Small Cell Neuroendocrine Carcinoma of the Gallbladder: A Case Report and Literature Review

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1. Abstract
Neuroendocrine carcinoma of the gallbladder (NECGB) is a rare and aggressive tumor with a poor prognosis. The clinical presentation is non-specific, but it occurs more frequently in women with gallstones. Histological and immunohistochemical confirmation is required to establish a diagnosis. Treatment is mainly surgery with or without adjuvant chemotherapy. We present the case of a 32-year-old woman who was diagnosed with small cell neuroendocrine carcinoma (SCNEC) of the gallbladder after physical examination for gallbladder enlargement.

2. Introduction
Neuroendocrine neoplasms (NENs) are tumors that originate from neuroendocrine cells and are found in the digestive tracts, respiratory tracts, and thyroid gland [1]. Neuroendocrine carcinoma of the gallbladder (NECGB) is a rare and aggressive tumor that accounts for 2.3% of all gallbladder tumors [2]. The main treatment is surgery, and adjuvant chemotherapy is recommended depending on the stage of the tumor [3, 4]. Despite aggressive treatment, this type of tumor has a poor prognosis because it is usually diagnosed as distant metastasis at an advanced stage [5]. Small cell neuroendocrine carcinoma of the gallbladder (SCNEC) of the gallbladder are the poorly differentiated variant of neuroendocrine carcinoma. We present a 32-year-old woman who had an enlarged gallbladder and was diagnosed with SCNEC of the gallbladder upon further examination.

3. Case Presentation
Abdominal color Doppler ultrasound in a 38-year-old woman during routine physical examination revealed liver space occupying lesions, with no significant abnormalities in tumor markers such as CEA, CA-125, CA-153, CA19-9, CA-242, and CA-724. Ultrasound-guided liver puncture was performed to determine the occupying properties. Further improvement of chest and abdominal enhanced CT (Figure 1) results showed gallbladder space-occupying lesions, malignant in nature (about 4.6cm*3.7cm*5.5cm, obviously uneven enhancement after enhancement). The possibility of gallbladder cancer was considered, and the tumor involved adjacent liver parenchyma. Multiple hepatic sites were occupied (scattered in the hepatic parenchyma with slightly low density nodules and masses in more than 10 places, partially fused, the larger one was located in the liver S5 segment, the size was about 4.0cm*3.1cm, and the enhancement was uneven after enhancement). Metastatic tumors, multiple enlarged lymph nodes in the...
hepatic portal area, hilar space and retroperitoneal epigastric area were considered, and metastasis was considered. Left supraclavicular lymph node enlargement, metastasis is not excluded; Slightly thickened wall of the right lower abdominal colon. There were no obvious abnormalities in lung, pancreas, spleen and kidney. No enlarged lymph nodes were found in mediastinum, lower abdominal cavity or retroperitoneum.

Abdominal enhanced MRI results showed that the gallbladder volume increased, the gallbladder wall was irregularly thickened, and a mass formed on the bottom wall, with a size of about 4.5cm*4.3cm*5.7cm. Diffuse-weighted imaging presented a high signal, and the lowest ADC value was about 0.6*10^-3mm^2/s, with uneven enhancement. The local boundary between the mass and the hepatic parenchyma adjacent to the left inner lobe of the liver and the lower segment of the right anterior lobe of the liver was not clear. The shape of the liver was not regular, and the nodules and masses (more than 10) in the liver parenchyma were mostly diffused in the liver and partially fused, the larger one was located in the liver S5 segment, the size of which was about 3.9cm*2.7cm. Diffuse- weighted imaging showed high signal, and uneven enhancement after enhancement. MRCP showed no dilation of the intrahepatic and extrahaepatic bile ducts. There were multiple enlarged lymph nodes in the hilar area, hilar space and upper midabdominal retroperitoneum. The larger nodes were about 3.0cm*2.5cm (above the head of the pancreas), and the enhancement was uneven and enhanced. Normal scan of pancreas, spleen and adrenal glands showed no abnormality, and the enhanced parenchyma was uniformly enhanced. Bone scan showed no obvious signs of metabolic abnormality. Small focal cyan cells nests were observed under microscope in the punctured liver tissue, and immunohistochemical results showed CK(-), Vim(-), Ki67(+, about 90%), CK7(partial +), CK20(-), Villin(-), CDX-2(-), TIF-1(-), NapsinA(-), TG(-), PAX8(-), Hept1(-), GATA3(-), p40(-), p63(-), CK5/6(-), SYN(-), CGA(-), CD56(+), combined with HE staining and immunohistochemical results, consider small cell neuroendocrine carcinoma (Figure 2).

Figure 1: chest and abdominal enhanced CT: The primary gallbladder lesions and liver metastases were observed.

Figure 2: HE staining of liver tissue

4. Discussion

In 1995, Capella first gave the nomination of “neuroendocrine tumor (NET)”, which quickly became widely accepted [6]. Subsequently, the 2000 WHO classification of gastrointestinal tract NET was established based on Capella classification. Taking into account tumor size, vascular and neuronal invasion, proliferative activity, local invasion, lymph node, and distant metastasis, NETs were separated into well-differentiated NET with benign behavior, well-differentiated NET with uncertain behavior, well- differentiated neuroendocrine carcinoma (NEC), and poorly differenti-ated NEC. Nevertheless, the classification uses a mix of grading and staging, with no independent assessment. Given that tumor grade and stage are considered separate parameters of independent prognostic significance, the 2010 WHO classification defines G1-G3 grading and staging of the TNM program. Well-differentiated tumors were divided into G1 (low grade) and G2 (intermediate grade), and all poorly differentiated NETs (mitotic figures > 20/10 HPF and Ki-67 staining > 20% positive) were graded G3 (NEC) [3]. Poorly differentiated varieties were again classified as large cell carcinoma, small cell carcinoma, and mixed adenocarcinoma neuroendocrine carcinoma [7].
The most common sites of primary NET in the gastrointestinal tract are usually the appendix, jejunum, and rectum. Other sites include the duodenum, colon and stomach. Lymph nodes are the most common sites of metastasis, followed by the liver, lungs and peritoneum. In particular, the gallbladder is thought to be a rare NET site in the gastrointestinal tract [3]. The origin of gallbladder NEC is controversial. Many researchers have proposed that tumors arise from metaplasia of the gallbladder epithelium, and that inflammation may promote metaplasia of neuroendocrine cells, as most NEC is accompanied by cholelithiasis. Normally, neuroendocrine cells are not present in the gallbladder; However, many gallstone patients do have intestinal or gastric metaplasia in their gallbladder [8]. Sakamoto et al. found that 11.7% of cholelithiasis patients developed metaplasia, 83.3% showed positive staining for chromogranin A, and 50.0% positive staining for serotonin [9]. These two antigens are expressed specifically in neuroendocrine cells.

Another school of thought coexists, NEC is thought to have evolved from gallbladder adenocarcinoma. Interestingly, this theory is possible with similar coexisting hybrid tumors in the literature [10]. In addition, a series of less than 50 reported cases hypothesized that ectopic pancreatic tissue in the gallbladder was a potential carcinogen for that organ [11].

Furthermore, from a genetic point of view, no association with other traits was found except for one case of clear cell gallbladder NET with Von Hippel-Lindau disease [11].

The clinical manifestations of gallbladder NEC vary. No concrete signs to report. In general, the main complaint is right upper abdominal discomfort, including distending pain and tenderness. However, pain is indistinguishable from cholelithiasis. Functionally, gallbladder NEC can be classified into secretory and non-secretory types based on tumor-producing peptides. Non-secretory tumors often show signs of malignancy. However, functional NET is able to secrete peptides such as histamine and serotonin. Due to the first-pass effect of the liver, in rare cases, these peptides do not fully degrade, the functional tumors might show a definite syndrome mimicking carcinoid syndrome, resulting in clinical manifestations such as dilation, diarrhea, flushing, edema, and wheezing [12].

The patient initially underwent radiological studies in the form of CT abdominal and pelvic ultrasonography with baseline abdominal ultrasonography to stage the disease and evaluate the possibility of surgical resection [13]. In addition, the patient received a positron emission tomography CT scan to detect any possible distant metastases. MRI will be the preferred method, combined with a magnetic resonance cholangiopancreatography, would report sensitivities of nearly 100% for staging and invasion assessment [14]. Nevertheless, imaging modalities cannot distinguish specific pathological types, so histological, cytological, and immunohistochemical analyses help to arrive at a definitive diagnosis. A guided biopsy or fine needle aspiration (FNA) is usually performed to complete the diagnosis. Histological examination and immunohistochemical staining associated with SCNEC which include neuron-specific enolase, chromogranin A and synaptophysin are essential for a definitive diagnosis [15]. Tumor markers have not been recognized as reliable in establishing a diagnosis of gallbladder SCNEC [16].

Small cell neuroendocrine carcinoma (SCNECs) is a type of poorly differentiated neuroendocrine tumors (NETs) [17]. Although SCNECs is one of the most common pathological patterns of lung cancer, the occurrence of SCNECs in the biliary system is extremely rare. Publications on gallbladder SCNEC are limited in number and consist mainly of individual case reports or small review series [18].

SCNEC is a very rare pathology, occurring in 0.2% of all neuroendocrine tumors [19]. The median age of patients was 64 years, with a 2:1 female predominance. Median survival of the gallbladder with SCNEC is 8-13 months [20]. SCNEC of the gallbladder lacks specific clinical symptoms, radiological features, and laboratory findings, which makes non-invasive early preoperative diagnosis still difficult. In about two-thirds of patients, stage IV disease is diagnosed at the time of presentation [21, 22]. In the published literature, SCNEC has highly invasive features, including early lymph node metastases and most often distant metastases to the liver and lungs, leading to a discouraging prognosis. The patient in this case had multiple metastases of liver and lymph nodes.

Till now, there is still no standard treatment defined for SCNEC of the gallbladder. Surgery, chemotherapy, and radiation are all selective treatments that may help improve overall survival [23]. There is no doubt that in patients with SCNEC of the gallbladder without serious contraindications and well-defined distant metastases, radical surgical resection remains the primary treatment option for local tumors. For patients with distant metastases, surgical treatment remains controversial. In general, local liver invasion requires early radical dissection to improve quality of life and reduce complications caused by the tumor [24]. However, evidence of the benefits of surgery for advanced disease is limited [21]. Because of the high degree of malignancy of SCNEC, many patients are in an advanced stage at diagnosis. Surgery alone is not enough. Due to the low sensitivity of SCNEC, the management of chemotherapy remains uncertain. According to the small cell lung Cancer guidelines, a platinum-based chemotherapy regimen was used to treat SCNEC and achieved an impressive response [25, 26]. Commonly used chemotherapy drugs include cisplatin, etoposide, and 5-fluorouracil. In addition, radiation therapy and endocrine therapy are also used for SCNEC management [27].
5. Conclusion
Small cell variation in gallbladder neuroendocrine carcinoma is the rarest tumor type. It has a poor prognosis compared to any other gastrointestinal neuroendocrine cancer. Diagnosis depends on pathological and immunohistochemical findings. For T1N0M0 SCNEC of the gallbladder, a cholecystectomy may be sufficient. For patients in later stages, the management of combination therapy may be optimal.

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