


# Combined Undifferentiated and Neuroendocrine Carcinomas of the Gallbladder Appearing as Two Separate Lesions: A Case Report with Radiological-Pathological Correlation

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## ABSTRACT

We report herein a rare case of incidentally detected combined undifferentiated and neuroendocrine carcinomas of the gallbladder. An incidental gallbladder malignancy was revealed on abdominal ultrasound and multi-detector computed tomography in a 54-year-old man. A short distance from the main polypoid hypoechoic mass at the fundus of the gallbladder, focal wall thickening was noted with prominently increased power Doppler flow. Extended cholecystectomy was performed, and histology confirmed the main polypoid mass as undifferentiated carcinoma and the separate nodule as neuroendocrine carcinoma. To our knowledge, this is the first report presenting two separate lesions of combined gallbladder carcinomas by radiological features.

## CASE REPORT

### CASE REPORT

An incidental mass in the gallbladder was revealed in a 54-year-old man during abdominal ultrasound screening. His medical history was unremarkable except for hypertension. He was asymptomatic and showed no evidence of jaundice. Routine laboratory tests, including liver function tests, were unremarkable.

Upper abdominal ultrasound examination revealed a 3.5 × 3.8 cm sized, heterogeneously hypoechoic mass at the fundus of the gallbladder with subtle increased power Doppler flow (Fig. 1a, b). A short distance from this mass, focal wall thickening of the gallbladder with prominently increased power Doppler flow was noted (Fig. 1c, d). Triphasic multi-

detector computed tomography (MDCT) examination was performed. Venous phase imaging showed a polypoid mass at the fundus of the gallbladder that revealed heterogeneous enhancement similar to that of the fatty liver parenchyma and included a central necrotic portion (Fig. 2a). Focal marginal blurring was noted at the fundus of the gallbladder with suspected pericholecystic infiltration. A short distance from this mass, focal nodular thickening of the gallbladder wall corresponding to the lesion on ultrasound revealed more intense enhancement during all phases compared with the main mass (Fig. 2b). There was a subtle focal low-density lesion in segment 5 of the liver adjacent to the gallbladder fossa on arterial and venous phase images (Fig. 2c), which was appeared as 1 cm sized hypoechoic nodule on ultrasound. This lesion should rule out metastasis. A 2.5 x 1 cm sized

homogeneously enhancing portocaval lymph node was detected without evidence of necrosis (Fig. 2d).

With preoperative diagnosis of a malignant gallbladder tumor, extended cholecystectomy was performed. The resected fungating tumor, measuring 4 × 3 × 2.5 cm, showed surface necrosis with extension to the pericholecystic fat tissue (Fig. 3a). The histopathological diagnosis was anaplastic undifferentiated carcinoma with rhabdoid features. There was another separate whitish yellow infiltrative nodule measuring 2 × 1.5 cm a short distance from the main mass (Fig. 3b). The histopathological diagnosis of this nodule was neuroendocrine carcinoma with positive staining for synaptophysin, chromogranin, and CD56 and negative staining for CD7 and CD20 by immunohistochemical studies (Fig. 4). There was one metastatic lymph node. A liver parenchyma about 7 × 6 × 2 cm in size was also resected and histologically determined to be an abscess without evidence of metastasis. The patient was given concurrent chemoradiotherapy (CCRT) after the extended cholecystectomy. The patient refused adjuvant therapy after two cycles of CCRT due to nausea, vomiting and poor oral intake. No evidence of tumor recurrence was found on follow up CT scans and the patient is alive 33 months after the initial operation.

## DISCUSSION

### Epidemiology & Risk factors

The incidence of the gallbladder carcinoma varies geographically and in different ethnic groups within the same country. From 1985 to 2005, the incidence in the USA was 0.9 per 100,000 males and 1.6 per 100,000 females, accounting for 0.16% and 0.39% of all cancers, respectively [1]. In Korea, the incidence of gallbladder carcinoma including the biliary tract carcinoma (cholangiocarcinoma) was 9.8 per 100,000 during 2010 [2]. Most patients with gallbladder carcinoma are in the sixth or seventh decade of life. Cigarette smoking, female sex, age, and postmenopausal status are risk factors for the development of the gallbladder carcinoma [3]. Also, chronic *Salmonella typhi* infection, exposure to chemicals used in the rubber, automobile, wood finishing, and metal fabricating industries, cholelithiasis, porcelain gallbladder, choledochal cyst, anomalous junction of the pancreaticobiliary ducts, and low insertion of the cystic duct are associated with a higher prevalence of the gallbladder carcinoma [4].

### Histological classification

Adenocarcinomas are known to be the most common malignant neoplasms arising in the gallbladder and account for 90% of gallbladder carcinomas [4]. There are several histologic variants of adenocarcinoma including papillary, intestinal, mucinous, signet-ring cell, and clear cell. The remaining epithelial cell types of the gallbladder carcinoma include adenosquamous, squamous cell, small (oat) cell, and undifferentiated carcinoma. Among primary gallbladder malignancies, the frequency of undifferentiated carcinoma is relatively low, with 1.8% reported by Ogura et al [5, 6]. The remainder of the gallbladder malignancy include

neuroendocrine tumors, sarcomas, lymphomas, metastases, and other unusual malignancies.

Neuroendocrine tumors of the gallbladder, which are very rare, account for 0.5% of all neuroendocrine tumors and 2% of all gallbladder carcinomas [7]. Neuroendocrine tumors may occur in the gallbladder in a pure form or may be combined with other types of gallbladder malignancies, such as adenocarcinoma [8]. Because neuroendocrine cells do not normally exist in the mucosa of the gallbladder, neuroendocrine tumors would not be expected to occur in this organ. Three hypotheses have been proposed for the histogenesis of neuroendocrine carcinoma [9]. First, intestinal metaplasia of the gallbladder mucosa, which occurs under chronic inflammatory conditions, may contain neuroendocrine cells. Second, neuroendocrine tumors can arise from endodermal stem cells or progenitor cells with multidirectional differentiation potential. Third, the neuroendocrine component may be derived from the aberrant differentiation of adenocarcinoma through the process of neometaplasia or transdifferentiation. There have been several reports of mixed adenoneuroendocrine carcinoma in the gallbladder, but these two different components were not distinguishable on either preoperative imaging or gross specimen [9-13]. Only histopathology demonstrated the collision tumor consisted of adenocarcinoma cells and neuroendocrine carcinoma cells with intermingled areas. However, in our case, two different forms of gallbladder malignancy showed as separate lesions on preoperative ultrasound and CT images, corresponding to the pathologic diagnosis.

### Clinical findings

The signs and symptoms of gallbladder carcinoma are not specific, often resembling those of cholecystitis. Abdominal pain, anorexia, or weight loss are common clinical features in gallbladder carcinoma [4]. Unfortunately, the majority of patients with gallbladder carcinoma present at a late state. Gallbladder carcinoma may be noticed by palpable mass, hepatomegaly, and jaundice on physical examination. Jaundice usually happens as a result of malignant obstruction of biliary tree rather than hepatic metastasis or accompanying choledocholithiasis [14].

### Imaging findings & Differential diagnoses

Imaging patterns of adenocarcinoma have been well described as follows: a mass replacing the gallbladder in 40%-65% of cases, focal or diffuse gallbladder wall thickening in 20%-30%, and an intraluminal polypoid mass in 15%-25% [4]. Adenocarcinomas replacing the gallbladder or shown as intraluminal mass have heterogeneous echotexture on ultrasound, which reflects varying degrees of tumor necrosis, and present as hypo- or iso-attenuating mass on CT images. Wall thickening is the most diagnostically challenging of these three patterns because it mimics the appearance of benign inflammatory conditions of the gallbladder which are more common. CT scan is helpful for distinguishing complicated cholecystitis from gallbladder carcinoma. CT demonstration of associated lymphadenopathy, soft tissue extension into the liver, and hematogeneous metastases favors the diagnosis of gallbladder carcinoma [4]. On MR images, gallbladder carcinoma shows low signal intensity on T1-weighted images

and high signal intensity on T2-weighted images compared with the surrounding liver parenchyma. On gadolinium-enhanced images, malignant lesions typically demonstrate early and persistent enhancement. Gallbladder carcinoma shows significant diffusion restriction and appears high signal intensity on high b value DWI due to its high cellularity [15].

Only a few articles have reported the radiologic findings of unusual gallbladder malignancies including undifferentiated carcinoma and neuroendocrine carcinoma [16]. Undifferentiated carcinoma of the gallbladder tends to form a large mass with central necrosis and grows rapidly with direct invasion into an adjacent organ. Lymph node metastasis and peritoneal dissemination is more commonly noted in this tumor.

Neuroendocrine tumors rarely occur in the gallbladder, and only a few radiology reports have described the imaging features [8,17]. They reported that neuroendocrine carcinomas of the gallbladder showed enhancement similar to or slightly lower than that of the liver parenchyma on contrast-enhanced CT images, and there was no significant difference between the CT findings of neuroendocrine carcinoma and adenocarcinoma. Obuz et al reported a case of poorly differentiated neuroendocrine carcinoma appeared as hypovascular mass replacing the gallbladder [8]. This was consistent with histopathologic findings of necrosis and fibrosis. In our case, the neuroendocrine carcinoma showed intense homogeneous enhancement on contrast-enhanced CT images and increased power Doppler flow on ultrasound since the tumor was less than 2cm in size and had no necrotic area. Furthermore, most neuroendocrine tumors of the gastrointestinal tract manifest as small masses with avid enhancement on contrast-enhanced CT images because of their hypervascularity [18]. MR characteristics for neuroendocrine tumor of the gallbladder have been rarely reported. Nau et al reported a case report of neuroendocrine tumor of the gallbladder, appearing as a large heterogeneous mass on MR image [19].

Among the remainder of the unusual gallbladder malignancy, sarcoma is also rarely reported. Kim et al reported a case of malignant fibrous histiocytoma which showed a large ill-defined mass with extensive central necrosis. On MR images, this huge mass showed peripheral high signal intensity and central bright signal intensity on T2-weighted images, and showed peripheral rim enhancement after administration of gadolinium-based contrast material [16]. Primary lymphoma of the gallbladder presents as an intraluminal mass, a large mass replacing the gallbladder, or diffuse wall thickening, which is similar to adenocarcinoma [20]. On MR images, lymphoma appears homogeneous and slightly hypointense lesion in comparison with the adenocarcinoma on T2-weighted images. Intact mucosa which correlates with submucosal infiltration of the tumor is also a characteristic finding [21].

The most common metastatic tumor of the gallbladder is malignant melanoma and presents as focal, irregular wall thickening or a polypoid enhancing mass. Most metastatic lesions are from peritoneal implantation and located on the

serosal surface of the gallbladder. Some lesions appear as an intraluminal mass [22].

#### Treatment & prognosis

In general, the therapeutic options for gallbladder carcinoma are limited because of the advanced stage of disease at presentation in most cases. Although surgical resection is the mainstay of treatment, the extent of resection remains controversial. Extended cholecystectomy including en bloc segmental hepatic resection, and lymph node dissection is usually performed for patients with gallbladder carcinoma. Some authors agree that early disease with tumor confined to the lamina propria or muscular layer requires a simple cholecystectomy [4]. In recent studies, adjuvant chemoradiotherapy has shown an increase in survival time [23, 24].

The prognosis for patients with gallbladder carcinoma depends on the extent of disease and histologic type. For invasive adenocarcinomas that extend through the entire thickness of the gallbladder wall, the 10-year relative survival rate is about 30% [1]. The prognosis of undifferentiated carcinoma is poorer than the differentiated carcinoma [6]. In patients with neuroendocrine carcinoma, about 40-50% of patients have disseminated disease at the time of diagnosis and have poor prognosis. Mixed adenoneuroendocrine carcinomas behave as adenocarcinomas and should be managed accordingly, being clinically more aggressive than neuroendocrine tumors [1].

To our knowledge, this is the first report presenting two separate lesions showing undifferentiated and neuroendocrine carcinomas of the gallbladder with distinguishable radiologic features on ultrasound and CT images corresponding to the pathologic diagnosis. These findings may be helpful in predicting or differentiating the type of gallbladder malignancy on preoperative imaging modalities.

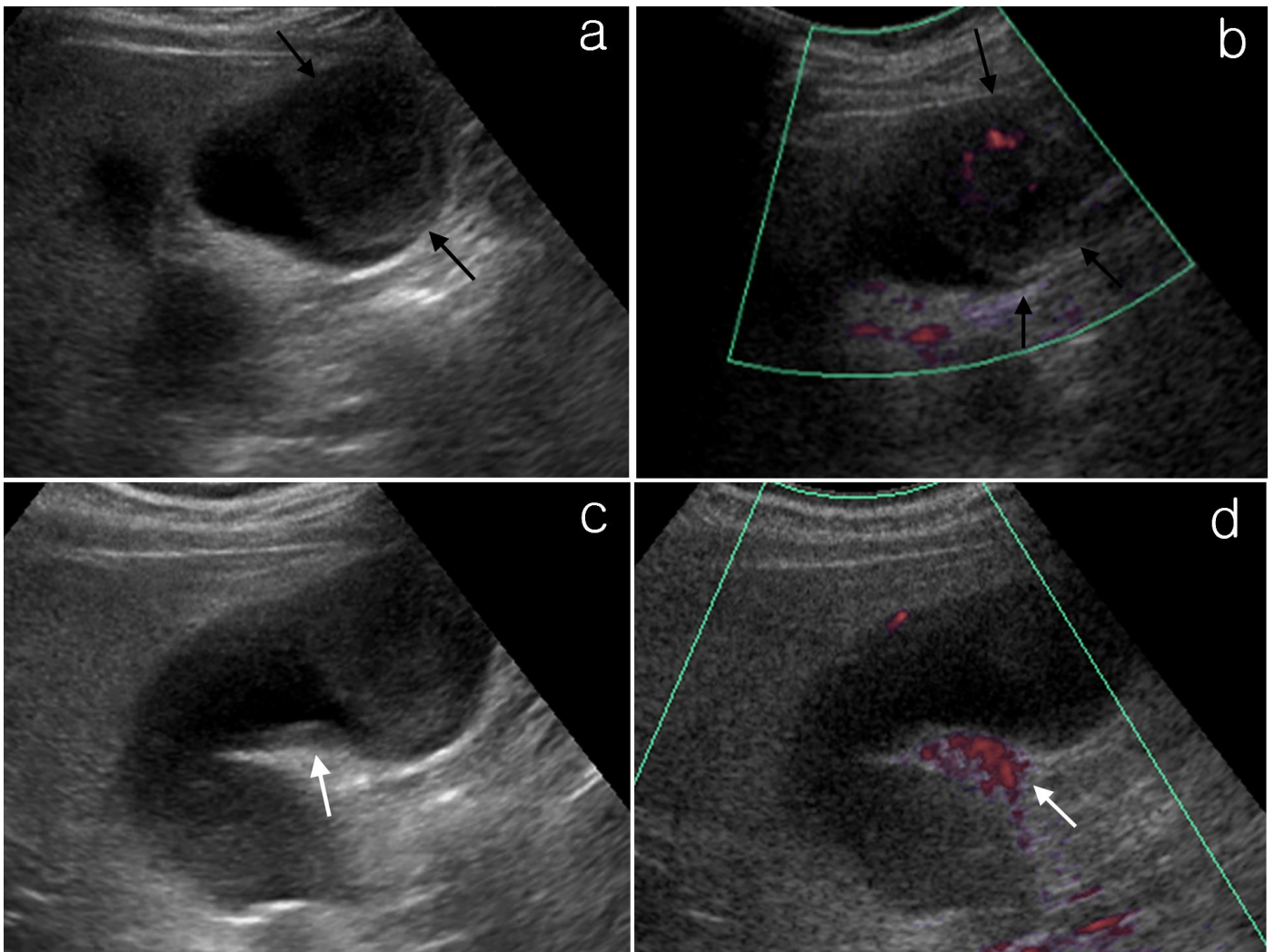
#### TEACHING POINT

In addition to the adenocarcinoma, known to be the most common malignant neoplasm arising in the gallbladder, there are several other types of gallbladder tumor including undifferentiated carcinomas, neuroendocrine tumors, sarcomas, lymphomas, and metastases. Gallbladder tumors can arise concurrently with distinguishable radiologic features. Broad familiarity with rare variations of gallbladder tumor may be helpful in improving diagnostic accuracy and differentiating the types of gallbladder malignancy.

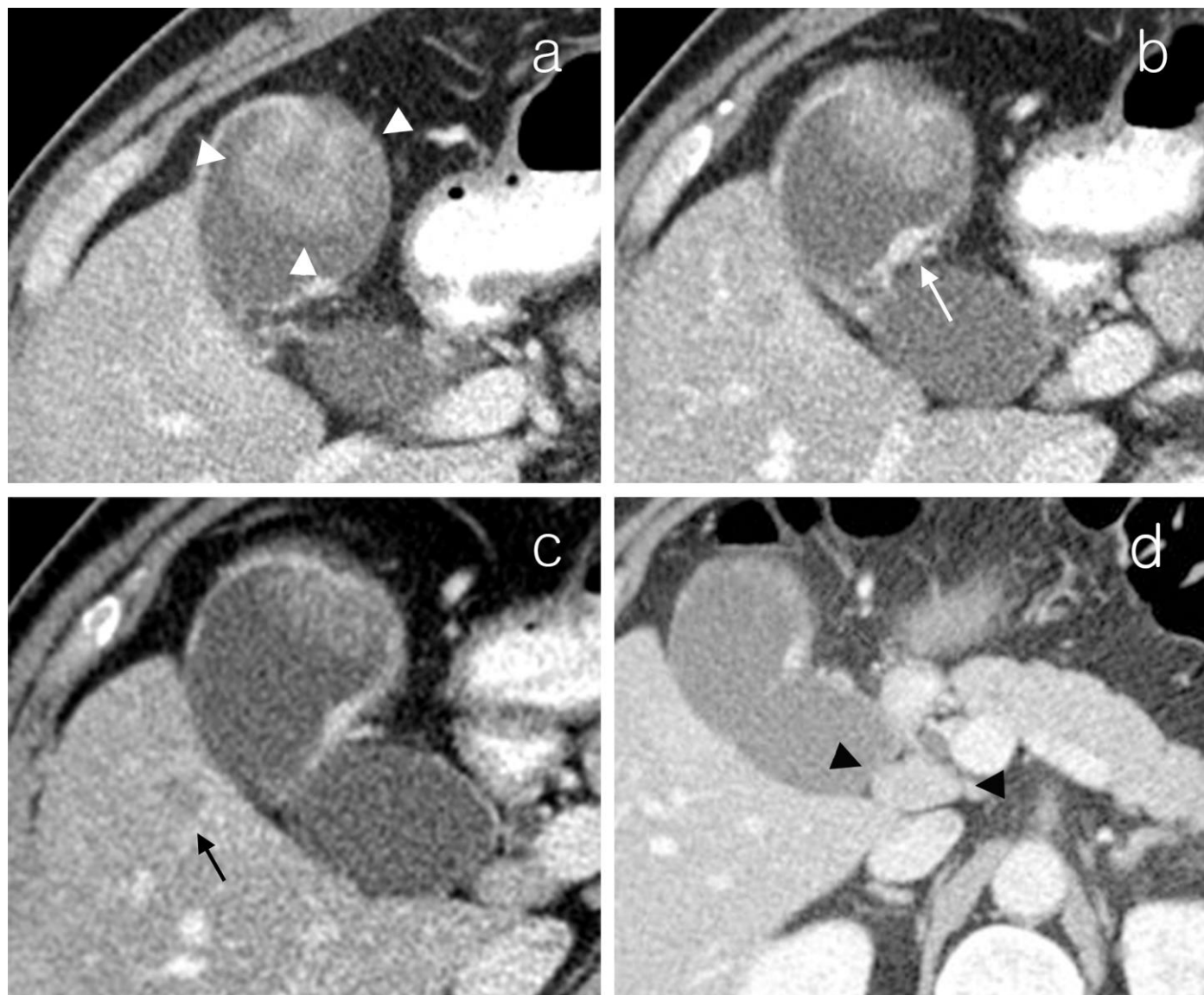
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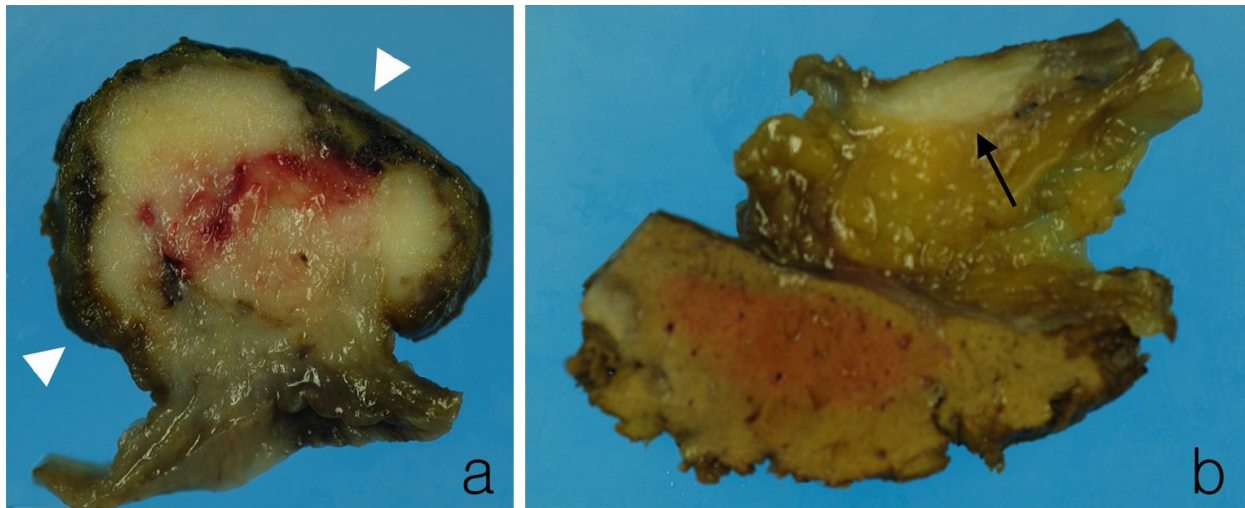
FIGURES



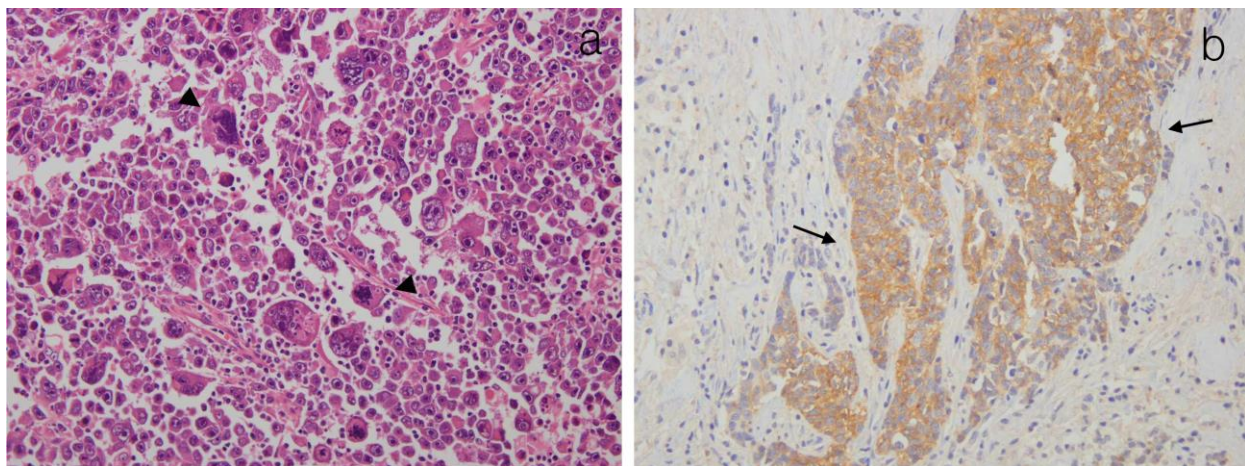
**Figure 1:** 54-year-old man with combined undifferentiated and neuroendocrine carcinoma of the gallbladder.  
**FINDINGS:** Abdominal ultrasound shows a heterogeneously echogenic polypoid mass at the fundus of the gallbladder with subtle increased power Doppler flow (black arrows, a, b). A short distance from the main mass, focal nodular thickening of gallbladder wall was noted with prominently increased power Doppler flow (white arrow, c, d). The histology confirmed the main polypoid mass as undifferentiated carcinoma and the separate nodule as neuroendocrine carcinoma.  
**TECHNIQUE:** Philips, HDI 5000; 2-5-MHz convex transducer



**Figure 2:** 54-year-old man with combined undifferentiated and neuroendocrine carcinoma of the gallbladder.  
FINDINGS: Venous phase MDCT image confirmed a polypoid mass at the fundus of the gallbladder with heterogeneous enhancement similar to that of the fatty liver parenchyma, including a non-enhancing central necrotic portion (white arrowheads, a). A short distance from this mass, focal nodular wall thickening of the gallbladder revealed more intense enhancement (white arrow, b) compared with the main mass. The histology confirmed the main polypoid mass as undifferentiated carcinoma and the separate nodule as neuroendocrine carcinoma. There was a subtle focal low-density lesion in segment 5 of the liver adjacent to the gallbladder fossa (black arrow, c), which was histologically confirmed to be an abscess after resection. A 2.5 x 1 cm sized homogeneously enhancing portocaval lymph node was detected (black arrowheads, d).  
TECHNIQUE: Siemens Healthcare, SOMATOM Definition Flash, Axial CT. 80~165mA, 120kV, 3mm slice thickness, Intravenous contrast: 120 mL of contrast medium (Iopromide, Ultravist 370, Bayer HealthCare), in venous phase.



**Figure 3:** 54-year-old man with combined undifferentiated and neuroendocrine carcinoma of the gallbladder.  
FINDINGS: The gross resection specimen showed the main polypoid mass as whitish mass with hemorrhage and necrosis (arrowheads, a). The histopathological diagnosis was anaplastic undifferentiated carcinoma with rhabdoid features. Another small whitish nodule was found in the wall of the gallbladder (arrow, b). The histopathological diagnosis of this nodule was neuroendocrine carcinoma.



**Figure 4:** 54-year-old man with combined undifferentiated and neuroendocrine carcinoma of the gallbladder.  
FINDINGS: Histopathologic examination (hematoxylin-eosin, x200) showed bizarre shaped pleomorphic tumor cells with atypical mitoses and tumor giant cells, suggesting anaplastic undifferentiated carcinoma (arrowheads, a). The separate nodule showed positive staining for CD56 by immunohistochemistry (arrows, b) and was confirmed to be neuroendocrine carcinoma.

<b>Incidence</b>	0.9/100,000 males and 1.6/100,000 females, accounting for 0.16% and 0.39% of all cancers, respectively in the USA
<b>Gender ratio</b>	Female 3 : male 1
<b>Age predilection</b>	Sixth or seventh decades
<b>Risk factors</b>	Female sex, age, postmenopausal status, cigarette smoking, chronic Salmonella typhi infection, exposure to chemicals used in the rubber, automobile, wood finishing, and metal fabricating industries, cholelithiasis, porcelain gallbladder, choledochal cyst, anomalous junction of the pancreaticobiliary ducts, and low insertion of the cystic duct
<b>Treatment</b>	Extended or simple cholecystectomy Chemotherapy and radiation may also be used with surgery
<b>Prognosis</b>	Depends on the extent of disease and histologic type For invasive adenocarcinomas, the 10-year relative survival rate is about 30%
<b>Imaging findings</b>	Mass replacing the gallbladder, diffuse or focal wall thickening, or polypoid intraluminal mass

**Table 1:** Summary table of gallbladder carcinoma.

Differential diagnosis	Type of mass	Imaging features		
		US	CT	MR
Adenocarcinoma	Mass replacing the gallbladder	Heterogeneous echotexture, which reflects varying degrees of tumor necrosis	Hypo- or iso-attenuating mass in the gallbladder fossa and soft tissue invasion of the liver	T1-hypointense, T2-hyperintense compared with the surrounding liver parenchyma On gadolinium-enhanced image, early and persistent enhancement Hyperintense on high b value DWI, low ADC value
	Diffuse or focal wall thickening	Pronounced wall thickening demonstrated with associated mural irregularity or marked asymmetry	Helpful for distinguishing complicated cholecystitis from gallbladder carcinoma; CT demonstration of associated lymphadenopathy, soft tissue extension into the liver, and hematogeneous metastases favors the diagnosis of gallbladder carcinoma	
	Polypoid intraluminal mass	Heterogeneous echotexture, which reflects varying degrees of tumor necrosis Immobile with changes in patient position	Hypo- or iso-attenuating mass in the gallbladder	
Undifferentiated Carcinoma	-	Tends to form large mass with central necrosis Rapid growth with direct invasion into adjacent organ		-
Neuroendocrine tumor	Mass replacing the gallbladder	Heterogeneous echotexture, which reflects varying degrees of tumor necrosis	Enhancement similar to or slightly lower than that of the liver parenchyma Hypovascular mass replacing the gallbladder, reflects necrosis and fibrosis	Large mass with heterogeneous signal intensity
	Focal wall thickening	Increased power Doppler flow	Intense homogeneous enhancement	
Sarcoma (Malignant fibrous histiocytoma)	-	Large ill-defined mass with extensive central necrosis		Large mass with peripheral high signal intensity and central bright signal intensity on T2-weighted image On gadolinium-enhanced image, peripheral rim enhancement
Lymphoma	Similar to adenocarcinoma	Similar to adenocarcinoma		Slightly T2-hypointense compared with adenocarcinoma Intact mucosa, correlates with submucosal infiltration of the tumor
Metastasis (Malignant melanoma)	Polypoid enhancing mass or focal, irregular wall thickening	Mostly located on the serosal surface because of peritoneal implantation Some appeared as an intraluminal mass		-

Table 2: Differential diagnosis table for gallbladder malignancy.

ABBREVIATIONS

CCRT = concurrent chemoradiotherapy  
MDCT = multi-detector computed tomography

KEYWORDS

Gallbladder malignancy; combined gallbladder carcinoma; neuroendocrine carcinoma

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