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Case Report

Miliary lung adenocarcinoma: a case report

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Abstract: Background: Miliary lung adenocarcinomas are rare and highly aggressive in nature. There is currently no effective treatment for this carcinoma. Case presentation: We report a very rare case of a 48-year-old man with a lung adenocarcinoma. CT findings were indicative of miliary tuberculosis. Whole body bone scans and head MRI showed multiple multiple brain and bone metastases. The patient underwent two cycles chemotherapy of paclitaxel combined with cisplatin, followed by two cycles of pemetrexed plus cisplatin and Endostar; however, this was ineffective. The patient is currently being treated with icotinib. The aggressive form of this cancer in this patient may represent a new subtype of lung adenocarcinoma. Conclusion: Miliary lung adenocarcinomas have unique characteristics that need to be studied further in order to understand the underlying molecular mechanism, pattern of development and metastasis, and therefore establish effective treatment strategy.

Keywords: Case report, lung adenocarcinomas, miliary, tuberculosis

Introduction

Lung cancer is the most frequently diagnosed cancer and the leading cause of cancer-related death worldwide [1]. Lung cancers are typically classified as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLCs are further divided into three major subtypes: squamous cell carcinoma, adenocarcinoma and large cell carcinoma. Lung adenocarcinoma is the most frequent type in no-smokers, and its incidence has been increasing in the past few years in this population [1-3].

Lung adenocarcinomas typically originate in the bronchial epithelium or bronchial glandular epithelium. They are often asymptomatic, so they are often detected incidentally while examining for other conditions [4]. Their radiological presentations include ground glass nodules, part-solid nodules and solid nodules on chest CT scans [5]. Miliary mottling on chest radiographs is rare, and it is a common presentation of miliary tuberculosis. It is also observed in certain fungal infections, sarcoidosis, silicosis, hemosiderosis, fibrosing alveolitis, pulmonary eosinophilic syndrome, and pulmonary alveolar proteinosis, and it is rarely observed in hematogenous metastases of primary cancers of the thyroid, kidney, trophoblasts, and sarcomas [6-8]. Further, presentation of primary lung cancer as miliary nodules is very rare [9-11]. Here, we present a rare case of lung adenocarcinoma in which the chest CT scans depicted numerous tiny nodular lesions in both lung fields without a primary larger lesion, which were considered as miliary tuberculosis or pneumoconiosis usually.

Case presentation

The present study describes the case of a 48-year-old man who had a cough, thoracodynia and chest congestion for one month. During this period, he underwent CT at the outpatient department of the hospital on the advice of a specialist. The chest CT scan revealed diffuse nodular shadows in both lungs, which were indicative of miliary tuberculosis or pneumoconiosis usually (**Figure 1**). However, the patient agreed to undergo only symptomatic treatment. Because the symptoms were not alleviated and gradually became severe, the patient consulted the Department of Respiratory Medicine of the First Affiliated Hospital of Henan University of

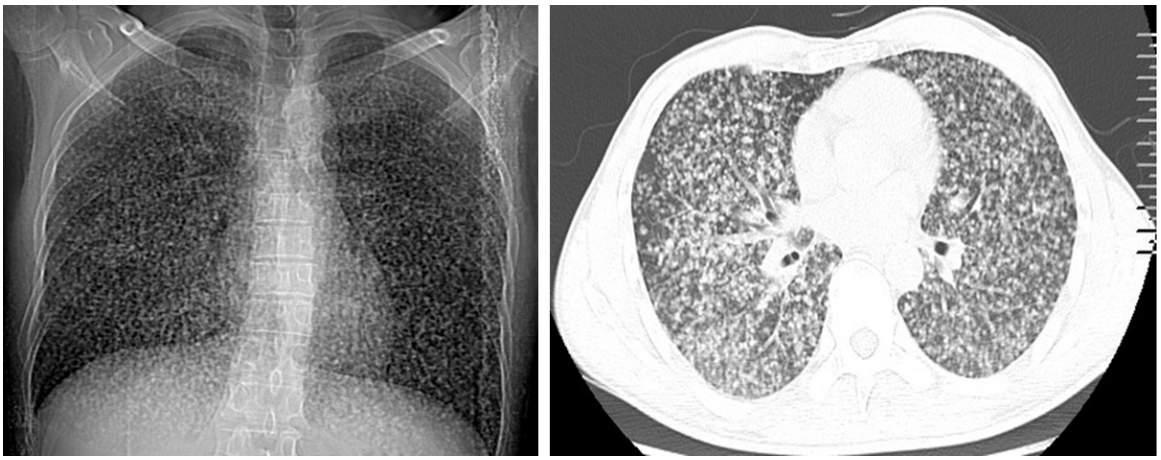

Figure 1. Chest CT scans showed numerous tiny nodular lesions scattered in both lung fields without a primary larger lesion.

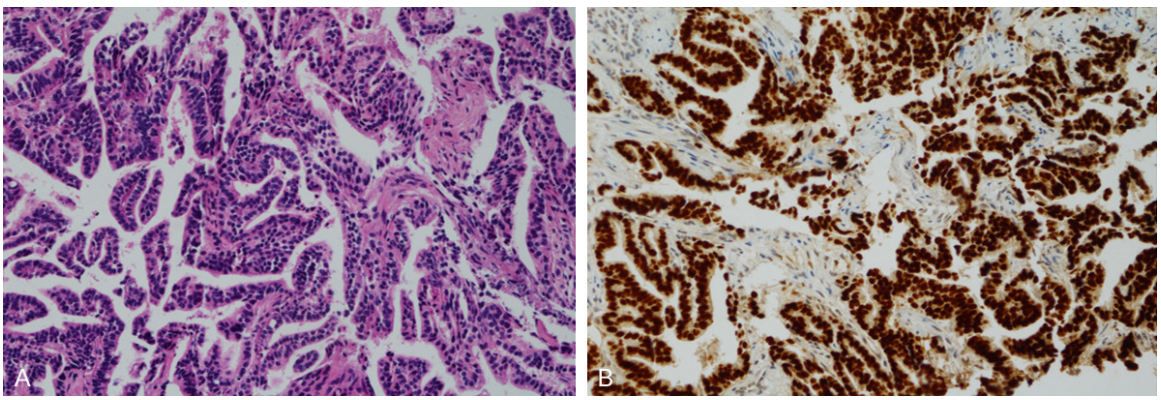

Figure 2. A. HE-stained biopsy sample obtained from the patient (magnification, 200×); B. Immunohistochemical staining of TTF-1 (magnification, 200×).

Science and Technology (Luoyang, China) ten days later. A peanut-sized lymph node that was tough and removable was touched in the right supraclavicula. A few fine rales were found on examination of both lungs. He had a 30-year history of hepatitis B, but no history of smoking, no family history of cancer, no history of exposure to activities related to silicosis and no close contact with tuberculosis. The results of relevant laboratory studies were: carcinoembryonic antigen (CEA) 19.7 ng/ml (normal range, <4.3 ng/ml), carbohydrate antigen (CA) 125, 14.21 U/ml (normal range, <35 U/ml, neuron specific enolase (NSE) 58.84 ng/ml (normal range, <16.3 ng/ml), CYFRA21-1 22.61 ng/ml (normal range, <3.3 ng/ml), erythrocyte sedimentation rate 2 mm/h (normal range, <15 mm/h). Examination of blood tumor markers showed significant higher than normal. The results of tuberculin purified protein derivative test and erythrocyte sedimentation rate are negative. Electronic fibre bronchoscopy did not indicate the presence of any neoplasm in the airway lumen, but pathological examination and immunohistochemistry of a blind biopsy sample of the right side of the back section of the bronchial lumen were indicative of lung adenocarcinoma (**Figure 2**). The Ki67 index was only 5%. He was administered two cycles of chemotherapy with paclitaxel combined with cisplatin from October to November 2014. This was found to be ineffective, so two cycles of pemetrexed plus cisplatin and Endostar were administered; however, this was also ineffective. Moreover, multiple brain and bone metastases were found. The patient is currently being treated with icotinib. Because of ostealgia caused by the metastases, he received pallia-

tive radiationtherapy on thoracic and lumbar spine from July to August 2015.

Discussion

Miliary masses occasionally appear in association with bronchioloalveolar carcinoma, a rare subtype of adenocarcinoma that develops in the alveoli without invasion into other tissues [12]. However, these characteristics of miliary masses are obviously different to those found in the present case and those reported in 11 other cases of lung adenocarcinoma reported previously [4, 13, 14]. Miliary masses have unique clinical and biological feature and unfavorable treatment response and poor prognosis. They therefore need to be classified into a new subtype. In the present case, a unique characteristic that separates this case from the other 11 cases was that the tubercles were uniform without a primary larger carcinoma, which was earlier thought to be the origin of miliary tubercles. Moreover, the tubercles showed homogeneous distribution. This case therefore presents a new and possibly rare feature of miliary lung adenocarcinoma that will be highly useful for future diagnosis of this condition.

As early as 1993, Umeki reported five cases of non-smoking bronchogenic adenocarcinoma with bone and miliary pulmonary metastases [14]. He audaciously concluded that the miliary lung metastases were produced by bone metastases of the bronchogenic carcinomas, as the carcinoma might have the ability to produce and release showers of emboli. However, after reviewing six other cases reported in two studies [4, 13], we found that bone metastases was present in two cases, while the other four cases had no metastasis. However, liver metastasis was present in the two cases with bone metastasis. Therefore, it seems unlikely that bone metastases of bronchogenic carcinomas alone are responsible for the formation of miliary masses. It seems that miliary pulmonary metastases may originate from bone or liver metastases, which may progress from primary lesions through blood circulation.

The metastatic process of tumor cells consists of a series of steps, i.e., escape from the primary microenvironment, circulation in the blood, reaching an organ/system, and eventually developing into an overt metastasis. However, during these processes, they need to successfully overcome anoikis, the host's immunologic defenses and systemic therapy [15, 16]. Recent experimental models indicate that millions of tumor cells are continuously dispersed through the body. Some of them reach a secondary organ, but may not progress enough to become a clinical overt metastasis [17, 18]. Thus, miliary lung adenocarcinoma cells need to have a high capacity for escape and acclimatization. They need to grow in situ and get dispersed through blood circulation at the same time. In the present case, as the masses were small, distributed throughout both lungs, and insensitive to Endostar (a recombinant human endostatin), it is possible that these masses were dispersed through the pulmonary vasculature. However, the underlying mechanism is still unclear. It would be interesting to study the properties of these cancer cell lines by culturing them and investigating the underlying molecular mechanism.

Lung adenocarcinoma with miliary pulmonary metastases is unresponsive to the platinum drugs paclitaxel, pemetrexed, recombinant human endostatin, etc., which makes it difficult to stop the progression of this cancer. In 2011, Eckart et al. reported five such cases of patients in whom gene sequencing of epidermal growth factor receptor (EGFR) mutations identified a deletion in exon 19 of the EGFR gene; all five patients had a significant response to EGFR tyrosine kinase inhibitors [4]. Therefore, EGFR tyrosine kinase inhibitors combined with multidisciplinary synthetic therapy are probably useful for the treatment of this carcinoma [19]. On account of their high transfer rate through blood circulation, we strongly suggest that clinicians conduct tests for detection of circulating tumor cells to monitor the state of the illness in "real time" during the administration of systemic therapies [20]. In the reported cases so far (including the present one), 8 of the 12 patients had bony metastases. Thus, using drugs that target the bone marrow (e.g., bisphosphonates or antibodies against the RANK ligand [21-24]) in the early stages might help prevent metastasis or even local relapse.

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Disclosure of conflict of interest

None.

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