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Case Report

Colonic Metastasis with Epidermal Growth Factor Receptor Mutation from Primary Lung Adenocarcinoma: a Case Report and Review of the Literature -

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ABSTRACT

Colon cancer with lung metastasis is very common clinically, but lung cancer with colon metastasis is relatively rare. More than half of lung cancers have distant metastasis at the time of the initial diagnosis. Despite patients undergoing resection for potential cure of lung cancer, silent metastatic disease is also considered. Gastrointestinal metastasis had rarely been reported, whereas colonic metastasis seems to be particularly rare. Although the majority of reported patients lack abdominal symptoms, we need to be aware of gastrointestinal metastasis in lung cancer patients who have gastrointestinal symptoms. This report presents a clinical case with colonic metastasis with Epidermal Growth Factor Receptor (EGFR) Mutation from primary lung adenocarcinoma. Immunohistochemistry and molecular genetics can provide important information in the practice of clinical medicine.

Keywords: Lung cancer; Colon metastasis; Epidermal Growth Factor Receptor (EGFR) Mutation.

INTRODUCTION

Colon cancer with lung metastasis is very common clinically, but lung cancer with colon metastasis is relatively rare. Malignancies of the lung are the leading cause of cancer-related mortality in the world [1]. Non-Small Cell Lung Cancer (NSCLC), especially adenocarcinoma, constitutes the majority of all histological subtypes. Cancer metastasis is the most critical prognostic factor and a highly complex phenomenon. More than half of cases of primary lung cancer have distant metastasis at the time of the initial diagnosis [2]. The most frequent destinations for lung cancer metastasis include lymph nodes, pleura, contralateral lung, liver, bones, brain and adrenal glands [3,4]. The Gastrointestinal (GI) tract is an exceptionally rare site of metastasis from primary lung cancer in the published literature [5-7]. We present a clinical case with colonic metastasis with Epidermal Growth Factor Receptor (EGFR) mutation from primary lung adenocarcinoma and also review the current literature of lung cancer with gastrointestinal metastasis.

CASE REPORT

A 73 year old man, former smoker with a 20 pack year smoking history and multiple co-morbidities including type 2 diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation and chronic hepatitis C post interferon treatment, was admitted to the hospital because of dizziness, slurred speech, easily choking, drooling and unsteady gait with tilting to left side recently. Magnetic resonance imaging of the brain with contrast revealed multiple abnormal signals and enhanced lesions in the pons, bilateral cerebellar hemispheres and bilateral cerebral hemispheres with peri-focal edemas which miliary metastasis was considered. Chest X-ray (Figure 1A) and computed tomography (CT) scan (Figure 1B), revealed a 21 mm round mass in the left upper lung superimposed with left first rib and increased interstitial infiltrates with peribronchial cuffing and “dirty chest” appearance in the right lower lung which aspiration pneumonia was highly suspected. In addition, patient had bowel habit change and obvious body weight loss about 8kg within recent half year. Colonoscopy (Figure 2) revealed sub epithelial tumor with central ulcer over ileum and ascending colon (90cm from anal verge) which metastasis was considered.

The pathology from CT-guided lung biopsy confirmed adenocarcinoma with positive Thyroid Transcription Factor-1 (TTF-1) on Immunohistochemistry (Figure 3A, 3B). The pathology from colonoscopic polypectomy demonstrated metastatic adenocarcinoma with TTF-1 (+), CK7 (+), CK20 (-), CDX2 (-) and Hep-par-1 (-) of the tumor cells on Immunohistochemistry (Figure 3C, 3D, 3E, 3F, 3G). EGFR mutation test from both primary lung cancer and metastatic colon tumor showed the same mutation locus at L858R on EGFR exon 21.

After complete staging works up, the final diagnosis was stage IV (T4N3M1b) lung adenocarcinoma in LUL with contralateral lung, pleura, liver, brain, bones and colon metastasis. Target therapy, EGFR-tyrosine kinase inhibitor (EGFR - TKI; 150 mg erlotinib once daily), had been prescribed as first-line therapy. One month later, patient’s condition became better clinically. Followed chest X-ray revealed lung cancer in LUL in stable status. But, because of a worsening clinical course related to severe diarrhea and lower gastrointestinal bleeding with hypovolemic shock, patient and his family opted for hospice care eventually. Finally, he passed away less than 2 months after the initial lung cancer diagnosis.

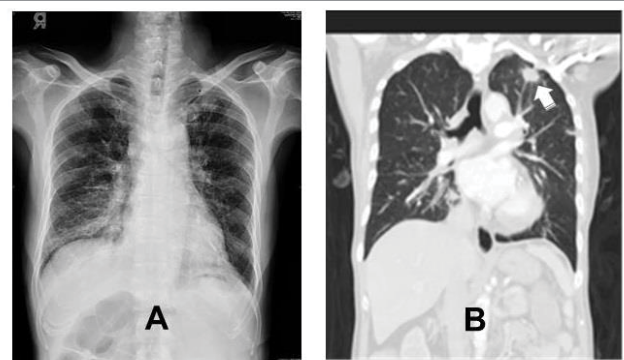


Figure 1: A pulmonary nodule in the left upper lung.
(A) Chest X-ray shows round ground-glass opacity in the left upper lung superimposed with left first rib and increased interstitial infiltrates in the right lower lung which aspiration pneumonia was highly suspected.
(B) Chest CT scan reveals a soft tissue density lesion with size about 21 x 15 mm in the left upper lung (white arrowhead) and multiple variable size micronodules in bilateral lobes of lungs which are highly suspicious metastasis.

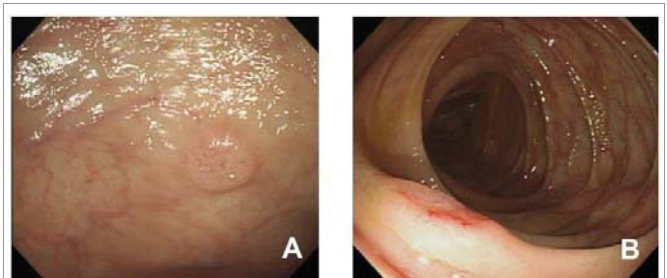


Figure 2: Subepithelial tumor with central ulcer over terminal ileum (A: estimated 0.5cm) and ascending colon (B: 90cm from anal verge; estimated 1.0cm) which are highly suspicious metastasis on colonoscopy examination.

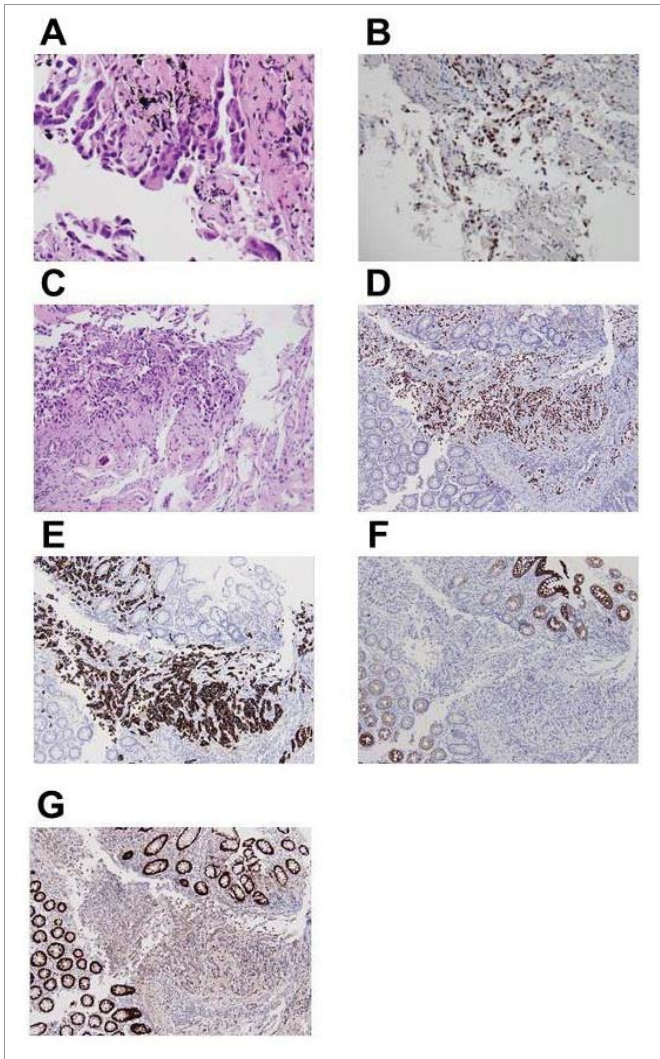


Figure 3: Representative pictures of primary lung adenocarcinoma and metastatic lung adenocarcinoma in colon tissue.
 (1) Primary lung adenocarcinoma: H&E section (A) and TTF-1 (B) immunostains;
 (2) Metastatic lung adenocarcinoma in colon tissue: H&E section (C), TTF-1(D), CK7(E), CK20(F) and CDX2(G) immunostains.

DISCUSSION

Metastatic spread occurs in approximately half of lung malignancies. The most frequent metastatic organs include lymph nodes, adrenal glands, liver, brain and bones. The incidence of metastatic lesions to the GI tract is under speculation because it did not be examined routinely for lung cancer staging. The mechanisms of spread of lung cancer to the GI tract occurs through deposition of malignant cells in the subserosal layer of the bowel [8] through the spinal vein hematogenous route or retroperitoneal and mesenteric lymphatic routes [9], with subsequent proliferation of these new foci [10]. The majority of reported patients lack abdominal symptoms and lesions are later diagnosed at autopsy. The most common abdominal symptom is abdominal pain which occurs in about half of patients [11] but lacks specificity. Other abdominal symptoms may be presented as nausea, vomiting, weight loss, obstruction, perforation, GI bleeding, dysphasia, anemia, jaundice or bowel habit change.

Primary lung cancer that metastasizes to the GI tract usually presents as a solitary nodule, with the preponderance for the male

sex [12]. According to different manifestations, diagnosis tools may include fecal occult blood testing, abdominal CT scan, positron emission tomography scanning, Tc-99m red blood cell-labelled scintigraphy, endoscopy studies and immunohistochemical staining. A positive TTF-1 stain on immunohistochemistry, with a sensitivity of 57.5 ~ 76% and a specificity of 99 ~ 100% [13], differentiates between an adenocarcinoma of lung from colorectal origin. In addition, positive staining for CK5/6 or p63 with negative staining for CK20 and CDX-2 typically represents adenocarcinoma of the lung.

Generally, advanced lung malignancies with metastasis to the GI tract imply poor prognosis. McNeill et al. estimated survival of fewer than 16 weeks and Lou, et al. [14] determined an overall survival ranging from 5 weeks to 1 year with a median of 3 months post-diagnosis with colonic metastasis [6]. In current literature review, Jevremovic estimated that the total number of cases reported metastasizing to the stomach is less than 60, to the small intestine is 58 and to the colon is 14 [15]. A number of clinical studies about symptomatic GI metastasis have estimated the incidence to range from 0.2 ~ 1.7% [2,6,11,16], but there is a 4.6 ~ 14% incidence of GI metastasis found at autopsy [6, 17-19]. From clinical studies and autopsy data, squamous cell carcinoma and large cell carcinoma of lung are the most commonly histological sub types' involved GI metastasis [15].

Treatment of patients with lung cancer depends upon the cell type, molecular characteristics, tumor stage, and an assessment of the patient's overall medical condition. The identification of oncogenic activation of particular tyrosine kinases in some advanced NSCLC tumors, most notably mutations in the EGFR or rearrangements of the Anaplastic Lymphoma Kinase (ALK) gene or ROS1 gene, has led to the development of specific molecular treatments for patients. EGFR-TKI significantly prolongs progression-free survival in patients with advanced NSCLC that contains an activating mutation in EGFR compared with platinum-based chemotherapy doublets. However, there is no available data about the treatment response of EGFR-TKI to patients with colonic metastasis with EGFR mutation from primary lung adenocarcinoma at present. In addition, diarrhea is a common symptom in patients receiving small molecule EGFR-TKIs, such as erlotinib, gefitinib, and afatinib. Although diarrhea is reported in up to 90% of patients, especially those treated with afatinib in phase III study [20], it is severe in fewer than 15% and typically can be easily managed by the use of loperamide. Because diarrhea is an uncommon symptom of GI metastasis, the mortality of the presented patient may be related to the side effect of EGFR-TKI combined with laxative agents for constipation and hemorrhoid.

Many experts believe that patients undergoing resection for potential cure of lung cancer have silent metastatic disease sometimes. Colonic metastasis seems to be particularly rare. The majority of reported patients lack abdominal symptoms. We must be aware of GI metastasis in patients who have NSCLC, especially squamous cell carcinoma and large cell carcinoma, with GI symptoms or a solitary sub-epithelial tumor on colonoscopy examination. In the era of molecular and personalized therapeutics, targeted therapy has provided a successful avenue for treatment of high-stage lung adenocarcinomas through the analysis of immunohistochemistry and molecular genetics.

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