

Case Report

Long-Term Survival Following Extended Cholecystectomy for Synchronous Gallbladder and Regional Lymph Node Metastasis of Lung Adenocarcinoma, with Subsequent Pulmonary Lobectomy

Mao Yoshikawa^{a,b*}, and Hiroyuki Tao^b

^aDepartment of General Thoracic Surgery, Okayama University Hospital, Okayama 700-8558, Japan,

^bDepartment of Thoracic Surgery, Japanese Red Cross Society Himeji Hospital, Himeji, Hyogo 670-8540, Japan

An 80-year-old male underwent an extended cholecystectomy for node-positive gallbladder adenocarcinoma. Two weeks later, hemoptysis revealed a left hilar tumor obstructing the bronchus, which was diagnosed as adenocarcinoma. Three months post-cholecystectomy, a left upper pulmonary lobectomy was performed. Histological similarity and positive thyroid transcription factor-1 (TTF-1) immunostaining in both tumors confirmed lung adenocarcinoma with gallbladder metastasis. Despite the generally poor prognosis for gallbladder metastasis from lung cancer, the patient achieved 3 years of survival. Patients with isolated synchronous gallbladder metastasis from lung cancer may benefit from oligometastectomy.

Key words: gallbladder metastasis, lung cancer, oligometastatic disease

Non-small cell lung cancer (NSCLC) is usually asymptomatic and is often detected based on symptoms from metastatic lesions. The most frequent metastatic sites for lung cancer include the liver, nervous system, bones, respiratory system, and adrenal glands [1]. Gallbladder metastasis from lung cancer is extremely rare, with a reported frequency of only 1.9% in autopsy cases [2]. While systemic therapy is the standard treatment for lung cancer with distant metastases, there has been ongoing debate about whether local treatments, such as surgery or radiotherapy, can be considered when metastatic lesions are limited [3]. Retrospective studies of local therapy for solitary brain or adrenal metastases have shown favorable outcomes [4,5]. Although there have been reports on the resection of gallbladder metastases from lung cancer for symptomatic palliation [6], long-term survival following simultaneous resection of gallbladder metastasis and

primary NSCLC is exceedingly rare. Here, we report a case of hilar lung adenocarcinoma that manifested after the resection of a gallbladder metastasis identified due to right hypochondriac pain.

Case Presentation

An 80-year-old male presented with right hypochondriac pain. An abdominal computed tomography (CT) scan revealed a 10 mm diameter mass at the gallbladder fundus and regional lymph node enlargement (Fig. 1). No lung field lesions were noted on plain chest CT, except for left hilar enlargement, prompting a bronchoscopy after gallbladder treatment. Diagnosed with gallbladder cancer and portal (#12p) lymph node metastasis, the patient underwent an extended cholecystectomy. The postoperative course was uneventful, and the patient was discharged on the 18th postoperative day. Pathological analysis indicated poorly differ-

Received November 1, 2024; accepted March 18, 2025.

*Corresponding author. Phone: +81-86-235-7265; Fax: +81-86-235-7269
E-mail: me421099@s.okayama-u.ac.jp (M. Yoshikawa)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

entiated adenocarcinoma within the mucosal lamina propria and #12p lymph node metastasis.

Two weeks later, the patient was readmitted due to hemoptysis. An enhanced chest CT scan revealed obstruction of the left upper division of the bronchus, a left hilar tumor measuring 12 mm in diameter, and neighboring hilar lymph node enlargement (Fig. 2). A bronchoscopic biopsy confirmed adenocarcinoma. Positron emission tomography showed no FDG accumulation outside the pulmonary tumor and adjacent lymph nodes, and no metastatic lesions were detected on brain MRI. We considered lung adenocarcinoma as a second primary cancer, diagnosing it as cT1bN1M0. Subsequently, a left upper lobectomy with pulmonary artery plasty was performed via open thoracotomy 3 months after the cholecystectomy. The postoperative course was uneventful, except for transient atrial fibrillation on the 6th postoperative day. The patient was discharged on the 14th postoperative day. Pathological

examination identified the lung tumor as solid adenocarcinoma with pleomorphic atypical cell proliferation, which directly invaded the bronchial wall, pulmonary artery, and left upper lobar lymph nodes (#12u), with negative tumor margins also observed.

Based on histological similarities between the lung and gallbladder tumors, we suspected a metastasis between the two (Fig. 3A-C). Immunostaining was positive for thyroid transcription factor-1 (TTF-1) in the lung, gallbladder, and regional lymph node tumors (Fig. 3D-F). The final diagnosis was lung adenocarcinoma with gallbladder metastasis, classified as pathological T1bN1M1c stage IVB. The tumors exhibited high PD-L1 expression (80%).

Considering the patient's age and comorbidities, adjuvant therapy was not administered, and strict observation was continued. Currently, 3 years after chest surgery, the patient remains well, with no signs of recurrence.

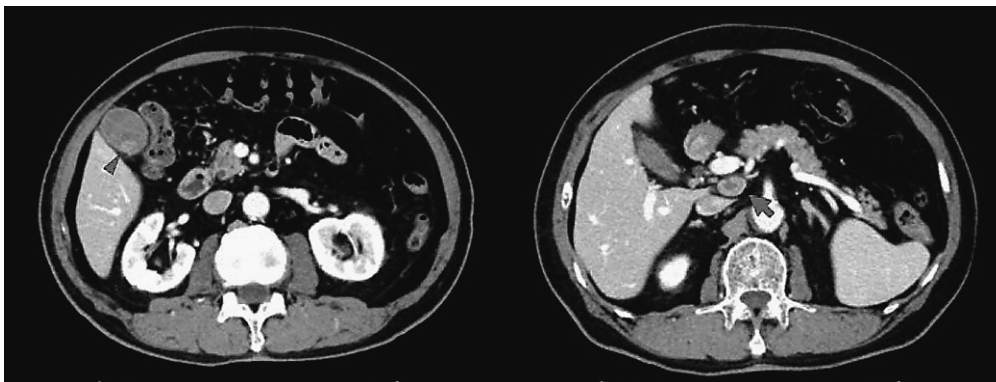


Fig. 1 Abdominal computed tomography showing a polypoid nodule on the gallbladder wall (arrowhead) and an enlarged regional lymph node with internal necrosis (arrow).

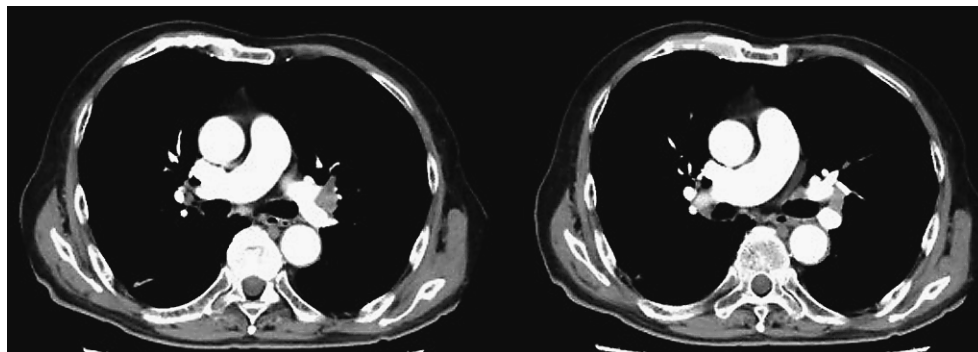


Fig. 2 Chest computed tomography showing a hilar tumor obstructing the left upper division bronchus.

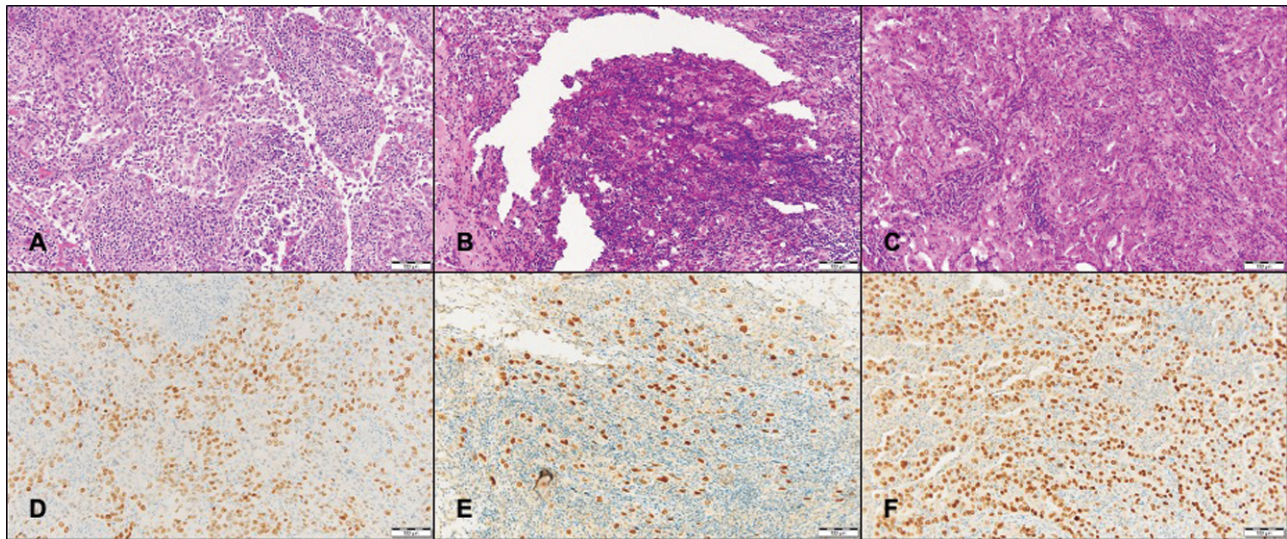


Fig. 3 Histological findings of lung (A), gallbladder (B), and portal (#12p) lymph node (C) tumors via H&E staining, showing similar atypical cells with weak cell-cell connectivity and pleomorphic features, consistent with poorly differentiated adenocarcinoma. The tumors of the lung (D), gallbladder (E), and portal (#12p) lymph node (F) are positive for TTF-1 staining. Scale bars: A-F, 100 μ m.

Discussion

To our knowledge, this is the first report of gallbladder metastasis accompanied by regional lymph node metastasis in a patient with lung cancer. Two possible patterns of metastasis to the gallbladder's regional lymph nodes include hematogenous spread from the gallbladder tumor and lymphatic flow from the lungs. Although the frequency is as low as 2.5%, gallbladder cancer within the mucosal lamina propria can metastasize to regional lymph nodes due to the absence of muscular and submucosal layers in the gallbladder wall [7]. Ryu *et al.* found that most NSCLC patients with abdominal lymph node metastasis had positive nodes draining directly into the trunk connected to the cisterna chyli, suggesting that the thoracic duct could be a potential route for lymphatic spread to the abdomen [8]. They also reported that pericholedochal lymph node metastasis is extremely rare. In this case, lymph node 8 (a common hepatic artery), which is closer to the thoracic duct, showed no metastatic lesions. Therefore, we hypothesize that hematogenous metastasis from lung cancer to the gallbladder occurred first, followed by regional lymph node metastasis from the gallbladder.

Metastatic lesions in the gallbladder from other organ cancers typically grow slowly as submucosal

nodules and often do not involve gallstones [9]. Consequently, these tumors are usually asymptomatic and are often detected during imaging examinations for surveillance or staging. In previous reports of gallbladder metastasis from lung cancer associated with acute cholecystitis [6,9-13], only 1 of 6 cases involved gallstones, while another case was attributed to tumor-induced obstruction of the gallbladder neck, and the remaining 4 cases showed no clear correlation between gallbladder metastasis and acute cholecystitis [6,9]. Because the gallbladder metastasis in our case was located at the bottom of the gallbladder, obstruction of the gallbladder neck by the tumor seemed unlikely. The reason for the development of acalculous cholecystitis in patients with gallbladder metastasis from original cancers remains unclear.

In adenocarcinoma cases, both primary lung and distant gallbladder tumors may be misdiagnosed as independent primary cancers because adenocarcinoma is the predominant histological type of primary gallbladder cancer. Immunostaining for TTF-1 can help indicate the possibility of metastasis from lung adenocarcinoma, as TTF-1 is frequently positive in lung adenocarcinoma but not in primary gallbladder adenocarcinoma [14]. To date, the relationship between gallbladder metastasis and lung cancer histology has not been clarified.

Despite recent advancements in outcomes for patients with metastatic lung cancer using targeted therapy and immunotherapy [15], selected oligometastatic patients might benefit from local treatments, given the challenges of drug resistance. Our case appears unique in that long-term survival was achieved compared to previous reports [6]; however, if the gallbladder is a solitary synchronous metastatic site from NSCLC, there may be justification for considering surgical resection of both the primary lung cancer and gallbladder metastasis. We emphasize that regional lymph node dissection should also be considered when surgery for gallbladder metastasis is performed.

Conclusions

This is the first report of gallbladder metastasis accompanied by regional lymph node metastasis in a patient with lung cancer. Surgical resection of both the primary lung cancer and gallbladder metastasis may be a viable therapeutic option for selected patients. Regional lymph node dissection should also be considered in cases where surgery for gallbladder metastasis is indicated.

Acknowledgments. We would like to thank KN International (<https://www.kninter.co.jp>) and Editage (<https://www.editage.com>) for English language editing.

References

1. Riihimäki M, Hemminki A, Fallah M, Thomsen H, Sundquist K, Sundquist J and Hemminki K: Metastatic sites and survival in lung cancer. *Lung Cancer* (2014) 86: 78–84.
2. Abrams HL, Spiro R and Goldstein N: Metastasis in carcinoma; analysis of 1000 autopsied cases. *Cancer* (1950) 3: 74–85.
3. Chen YH, Ho UC and Kuo LT: Oligometastatic Disease in Non-Small-Cell Lung Cancer: An Update. *Cancers* (2022) 14: 1350.
4. Hu C, Chang EL, Hassenbusch SJ 3rd, Allen PK, Woo SY, Mahajan A, Komaki R and Liao Z: Nonsmall cell lung cancer presenting with synchronous solitary brain metastasis. *Cancer* (2006) 106: 1998–2004.
5. Solaini L, Ministrini S, Tomasoni M, Merigo G, Gaverini G, Bertoloni GP and Tiberio GA: Adrenalectomy for metastasis: long-term results and predictors of survival. *Endocrine* (2015) 50: 187–192.
6. Imaoka K, Satoh D, Oshita K, Yano T, Kubota T, Ishida M, Choda Y, Yoshimitsu M, Nakano K, Harano M, Matsukawa H, Idani H, Shiozaki S and Okajima M: Acute cholecystitis caused by gallbladder metastasis from non-small cell lung cancer: a case report. *Clin J Gastroenterol* (2021) 14: 351–357.
7. Lee SE, Jang JY, Lim CS, Kang MJ and Kim SW: Systematic review on the surgical treatment for T1 gallbladder cancer. *World J Gastroenterol* (2011) 17: 174–180.
8. Ryu W, Lee MK, Park MH, Hyun IY, Lee M, No EJ, Yong SJ, Kim JS, Lim JH and Ryu JS: Abdominal lymph node metastasis by lymphatic spread through the thoracic duct in patients with non-small-cell lung cancer. *Thorac Cancer* (2021) 12: 2078–2084.
9. Jeong YS, Han HS, Lim SN, Kim MJ, Han JH, Kang MH, Ryu DH, Lee OJ, Lee KH and Kim ST: Gallbladder metastasis of non-small cell lung cancer presenting as acute cholecystitis. *Chin J Cancer Res* (2012) 24: 249–252.
10. Gutknecht DR: Metastatic lung cancer presenting as cholecystitis. *Am J Gastroenterol* (1998) 93: 1986–1989.
11. Nassenstein K and Kissler M: Gallbladder metastasis of non-small cell lung cancer. *Onkologie* (2004) 27: 398–400.
12. Jeong HT, Yun M, Hong HS, Lee JD and Kim KW: Unusual gallbladder metastasis from non-small cell lung cancer detected by F-18 FDG PET/CT with intravenous contrast enhancement. *Clin Nucl Med* (2010) 35: 635–636.
13. Yoshida Y, Shingyoji M, Ashinuma H, Itakura M and Tatsumi K: Coincidental detection of gallbladder metastasis of lung adenocarcinoma. *Jpn J Lung Cancer* (2014) 54: 73–77 (in Japanese).
14. Jagirdar J: Application of immunohistochemistry to the diagnosis of primary and metastatic carcinoma to the lung. *Arch Pathol Lab Med* (2008) 132: 384–396.
15. Arbour KC and Riely GJ: Systemic therapy for locally advanced and metastatic non-small cell lung cancer: a review. *JAMA* (2019) 322: 764–774.