Primary pulmonary invasive mucinous adenocarcinoma with sigmoid colon metastasis: a case report and literature review

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Case report

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Abstract

Background: Invasive mucinous carcinoma is a very rare tumor. The colonic metastasis of IMA is more infrequent. So far, no literatures are published.

Case presentation: We report a case of a patient with invasive mucinous adenocarcinoma. After serial months of chemotherapy, the sigmoid colonic metastasis was detected.

Conclusions: Symptoms and CT findings can initially be subtle, histological examination remains the gold standard for the definitive diagnosis. Patients with high grade primary lung cancer may have gastrointestinal metastases, therefore their gastrointestinal should be examined to allow early detection and treatment.

Background

Lung cancer remains the leading cause of cancer-related deaths globally[1]. Adenocarcinoma represents the most common lung cancer subtype[2]. Among all lung adenocarcinomas, invasive mucinous adenocarcinoma (IMA) is relatively rare, accounting for only 2 ~ 5% of lung invasive adenocarcinomas[3]. Nearly 50% patients with lung cancer have been found to have distant metastases at the time of death [4]. The common metastatic sites originating from lung cancer include lung itself, liver, brain, adrenal gland, and bone[5]. It is extremely rare to find colonic metastasis [6, 7], only a few case reports have been published[8–10]. But none have been reported of primary pulmonary mucinous adenocarcinoma with colonic metastasis, perhaps due to the rarity of IMA and colonic metastasis. In the present study, we report the first case of primary pulmonary mucinous adenocarcinoma with sigmoid colon metastasis. We also review the published literature of primary lung cancer with sigmoid colon metastasis.

Case Presentation

The patient was a 69-year-old Chinese female. One month ago, during her physical examination, lung lesions were found. Thus, she visited the respiratory out-patient department in May, 2020. Chest CT was performed which revealed multiple ground glass nodules and bilateral consolidation shadows in both lower lungs (Fig. 1). The initial diagnosis was pulmonary inflammation, and reexamination after treatment was recommended. So she was hospitalized for more detailed tests.

She complained cough of one-month duration, associated with white mucus. Her vital signs were normal. Auscultation revealed coarse crackles in both lower lung fields. A systemic review of the occupational and travel environments did not reveal the reason for the pulmonary infiltration. She has a family history of diabetes.

The white blood cell count was $3.10 \times 10^9/L$, C-reactive protein and procalcitonin were in the normal range. Routine blood chemistry tests were normal. Tumor markers in patients' serum were all negative. Flexible bronchoscopy was performed and no endobronchial lesions were detected. The sputum culture

was positive, gram-positive and gram-negative bacteria were found. Tuberculosis (TB) was ruled out. The remainder of the infectious work-up including AFB smear, mycobacterial cultures, BAL fluid bacterial cultures and HIV antigen/antibody combo were negative. An autoimmune panel, including ANA, ANCA and myositis autoantibodies was negative, except ANA and anti Ro-52 (+). The patient was therefore started on cefoperazone- sulbactam and levofloxacin in addition to broad spectrum antibiotic therapy. After ten-days treatment, the patient's respiratory symptoms showed mild improvement, but the multifocal pulmonary infiltrations remained unchanged. Therefore CT-guided percutaneous lung biopsy in right lower lobe was performed. Histopathologically, the tumor consisted of abundant mucin filling the alveolar spaces and some tumor cells floating in mucin pools. Columnar mucinous epithelial cells lined thickened alveolar walls (Fig. 2), Immunohistochemistry (IHC) showed neoplastic cells positive for CK7, negative for TTF-1, CK20, CDX2, ALK(lung) and P63. We finally diagnosed invasive mucinous adenocarcinoma of the lung (moderate to poorly differentiated stage T4N2M0, stage IIIB). Further tumor mutation analysis was examined, EGFR mutation was negative and KRAS mutation at the 17 exon (p.G12 D mutation) was detected. Chemotherapy was started for pulmonary mucinous adenocarcinoma. After four cycles of treatment, in August, 2020, CT examination from chest to pelvis was performed which revealed localized thickening of sigmoid wall (Fig. 3). The patient was sent to an endoscopy room, and colonoscopy suggested the possibility of colon cancer, so biopsy was performed. IHC showed CK7(-), TTF-1(+), CK20(+), CDX2 (+) ,Ki-67(Li:80%)(Fig. 4), CerB-2(-). Finally, metastatic lung mucinous adenocarcinoma (enteric adenocarcinoma) was diagnosed. About a month later, the patient had severe abdominal pain and passed away finally. We speculated that she was died of enterobrosis and septic shock.

Discussion

Primary pulmonary invasive mucinous adenocarcinoma (IMA) is an adeno-

carcinoma variant according to the current World Health Organization (WHO) classification of lung tumors [11], formerly known as mucinous bronchioloalveolar carcinoma (BAC), which is relatively rare [3]. IMA has a range of differences from those of invasive non-mucinous adenocarcinoma (INMA), including genetic, clinical, radiological and pathological characteristics. The age of IMA patients ranged between 41 and 66 years and the majority were non-smoking females [12]. Clinical features are generally non-specific, such as cough, fever, expectoration and dyspnea etc. The symptom of coughing with white sputum may help early diagnosis of pneumonic-type adenocarcinoma[13]. In the present study, it was revealed that the patient was female and non-smoker, as well as mild coughing with white sputum when she was initially diagnosed, which were consistent with previous study[13].

IMC displays a variety of radiological presentations. According to the CT findings, IMC has been classified into three patterns[14]: ☐ solitary nodules or masses; ☐ localized consolidation, pneumonic types; ☐ multicentric or diffuse disease, most patients have a mixture of these features. The most common features on chest high-resolution computed tomography (HRCT) scan are predominant ground- glass opacities, consolidations, or multiple nodules[15]. Because of the nonspecific

radiographic findings, we may usually not differentiate them from other lung diseases, such as atypical pneumonia, tuberculosis, pulmonary lymphoma or metastatic lung cancer[15, 16]. However some studies [17–19] reported that the pneumonic types IMA had air bronchograms with stretched, sweeping, narrowed appearance and bulging of the interlobar fissure. In our report, the patient was initially misdiagnosed as focal organizing pneumonia, but after ten days of anti-inflammatory therapy, the lesions are not eliminated, ultimately we got an accurate diagnosis by percutaneous computer tomography (CT)-guided lung biopsy. we reviewed her chest CT imagings carefully, some signs were found, such as air bronchograms with a stretched, sweeping and bulging of the interlobar fissure, which can help the differential diagnosis. Percutan- eous computer tomography (CT)-guided lung biopsy appears to be an effective way to make a definitive diagnosis.

Almost 50% of non-small-cell lung cancer (NSCLC) patients present with metastatic disease at the time of diagnosis, the most common NSCLC metastatic site is bone (34%), followed by lungs (32%), brain (28%), adrenal glands (17%), liver (13%), and extrathoracic lymph nodes (9%) [8]. Colonic metastasis is extremely uncommon with an incidence of 0.1% [20], and about 50 unique case reports of lung cancer metastasizing to the colon have been published globally[4, 6–8, 10, 21–70], among them, squamous cell carcinoma(SqCC), lung adenocarcinomas, small cell lung carcinomas, Large-cell carcinoma, other primary lung histopathologic cell types such as sarcomatoid, pleomorphic, and unknown were confirmed as primary origins, SqCC is the most common origins, followed by lung carcinoma.

Immunohistochemistry is very valuable for determining the primary origins. Among those, CK7, CK20, CDX2, and TTF-1 has been proven to be diagnostic[6]. Most pulmonary adenocarcinomas are typically positive for TTF-1 and CK 7, and negative for CK 20[71–74]. Most colorectal adenocarcinomas are negative for TTF-1 and CK 7, and positive for CK 20[75–76]. However, up to 20% of lung adenocarcinomas are reported to be negative for TTF-1, and up to 30% may react positively with CK 20. Several studies showed CDX-2 to be highly sensitive for colorectal ACA, but among lung tumors, only a rare type of pulmonary ACA, the goblet cell variant of primary mucinous (so-called colloid) ACA, has been reported to be positive for CDX-2[77]. TTF-1 is expressed only in lung cancer and thyroid cancer [77– 81]. The expression of TTF-1 rate in IMA is often lower than that in non-mucinous adenocarcinoma. In addition, according to the report of Su et al [12], the positive rates of primary lung adenocarcinoma were 73% for TTF-1, 75% for CK7, and 0% for CK20, the positive rates of primary colon cancer were reported to be 0% for TTF-1, 7% for CK7, and 86% for CK20. Thus, since TTF-1 expression is lacking in all adenocarcinoma types except for lung adenocarcinoma, which is very important to distinguish between primary adenocarcinoma and metastatic adenocarcinoma.

KRAS mutations are the most frequent oncogenic driver mutations in IMAs (up to 86%) [82, 83]. the most common types are G12D and G12V in IMAs [83]. KRAS mutation has been reported to be associated with invasive mucinous adenocarcinoma, formerly known as mucinous BAC [84]. For our patient, the lung lesion was immunoreactive for CK7, favoring the diagnosis of lung adenocarcinoma. Negative staining of p63 rules out squamous cell carcinoma of the lung. KRAS mutation (p.G12 D mutation) was positive. The sigmoid lesion was immunoreactive for TTF-1, CK 20, CDX2. The positive expression of TTF-1

indicated that her sigmoid tumor was metastatic from pulmonary carcinoma. Because of the primary pulmonary mucinous adenocarcinoma, CDX2 can be positive. These IHC stains can help determine the primary tumor and distinguish metastatic carcinoma from primary tumor.

Conclusion

Our report represents an exceedingly rare case of primary pulmonary invasive mucinous adenocarcinoma metastatic to sigmoid colon. Symptoms and CT findings can initially be subtle, histological examination remains the gold standard for the definitive diagnosis. Patients with high grade primary lung cancer may have gastrointestinal metastases, therefore their gastrointestinal should be examined to allow early detection and treatment.

Abbreviations

IMA : invasive mucinous adenocarcinoma; CDX2: Caudal-type homeobox 2;

CK: Cytokeratin; CT: Computed tomography; SqCC: squamous cell carcinoma

TTF: Thyroid transcription factor-1; BAC: bronchoalveolar carcinoma

NSCLC : non-small-cell lung cancer; IHC: immunohistochemical

Declarations

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Availability of data and materials

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Authors' contributions

Fang J contributed to CT scanning of the patient , collection of the clinical data and writing of the manuscript. Hu HJ contributed to edit, revised and approved the manuscript. Cao H contributed to histological diagnosis. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

The consent for publication of the manuscript and the related images from the patients and/or their relatives have been obtained.

Ethics approval and consent to participate

The ethical approval has been received by the Medical Ethics Committee, Zhongnan Hospital of Wuhan University concerning the publication of this manuscript and any accompanying images(No2019056). A copy of this document is available for review by the Editor-in-Chief of this journal.

New software

The authors declare that no new software has been used.

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Figures

Figure 1

Chest tomography reveals lobular consolidation and ground-glass attenuation with crazy-paving appearance and subpleural dominance in both lung fields (a–b). Dense peribronchial consolidation in the left lower lobe(b) .

Figure 2

Microscopic examination at a magnification of $\times 200$ shows mucinous tumor cells consisting of tall columnar cells with abundant apical mucin.

Figure 3

Abdomen and pelvic CT shows the thickened sigmoid wall with surrounding fatspace blurred. Mucosal involvement can be seen contributing to marked narrowing of the sigmoid colon. (a. non-contrast CT b. arterial phase of enhancement c. venous phase of enhancement)

Figure 4

The IHC of the colon. The carcinoma cells were positive for TTF-1, CK20 and CDX2, Ki-67(Li:80%).