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Metastatic large-cell neuroendocrine carcinoma of the lung masquerading as a primary gallbladder carcinoma: A case report

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Abstract

Gallbladder neuroendocrine carcinoma is rare, representing ~4% of all primary malignant gallbladder neoplasms. We report the case of a 75-year-old female who presented for radiologic restaging for lung adenocarcinoma diagnosed elsewhere, demonstrating a hypermetabolic gallbladder mass. With concern for a gallbladder primary, radical cholecystectomy followed. Gross showed a 2-cm polypoid fundic mass; microscopically, tumor cells were arranged in sheets, with organoid features and necrosis, variable cytoplasm, vesicular-granular chromatin, prominent nucleoli, frequent mitoses, and apoptotic figures. Immunohistochemically, synaptophysin, chromogranin, CK7, and TTF-1 were positive; Ki67 was 80%. The combined findings were diagnostic of large-cell neuroendocrine carcinoma. Further investigation including outside slide review with additional stains revealed the lung primary to be classified large-cell neuroendocrine carcinoma, thus the gallbladder tumor representing metastasis. Within 4 months, the patient expired with widespread metastases. To our knowledge, this is the first reported case of metastatic lung large-cell neuroendocrine carcinoma to gallbladder in the English literature.

Keywords

Large-cell neuroendocrine carcinoma, metastasis, gallbladder

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Introduction

Neuroendocrine carcinoma (NEC) of the gallbladder (GB) is a rare primary tumor, accounting for approximately 4% of all GB cancers[1] and approximately 0.2% of all NECs of gastrointestinal origin. Metastases to the GB are also uncommon with, 5.8% seen in a large autopsy study by Abrams et al. and 4.8% in a retrospective institutional study.[2,3] The most common metastatic neoplasms to the GB include melanoma, renal cell carcinoma (RCC), and breast carcinoma more commonly reported in Western countries; with gastric, liver, and colorectal carcinomas more commonly seen in Eastern countries.[4] Metastatic cases of non-small-cell lung carcinoma are few (four reported cases).[5] Herein we report a case of metastatic large-cell neuroendocrine carcinoma (LCNEC) from a lung primary in a patient undergoing treatment for lung adenocarcinoma previously diagnosed elsewhere. To our knowledge, we present the first instance of metastatic lung LCNEC to the GB reported in the English literature.

Case report

A 75-year-old female presented for positron emission tomography/computed tomography (PET/CT) imaging for follow-up restaging for a lung adenocarcinoma, diagnosed elsewhere 2 months prior, with brain metastases, for which chemotherapy and radiation had been ongoing. Her treatment regimen over the prior 2 months included weekly chemotherapy with paclitaxel (45 mg/m^2) and carboplatin AUC (area under the curve; 2 mg/mL) with concurrent radiation therapy to the lung. She additionally received stereotactic body radiation therapy (SBRT) to the brain metastases over 5 fractions administered concurrently with the aforementioned chemoradiation for her lung cancer (Table 1). The patient was a former smoker with a 25 pack per year history. She had quit 31 years prior to her diagnosis of a lung malignancy. There was no history of alcohol or illicit drug use. This PET/CT scan demonstrated a decrease in the size of her lung mass and a 2 cm hypermetabolic polypoid mass in the GB (Figure 1) highly concerning for a primary GB carcinoma that was first seen on

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Table 1. Oncologic treatment summary.

Oncologic treatment summary								
Diagnosis of lung malignancy with brain metastases Paclitaxel Carboplatin Radiation to Lung Stereotactic body radiation therapy to brain metastases Durvalumab initiated Suspected primary gallbladder cancer seen on imaging	2 months later	Cholecystectomy Performed Durvalumab stopped	2 weeks later	Numerous new brain metastases developed and whole brain irradiation given	4 weeks later	Disease progression with multiple vertebral body osseous metastases, palliative spinal radiation given Patient transitioned to hospice care	9 weeks later	Patient expired

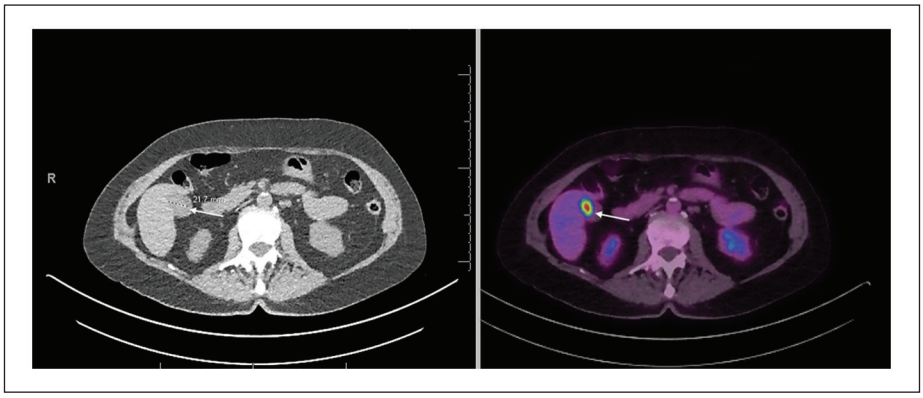

Figure 1. Representative axial positron emission tomography/computed tomography (PET/CT) images demonstrating the gallbladder mass (arrows, CT image on left with corresponding PET image on right).

prior PET/CT. The patient endorsed recurrent right upper quadrant pain with spontaneous resolution. Her past medical history was also significant for a remote history of triple-negative left breast cancer, diagnosed at 45 years of age and previously treated with mastectomy and chemoradiation (additional prior treatment details unknown). Her family history was significant for breast cancer in her maternal grandmother (age 85), esophageal cancer in her maternal grandfather (age 65), colon cancer in her maternal uncle (age 71), and colon cancer in her mother (age 80). Due to the patient's history and family history, obtaining genetic testing to rule out a hereditable cancer syndrome was discussed with oncology, although there is no record of this testing being completed. Hepatobiliary surgical consultation was subsequently obtained, and radical cholecystectomy was performed.

The GB grossly demonstrated a polypoid fundic mass on the hepatic side of the GB wall, with focal discoloration of the overlying mucosa (Figure 2). Histologically, sections demonstrated a hypercellular tumor with areas of geographic necrosis the adjacent GB mucosa was unremarkable (Figure 3(a)). On higher power, a sheet-like arrangement and vague organoid pattern could be appreciated. Cytologically, the cells demonstrated variable amounts of cytoplasm, with

Figure 2. Gross photograph of polypoid fundic gallbladder mass.

vesicular–granular chromatin, prominent nucleoli, frequent mitotic figures, apoptotic bodies, and pleomorphism (Figure 3(b)). Immunohistochemical (IHC) analysis demonstrated the cells were positive for synaptophysin (Figure 3(c)), chromogranin, cytokeratin 7, and TTF1; with a Ki67 proliferative

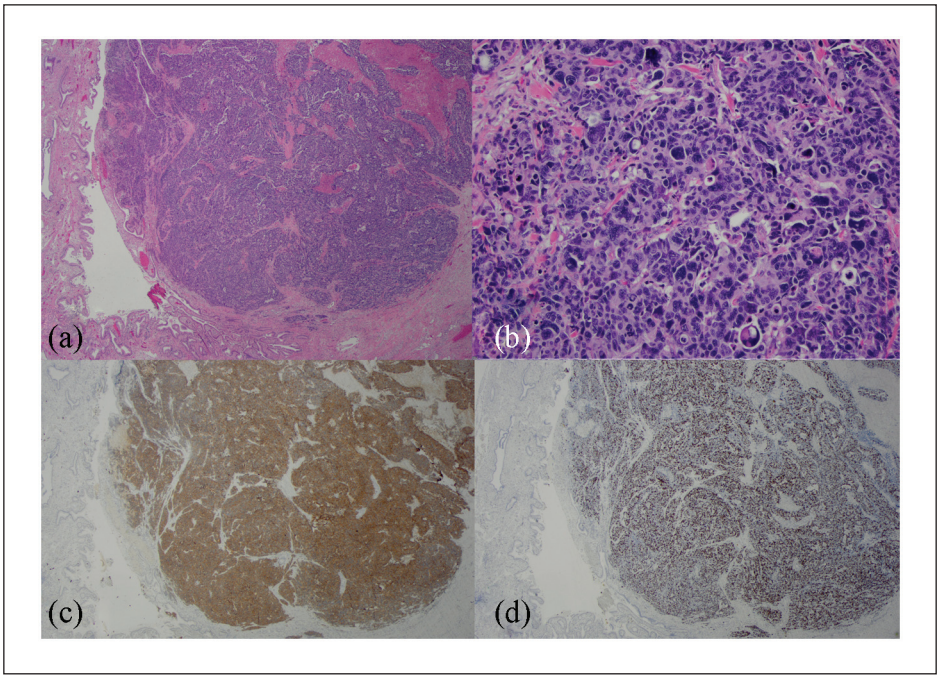

Figure 3. Hematoxylin & eosin (H&E) and immunohistochemical (IHC) stains of the gallbladder mass. (a) Low-power H&E image showing adjacent normal gallbladder mucosa and the hypercellular tumor with geographic necrosis visible (20×). (b) High-power H&E image demonstrating vaguely organoid cellular architecture, the cells show variable cytoplasm with frequent mitoses and apoptosis (200×). (c) IHC stain for synaptophysin is diffusely positive (20×). (d) IHC stain for Ki67 demonstrates a proliferative index of approximately 80% (20×).

index of approximately 80% (Figure 3(d)). The findings were most consistent with an LCNEC involving the GB. No neoplastic precursor lesions were seen in the surrounding GB. Due to the rarity of this neoplasm, and the patient's clinical history, a metastasis could not be entirely excluded. Further investigation including review of outside pathology slides in conjunction with additional stains revealed the lung primary to be best classified as an LCNEC, with the GB tumor thus, representing a metastasis.

The patient's post-operative course was largely unremarkable, and she was discharged after a short hospital stay. However, 2 weeks following her surgery, additional brain metastases developed, for which whole brain radiation was administered and platinum-based chemotherapy was discussed. Approximately 1 month after this, unilateral hip and leg pain ensued. A restaging PET scan demonstrated new widespread hypermetabolic lesions in the thoracic and lumbar spine, ribs, pelvis, and thyroid. Palliative spinal radiation was administered before transitioning to hospice care; the patient passed away shortly thereafter. The interval between the diagnosis of her metastatic GB NEC and death was 112 days (Table 1).

Discussion

NEC is a rare primary tumor of the GB, of which the most common primary malignant neoplasm encountered is adenocarcinoma.[6,7] GB NECs typically present in older adults during the seventh decade of life, more frequently in females than males.[8] These may arise anywhere within the GB, are more commonly small cell in morphology rather than large cell, with up to one-third displaying mixed morphology with an adenocarcinoma component.[8] A precursor lesion (intracholecystic papillary neoplasm, ICPN) may be seen in up to 17% of cases.[6,7] These highly aggressive neoplasms have a poorer prognosis than conventional adenocarcinoma, most present with advanced disease at diagnosis, with a median survival time <1 year, and 5 and 10-year survival rates of 20% and 0%.[8] Neuroendocrine cells are not normal constituents of the GB mucosa, which has confounded understanding of the pathologic sequence of events in GB-NEC. Hypothetical etiologies include differentiation from GB stem cells, metaplasia of the GB epithelium from chronic cholecystitis, and the transdifferentiation of GB adenocarcinomas into NECs.[7,9,10] Immunohistochemically, GB NECs express typical neuroendocrine markers synpatophysin (94%) and chromogranin (71%), CK7 (67%), and TTF1 (31%), with a high Ki67 (median 75%).[6,7]

Metastases to the GB are also rare occurrences (Table 2). One post-mortem study demonstrated only 5.8% of patients with cancer to have GB metastasis at time of autopsy.[3] An institutional retrospective study evaluated 417 malignant cholecystectomies of which 20 (4.8%) were metastases, most commonly being gastric, colonic, and hepatic in

Table 2. Summary of metastases to gallbladder from literature.

Study	GB metastases reported
Abrams et al.[3]	Stomach cancer (17 of 119 (14.3%) stomach cancer autopsy cases) Pancreatic cancer (4 of 32 (13%) pancreatic cancer autopsy cases) Ovarian cancer (7 of 64 (11%) ovarian cancer autopsy cases) Breast cancer (11 of 167 (6.6%) breast cancer autopsy cases) Colon cancer (6 of 118 (5.1%) of colon cancer autopsy cases) Rectal cancer (3 of 87 (3%) rectal cancer autopsy cases) Lung cancer (3 of 160 (1.9%) lung cancer autopsy cases)
Yoon et al.[2]	Stomach cancer (n = 8) Colorectum cancer (n = 3) Liver cancer (n = 2) Kidney cancer (n = 2) Skin cancer (n = 2) Extrahepatic bile duct cancer (n = 1) Uterine cervical cancer (n = 1) Appendix cancer (n = 1)
Tanaka et al.[11]	Large-cell carcinoma from lung
Jeong et al.[5]	Non-small cell lung cancer (squamous cell carcinoma) 3 additional cases of non-small cell lung cancer cited Melanoma (in up to 20% of cases)
Choi et al.[4]	Stomach cancer (n = 8) Renal cell carcinoma (n = 4) Hepatocellular carcinoma (n = 3) Colon cancer (n = 2) Ovarian cancer (n = 1) Skin cancer (n = 1) Duodenual cancer (n = 1) Uterine cervical cancer (n = 1)

origin.[2] Subsequently, Choi et al.[4] looked at GB metastases with a focus on evaluating differing computed tomography (CT) characteristics whereby adenocarcinomas tended to display an infiltrative appearance with wall thickening on CT, while non-adenocarcinomas tended to form a polypoid mass; gastric, renal, and liver origin were most commonly seen. In both of these Eastern studies, none of the reported GB metastases were of pulmonary origin.[2,4] Other common reported GB metastases include breast and melanoma, with rare cases of lung primaries.[5] Tanaka et al.[11] have previously reported a case of a metastatic lung LCNEC to the GB, with this current case representing the first reported the in the English literature.

Conclusion

Given the rarity of primary NECs of the GB, it is imperative to rule out a metastatic etiology in this scenario. IHC analysis does not aid in definitively excluding metastasis as the IHC profile described earlier is seen in primary lung NECs in addition to extrapulmonary visceral NECs. If a precursor lesion such as ICPN is present, this is helpful to support a primary GB NEC; however, a precursor lesion is not seen in the majority of cases. In addition, molecular analysis may not offer additional benefit as some of the molecular aberrations in both lung and GB NECs are shared, some of which may also be seen in their adenocarcinoma counterparts.[6,12] Hence, clinical and radiologic correlation is paramount with comparison to prior diagnosed malignancies if applicable.

Author contributions

All authors whose names appear on the submission (CS and DA-V) made substantial contributions to this manuscript. All authors read and approved the final manuscript.

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Informed consent

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