

## Case Report

## Neuroendocrine Tumor of the Gallbladder

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## Abstract

Neuroendocrine tumors (NET) arise from neuroendocrine cells and are an exceedingly rare malignancy in the gallbladder. In this case report, a 52-year-old woman with complaints of episodic abdominal pain for two months prior was admitted to our hospital. She had no other signs and symptoms and her laboratory tests were within normal limits. Ultrasonography showed a broad-necked mass (26 × 12 mm) in the gallbladder for which she underwent laparoscopic cholecystectomy. The final pathological diagnosis was a high grade neuroendocrine carcinoma of the gallbladder with involvement of the lymph nodes and omentum. The patient received the chemotherapy regimens of gemcitabine plus cisplatin, followed by docetaxel plus sunitinib for her metastatic liver lesions. She also underwent radiofrequency ablation. Serial CT-scans revealed metastatic liver lesions that had decreased in size, with no significant improvement. The patient refused additional treatment and at 46 months, she was doing well with no complaints of any pain, disease recurrence, or metastatic progression.

**Keywords:** Case report, chemotherapy, gallbladder, neuroendocrine tumor, radiofrequency ablation.

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## Introduction

Neuroendocrine tumors (NET) are a heterogeneous group of rare malignancies with variable histories and biological behaviors<sup>1</sup> that arise from neuroendocrine cells. Neuroendocrine cells are defined as cells that have the ability to produce neurotransmitters, neuromodulators, or neuropeptide hormones. In addition, they contain dense core secretory granules and lack axons and synapses. Most neuroendocrine cells are located in the mucosal layer of the gastrointestinal and respiratory tracts, forming one of the largest endocrine organs of the human body. They are located throughout the body, such as the skin, mucosal membranes, and all solid organs. Therefore a NET may originate anywhere within the body.<sup>2</sup>

The majority of malignant epithelial tumors of the gallbladder are well or moderately differentiated adenocarcinomas that lack distinctive features. Small cell carcinoma is a distinct but very unusual neoplasm of the gallbladder. The prevalence of gallbladder small cell NET is 1% to 5% of all gastrointestinal carcinoids.<sup>3</sup>

Herein we report the diagnosis, natural history, therapy, and follow up of a patient with small cell NET who was doing well 46 months after diagnosis.

## Case Report

A 52-year-old woman with episodic abdominal pain two months prior to admission was referred to a general hospital for additional evaluation in September 2007. She had no other complaints and

her general physical exam was normal. Ultrasonography showed a broad-necked mass (26 × 12 mm) in the gallbladder (Figure 1). She was admitted for further investigation with the impression of a gallbladder polyp. There were no abnormal laboratory findings. Levels of the tumor markers, carcinoembryonic antigen (CEA) and 19-9 carbohydrate antigenic determinant (CA19-9) were within normal ranges. She underwent laparoscopic cholecystectomy for gallbladder resection and a definitive diagnosis. During the surgery there was no evidence of any metastases to the liver, peritoneum, or lymph nodes observed. A mass with an approximate size of 35 × 25 × 10 mm was observed in the neck of the resected gallbladder and sent for pathology. Following surgical intervention there were no complications observed during the recovery period. After the pathology report of gallbladder carcinoma, the patient underwent CT scans of the chest, abdomen, and pelvis to assess for metastases. There was no sign of metastasis in the CT scans, thus the tumor was diagnosed as a primary carcinoma of the gallbladder according to standard characteristics.

## Pathology findings

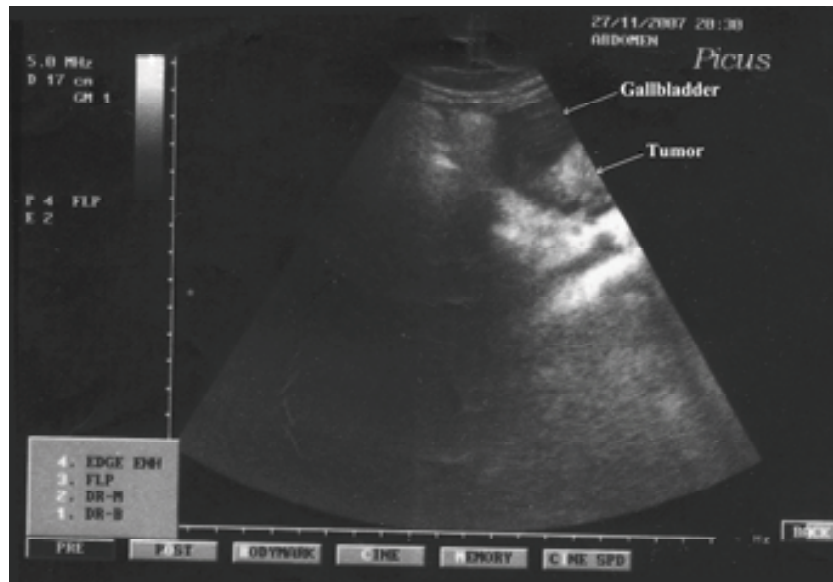
The first pathology results performed in Iran revealed a poorly differentiated carcinoma arising from the gallbladder, with full-thickness invasion and into the lymph nodes near the neck of the gallbladder and omental tissue. The pathology material from the cholecystectomy was forwarded to Hammersmith Hospital in London which reported an invasive carcinoma composed of polygonal and spindle cells with only focal glandular differentiation and “solid growth” as the dominant pattern. The pattern suggested neuroendocrine differentiation as confirmed by strong but patchy chromogranin immunoreactivity. Synaptophysin and chromogranin A stains were immunoreactive with the tumor cells (Figure 2). C-kit (CD 117) had a strong membranous expression, thus the tumor was classified as at least an intermediate grade. The final diagnosis was a high grade neuroendocrine carcinoma of the gallbladder.

Pathology was additionally submitted to King’s College Hospital in London, and the result was “neoplasm with two compo-

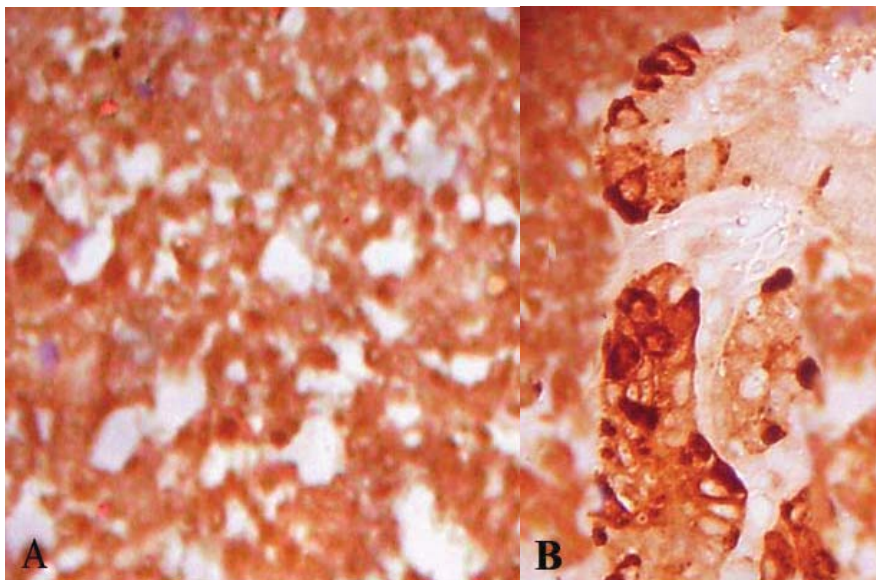
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**Figure 1.** Ultrasonography findings of a broad-necked mass (26 × 12 mm) in the gallbladder.



**Figure 2.** A) Chromogranin immunoreactive stain (x10). B) Nests of neuroendocrine cells in the gallbladder mucosa (x40).

nents” as follows: 1) moderately differentiated adenocarcinoma large cells in situ or micro invasive and 2) small cell neuroendocrine-like carcinoma of the gallbladder. The latter formed the bulk of the lesion with transmural infiltration and involvement of the lymph nodes and omentum.

#### Treatment

Following cholecystectomy the patient refused additional surgical intervention, so our therapeutic efforts were limited to chemotherapy. The patient underwent six cycles of gemcitabine (1250 mg/m<sup>2</sup> on days 1 and 8, repeated every 21 days) and cisplatin (75 mg/m<sup>2</sup> on day 1, repeated every 21 days). After nine months, the patient had evidence of liver lesions as noted on a CT scan and was treated with six cycles of docetaxel (100 mg/m<sup>2</sup> every 3 weeks) and sunitinib [50 mg qd for 4 weeks out of the 6-week treatment cycle (4 weeks on, 2 weeks off)]. In August 2010, the patient underwent radiofrequency ablation as treatment for her

liver metastases. Serial CT-scans of the pelvis and abdomen revealed liver metastatic lesions that were smaller, but there was no significant improvement. The patient refused additional treatment. As of July 2011, she was alive, with stable disease and no progression or improvement in the metastatic lesions.

#### Discussion

This case has been classified as a heterogeneous neuroendocrine cell carcinoma. Heterogeneous carcinoma is indicative of a simultaneous occurrence of more than one histological differentiation. As with most other small cell carcinomas, this patient had a non-secretory tumor with no overt clinical signs of secreted peptides or any specific characteristics observed on the radiological studies.

In 2000, Matsuo et al. have suggested that the combination of the tumor’s immunohistochemical activity with pathology findings is necessary for a definite diagnosis.<sup>4</sup> Our case was diagnosed

by both methods as a small cell carcinoma of the gallbladder.

As the normal gallbladder does not contain neuroendocrine cells, thus these tumors are very rare. Neuroendocrine cells have been observed in mucosal metaplasia of the gallbladder, often accompanied by cholelithiasis and cholecystitis.<sup>5</sup> This hypothesis is supported by the presence of metaplasia in the gallbladder with chronic cholecystitis.<sup>6</sup>

The histogenesis of small cell carcinoma is currently believed to be of an epithelial origin.<sup>5</sup> A literature search of gallbladder carcinomas has revealed reports of 28 (78%) pure small cell carcinomas and 8 (22%) small cell carcinomas combined with adenocarcinomas.<sup>5</sup>

The clinical behavior of this disease includes an increased incidence in the elderly population, female preponderance, an association with cholelithiasis, and metastases as frequent as 75% of the time to the lymph nodes, liver, lungs, and peritoneum.<sup>5,7</sup> According to signs and symptoms and behavior of disease, our patient is consistent with the picture reported in other cases of small cell carcinomas of the gallbladder.

In gallbladder carcinomas, adjuvant chemotherapy is often used without a well-defined protocol. Therapeutic interventions are currently limited to complete surgical resection with negative margins.

Gallbladder polyps larger than 2 cm are best treated with open cholecystectomy rather than laparoscopic cholecystectomy, as they are considered to be at very high risk for gallbladder cancer and to reduce the risk of seeding associated with laparoscopic surgery.<sup>8,9</sup> On the other hand, a resection is feasible in less than 25% of patients because of the advanced stage of the disease at diagnosis.<sup>6</sup> However, surgical excision with adjuvant chemotherapy remains the best option to treat a small cell carcinoma of the gallbladder. The necessity of a radical resection and removal of marginal tissue has been debated in the literature.<sup>10</sup> Although different chemotherapy regimens have been described in patients who are not amenable to curative surgery,<sup>11-14</sup> to date there is no blinded randomized clinical trial that has validated a particular regimen as the gold standard for treatment.<sup>15</sup>

The prognosis of small cell gallbladder carcinoma appears to be very poor with a median survival in a series of 53 cases with disseminated disease of eight months, a one-year survival rate of 28%, and two-year survival rate of 0%.<sup>13</sup> In another literature review of 32 small cell gallbladder carcinoma cases, only one case survived for 28 months.<sup>4</sup> According to another literature review, the median survival time of combined small cell carcinoma and adenocarcinoma following surgery was reported to be 4.5 months. In patients who underwent cholecystectomies, the median sur-

vival time was slightly better than those who underwent radical tumor resection. Chemotherapy following surgery also increased the survival time to an average of 13 months.<sup>5</sup>

In our case, after 46 months the patient was doing well with no complaints of any type of pain and no evidence of disease recurrence following radiofrequency ablation of the liver, which was performed 36 months after her diagnosis.

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