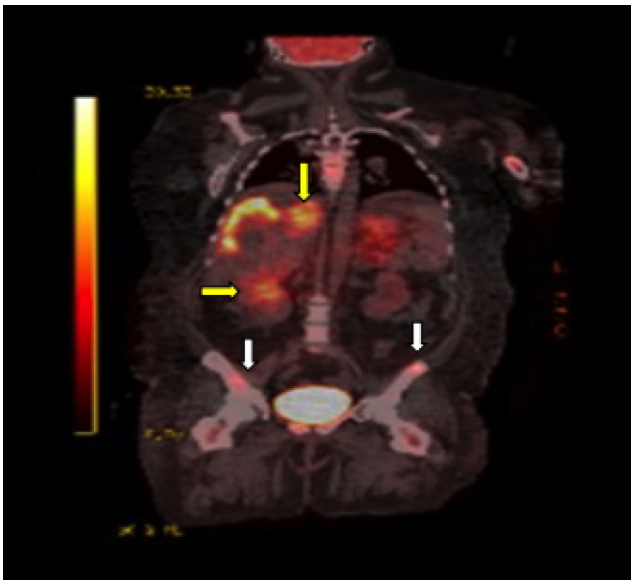

Figure 4. PET scan showing multiple liver and bone lesions. White arrows indicate the bone metastases and yellow arrows indicate the liver metastases.

An open cholecystectomy with intraoperative biopsies of her liver lesions was performed. On histology, the gallbladder specimen revealed mixed adenoneuroendocrine carcinoma (MANEC) and the liver lesions revealed high grade neuroendocrine carcinoma compatible with metastatic disease from the aforementioned MANEC.

A PET/CT showed multiple heterogeneous focally increased masses within the liver with areas of central hypodensity and multifocal areas of osseous uptake compatible with osseous metastatic disease (Figure 4). An MRI of the spine revealed enhancing osseous lesions within the T4-T6 as well as the T9 vertebral bodies. Epidural extension of soft tissue was seen resulting in severe spinal canal narrowing at the level of T5. Octreotide scan revealed multifocal octreoscan-avid foci throughout the liver and skeleton, compatible with neuroendocrine metastatic disease.

The patient received palliative radiotherapy to the humerus and pelvis as well as palliative chemotherapy with carboplatin/etoposide given once as inpatient and palliative XELOX and Zometa as outpatient. A new PET/CT revealed new and increasing osseous metastases as well as decreased size of multiple hepatic metastases. She then developed left elbow swelling due to metastatic disease and received palliative radiotherapy.

Histologically, the gallbladder had diffuse involvement by an adenocarcinoma deep in the wall and up to the serosal surface. The majority of the gallbladder lumen contained a high grade neuroendocrine carcinoma with necrosis and abundant mitoses (greater than 20 per 10 HPF). The liver (both on biopsy and in the cholecystectomy specimens) contained the high grade neuroendocrine carcinoma component. The most likely diagnosis was a gallbladder primary with metastatic disease to the liver although no definitive dysplasia or *in situ* disease was identified due to extensive luminal necrosis.

Discussion

According to the European Neuroendocrine Society and the 2010 World Health Organization, classification of gastroenteropancreatic neuroendocrine tumors is based on tumor differentiation and grade with the latter being dependent on mitotic activity and/or Ki-67 labeling index [5]. Four main categories of GB-NEN have been proposed; (1) well-differentiated NEN or grade 1 (low grade) tumor: <2 mitoses/10 HPF and <3% Ki-67 labeling index; (2) well-differentiated or grade 2 (intermediate grade) tumor: 2-20 mitoses/10 HPF or 3-20% Ki-67 labeling index; (3) poorly-differentiated NEC or grade 3 (high grade) tumor: >20 mitoses/10 HPF

or >20% Ki-67 labeling index; and finally (4) mixed adenoneuroendocrine carcinoma (MANEC), histologically exhibiting adenocarcinoma (or other components) and NEC concomitantly.

Very little is known about the origin of GB-NENs; normally, the gallbladder mucosa is devoid of neuroendocrine cells. The leading theory is that GB-NENs derive from either a multipotent stem cell or neuroendocrine epithelial cells that underwent intestinal or gastric metaplasia secondary to cholelithiasis-related chronic inflammation [2]. In fact, almost all published reports on gallbladder NENs describe coexisting gallstones and chronic cholecystitis [2].

Most patients present with nonspecific findings. Vague abdominal pain and discomfort are the most common initial symptoms followed by jaundice and weight loss. In fact, most NECs are identified incidentally at the time of cholecystectomy for cholelithiasis. The presence of the carcinoid syndrome is very rare (<1%). In our cases, the first patient presented with symptoms of gallstone pancreatitis, whereas the second presented with liver masses initially thought to be adenomas.

Imaging techniques, such as US, CT scan, MRI and PET/CT can help identify the gallbladder lesion; however, it is not possible to preoperatively differentiate NEC from other subtypes of gallbladder carcinomas [2]. Both transabdominal ultrasound and EUS enable fine needle aspiration (FNA) of the primary tumor, lymph nodes, or liver for cytology and improve the diagnostic sensitivity from 74 to 90% as compared to transabdominal US alone. Since most NETs exhibit overexpression of somatostatin receptors, somatostatin analogue scintigraphy (SRS) may be of help in identifying such tumors [6].

Nevertheless, definite diagnosis of GB-NECs requires pathological examination and immunohistochemical (IHC) staining with CGA and SYN. In a report of 10 GB-NECs, IHC showed a positivity in 100% of cases for CgA, NSE, and CK, while the respective rates for Syn, EMA, and CD56 were 88.9, 87.5, and 75%, respectively [7]. Our LCNEC case revealed strong positivity for SYN, CgA, pancytokeratin, and weak positivity for CDX2, CK7, and negativity for CK20 and TTF-1, while our MANEC case revealed strong positivity for pancytokeratin, synaptophysin, chromogranin, CD56, and CDX2 (faint) and it was negative for HMB-45, CD45, S-100, TTF-1, PAX8, CK20, and WT-1. The liver biopsy demonstrated that the tumor was positive for pancytokeratin and negative for CD45.

Interestingly, NECs are usually combined with other histological carcinoma elements, such as adenocarcinoma or squamous cell carcinoma. Diagnosis of MANECs is established only when both adenocarcinoma and NEC features account for more than 30% of the pathology specimen under examination [3]. In our MANEC case, the gallbladder had a diffuse involvement by an adenocarcinoma deep in the wall and up to the serosal surface while the majority of the gallbladder lumen contained a high grade neuroendocrine carcinoma with necrosis and abundant mitoses, thereby fulfilling the criteria of MANEC.

Of note, pure large cell NECs (LCNECs) of the gallbladder are exceedingly rare with only 8 cases reported in the literature so far [8,9]. LCNEC is thought to exhibit aggressive behavior and early metastasis with either direct invasion of the liver or metastasis to the lymph nodes, liver or bone [10]. In our case, the patient with LCNEC did not reveal any metastatic foci in the resected liver segments 4 and 5 or in the hilar lymph nodes. Based on a previous review [9], only 8 cases of pure LCNECs have been reported to date. Therefore, our case represents the 9th reported LCNEC case in the literature and the youngest ever reported patient with LCNEC (29 years old).

Given the rarity of the disease and the limited understanding of its biology, there are currently no guidelines pertaining to the optimal therapeutic management of these patients. However, surgery is the preferred treatment method for GB-NECs. The surgical procedure varies widely, from simple cholecystectomy to extensive surgical resection including local lymph node dissection and resection of metastases [2,11,12]. Most centers utilize the same approach as in case of other gallbladder carcinomas: cholecystectomy for T1 or *in situ* tumors and aggressive radical operative therapy including cholecystectomy, regional lymphadenectomy and hepatic resection for advanced GB-NENs (≥T2/N0–N2) [2]. Aggressive surgical approaches seem to be associated with more favourable outcomes [2]. While patients with GB-NECs do not seem to benefit from traditional radiotherapy, chemotherapy stands as the best form of palliation, especially in high-grade GB-NECs [2]. In addition, biological targeted therapies (i.e. somatostatin analogs) may prove effective in achieving symptom control in GB-NENs, as it happens in other gastroenteropancreatic NENs [13].

In terms of prognosis, evidence of elevated Ki67 and high mitotic index are predictive of a poor outcome, as is invasion to adjacent structures [14]. According to the SEER database, survival rates for all GB-NENs are relatively low: 1-year (43-45%), 2-year (30-33%), 3-year (28-31%), 4-year (22-26%), and 5-year (22-25%) [1,2]. Our patients are alive at 4 and 6 months of follow-up respectively.

Conclusion

GB-NECs are very rare, aggressive tumors associated with poor prognosis. Presentation may vary from incidental finding to metastatic disease. Aggressive surgical approach, including cholecystectomy, lymphadenectomy and hepatic resection followed by adjuvant chemotherapy are recommended in advanced disease; however, survival is still poor. The better understanding of the tumor biology and the development of effective targeted therapies will help increase the lifespan of these patients.

Conflict of interests

The authors declare no conflict of interests.

References

1. Yao JC, Hassan M, Phan A et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063-72.
2. Eltawil KM, Gustafsson BI, Kidd M, Modlin IM. Neuroendocrine tumors of the gallbladder: an evaluation and reassessment of management strategy. J Clin Gastroenterol 2010;44:687-95.
3. Deehan DJ, Heys SD, Kernohan N, Eremin O. Carcinoid tumour of the gall bladder: two case reports and a review of published works. Gut 1993;34:1274-6.
4. Pandey M, Sood BP, Shukla RC et al. Carcinoma of the gallbladder: role of sonography in diagnosis and staging. J Clin Ultrasound 2000;28:227-32.
5. Klimstra DS, Modlin IR, Coppola D et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas 2010;39:707-12.
6. Schillaci O, Scopinaro F, Angeletti S et al. SPECT improves accuracy of somatostatin receptor scintigraphy in abdominal carcinoid tumors. J Nucl Med 1996;37:1452-6.
7. Chen C, Wang L, Liu X et al. Gallbladder neuroendocrine carcinoma: report of 10 cases and comparision of clinicopathologic features with gallbladder adenocarcinoma. Int J Clin Exp Pathol 2015;8:8218-26.
8. Liu W, Wang L, He XD et al. Mixed large cell neuroendocrine carcinoma and adenocarcinoma of the gallbladder: a case report and brief review of the literature. World J Surg Oncol 2015;13:114.
9. Buscemi S, Orlando E, Damiano G et al. "Pure" large cell neuroendocrine carcinoma of the gallbladder. Report of a case and review of the literature. Int J Surg 2016;28 (Suppl 1):S128-32.
10. Jun SR, Lee JM, Han JK, Choi BI. High-grade neuroendocrine carcinomas of the gallbladder and bile duct: Report of four cases with pathological correlation. J Comput Assist Tomogr 2006;30:604-9.
11. Modlin IM, Kidd M, Latich I et al. Current status of gastrointestinal carcinoids. Gastroenterology 2005;128:1717-51.
12. Moris D, Tsilimigras DI, Ntanasis-Stathopoulos I et al. Liver transplantation in patients with liver metastases from neuroendocrine tumors: A systematic review. Surgery 2017;162:525-36.
13. Nikou GC, Lygidakis NJ, Toubanakis C et al. Current diagnosis and treatment of gastrointestinal carcinoids in a series of 101 patients: the significance of serum chromogranin-A, somatostatin receptor scintigraphy and somatostatin analogues. Hepatogastroenterology 2005;52:731-41.
14. Chen H, Shen YY, Ni XZ. Two cases of neuroendocrine carcinoma of the gallbladder. World J Gastroenterol 2014;20:11916-20.