Case Report

Gallbladder Metastasis of Non-small Cell Lung Cancer Presenting as Acute Cholecystitis

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ABSTRACT

Although non-small cell lung cancer (NSCLC) can metastasize to almost any organ, metastasis to the gallbladder with significant clinical manifestation is relatively rare. Here, we report a case of gallbladder metastasis of NSCLC presenting as acute cholecystitis. A 79-year-old man presented with pain in the right upper quadrant and fever. A computed tomography (CT) scan of the chest and abdomen showed a cavitary mass in the right lower lobe of the lung and irregular wall thickening of the gallbladder. Open cholecystectomy and needle biopsy of the lung mass were performed. Histological examination of the gallbladder revealed a moderately-differentiated squamous cell carcinoma displaying the same morphology as the lung mass assessed by needle biopsy. Subsequent immunohistochemical examination of the gallbladder and lung tissue showed that the tumor cells were positive for P63 but negative for cytokeratin 7, cytokeratin 20 and thyroid transcription factor-1. A second primary tumor of the gallbladder was excluded by immunohistochemical methods, and the final pathological diagnosis was gallbladder metastasis of NSCLC. Although the incidence is extremely rare, acute cholecystitis can occur in association with lung cancer metastasis to the gallbladder.

Key words: Cholecystitis; Gallbladder; Non-small cell lung cancer; Metastasis

INTRODUCTION

Non-small cell lung cancer (NSCLC) can metastasize to any location in the body, and approximately two-thirds of NSCLC patients present with advanced disease at the time of diagnosis. The frequent metastatic sites of NSCLC are the pleura, contralateral lung, bone, liver, adrenal glands and brain. Extrathoracic metastatic disease is found at autopsy in >50% of patients with squamous cell carcinoma and 80% of patients with adenocarcinoma and large cell carcinoma[1]. By contrast, gallbladder metastasis is extremely rare in NSCLC patients: the gallbladder was recognized as a site of metastasis in only 1.9% of 160 lung cancer cases in large autopsy reviews[2], and there are only a few clinical reports of cases in which metastatic lung cancer of the gallbladder was detected when the patients were alive[3-5]. Here, we report the unusual case of a 79-year-old man with synchronous NSCLC metastasis to the gallbladder presenting as acute cholecystitis. The clinico-pathological features of three previously published cases of NSCLC metastasis to the gallbladder are reviewed in addition to the present case.

CASE REPORT

A 79-year-old man presented in January, 2010 with a 3-day history of progressively worsening abdominal pain in the right upper quadrant, fever and headache. He had no relevant previous medical history. On physical examination, body temperature was 38.9℃, blood pressure 130/75 mmHg, and pulse rate 105/min. Abdominal examination revealed tenderness in the right upper abdomen and rigidity of the abdominal wall with positive Murphy's sign. Laboratory testing revealed a hemoglobin level of 11.0 g/dl, a white cell count of 17,500/μl with 90.4% neutrophils, and a platelet count of 272,000/μl. Blood chemistry findings were as follows: alanine aminotransferase, 65 IU/L;

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aspartate aminotransferase, 40 IU/L; total bilirubin, 0.4 mg/dl; and alkaline phosphatase, 218 IU/L. A computed tomography (CT) scan of the abdomen and pelvis revealed irregular thickening of the gallbladder wall (Figure 1A). A CT scan of the chest showed a 5 cm × 4 cm irregular cavitary mass in the right lower lobe of the lung (Figure 1B) and lymph node enlargement in the right hilar and paraesophageal areas. Magnetic resonance imaging of the brain revealed a 1.5 cm well-defined peripheral enhancing necrotic nodule with significant surrounding edema. The patient underwent open laparotomy and cholecystectomy without complication. The tumor was palpable and movable within the body of the gallbladder, without gross involvement of the liver or regional lymph nodes. Examination of the abdominal cavity showed no signs of peritoneal metastases. On gross examination, the gallbladder wall was thickened, with a 3.5 cm palpable mass on the body (Figure 2). There were no gallstones in the bile. Microscopic examination of tumor morphology by hematoxylin and eosin (H & E) staining provided a histological diagnosis of moderately-differentiated squamous cell carcinoma (Figure 3A). Immunohistochemical staining showed that the tumor cells were positive for P63 (1:100; Leica, Newcastle-upon-Tyne, UK) (Figure 3B), but negative for cytokeratin 7 (1:400; NeoMarkers, California, USA), cytokeratin 20 (1:100; Leica) and thyroid transcription factor-1 (TTF-1) (1:200; Leica). A percutaneous needle biopsy of the lung mass was then performed, which revealed a moderately-differentiated squamous cell carcinoma (Figure 3C) with an immuno-histochemical profile consistent with that obtained previously for the gallbladder tumor (Figure 3D). Pathological and immunohistochemical examination revealed that the tumors in the lung and gallbladder were of the same histological type. Therefore, the final diagnosis was NSCLC with synchronous gallbladder and brain metastases.

The patient was treated with palliative whole brain radiotherapy but elected not to undergo palliative chemotherapy. The patient died of progressive disease 4 months after diagnosis.

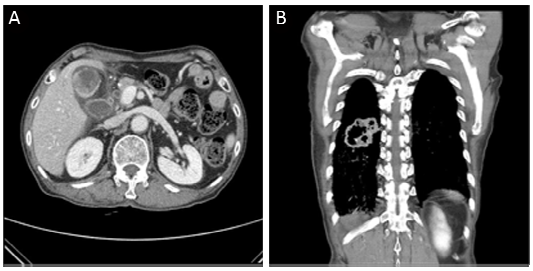

Figure 1. CT scan of the abdomen and chest. **A:** CT scan of abdomen showing irregular wall thickening of the gallbladder; **B:** CT scan of chest showing a 5 cm × 4 cm irregular cavitary mass in the right lower lobe of the lung.

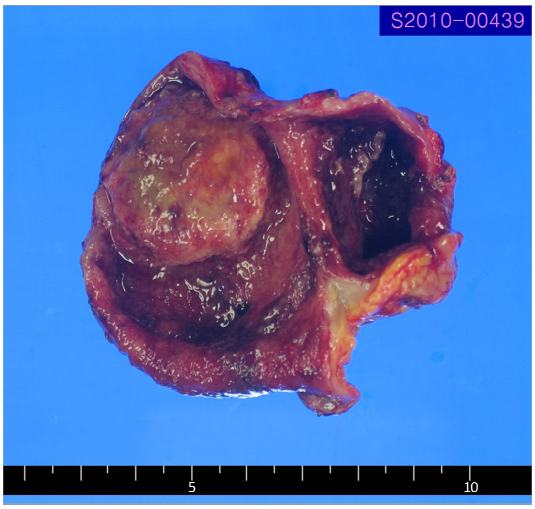

Figure 2. Resected gallbladder specimen. The resected specimen showed a 3.5 cm polypoid tumor capped with necrotic tissue.

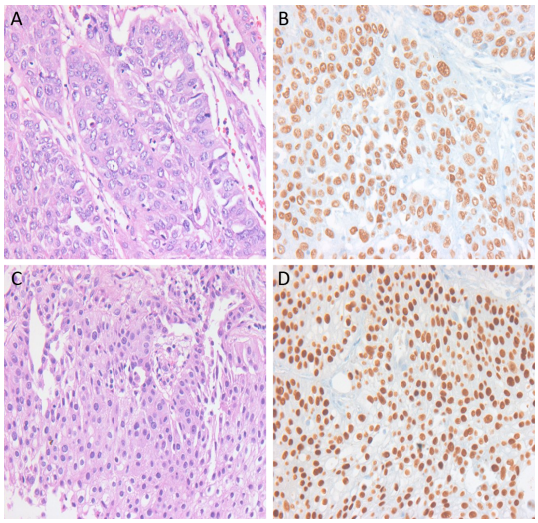

Figure 3. Pathological features of resected gallbladder tumor and needle biopsy of the lung mass. Histological examination of the resected gallbladder tumor **(A)** showed moderately-differentiated squamous cell carcinoma (H & E; ×400), and Immunohistochemistry **(B)** showed that the tumor cells were positive for P63 (×400), but negative for cytokeratin 7, cytokeratin 20 and TTF-1. Histological examination of needle biopsy of the lung mass **(C)** also showed moderately-differentiated squamous cell carcinoma (H & E; ×400), and the immunohistochemical profile **(D)** was consistent (positive for P63, but negative for cytokeratin 7, cytokeratin 20 and TTF-1) with that obtained previously for the gallbladder tumor.

DISCUSSION

Metastases to the gallbladder are thought to be rare,

but were found in 5.8% of cancer patients in a review of one large autopsy series[2]. Different types of cancer can spread to the gallbladder. The tumor most likely to metastasize to the gallbladder is malignant melanoma, which may do so in up to 20% of cases[2, 6]. Other tumors that show clinically significant metastasis to the gallbladder include renal cell carcinoma, adenocarcinoma of the breast, gastric cancer, squamous cell carcinoma of the cervix and hepatocellular carcinoma[7-11]; however, gallbladder metastasis in patients with lung cancer is very rare. Autopsy findings reported by Abrams, et al. indicated involvement of the gallbladder in 1.9% of lung cancer patients[2]. To the best of our knowledge, only three cases of clinical NSCLC metastasis to the gallbladder have been reported in the English language literature[3-5]; these cases, along with the present case, are summarized in Table 1.

Table 1. Reported cases of metastatic non-small cell lung cancer to the gallbladder

Case No.	1	2	3	4
Age (year) / Sex	69/M	45/M	70/M	79/M
Histological type	Squamous cell carcinoma	Adenocarcinoma	Poorly-differentiated NSCLC	Squamous cell carcinoma
Site	Left upper lobe	Right upper lobe	Right upper lobe	Right lower lobe
Immunohistochemistry	NA	TTF-1 (+)	TTF-1 (+)	P63 (+) TTF-1/CK 7/CK 20 (-/-/-)
Type of metastasis	Metachronous	Metachronous	Synchronous	Synchronous
Site of metastasis	Mediastinal LN	Brain	Paratracheal LN	Hilar, paraesophageal LNs, brain
Evidence of cholecystitis	Yes	Yes	Yes	Yes
Evidence of cholelithiasis	Yes	No	No	No
Intervention	Cholecystectomy	Cholecystectomy	Chemotherapy followed by cholecystectomy	Cholecystectomy
Reference	Gutknecht DR[3]	Nassenstein K, et al.[4]	Jeong HT, et al.[5]	Jeong Y, et al.

NSCLC: non-small cell lung cancer; NA: not available; TTF-1: thyroid transcription factor-1; CK: cytokeratin; LN: lymph node.

Primary tumors can metastasize to the gallbladder either by direct invasion of the porta hepatis or by hematogenous spread. Hepatocellular carcinoma and pancreatic tumors have been reported to invade the gallbladder by direct invasion. Hematogenous metastasis to the gallbladder has been reported in association with melanoma and other primary tumors, such as renal cell, cervical, gastric, breast and lung cancer[7-11]. Hematogenous metastases to the gallbladder initially occur as small flat nodules below the mucosal layer and then grow as pedunculated nodules, rarely surpassing several millimeters in size[10]. This explains why most gallbladder metastases do not cause any symptoms; gallbladder metastases are usually diagnosed by imaging performed for surveillance or staging purposes. Only few metastatic tumors within the gallbladder manifest symptoms. The most frequent symptomatic presentation is acute cholecystitis. Indeed, in all cases of NSCLC gallbladder metastasis described in Table 1, as in the present case, patients presented with abdominal pain diagnosed as acute cholecystitis related to the metastatic involvement of the gallbladder. These findings may be due to the aggressiveness of lung cancer. NSCLC progresses more rapidly than malignant melanoma or renal cell carcinoma, which shows a high incidence of symptomatic gallbladder metastases.

The identification of primary vs. secondary gallbladder cancer can be challenging. Since primary tumors of the gallbladder often coexist with gallstones, acalculous gallbladder is more consistent with metastasis than a primary tumor[7]. Most of the patients with gallbladder metastases of NSCLC presented with acalculous cholecystitis, except one case: in 1997, Gutknecht reported the case of a patient with squamous cell carcinoma of the lung who developed acute cholecystitis and whose gallbladder contained two pigmented calculi[3]. Histologically, primary tumors of the gallbladder are most often adenocarcinomas; however, immunohistochemical staining is necessary for precise differential diagnosis between primary and metastatic gallbladder tumor[11]. Although there is no "lung-specific tumor marker", TTF-1 can be used to discriminate between a primary lung tumor and a primary gallbladder tumor with a reasonable degree of certainty[12]. Two patients with gallbladder metastases of NSCLC were diagnosed by immunohistochemical TTF-1 positivity[4, 5]; however, TTF-1 lacks sensitivity for squamous cell carcinoma or large cell carcinoma, and is negative in more than 90% of lung squamous cell carcinomas, which was diagnosis in the present case.

Since it is a rare metastatic site, treatment options for metastatic tumors within the gallbladder are not clear. Whether the gallbladder tumor is primary or secondary, cholecystectomy is necessary in patients with symptomatic gallbladder to avoid symptoms or complications. All the patients with gallbladder metastases of NSCLC listed in Table 1 underwent

cholecystectomy because of acute cholecystitis. In asymptomatic cases, cholecystectomy may achieve longer survival in patients with an isolated, resectable metastatic lesion. Aoki, et al. report that outcomes for patients with solitary gallbladder metastasis who underwent cholecystectomy appear to be similar to those of patients with renal cell carcinoma and a solitary metastatic site treated with metastatectomy[11].

Our experience and review of the published cases suggests the need for careful evaluation of abdominal symptoms and closer surveillance of the gallbladder during routine imaging examinations in NSCLC patients. Although metastatic gallbladder involvement is rare in NSCLC patients, NSCLC has the potential to metastasize to the gallbladder, and clinicians caring for patients with NSCLC who present with signs or symptoms of cholecystitis should be alert to the possibility of gallbladder metastases.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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