（肺癌．2014;54:73-77）

CASE REPORT

Coincidental Detection of Gallbladder Metastasis of Lung Adenocarcinoma

Yasushi Yoshida[1]; Masato Shingyoji[1]; Hironori Ashinuma[1];
Meiji Itakura[1]; Koichiro Tatsumi[2]

ABSTRACT —— ***Background.*** It is uncommon to detect gallbladder metastasis of lung cancer prior to death. ***Case.*** A 49-year-old male with a diagnosis of primary lung adenocarcinoma T1bN3M1b stage IV and a L858R point mutation was referred to our department for chemotherapy. The course of chemotherapy was uneventful, and he achieved stable disease. The treatment regimen was subsequently switched to maintenance therapy; however, the patient was suddenly admitted for acute cholecystitis. Conservative treatment was ineffective, and laparoscopic cholecystectomy was performed. A histopathological examination of the resected gallbladder revealed metastasis of the lung adenocarcinoma. ***Conclusions.*** Physicians should consider the possibility of gallbladder metastasis in cases of cholecystitis among lung cancer patients.

(*JJLC.* 2014;54:73-77)

KEY WORDS —— Lung adenocarcinoma, Gallbladder metastasis, Cholecystitis

INTRODUCTION

Evaluating the stage of lung cancer is important in order to avoid useless surgical intervention. Common sites for lung cancer metastasis include the adrenal glands, liver, brain and skeletal system. However, metastasis to the gallbladder is rarely detected, especially while the patient is alive, with the incidence of gallbladder metastasis in autopsy cases reported to be as low as 1.9%.[1] In previously reported cases, metastasis was detected via investigations of acute cholecystitis due to the presence of metastatic nodules.[2,3] We encountered a patient diagnosed with lung adenocarcinoma who developed acute cholecystitis in whom a histopathological examination of the resected gallbladder coincidentally detected small metastases of lung cancer to the gallbladder.

CASE PRESENTATION

A 49-year-old male patient was referred to the Department of Thoracic Disease at Chiba Cancer Center for the treatment of lung adenocarcinoma. One month prior to presentation, a medical checkup revealed an abnormal shadow on a chest X-ray and multiple liver masses on abdominal ultrasonography. The patient was therefore transferred to the hospital, where a chest X-ray showed a nodular shadow in the left upper lung field (Figure 1) and chest computed tomography (CT) demonstrated a mass measuring 22 × 20 mm in left S^3b, as well as trivial pericardial effusion and lymphadenopathy in #4L, #5, #11L and the left supraclavicular region. Abdominal CT confirmed multiple masses in the liver suspicious of metastases. Subsequently, whole-body ^{18}F-2-deoxy-fluoro-D-glucose (FDG) positron emission tomography (PET) showed an intense uptake corresponding to the lesions on CT (Figure 2, 3). Bronchoscopy was performed, and the histology of the transbronchial lung specimens was consistent with that of lung adenocarcinoma. An epidermal growth factor receptor (EGFR) exon 21 point mutation (L858R) was also identified in the specimens. The final diagnosis was primary lung adenocarcinoma T1bN3M1b stage IV with a L858R point mutation. The patient requested to be referred to our department to receive chemotherapy.

At presentation, a physical examination revealed no

[1]Division of Thoracic Disease, Chiba Cancer Center, Japan; [2]Department of Respirology, Graduate School of Medicine, Chiba University, Japan.

Reprints: Yasushi Yoshida, Division of Thoracic Disease, Chiba Cancer Center, 666-2 Nitona, Chiba City, Chiba 260-8717, Japan (e-mail: pmdht627@yahoo.co.jp).

Received November 24, 2013; accepted March 7, 2014.

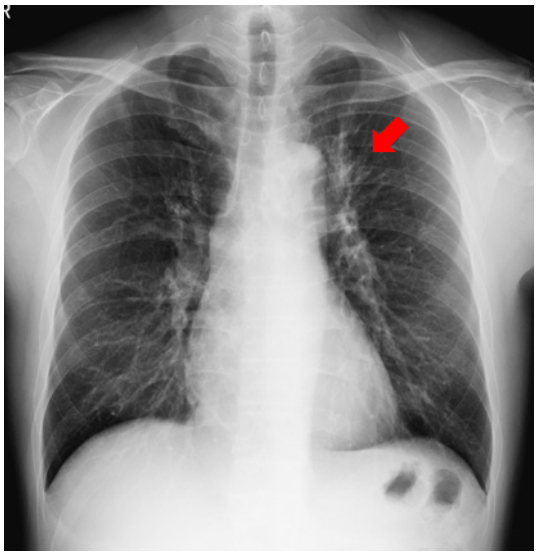

Figure 1. Chest X-ray showing a nodule shadow on the mediastinal side of the left upper lung field (arrow).

special findings, including superficial lymphadenopathy. His medical history was unremarkable. He had smoked one package of cigarettes per day starting at 22 years of age until the medical checkup detected the above abnormalities. The laboratory data showed remarkable elevations of CEA (1,843.0 ng/ml), CA19-9 (3,781.09 U/ml) and SLX (820 U/ml), with slight elevation of NSE (12 ng/ml). Treatment with carboplatin, paclitaxel and bevacizumab was subsequently administered as first-line chemotherapy. After six cycles of treatment, CT showed stable disease according to the Response Evaluation Criteria in Solid Tumor (RECIST), and the CEA level decreased remarkably (267 ng/ml). The only adverse reaction was bilateral lower limb pain of grade 2, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Therefore, maintenance therapy with bevacizumab alone was initiated. After four consecutive cycles of treatment, the pa-

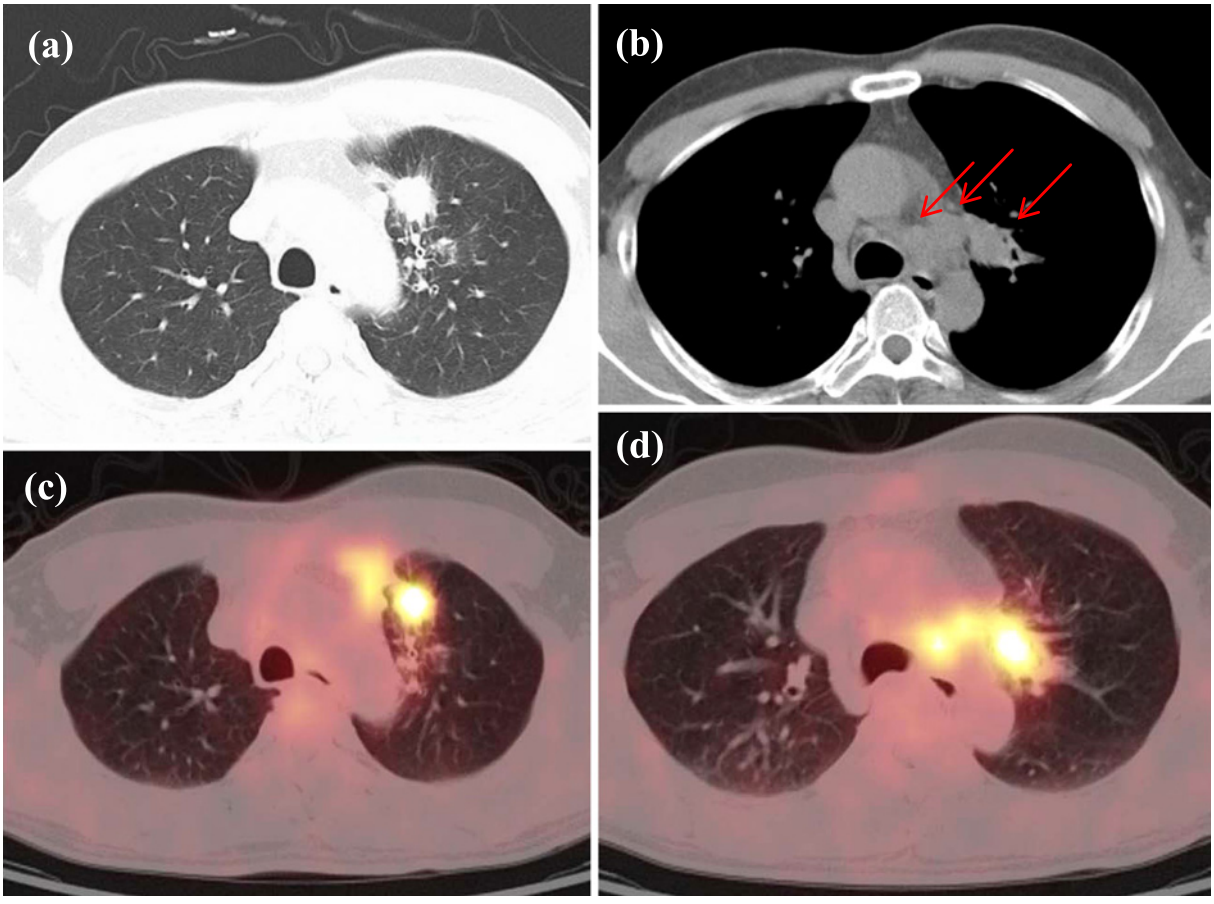

Figure 2. **a, b:** Chest computed tomography showing a nodule measuring 22×21 mm in left S^3, as well as #4L, #5 and #11L lymphadenopathy (arrows). **c, d:** A PET/CT scan showing an avid FDG uptake in the nodule **(c)** with lymphadenopathy **(d)**.

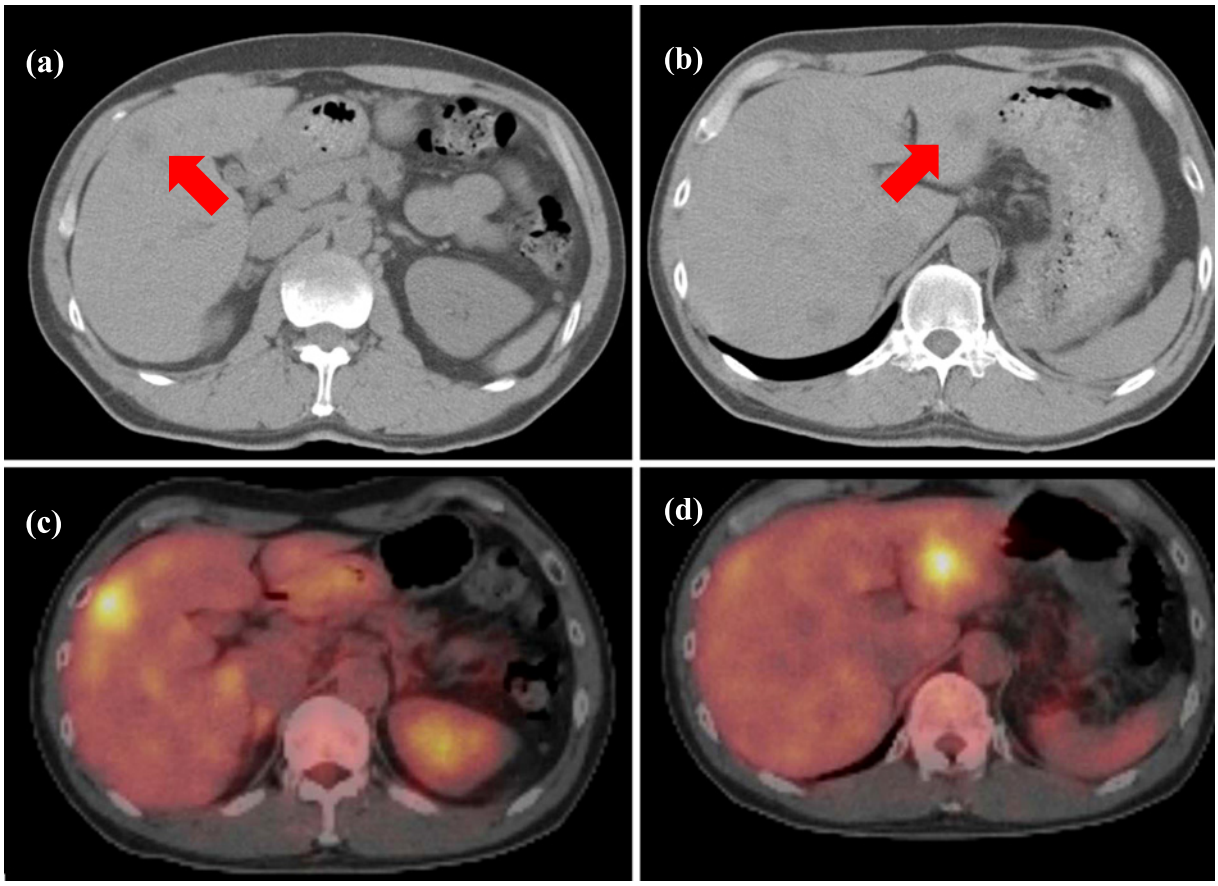

Figure 3. **a, b:** Abdominal CT showing multiple round, low-density areas in the liver (arrows). **c, d:** A PET/CT scan showing an intense FDG uptake corresponding to the lesions observed on CT.

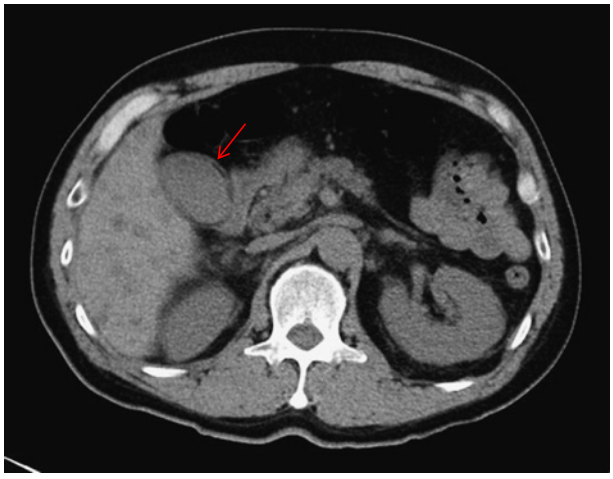

Figure 4. An enhanced abdominal CT scan showing dilatation of the gallbladder with a thick gallbladder wall (arrow).

tient developed acute abdominal pain in the right upper region and was admitted to the emergency department of our hospital. Murphy's sign was positive on a physical examination, and the laboratory data showed a white blood cell count of 12,000/μl (neutrophils: 82.9%), an aspartate aminotransferase level of 118 IU/*l*, an alanine aminotransferase level of 137 IU/*l*, a γ-glutamyl transpeptidase level of 1,236 IU/*l*, an alkaline phosphatase level of 1,287 IU/*l*, a total bilirubin level of 1.0 mg/dl, a C-reactive protein (CRP) level of 16.6 mg/dl and a CEA level of 11,945.6 ng/ml. Enhanced abdominal CT (Figure 4) disclosed a distended gallbladder with obvious wall thickness, although no gallstones were detected. Initially, intravenous antibiotics were administered; however, the patient's condition did not sufficiently improve. Percutaneous transhepatic gallbladder drainage (PTGBD) was therefore performed four days later. The patient's condition transiently was ameliorated, although the CRP level again gradually increased. Finally, he underwent laparoscopic cholecystectomy one week after PTGBD. The resected gallbladder measured 6.0 × 3.0 × 2.5 cm in size. Histologically, the gallbladder wall was remarkably thickened due to edema, while floating

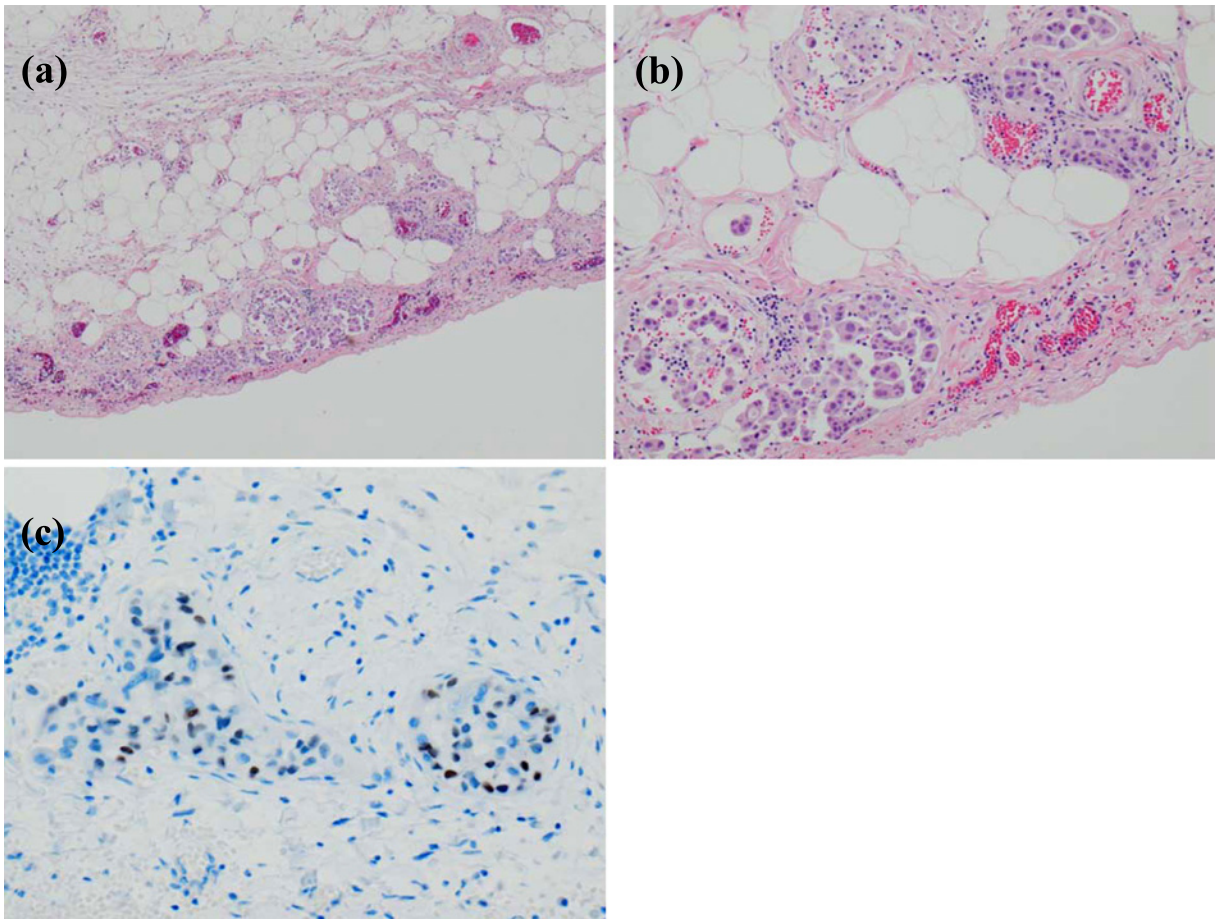

Figure 5. **a, b:** Histological findings of the resected gallbladder showing a significantly thickened gallbladder wall due to edema, as well as atypical cells with round, densely stained nuclei and fine chromatin suspended in the lymphoid duct forming a small papillary lump (hematoxylin and eosin staining). Magnification 10×(**a**) and 20×(**b**). **c:** Immunohistochemical study of TTF-1 showing positive staining for adenocarcinoma cells, 20×.

atypical cells with round densely stained nuclei and fine chromatin formed a papillary mass in the lymphoid duct (Figure 5). Immunohistochemically, the tumor cells were positive for thyroid transcription factor-1 (TTF-1), which strongly suggested that these cells had originated from the lung adenocarcinoma. The patient developed multiple cerebral infarctions, likely due to dehydration, one week after cholecystectomy, although no apparent cerebral metastasis was noted. He received palliative care for five months before ultimately dying of the disease.

DISCUSSION

In one large autopsy study of patients with known malignancies, metastatic involvement of the gallbladder was found in only 5.8% of patients, and the frequency was especially low in lung cancer patients, at 1.9%.[1] In living patients, the detection of metastasis to the gallbladder is even more rare, and only limited case reports are found in the literature. Some reports have described melanoma as being the most prevalent malignancy with a tendency to metastasize to the gallbladder, exhibiting a prevalence of up to 20% of cases.[1,4] Regarding metastasis to the gallbladder, another reported stated that primary malignancies tend to originate from various organs, including the stomach, colorectum, liver, kidney and skin.[5] With respect to lung cancer, our search identified only four cases reported in the English literature.[2,3,6,7] Lung cancer undoubtedly can spread to any organ; however, it is extremely unusual to observe metastasis to the gallbladder while the patient remains alive.

Metastasis to the gallbladder may occur via the hematogenous route or direct invasion.[3] Hematogenous spread is expected to be the most probable route by

which lung cancer metastasizes to the gallbladder. In our review of the literature regarding lung cancer, all reports suggested that metastasis to the gallbladder occurs via the hematogenous route. In the present case, metastasis to the gallbladder may have occurred via the lymphogenous, in addition to the hematogenous, route based on the results of the histological examination, as histologically, we found tumor cells only in the lymphoid ducts, with no apparent lesions through which the tumor cells could have penetrated and invaded directly from the serosa side.

All previous reports have documented the development of acute cholecystitis, which is closely related to metastatic involvement of the gallbladder. Usually, hematogenous metastasis to the gallbladder initially manifests as a small flat nodule below the mucosal layer, which then grows to a pedunculated nodule measuring less than several millimeters in size.[8] Such small metastatic lesions rarely cause overt symptoms. Consequently, it may be impossible to make a clinical diagnosis of early metastasis to the gallbladder. In most previously reported cases, gallbladder metastasis was detected due to the development of acute cholecystitis induced by obstruction of the gallbladder by metastatic cancer cells. In the present case, although the volume of malignant cells was not so bulky as to cause acute cholecystitis, the gallbladder metastasis may have been associated with the acute cholecystitis, considering the lack of gallstones.

When gallbladder malignancy is diagnosed, it is often a challenge to differentiate metastatic gallbladder carcinoma from primary gallbladder carcinoma. The majority of patients with primary gallbladder cancer present with advanced disease showing extension and metastasis to the liver and lymph nodes; the poor prognosis of such tumors is widely recognized.[9] The most common histologic type of primary gallbladder cancer is adenocarcinoma (75.8%), with other less common types being papillary adenocarcinoma (5.8%) and mucinous (4.8%), adenosquamous (3.6%) and squamous (1.7%) carcinoma.[10] Among the gallbladder metastasis cases reported to date, including the present case, two involved adenocarcinomas, two involved squamous cell carcinomas and one involved poorly-differentiated non-small cell lung cancer (NSCLC). Therefore, histology is not useful for differentiating between these lesions. In one case of adenocarcinoma and one case of poorly-differentiated NSCLC, the immunohistochemical finding of TTF-1 positivity was used to make a diagnosis of gallbladder metastasis of lung cancer. In addition, in the present case, the tumor cells in the lymphoid duct were clearly positive for TTF-1, thereby confirming that the gallbladder adenocarcinoma originated from lung adenocarcinoma. TTF-1 plays an essential role in discriminating cancer of lung origin, with a high degree of reliability,[11] with the exception of cases of squamous cell carcinoma.

In conclusion, we herein reported an unusual case of gallbladder metastasis of lung cancer detected while the patient was alive. When a patient with lung cancer presents with acute cholecystitis, the potential for rare metastasis to the gallbladder should be considered.

本論文内容に関連する著者の利益相反：なし

REFERENCES

1. Abrams HL, Spiro R, Goldstein N. Metastases in carcinoma; analysis of 1000 autopsied cases. *Cancer.* 1950;3:74-85.
2. Gutknecht DR. Metastatic lung cancer presenting as cholecystitis. *Am J Gastroenterol.* 1998;93:1986-1989.
3. Jeong YS, Han HS, Lim SN, Kim MJ, Han JH, Kang MH, et al. Gallbladder Metastasis of Non-small Cell Lung Cancer Presenting as Acute Cholecystitis. *Chin J Cancer Res.* 2012;24:249-252.
4. Goldin EG. Malignant melanoma metastatic to the gallbladder. Case report and review of the literature. *Am Surg.* 1990;56:369-373.
5. Yoon WJ, Yoon YB, Kim YJ, Ryu JK, Kim YT. Metastasis to the gallbladder: a single-center experience of 20 cases in South Korea. *World J Gastroenterol.* 2009;15:4806-4809.
6. Nassenstein K, Kissler M. Gallbladder metastasis of non-small cell lung cancer. *Onkologie.* 2004;27:398-400.
7. Jeong HT, Yun M, Hong HS, Lee JD, 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.
8. Nojima H, Cho A, Yamamoto H, Nagata M, Takiguchi N, Kainuma O, et al. Renal cell carcinoma with unusual metastasis to the gallbladder. *J Hepatobiliary Pancreat Surg.* 2008;15:209-212.
9. Beltz WR, Condon RE. Primary carcinoma of the gallbladder. *Ann Surg.* 1974;180:180-184.
10. Henson DE, Albores-Saavedra J, Corle D. Carcinoma of the gallbladder. Histologic types, stage of disease, grade, and survival rates. *Cancer.* 1992;70:1493-1497.
11. Jagirdar J. Application of immunohistochemistry to the diagnosis of primary and metastatic carcinoma to the lung. *Arch Pathol Lab Med.* 2008;132:384-396.