Case Report

Rapidly growing neuroendocrine carcinoma of the gallbladder: A case report

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ABSTRACT

Gallbladder neuroendocrine carcinomas are rare tumors with a prognosis poorer than that of other gallbladder carcinomas. These tumors are often detected late and are difficult to treat. We present the case of a 68-year-old woman with small-cell gallbladder neuroendocrine carcinoma. Abdominal sonography and dynamic contrast-enhanced MRI performed at different points in time showed rapid growth. Treatment with surgical resection and adjuvant chemotherapy was instituted. In view of the rapid growth of these tumors, suspicious cases should at least be considered for close follow-up with appropriate imaging studies.

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Introduction

Gallbladder neuroendocrine carcinomas (GBNECs) are uncommon and represent 0.3%-3% of all primary malignant gallbladder tumors [1–3]. Their prognosis is poorer than that of other gallbladder carcinomas (GBCs) [4]. Abdominal ultrasonography (AUS), in general, is useful in detecting gallbladder tumors, and if the tumor seems to be malignant, contrast-enhanced computed tomography (CECT) can detect lymph node and remote metastases [5]. It is difficult to distinguish GBNECs from other GBCs preoperatively [6]. CECT is useful in making the distinction only in advanced cases of malignancy [4,7]. There are no reports regarding the role of magnetic resonance imaging (MRI) in the diagnosis and follow-up of patients with GBNECs.

The purpose of this case report was to present the MRI features of early stage GBNEC, which can facilitate early detection and timely treatment. Further, this case illustrates the aggressive nature of the tumor that necessitates close follow-up in the event of early surgery being deferred.

Case report

A 68-year-old woman breast cancer survivor was found to have wall thickening of the gallbladder fundus on routine
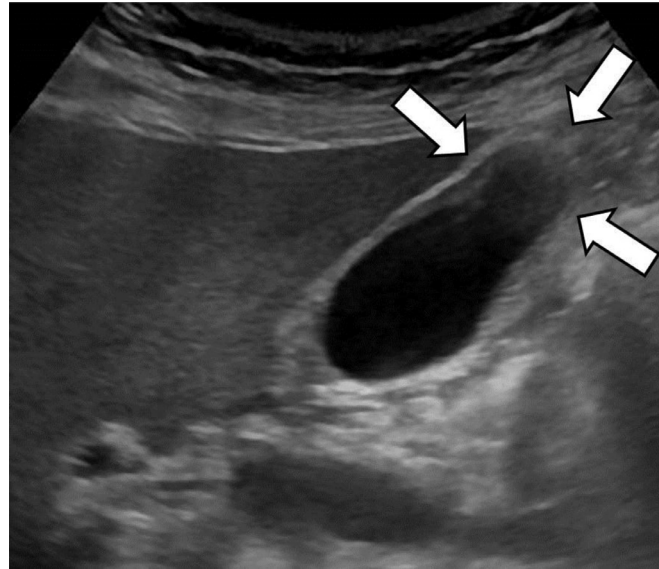
Fig. 1 – First abdominal ultrasonography image of a 68-year-old female patient.
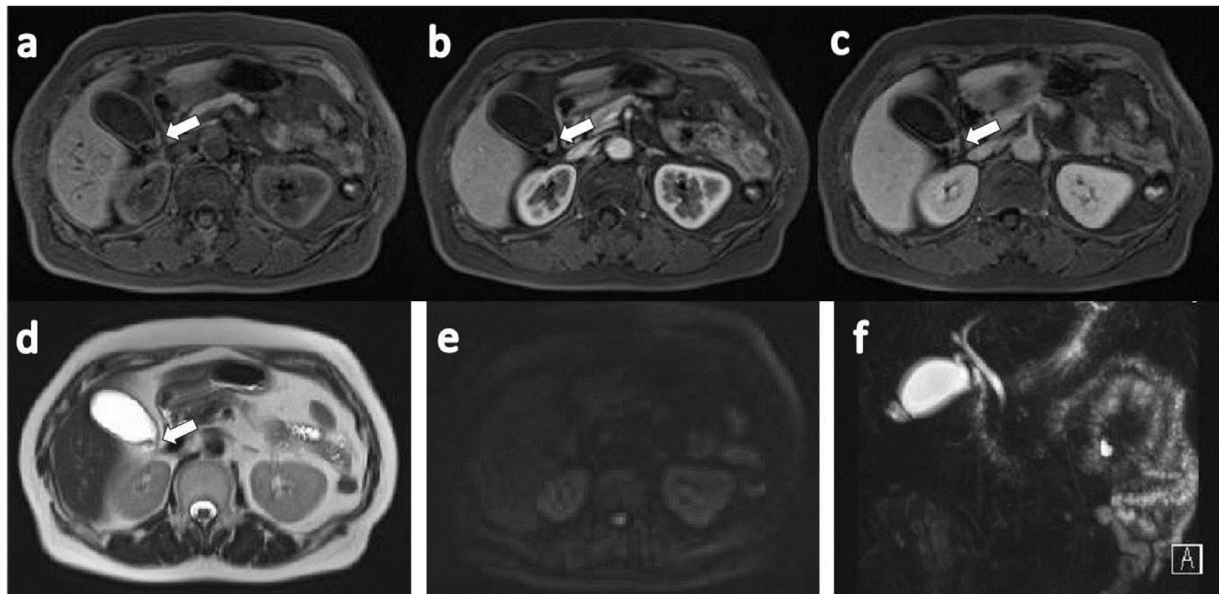Gallbladder wall thickening is observed (arrow).

Fig. 2 – Findings from the first magnetic resonance imaging scan (2 months after the first ultrasonography).
Uniform wall thickening of the gallbladder neck is observed on fat suppression T1-weighted (a), arterial phase (b), and equilibrium phase of dynamic contrast-enhanced magnetic resonance imaging (MRI) (c) (arrows). The thickening wall of the gallbladder neck is low density on T2-weighted imaging (d). No diffusion restriction is observed on diffusion-weighted imaging (e) (arrows). The thickened wall cannot be detected on 3D MRI reconstruction (f).

AUS performed to identify liver metastasis after mastectomy (Fig. 1). She had no abdominal symptoms at that time. Dynamic contrast-enhanced MRI, which was performed after 2 months, revealed adenomyomatosis at the gallbladder fundus. Further, uniform wall thickening of the gallbladder neck was identified in the equilibrium phase of the dynamic MRI, which did not shown restricted diffusion on diffusion-weighted images (Fig. 2). In view of the indetermi-

nate diagnosis, cholecystectomy was offered to the patient, which she refused. A follow-up AUS, which was performed after 6 months, revealed a large irregular lesion at the gallbladder neck (Fig. 3). This patient was then, referred to our department with a diagnosis of gallbladder cancer.

At assessment, the patient did not complain of any abdominal symptoms or weight loss. Her body mass index was 23.1 kg/m^2, and blood tests were negative for elevated tumor mark-
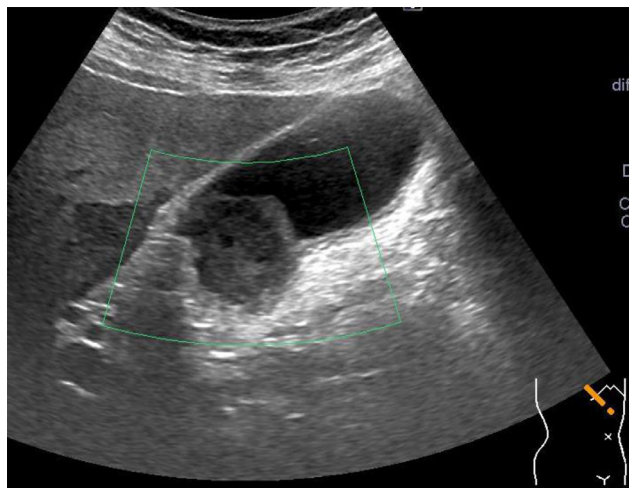
Fig. 3 – Findings from the second abdominal ultrasonography (6 months after the first magnetic resonance imaging scan).
A large irregular lesion is seen at the gallbladder neck (arrow).

ers. A second dynamic contrast-enhanced MRI was performed (7 months after the first MRI) at our center that confirmed a well-defined isointensity tumor measuring 3 cm in diameter, involving the gallbladder neck and body in the equilibrium phase (Fig. 4c). Malignancy was suspected based on an iso-signal intensity on T2-weighted images (Fig. 4d), a low signal intensity on fat suppression T1-weighted images (Fig. 4a), diffusion restriction on diffusion-weighted images (Fig. 4f), and a high signal intensity in the arterial phase (Fig. 4b). CECT demonstrated a well-circumscribed, enhancing tumor (Fig. 5). On positron emission tomography-CT (PET-CT), abnormal uptake was noted only at the tumor, and no metastases were observed (Fig. 6).

Open cholecystectomy, gallbladder bed resection, and lymphadenectomy were performed with a preoperative diagnosis of gallbladder cancer. Intraoperative findings revealed no obvious liver infiltration or lymphadenopathy. The total operating time was 3 hours 28 minutes and the total intraoperative blood loss was 260 mL. The patient had no postoperative complications and was discharged on the 13th postoperative day. The resected specimen was found to have a dome-shaped sessile polypoid tumor, measuring 37 × 32 mm (Fig. 3). The liver bed was free from neoplasia and none of the surgical margins were involved in the tumor.

The diagnosis of small-cell GBNEC was made based on histopathology examination. The non-neoplastic part of the specimen was found to have mild inflammatory-cell infiltration. On immunohistochemical examination, the tumor was positive for neuron-specific enolase, CD56, and chromogranin, and negative for synaptophysin. Lymph node metastases were present (9 of 14 resected lymph nodes were positive), with evidence of extra-nodal spread of the tumor in some of them. Adjuvant chemotherapy with cisplatin and etoposide was initiated 1 month after her surgery. However, in view of the disease progression in the form of liver metas-

tasis that appeared 10 months postoperatively, cisplatin was replaced with carboplatin.

Chemotherapy was stopped when the liver metastases resolved and the patient went into complete remission 13 months postoperatively. The patient refused additional focal radiotherapy owing to the potential adverse effects. She remained in complete remission for 3 months; however, hilar lymph node metastases appeared 16 months postoperatively. Thereafter, she was referred to another hospital for enrollment into a clinical trial.

Discussion

We present the clinical course, diagnostic features, and management of GBNECs to emphasize the aggressive nature of the tumor and the need for close monitoring, especially when early surgery is deferred. GBNECs are rare among gastrointestinal neuroendocrine carcinomas, perhaps because neuroendocrine cells are normally not present in the gallbladder mucosa. They may be derived directly from adenocarcinomas, similar to gastric neuroendocrine carcinomas [6,8]. However, chronic inflammation, such as that seen in cholelithiasis, may induce intestinal and/or gastric metaplasia of the gallbladder mucosa. This may result in the expression of a variety of different neuroendocrine cells that have the potential to undergo dysplasia and malignant transformation. Furthermore, GBNECs may occur due to pathways related to undifferentiated stem cells and ectopic pancreatic tissue [6,8–11]. Gallstones are present in 74%-92% of patients with GBCs and most patients with GBNECs [6,10,12,13]. Further, chronic biliary reflux of pancreatic secretions, which occurs in congenital cystic dilatation of the biliary tree, choledochal cysts, and anomalous junction of the pancreaticobiliary ducts, also contributes to mucosal metaplasia and consequent GBCs. There are reports documenting an association between GBNEC and pancreaticobiliary maljunction [14]. Thus, GBNECs may not always be accompanied by gallstones [15,16]. The cause of GBNEC in our case is unclear because the patient had neither gallstones nor pancreaticobiliary maljunction.

Patients with advanced GBNEC present with abdominal pain, sometimes accompanied by jaundice and weight loss [9,14,15]. GBNECs may be associated with endocrine manifestations, such as Cushing syndrome or paraneoplastic sensory neuropathy [10].

The most sensitive immunohistochemical markers for small cell type of GBNECs are neuron-specific enolase, which is positive in 75% of cases; synaptophysin; and chromogranin [8].

AUS is most often the first imaging modality used to investigate gallbladder disease because it is cost-effective and does not involve radiation exposure. The image contrast between the anechoic bile and gallbladder wall, wall lesions, and adjacent liver can be well-examined with AUS. Although AUS can detect late-stage GBCs with a high sensitivity, its use is limited in the diagnosis and staging of early-stage GBCs [5,17]. On contrast-enhanced US, an enhanced pattern displaying branched, tortuous, or linear intralesion vessels as well as destruction of the gallbladder wall were reported to be strong
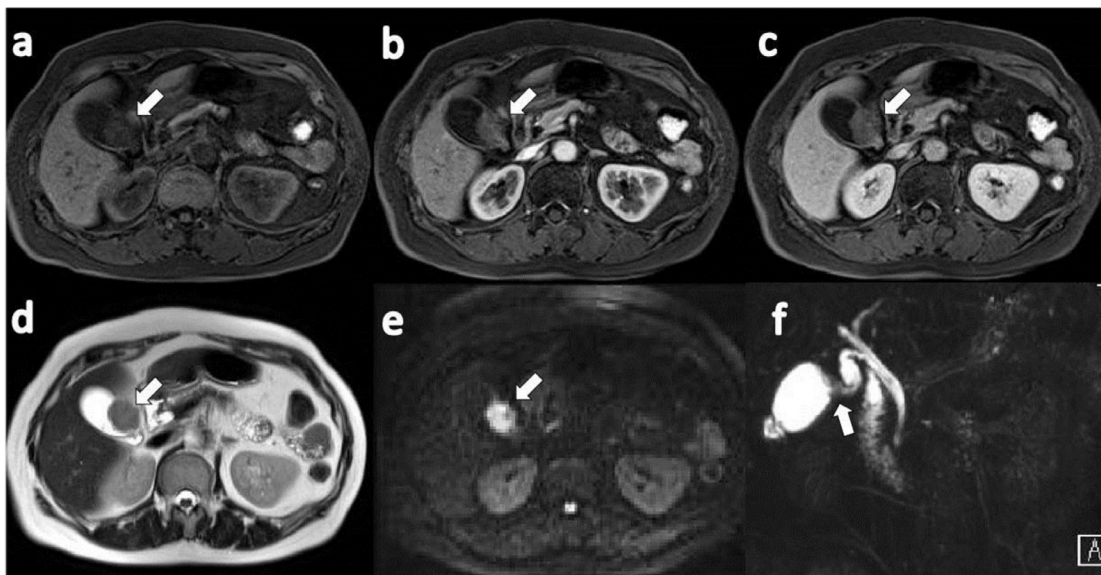
Fig. 4 – Findings from the second magnetic resonance imaging (MRI) scan (7 months after the first MRI scan).
A well-defined isointensity tumor involving the neck and body of the gallbladder is observed on equilibrium phase of dynamic contrast-enhanced MRI (c), which shows a high signal intensity in the arterial phase of the dynamic contrast-enhanced MRI (b), low signal intensity on fat suppression T1-weighted images (a), isointensity on T2-weighted images (d), and diffusion restriction on diffusion-weighted images (e) (arrows). The tumor is seen limited in the gallbladder on 3D MRI reconstruction (f) (arrow).

Fig. 5 – Contrast-enhanced computed tomography scan in the arterial phase (7 months after the first magnetic resonance imaging scan).
A well-circumscribed enhancing tumor is seen (arrow).

indicators of malignancy [17]. Endoscopic ultrasound enabled the assessment of the depth of tumor invasion into the gallbladder wall and lymphadenopathy at the porta hepatis and peripancreatic regions, as well as the collection of bile for cytological analysis in the diagnosis of GBCs [5].

GBCs have 3 major imaging features on CT, namely, focal or diffuse wall thickening with or without irregularity of the gallbladder; polypoidal intraluminal mass; and large mass obscuring and replacing the gallbladder, often extending to the liver [18]. CECT can detect gallbladder neoplasms with a sensitivity of 90%, and is effective in detecting T2 or high stage GBCs [5]. CECT is useful to determine the resectability of GBCs, with a pooled sensitivity of 99% and pooled specificity of 76%. [19] Although local and vascular invasion as well as hematogenous and lymph node metastases can be detected with CECT, its reliability in staging lymph node disease is not always accurate [5]. A quantitative method wherein the delayed-phase CT value is subtracted from the portal venous phase CT value may help in detecting malignant tumors. ∆CT (portal venous phase CT value minus delayed phase CT value) is reported to be an effective index for differentiating between benign and malignant gallbladder polypoid lesions. A value of ∆CT smaller than 10 Hounsfield units would indicate a malignancy [16].

Focal or diffuse mural thickening of more than 1 cm as well as asymmetric thickening are highly suggestive of the diagnosis of GBCs on MRI. GBCs are usually heterogeneously hyperintense relative to the liver on T2-weighted images and relatively iso- or hypointense on T1-weighted images. In the early phase of dynamic contrast-enhanced imaging, the outer margin of the enhancement of GBCs is irregular. Gadolinium-enhanced fat-suppressed T1-weighted images are useful in diagnosing the tumor extent, direct invasion into the surrounding organs, liver metastases, and involvement of critical vascular structures such as the portal vein and hepatic artery [20]. MRI has been shown to be superior to CT in differentiating T1a lesions from T1b or greater lesions, which may be useful in preoperative management planning [21]. Addition of
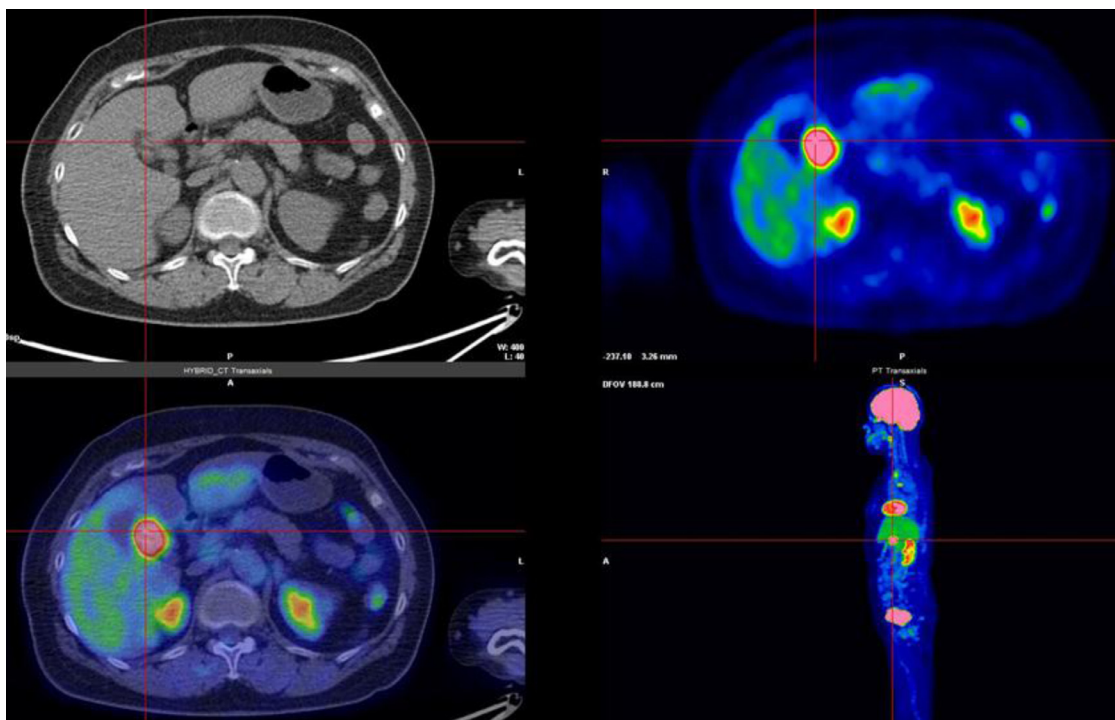
Fig. 6 – Positron-emission tomography-computed tomography scan (7 months after the first magnetic resonance imaging scan).
There is abnormal uptake in the region of the gallbladder tumor.
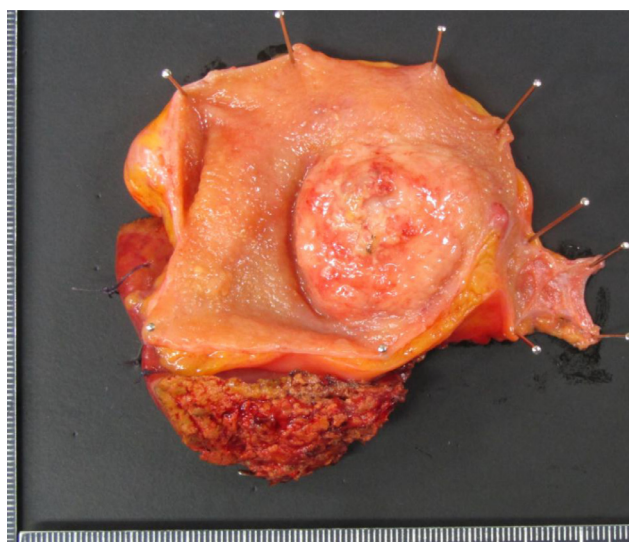

Fig. 7 – Specimen photograph showing a dome-shaped sessile polyploid tumor, measuring 37 x 32 mm.

diffusion-weighted imaging may aid in the differentiation of malignant from benign gallbladder diseases [21].

[18]F-fluorodeoxyglucose (^{18}F-FDG) PET/CT may be effective in the prognosis of patients with gallbladder cancer. SUV max data from PET/CT imaging were reported to be prognostic and independent predictors of the overall survival of GBCs [22].

However, preoperative distinction between GBNECs and GBCs is difficult [6,23]. Small-cell GBNECs usually present as a large mass containing extensive necrosis with a marked propensity for invasive submucosal growth [21,24]. CECT findings for GBNECs are typically demonstrated by a lesion with an enhancing periphery around a nonenhancing center representing central necrosis [7]. The degree of contrast enhancement may possibly distinguish GBNECs from GBCs [4]. However, these features are reported only in advanced cases. There are no reports of imaging findings of early-stage GBNECs.

In our case, the availability of MRI images from an earlier date offered us the opportunity to describe the MRI findings of early-stage GBNEC. Although the initial MRI demonstrated uniform thickening of the gallbladder wall, it was not identified as a malignant tumor. In hindsight, a similar finding should help in making a strong recommendation for cholecystectomy. Alternatively, if immediate cholecystectomy is not considered, attempts should be made to perform imaging at shorter intervals to identify rapid growth, if any. Since PET scans detect the accumulation of ^{18}F-FDG in GBNECs, combinations of PET with CECT or MRI are especially effective in detecting neuroendocrine tumors [6,16]. However, this may be limited as this combination of imaging is an expensive diagnostic technique. Endoscopic ultrasonography-guided fine-needle aspiration of the primary tumor, lymph nodes, or liver for cytology has a diagnostic sensitivity of 86% and a specificity of 100%, but with the risk of peritoneal seeding [10].

There is no standard indication for adjuvant therapy in patients with biliary neuroendocrine tumors. Patients with neuroendocrine carcinoma (NEC) or mixed adenoneuroendocrine carcinomas are usually considered for adjuvant therapy based on their clinical condition [25]. The recommended chemotherapy for poorly differentiated NEC is a combination of cisplatin and etoposide. Carboplatin, another alternative to cisplatin, is also found to be effective in both objective tumor response and overall survival in patients with NEC [26]. Patients with GBNEC and distant metastases, as in lymph nodes or liver, have a poorer prognosis than similarly staged cases of GBCs [4,25].

In conclusion, our case report illustrates the MRI findings of early-stage GBNEC. These findings may help in their early detection and timely cholecystectomy. In view of the rapid growth of these tumors, suspicious cases should at least be considered for close follow-up with appropriate imaging studies.

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