Case Report

Origin of Metastatic Colonic Adenocarcinoma Suspected from a Primary Lung Cancer: A Case Report and Literature Review

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Lung cancer with gastrointestinal metastasis is uncommon; however, when such metastasis occurs, the small bowel is the most common metastatic site. There are few case reports of colonic metastasis developing from a primary lung adenocarcinoma. We report a case of metastatic adenocarcinoma in the colon, complicated by bowel obstruction and hydropneumothorax, in a 67-year-old woman. The primary cancer was highly suspected to have originated from the lung, based on immunohistochemistry assessments. Immunohistochemistry was positive for thyroid transcription factor-1 and cytokeratin 7, but negative for cytokeratin 20. The published literature, focusing on the differential diagnosis of the origin of the primary malignancy using immunohistochemistry, was reviewed.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2015;26:38-43*]

Key Words
Adenocarcinoma;
Lung;
Colon;
Metastasis;
Immunohistochemistry

Lung cancer is the leading cause of death, worldwide. Gastrointestinal (GI) metastasis is rarely encountered, but when it does occur, most cases involve metastasis to the small intestine. Metastasis to the colon or rectum is rare, based on our review of the literature. We present a patient with metastatic adenocarcinoma in the colon, complicated with an obstruction. In addition, we reviewed the diagnosis and treatment of similar cases, with an emphasis on the application of immunohistochemistry to assist in the differentiation between primary or metastatic adenocarcinoma in the GI tract.

Case Report

A 67-year-old woman was admitted to our emergency department with complaints of diarrhea, ab-

Received: June 13, 2014. Accepted: November 17, 2014.
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dominal fullness, tenesmus, and recent weight loss. Abdominal contrast-enhanced computed tomography (CT) showed a discrepancy in the caliber of the sigmoid colon and the upper rectum (Fig. 1), but enlarged lymph nodes, hepatic lesions, or ascites were not observed. Colonoscopy was performed, but failed to approach the obstructive level. Right hydropneumothorax was also found on a chest radiograph (Fig. 2).

A T-loop colostomy for the release of the obstruction and chest tube intubation were performed. Her right lung did not recover from the collapse, and a lung malignancy was suspected. A hidden neoplasm in the collapsed right lung could not be completely ruled out, based on chest contrast-enhanced CT, after chest tube intubation (Fig. 3A). There was no evidence of thyroid or breast neoplasms based on the chest contrast-enhanced CT scan or physical examination. Tumor marker tests revealed the levels of CEA (124.72 ng/mL), CA-125 (57.7 U/mL), and CA 19-9 (3.24 U/mL); a pleural effusion smear showed adenocarcinoma.

Ten days after T-loop colostomy, an anterior resection of the rectum and segmental resection of transverse colon were performed under the impression of synchronous primary lung and colon cancer. No abnormal lesions were detected, during the operation, over her genital tract. Adenocarcinoma of the lung, with metastasis to the transverse colon and rectum, was highly suspected based on the immunohistochemical staining results showing the expression of thyroid transcription factor (TTF)-1, cytokeratin (CK) 7, and the abscence of CK20, gross cystic disease fluid protein 15 (*GCDFP-15*), estrogen receptor, progesterone receptor or thyroglobulin expression (Fig. 4). No lung tumor tissue was available due to the patient's refusal of a bronchoscopy or surgical biopsy. A chest contrast-enhanced CT, performed 4 months after the operation, showed an enhanced central type pulmonary carcinoma over right lung with progression of the invasion to the mediastinum, and media-

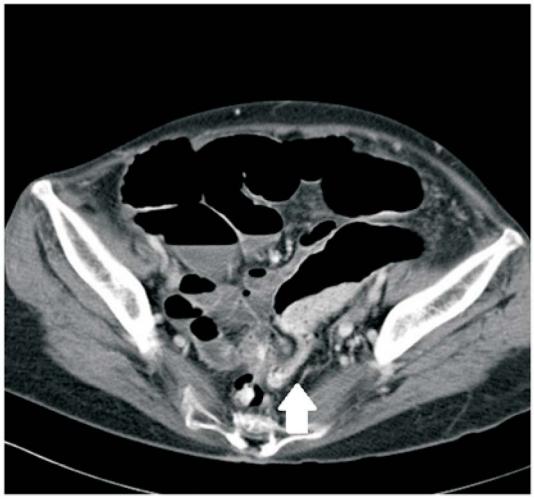

Fig. 1. Contrast-enhanced computed tomography of the abdomen showing a discrepancy in the caliber of the sigmoid colon and the upper rectum (arrow).

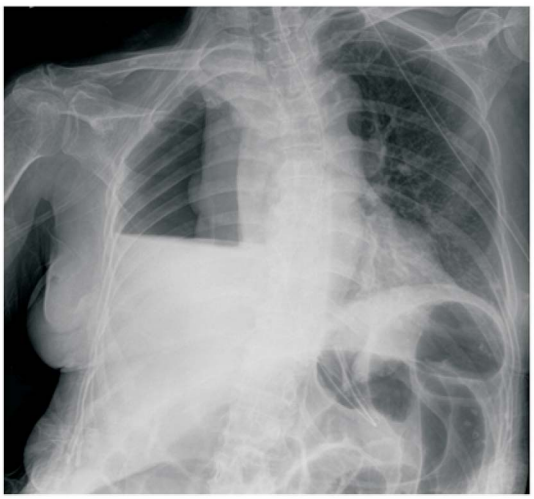

Fig. 2. A chest radiograph reveals right hydropneumothorax.

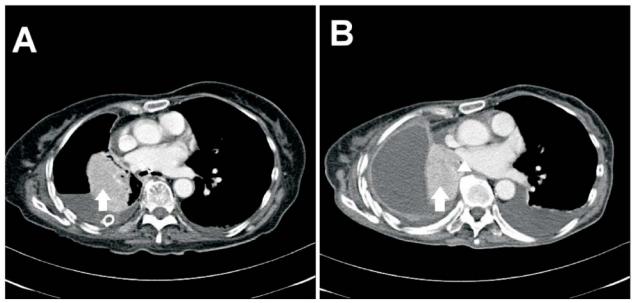

Fig. 3. (A) Contrast-enhanced computed tomography of the chest shows persistent collapse of right lung after chest tube intubation (arrow). (B) Contrast-enhanced computed tomography of the chest, performed 4 months after the operation, reveals a contrast-enhanced carcinoma over the right lung (arrow) and tumor invasion to the mediastinum (arrowhead)

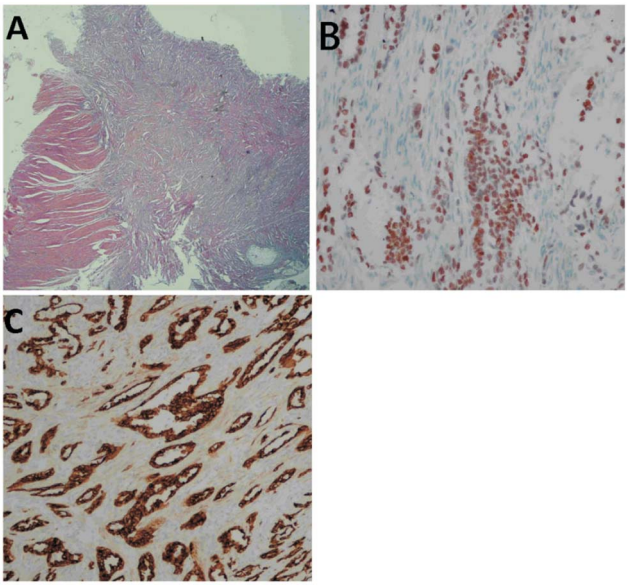

Fig. 4. (A) Hematoxylin and eosin-stained pathological section from the colonic tumor reveals neoplastic glandular cells, with tubular and papillary infiltrates through the serosa to the muscular layer. (B) Immunohistochemical stain of the surgical specimen of the colonic tumor showing positive TTF-1 expression. (C) Immunohistochemical stain of the surgical specimen of the colonic tumor is positive for cytokeratin 7 expression.

stinal lymphadenopathies (Fig. 3B). Although chemotherapy was prescribed, the patient died of respiratory failure 9 months after the operation.

Discussion

Few cases of lung cancer with GI metastasis have been diagnosed prior to the patient's death. Previous reports have indicated that the incidence of GI metastasis is 0.19-1.77%,[1-4] although the prevalence at autopsy has been reported to be approximately 4.7-14.0%.[5,6] Lung cancer patients demonstrating GI metastasis are deemed to be in the late stages of disease,[1,7-9] with the average time from a diagnosis of GI metastasis to death being approximately 3-4 months.[1-3] However, Kim et al. reported a patient with sarcomatoid carcinoma of the lung, with small bowel metastasis, who survived more than 5 years after surgical resection of the small bowel and lung tumors,[2] showing that appropriate treatment of these cases may extend the patient's life.

Literature reports indicate that most patients diagnosed with GI metastasis do not have any apparent GI symptoms; when symptoms are present, GI bleeding is the most common one.[1] However, GI tract obstruction, perforation, peritonitis, epigastric pain, anemia, polyp formation, and hyponatremia have also been reported in these patients.[1,10,11] Clinicians may mistake GI metastasis symptoms, such as abdominal pain and anemia, as chemotherapeutic side effects, and do not make accurate diagnosis. Thus, GI metastasis should be considered when GI bleeding, ulceration, enteritis, colitis, or perforation develop after chemotherapy.[3,9]

Colonoscopy, panendoscopy, small bowel enteroscopy, and abdominal CT can be helpful in diagnosing suspected GI metastatic lesions. However, endoscopically peculiar features of metastatic GI tumors, useful for distinguishing metastatic disease from primary GI tumors, have not been identified.[9] Kim et al. described wall thickening, intraluminal polypoid masses, exophytic masses, regional lymphadenopathy, ascites, obstruction, perforation, and intussusception as CT features indicative of GI metastasis.[4] Although early diagnosis of GI metastasis is difficult, especially when it involves small bowel metastasis, positron-emission tomography CT scans are useful for the early diagnosis of GI metastasis presenting with only a few symptoms.[7,12]

The dominant cancer cell type in lung cancer patients with GI metastasis is still in dispute, with most of the data being available from patients with small bowel metastasis. Squamous cell carcinomas,[3-6] adenocarcinomas,[1,13] or large cell carcinomas [9] were reported to be the most common cell type in various studies, although some reports did not show a dominant histological tumor type.[2] As mentioned previously, the small bowel was the most common site of GI metastasis from lung cancer,[2-6,9] although cases with metastasis to the stomach, duodenum, colon, anus, and appendix have also been reported.[10] Rare clinical cases involving colonic metastasis have been published, with the most common cell type in these cases being squamous cell carcinoma; limited num-

bers of lung adenocarcinomas with colonic metastasis have also been reported.[1,10,11,14-16]

Identifying a primary malignancy as a synchronous finding of pulmonary and GI lesions is difficult. The histological pattern of an adenocarcinoma involving the two sites is also difficult to discern. The presentation of inverted tumor-cell growth, from the serosa to the mucosa, and the absence of neoplasia or dysplasia over the mucosal surface, near the GI tumor, are regarded as peculiar features suggestive of metastatic GI carcinoma rather than a primary malignancy.[9]

However, immunohistochemical staining plays a role in making a definite diagnosis.[9,17] TTF-1 is a tissue-specific transcription factor specific for the lung, thyroid, and diencephalon. TTF-1 expression is generally applied as an assistive technique for distinguishing primary lung adenocarcinoma from metastasis. But recent studies have reported cases of adenocarcinomas of colonic origin as having positive TTF-1 expression; the rate was 1.8-5.8% in a recent summary.[18] These findings remind clinicians to carefully interpret positive TTF-1 expression for the origin site. Conjuction with their histological appearance, clinical histories and a combination of other immunohistochemical markers are helpful in making a precise diagnosis.[19] Su et al. studied the usefulness of a combination of TTF-1, CK7, and CK20 markers for differentiating primary and metastatic pulmonary adenocarcinomas. TTF-1$^+$ CK7$^+$ CK20$^-$ and TTF-1$^-$ CK7$^-$ CK20$^+$ cells are believed to represent adenocarcinoma of pulmonary and GI origins, respectively ($p < 0.001$).[20]

CDX2, a homeobox gene, present in epithelial cells from the duodenum to the rectum that encodes an intestine-specific transcription factor, was employed to detect adenocarcinoma of intestinal origin.[21,22] The sensitivity and specificity of *CDX2* for detecting colorectal adenocarcinomas in the lung, using fine-needle aspiration biopsies, were 75% and 100%, respectively. This marker assists clinicians in differentiating between primary and metastatic colorectal adenocarcinoma, but clinicians also need to be aware that poorly differentiated adenocarcinomas may present as false negatives.[21] Additionally, TA02 (napsin A), detected by two-dimensional polyacrylamide gel electrophoresis (2-DE), is also a useful method for distinguishing between primary and metastatic lung adenocarcinomas. Hirano et al. developed an immunohistochemical method using TMU-Ad02, a highly sensitive monoclonal antibody against TA02, to make the distinction easier. Their study suggested high positive rates (90.7%) for primary lung adenocarcinomas and no positive results in metastatic lung adenocarcinomas from the colon and rectum. The authors indicated that alveolar macrophages and hyperplastic type II pneumocytes around metastatic lung carcinomas would also stain positively, but that false positives would not interfere with the usefulness of the determination of the origin of the GI adenocarcinoma because of the absence of positively staining macrophages in other organs and the absence of pneumocytes in the GI tract.[23]

Peng and Gu also reminded clinicians to take multiple primary malignant neoplasms (MPMNs) into account as synchronous findings of colorectal and solitary cancers.[24] The therapeutic strategy and prognosis are different from those with metastasis. Unnecessary aggressive treatment, such as thoracotomy, and its resultant complications can be prevented following more accurate lung cancer staging.

Although GI metastasis occurs during the late stage of disease, surgical resection also plays a role in patients with lung cancer and GI metastasis;[1,9] for example, a patient with sarcomatoid carcinoma survived more than 5 years after surgery.[2] Patients with GI metastasis, suffering from bowel obstruction, perforation, or massive hemorrhage may also benefit from surgical treatment. Lee at el. showed a significant survival benefit of GI metastasis diagnosed preoperatively compared with those diagnosed postoperatively.[1]

Synchronous findings of pulmonary and GI malignancies present a puzzling scenario for clinicians. The puzzle becomes increasingly complex when the histological patterns of both lesions indicate the presence of adenocarcinoma. However, accurate diagnosis of the primary site can be achieved using immunohistochemistry. Only a few cases of lung cancer with colorectal metastasis have been previously reported,

and those demonstrating adenocarcinoma cell types are especially rare. We speculate that there are more obscure cases, without notable symptoms, across the span of patients with lung cancer. Physicians need to be alert to the possibility of colorectal metastasis in order to render optimal treatment.

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病例報告

疑似來自原發肺腺癌之大腸轉移：病例報告及文獻回顧

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肺癌合併腸胃道轉移並不常見，在文獻記載中最常轉移的腸胃道部位是小腸，而只有少數肺腺癌病例轉移至大腸的文獻報導。我們報告一個以免疫組織化學染色法而高度懷疑原發於肺部腺癌且轉移至大腸合併腸阻塞及水氣胸的六十七歲女性。免疫組織化學染色證實 thyroid transcription factor-1 和 cytokeratin 7 在癌細胞裡面，及 cytokeratin 20 並未表現於癌細胞。我們同時回顧了以免疫組織化學染色來診斷癌症原發位置之文章及其他相關的發表文獻。

關鍵詞 腺癌、肺、大腸、轉移、免疫組織化學。