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CASE REPORT

Small Cell Carcinoma of the Gallbladder: Report of Two Cases

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Two Taiwanese patients with gallbladder small cell carcinoma are reported. One is a 79 year-old male, the other, a 86 year-old female. They both presented with the symptom/signs of acute cholecystitis and underwent cholecystectomy. An intramural mass in the gallbladder neck region was found in the first patient, while the second patient had a transmural indurated tumor in the gallbladder body with extension to the neck region. Characteristic histological and immunohistochemical features of small cell carcinoma were present in both, and electron dense neurosecretory granules were identified in the second. To our knowledge, the second patient is the oldest ever reported. The first patient received chemotherapy directed toward the initial erroneous diagnosis of non-Hodgkin's lymphoma and developed liver metastasis in two months. The second patient did not receive chemotherapy due to her poor general condition and local recurrence occurred in six weeks. Both passed away three and five months after surgery, respectively. (Pathology Oncology Research Vol 5, No 3, 235–238, 1999)

Keywords: gallbladder, small cell carcinoma, endocrine cell carcinoma, neuroendocrine carcinoma

Introduction

Neuroendocrine tumors of the gallbladder are rare neoplasms and have been classified as carcinoid tumor and endocrine cell carcinoma or small cell carcinoma.[1,2] Small cell carcinoma usually occurs in elderly female patients with characteristic morphologic features, highly aggressive behavior, and occasional association with endocrine manifestations and chemosensitivity.[3] These distinct clinicopathological features justify its separation from ordinary gallbladder carcinomas.[3-8] In this report, we describe two such cases involving the gallbladder neck: To our knowledge, our second patient is the oldest in the English literature, thus extending the age range of this rare neoplasm.

Case Reports

Case 1

This previous healthy 79-year-old male patient visited our emergency service with cramping abdominal pain, fever, and chillness for one day on Jun 9, 1991. Physical examination revealed tenderness and rebound pain over bilateral upper quadrants of the abdomen with positive Psoas, obturator and Rousing signs. There were no paraneoplastic endocrine manifestations. Lab data showed WBC 13,100/ul, direct/total bilirubin 0.95/2.44 mg/dl, AST (SGOT)/ALT (SGPT) 55/30 IU/L.

Abdominal sonography and computed tomography (CT) at admission revealed an intramural tumor (3.5 cm) in the gallbladder with liver invasion and common bile duct (CBD) infiltration. No gallstone was found. Open cholecystectomy was carried out. The operative findings were distension and gangrene of the gallbladder with an intramural mass near the neck region and a distended CBD.

The original pathological diagnosis was non-Hodgkin's lymphoma of diffuse large cell type with involvement of both two regional lymph nodes despite the negative immunohistochemical result for LCA. Chemotherapy with cyclophosphamide, vincristine (Oncovin), procarbazine (Mutulane) and prednisolone were administered one month after operation. He was discharged without complication and was readmitted one month later for chemotherapy. Abdominal CT scan revealed local tumor recurrence with caudate lobe metastasis. Chemotherapy with the same agents was given. Unfortunately, he developed myelosuppression and his consciousness deteriorated with severe jaundice. He passed away three and half a months after the surgery. Autopsy was not performed.

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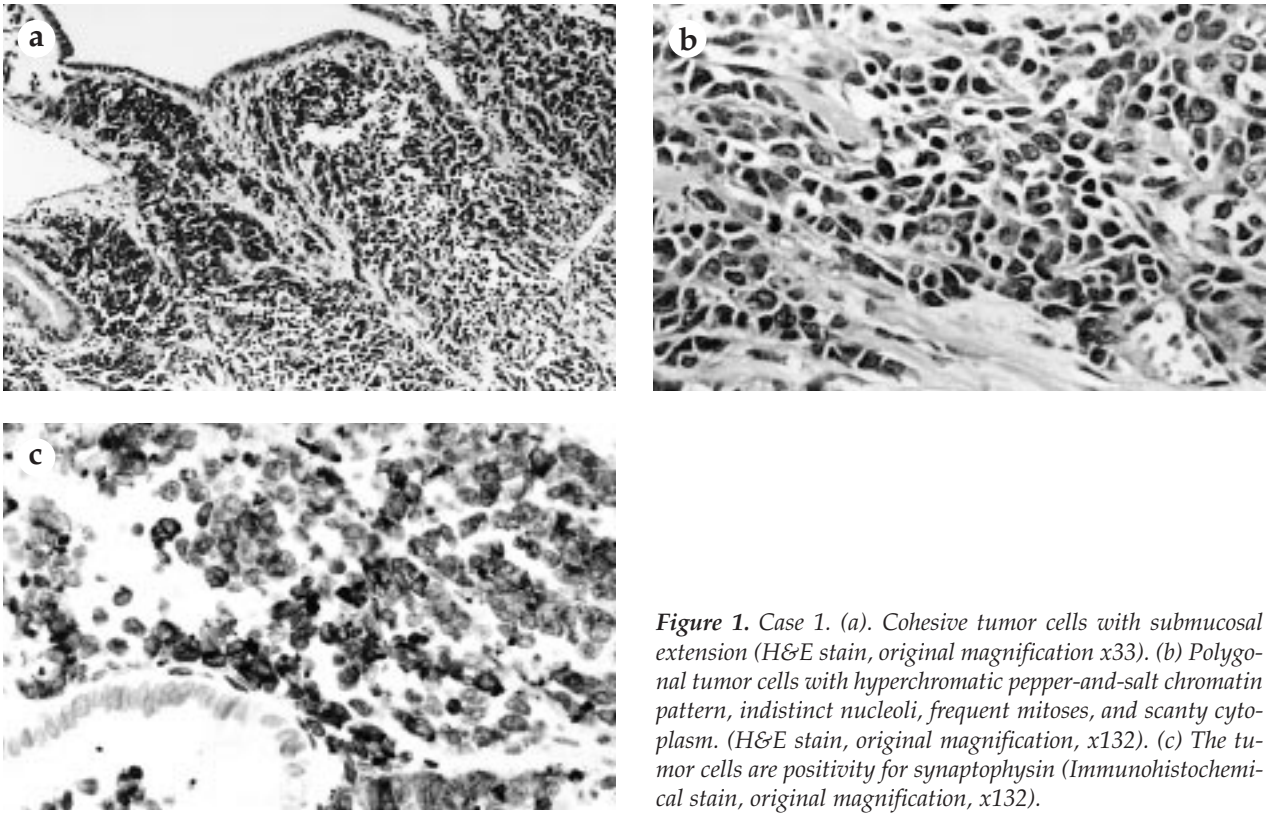

Figure 1. *Case 1. (a). Cohesive tumor cells with submucosal extension (H&E stain, original magnification x33). (b) Polygonal tumor cells with hyperchromatic pepper-and-salt chromatin pattern, indistinct nucleoli, frequent mitoses, and scanty cytoplasm. (H&E stain, original magnification, x132). (c) The tumor cells are positivity for synaptophysin (Immunohistochemical stain, original magnification, x132).*

Case 2

This 86-year-old female was admitted with the complaints of fever and epigastric pain radiating to the back for three days on Feb 3, 1998. Physical examination revealed severe right upper quadrant pain with a positive Murphy sign. There were no paraneoplastic endocrine manifestations. Abdominal sonography showed gallbladder stones with acute cholecystitis. Lab data revealed WBC 16,700/ul with 93% seg and normal liver function tests. At laparotomy, the gallbladder wall was markedly thickened with necrotic change. The lumen was filled with pus and several black stones. The post-operative course was smooth. Five weeks later, the follow-up ultrasound and CT scan revealed local tumor recurrence and regional nodal metastasis. No aggressive treatment was given due to her poor general condition. She passed away five months after the cholecystectomy. Autopsy was not performed.

Materials and Methods

The specimens were fixed in 10% formalin, embedded in paraffin, and stained with haematoxylin and eosin. Immunohistochemical studies on paraffin sections were performed using the peroxidase-antiperoxidase method. The monoclonal antibodies (MoAbs) used were cytokeratin (CK), epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), neuron specific enolase (NSE), synaptophysin, common leukocyte antigen (LCA) and chromogranin A. The LSAB kit and MoAb CK were obtaimed from Dako Corp, Carpinteria, CA, USA; the others from BioGenex, San Ramon, CA, USA. The specimen for ultrastructural study of case two was cut from the paraffin block and was processed routinely.

Pathology

Case 1

The gallbladder (12x5x4 cm) was coated with fibrinopurulent exudate. An intramural ill-defined grayish mass (3.5x2.7x2.5 cm) was found in the neck region with hemorrhagic necrosis of the adjacent mucosa. Two enlarged lymph nodes were dissected out at the peri-ductal region. The original sections were retrieved for a study of malignant lymphoma. Microscopically, loosely cohesive tumor cells accompanied by prominent necrosis were seen with extensive submucosal extension (*Figure 1a*). The polygonal tumor cells exhibited hyperchromatic nuclei with pepper-and-salt chromatin pattern, indistinct nucleoli, frequent mitotic figures and scanty cytoplasm (*Figure 1b*). Immunohistochemically, the tumor cells were positive for synaptophysin (*Figure 1c*) and NSE but negative for chromogranin A, EMA, CK, CEA

and LCA. The diagnosis was revised to be small cell carcinoma. There were no co-existing adenocarcinoma or squamous cell carcinoma.

Case 2

The gallbladder was 10x5.5x4 cm and was necrotic with pus coating. It was indurated (3.0 x 2.5 cm in dimensions) with grayish white cut surface at the body with extension to the neck. The adjacent bladder wall was necrotic and hemorrhagic. Under light microscopy, the gallbladder revealed acute cholecystitis with transmural tumor infiltration to the subserosal connective tissue (*Figure 2a*). The polygonal tumor cells with abundant mitotic figures, stippled chromatin, inconspicuous nucleoli and scanty amount of cytoplasm were arranged in solid sheets and trabecular pattern with focal tumor necrosis. The non-neoplastic mucosa didn't show metaplastic or dysplastic changes.

There was no co-existing adenocarcinoma or squamous cell carcinoma. Immunohistochemical stainings revealed that the neoplastic cells were strongly positive for chromogranin A (*Figure 2b*) and NSE but weakly positive for EMA and CEA. They were negative for CK and synaptophysin. A few intracytoplasmic electron-dense membrane-bound neurosecretory granules were identified in the second case by electron microscopy (*Figure 2c*).

Discussion

There have been several reports of gallbladder small cell carcinoma since the first description by Albores-Saavedra et al. in 1981.[2-4,6-9] This neoplasm is distinctive because of its characteristic morphologic features, predilection for elderly female patients, frequent association with cholelithiasis, highly aggressive clinical course, occasional endocrine manifestation and sensitivity to chemotherapy.[3] Combined small cell carcinoma and adenocarcinoma of the gallbladder has been reported with transitional areas between these two tumor types.[2,7] The tumor cells of small cell carcinoma tend to expand the lamina propria of the mucosal folds covered either by metaplastic or dysplastic intestinal epithelial cells. These findings suggest that the endocrine cell carcinoma is probably derived from the metaplastic epithelium of the gallbladder. In our both cases, however, the overlying mucosa was neither metaplastic nor dysplastic and therefore, they do not fit into this hypothesis. Experimental animal model seems to support a common endodermal stem cell origin

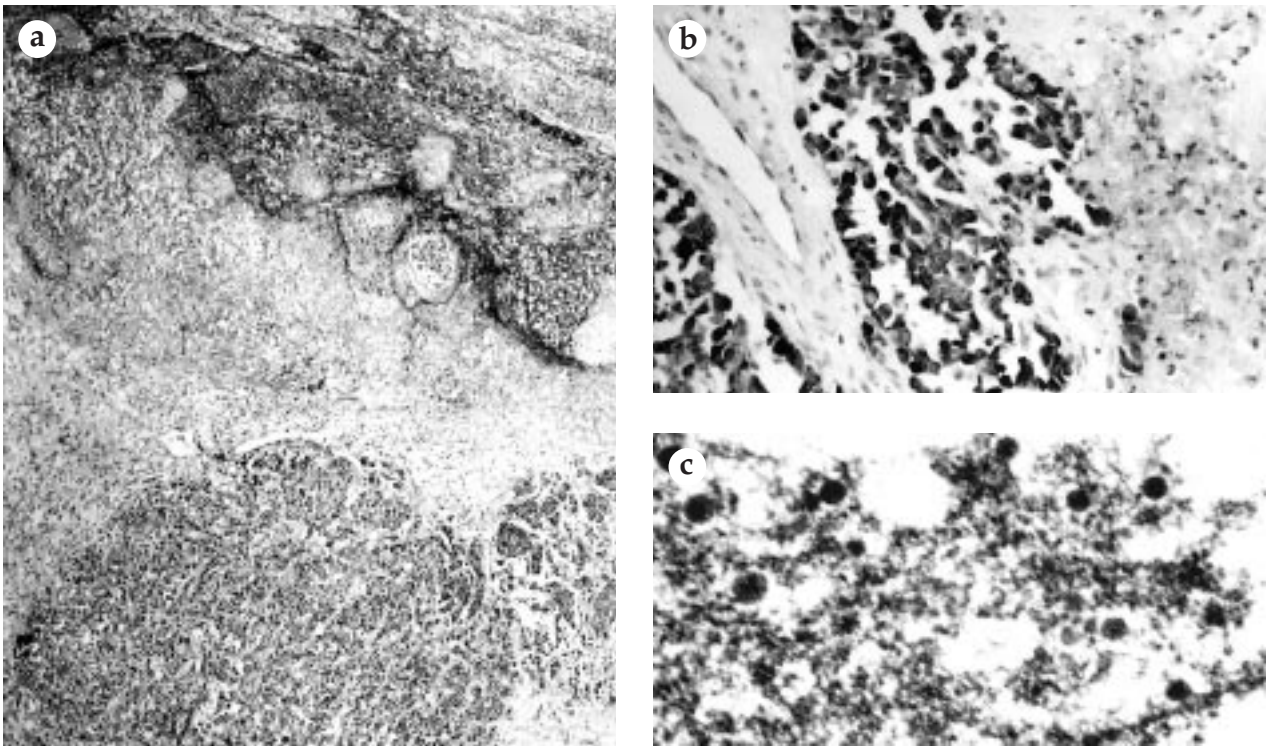

Figure 2. *Case 2. (a) Prominent mucosal necrosis at the upper portion with solid sheets and trabecular tumor nests at the bottom (H&E stain, original magnification x 33). b) The tumor cells are positive for chromogranin A (Immunohistochemical stain, original magnification, x132). (c) A few electron-dense neurosecretory granules in the cytoplasm (Transmission electron microscopy, magnification, x31700).*

of the gastrointestinal neuroendocrine tumors.[11] Moreover, the expression of neuroendocrine (chromogranin A, synaptophysin and NSE) markers with or withour the co-expression of epithelial (EMA and CEA) in our cases support the endodermal multipotent stem cell origin of the gastrointestinal neuroendocrine tumors including gallbladder small cell carcinoma.[12] Undifferentiated carcinoma and malignant lymphoma are the major differential diagnosis. The tumor cells in the former usually exhibit prominent nucleoli with focal glandular differentiation,[4] two features never seen in small cell carcinoma. Strong immunohistochemical positivity for cytokeratin and EMA but negativity for neuroendocrine markers is confirmative for the diagnosis of undifferentiated carcinoma. Malignant lymphoma can secondarily involve the gallbladder as part of a systemic disease. Primary malignant lymphoma of this organ is exceedingly rare and is probably limited to low grade lymphoma of mucosa-associated lymphoid tissue (MALT) type.[13] Primary high grade MALT type lymphoma of the gallbladder has not been reported yet. The diagnosis of this exceedingly rare entity must be very prudent and immunohistochemical support is mandatory to avoid misdiagnosis like our first case.

In conclusion, we report two cases of small cell carcinoma of the gallbladder with acute cholecystitis. The second patient is the oldest with this rare disease. Clinicians and especially pathologists must be aware of this entity to avoid misdiagnosis and erroneous treatment.

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