

Case Report

Cutaneous metastasis from lung adenocarcinoma presenting before discovery of the primary malignancy: a case report

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Received December 27, 2018; Accepted January 26, 2019; Epub February 1, 2019; Published February 15, 2019

Abstract: Cutaneous metastasis from lung adenocarcinoma is rarer than liver, adrenal, brain, bone and other distant metastases, and the prognosis is very poor. We report a case of a 42-year-old Asian male lung adenocarcinoma patient with lymph node metastases and cutaneous metastases to the right chest wall that appeared during the comprehensive treatments, without any lesion previously found in the lung. The patient was positive for the EGFR18 exon and had an excellent tumor response to the EGFR tyrosine kinase inhibitor (EGFR-TKI) with a duration of efficacy of up to 22 months. Then, the area of right chest wall lesions expanded with ulceration, and gene detection from peripheral blood indicated that the patient acquired resistance to the administered EGFR-TKI therapy. A bilateral pleural effusion occurred 1 month later upon changing treatment to the third generation of EGFR-TKI. Then, the pleural effusion was controlled, but a change in the chest wall skin lesions was not obvious until after treatment with bevacizumab combined with cisplatin pleural perfusion. Currently, the patient is administered S-1 for maintaining treatment. Current follow-up time is more than 48 months, and the KPS score is 80 points. Through this case and a review of relevant literature, we discuss the clinical manifestations, diagnosis, treatment and prognosis of this disease and intend to provide a reference for the clinical diagnosis and treatment of similar diseases.

Keywords: Lung adenocarcinoma, cutaneous metastasis, treatment, prognosis

Introduction

The incidence of cutaneous metastasis of malignancies is much lower than the rate of metastasis to other organs, at approximately 5-10% [1], but any malignant tumor can produce cutaneous metastasis, which yields a poor prognosis. Therefore, we should increase the study of metastatic carcinoma in the skin. The origin of cutaneous metastatic carcinoma depends on histopathology and immunohistochemistry, and lung, breast, mouth, colon, kidney, ovary and stomach metastatic tumors constitute 80 to 90% of adult malignant tumor cutaneous metastasis cases [2, 3]. A study by Singapore's National Dermatological Center [4] showed that the most common primary tumors of cutaneous metastasis in Asian populations were breast cancer (49%) and lung cancer (9%).

Lung cancer has become the most common type of malignancy and the leading cause of death from cancer [5, 6]. According to the report of Chinese cancer statistics, the incidence and mortality of lung cancer were the highest among all cancer types in China in 2015 [7]. Lung cancer frequently produces distant metastases in the liver, adrenals, brain and bones. The percentage of patients with lung cancer that develop cutaneous metastases ranges from 1 to 12% [8, 9]. All histologic types of lung cancer may metastasize to the skin, with the most common histologic diagnosis being adenocarcinoma, which is poorly differentiated and located in upper lobes of the lung [10, 11].

Cutaneous metastasis from lung cancer lacks a distinctive clinical appearance. It usually presents as single or multiple mobile nodules with abscesses, scales, ulcers, or local infection.

Lung adenocarcinoma cutaneous metastasis

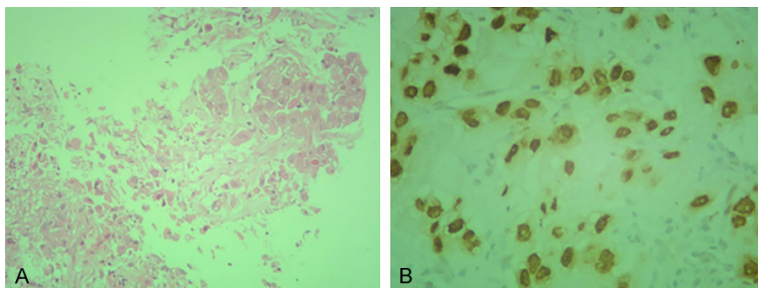


Figure 1. Pathologic images of lymph node puncture biopsy in the neck on December 16, 2013 in Yunnan Cancer Hospital. H&E \times 100 (A), TTF-1 (+) (B); support for low-differentiated adenocarcinoma, consider lung origin.

Cutaneous metastasis commonly occurs in sites such as the chest, back, head, and neck and can present at or before the discovery of the primary malignancy in 20-60% of cases, which increases the risk of misdiagnosis or missed diagnosis [11, 12]. The appearance of cutaneous metastasis in lung cancer indicates that the disease has entered the advanced stage, with an overall poor prognosis. The median survival time is approximately 5-6 months, with a few patients surviving for more than 1 year [11, 13].

We report a rare case that reached a relatively satisfactory result: a 42-year-old man with adenocarcinoma cutaneous metastasis presented before the primary malignancy of the lung was known, and with an EGFR18 exon mutation. At present, the disease is stable after multi-treatment, and the follow-up time has been over 48 months.

Case report

A 42-year-old man without prior pulmonary disease and smoking history sought treatment at our hospital in December 16, 2013 after finding swollen cervical lymph nodes 1 month ago. The results of immunohistochemistry taken from lymph node puncture in our hospital showed CK (+), Hck (-), P63 (-), CK5/6 (-), L-CK (+), CK20 (+), villin (-), TTF-1 (+), TG (-), CDX2 (-), PSA (-), PSAP (-), and Vim (-) (**Figure 1**), which supported poorly differentiated adenocarcinoma and putative lung origin. Therefore, the patient was diagnosed with poorly differentiated adenocarcinoma of the right neck (perhaps due to the primary lung) and no lesions in the lungs.

The patient underwent 4 cycles of TP regimen chemotherapy with minimal lesion shrinking

and IV degree myelosuppression (PLT $23 \times 10^9/L$) for a long period of time. Thus, chemotherapy was discontinued. Genetic testing revealed mutations in the EGFR 18 exon. The lesions remained stable when treated with icotinib, but a serious rash occurred. After a change of monotherapy chemotherapy with docetaxel 2 cycles, CT assessment indicated PD. Later, multiple nodules appeared on the right chest

wall with swelling and ulceration, and the biopsy taken from the skin lesions indicated poorly differentiated adenocarcinoma, which led to a diagnosis of cutaneous metastasis. Immunohistochemistry showed TTF-1 (+), Napsin (+), GATA-3 (-), CA125 (-), AR (-), ER (-), PR (-), Villin (-), PAX-8 (-), and E-cad (+), which was considered pulmonary in origin (**Figure 2**).

The patient's EGFR gene was tested again, yielding 18 exon G719X missense mutation and refusal to respond to EGFR-TKI treatment. The skin lesions progressed after accepting 1 cycle of chemotherapy with pemetrexed combined with cisplatin. Oral erlotinib was started in June 2015, and cutaneous metastasis subsided gradually. Three months later, a new lesion was found in the brain using MRI scans and was diagnosed as metastasis. Then, switching to afatinib, the size of the brain lesion decreased, and the skin lesions maintained their sizes. Lower extremity thrombus occurred after 9 months, after which afatinib was stopped, and maintenance treatment was given to erlotinib again. After 3 months, CEA, CA-724, Fer and other markers increased, the left axillary lymph node enlarged, and biopsy supported metastatic poorly differentiated adenocarcinoma that was considered to originate from the lung. The size of the brain lesion increased, which was measured using MRI scans, and the condition was evaluated as PD (**Figure 3**).

Then, after changing to oral dacomitinib, the condition stabilized again. After 7 months, the patient presented with chest tightness, palpitations, dyspnea, vomiting, increased heart rate of up to 120 beats/min, and an increase in size and rupture of the right chest wall nodules. The CT scans revealed that the right chest wall was

Lung adenocarcinoma cutaneous metastasis

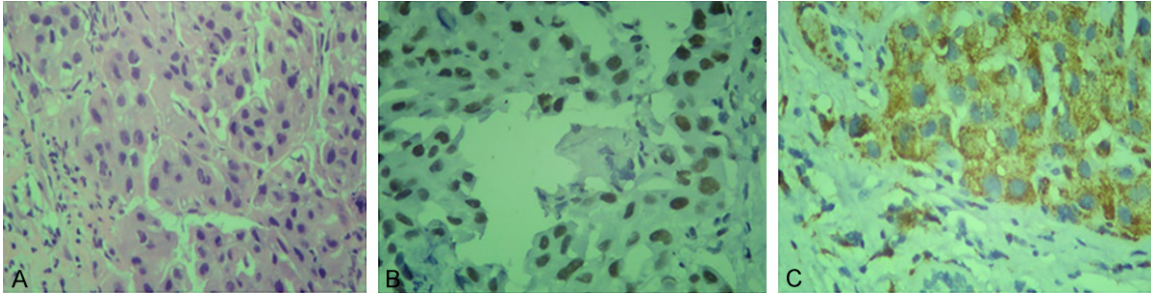


Figure 2. Right chest wall skin lesion puncture biopsy pathology in Yunnan Cancer Hospital. H&E $\times 100$ (A), TTF-1 (+) (B), Napsin A (+) (C): consider lung origin.

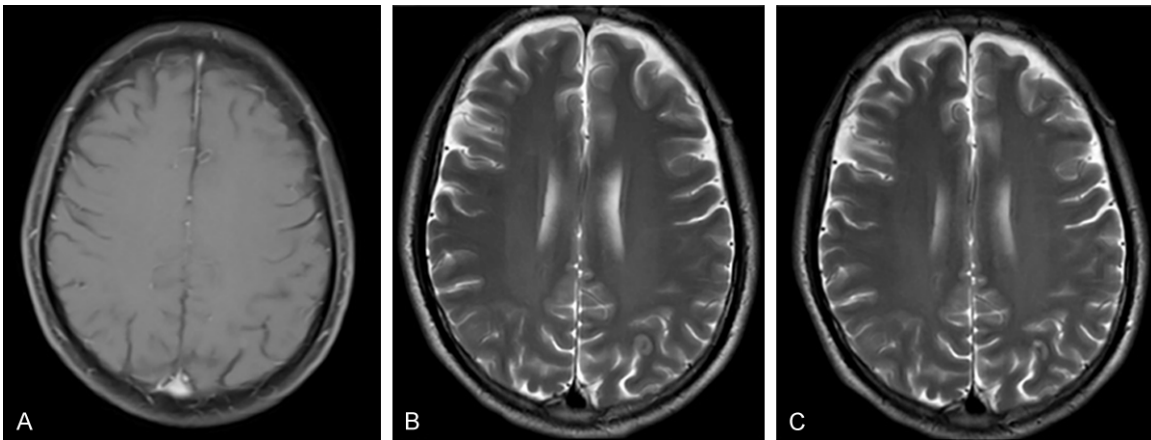


Figure 3. Magnetic resonance imaging (MRI) scan images. The size of the brain lesion during treatment was measured by using MRI scans in September 2015 (A): New brain lesions; August 2016 (B): Progress of brain metastases; Currently (C). The treatment of brain metastasis during disease is effective.

significantly thicker than before and that new nodules had appeared. The assessment was PD (**Figure 4**).

The genetic testing was performed on April 4, 2017, which was taken from peripheral blood, and revealed EGFR G719A and T790M mutations. The patient was administered osimertinib until the range of right chest wall lesions expanded after 1 month and symptoms became serious, such as chest tightness, palpitations, dyspnea, and vomiting. Bilateral pleural effusion was discovered using CT scans. Treatment of thoracentesis and drainage was carried out in the patient, and adenocarcinoma cells were found in the bloody pleural effusion. The assessment was PD. Later, the pleural effusion was controlled, but the change of chest wall skin lesions was not obvious after accepting 2 cycles of treatment with bevacizumab combined with cisplatin pleural perfusion. Currently, the patient is administered S-1 as maintenance, and the symptoms, such as chest

tightness, shortness of breath and multiple skin metastasis, have improved (**Figure 5**).

Diagnosis

The histopathology and immunohistochemistry, including right chest wall skin lesions and right neck and left axillary lymph nodes, revealed that the adenocarcinoma originated from the lung. The MRI scans suggested that brain lesion was a metastasis. PET/CT showed that right chest wall skin lesions and multiple lymph nodes must be metastases, but no lesions were observed in the lungs (**Figure 6**). Therefore, this patient was clearly diagnosed with metastatic adenocarcinoma of the right chest wall with multi-site lymph nodes and brain lesions (putative primary site in the lung).

Discussion

Cutaneous metastasis is rare in lung cancer, and skin lesions always appear to be indepen-

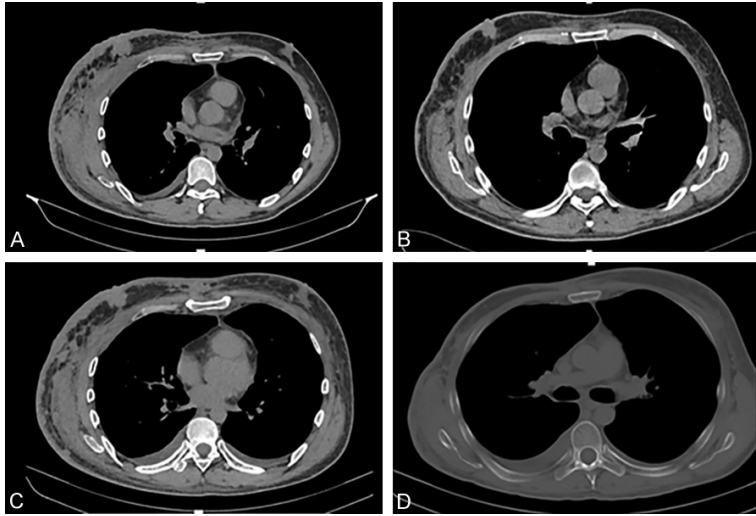


Figure 4. Computed tomography (CT) scan images. The size of cutaneous metastasis during treatment was measured by using CT scans in April 2015 (A), November 2016 (B), March 2017 (C), and Currently (D).



Figure 5. Photograph of cutaneous metastasis, taken on the day skin lesions were confirmed to be metastasis (A) and December 2017 (B). The treatment of cutaneous metastases was effective.

dent. However, it is easy to miss and delay diagnosis since its expression form is non-specific. This patient had no history of smoking, despite multiple skin lesions and rapid development. Biopsy of the skin metastases combined with immunohistochemistry led to diagnosis of skin metastasis of lung adenocarcinoma, which is rare, and reports of skin metastases preceded by primary lung lesions are rare. This suggests that when suspicious skin lesions are encountered in the clinic, the possibility of metastatic carcinoma to the skin should be considered, and skin biopsy should be performed as soon as possible to reach a definite diagnosis and delay illness.

of repeated genetic testing revealed the T790M mutation. The last 10 years of research showed that even for patients who are highly sensitive to EGFR-TKI, EGFR-TKI resistance will appear after 10-12 months of treatment. After acquired resistance, it is recommended to use EGFR-TKI combined with VEGFR inhibitors or directly use the third-generation EGFR-TKIs [20]. After developing EGFR-TKI acquired drug-resistance, the patient changed to the third-generation EGFR-TKIs drug, osimertinib. After a month, the skin lesions were locally relieved, but malignant pleural effusion appeared. The disease progressed, and the effective time of the drug was relatively short.

In recent years, the discovery of the EGFR mutation and successful cases of EGFR-TKI therapy have transformed the treatment of NSCLC from the experiential cytotoxic chemical therapy to molecular targeting therapy. EGFR-TKI has been established as a first-line treatment for terminal NSCLC with EGFR mutation, which greatly improves the prognosis and the quality of life for the patient [14-16]. Common EGFR mutations are deletions in exon 19 or exon 21 L858R point mutation. In this case, the exon 18 G719X point mutation is rare, accounting for only 3% of all EGFR mutations in the Asian population [17]. Previous studies have shown that the G719X mutation has moderate sensitivity to 1G-TKIs, and 2G-TKIs show high efficiency in patients with the G719X mutation [16, 18]. Terminal NSCLC patients receiving EGFR-TKI treatment, regardless of the short-term effect, inevitably develop resistance to TKI and failure to respond to treatment [15, 19]. This patient was treated with EGFR-TKI with good effect at first, and the disease remained stable for 22 months. After progression of the disease, the results

Lung adenocarcinoma cutaneous metastasis

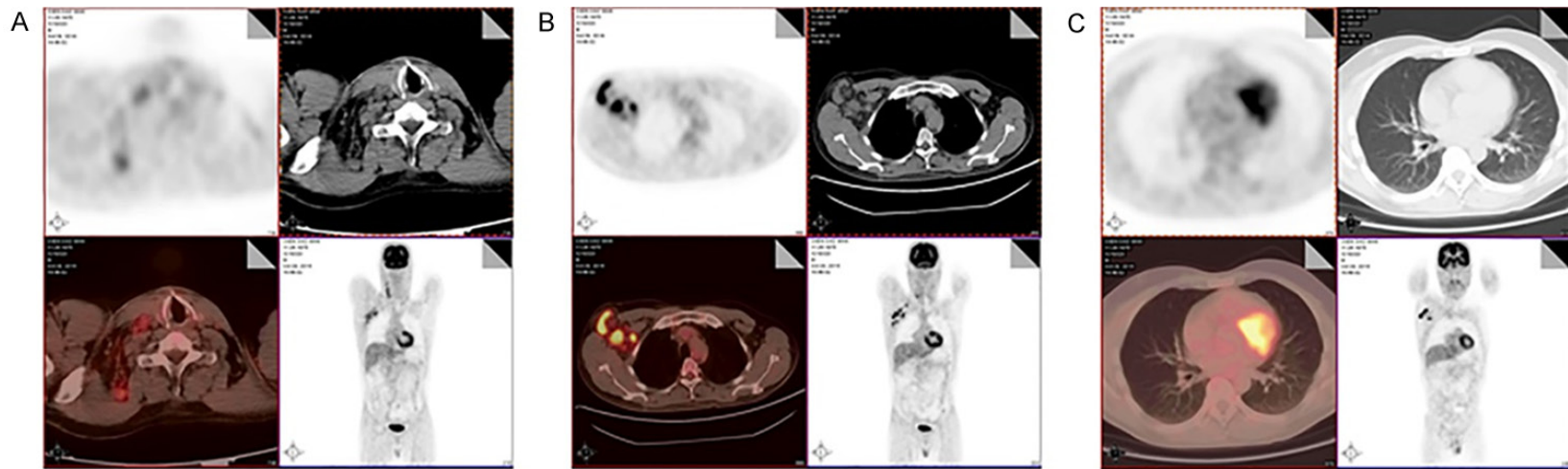


Figure 6. Positron emission tomography/Computed tomography (PET/CT) scan images in October 2014. Multiple lymph node metastases (A), right chest wall skin (B), no obvious lesions in the lungs (C).

The causes of malignant pleural effusion included the formation of neovascularization and increased pleural permeability, which are associated with elevated levels of VEGF. Correlation studies showed that [21-23] bevacizumab can block binding of VEGF to its receptor, whether administered by intravenous infusion or pleural injection, and can effectively control malignant pleural effusion. After 2 cycles of treatment with bevacizumab in combination with cisplatin intrapleural perfusion, the patient's pleural effusion was controlled; however, the right chest wall lesions were not any better. Currently, the patient is taking S-1 to maintain the treatment, and his multiple metastatic lesions of the skin are in remission.

Conclusion

The incidence of cutaneous metastasis in lung cancer is low. It is usually terminal. This patient has been diagnosed with cutaneous metastasis of lung adenocarcinoma for more than 48 months and is still in follow-up with a high quality of life. This is due to the timely diagnosis, multiple means of comprehensive treatment, real-time monitoring of the target site, and timely adjustment of drug use. EGFR-TKI can improve the prognosis of patients with terminal NSCLC and improve the quality of life. After acquiring resistance to EGFR-TKI, we should focus on different models of progression and implement individualized treatments to seek the best survival benefits.

Acknowledgements

This research was supported by grants from the National Natural Science Foundation of China (No. 81560471 and 81760520), the Joint Special Funds for the Department of Science and Technology of Yunnan Province-Kunming Medical University (No. 2017FE467(-073)). The author would like to thank the patient for his courage and determination in wanting to share his case in the hopes of creating awareness of this subject area. Further thanks to Rui Zhang and Chi Wang for their valuable assistance in the evaluation of the diagnostic images.

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Lung adenocarcinoma cutaneous metastasis

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