Case Report

Hereditary multiple exostoses complicated with lung cancer with cough as the first symptom: a case report

Xinyu Jia[1#], Ye Liu[2#], Chaojie Wu[1], Zhenzhen Wu[1], Ningfei Ji[1], Mao Huang[1]

[1]Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China; [2]Department of Geriatrics, Geriatric Hospital of Nangjing Medical University, Nanjing 210024, China

[#]These authors contributed equally to the work.

Correspondence to: Ningfei Ji, Mao Huang. Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China. Email: jiningfei@163.com; hm6114@126.com.

Abstract: Hereditary multiple exostoses (HME) is an autosomal dominant genetic disease. It mainly involves the extremities long bone metaphyseal and flat bone, with the cartilage cap covering the surface. The main clinical symptoms include the compression of the surrounding soft tissue caused by osteophyte hyperplasia, such as pain, dysfunction, and developmental deformity, etc. The cases of HME with lung cancer are rare. We performed a case of cough as the first symptom who had a paternal family history of HME. According to the results of positron emission tomography/computed tomography (PET/CT), pathology and immunohistochemistry, the case was finally diagnosed as right lung adenocarcinoma, T3N2M1a, stage IVA. At present, the patient was given pemetrexed with nedaplatin for 2 cycles and added anlotinib combined with chemotherapy for additional 3 cycles. The recent chest computer tomographic (CT) showed the right lung lesion was slightly smaller than before. When we meet patients of such multiple exostoses with lung occupying lesions, we need to think about many possibilities of the disease from various perspectives, such as primary lung cancer, lung metastasis or bone metastasis.

Keywords: Hereditary multiple exostoses (HME); lung cancer; case report

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Introduction

Hereditary multiple exostoses (HME) is a rare hereditary musculoskeletal disorder, which is a kind of benign bone tumors. It is mainly characterized by the exostosis formed in the perichondrium and covered by the cartilage cap (1). It mostly involves the long bone, rib, scapula, pelvis and vertebral body. Studies have shown that HME is related to the deletion mutation of exorosin-1 (EXT1) and exorosin-2 (EXT2) (2,3). The coding products of EXT1 and EXT2 genes can form heparan sulfate, further form heparan sulfate proteoglycan (4,5), and maintain the proliferation and differentiation of normal chondrocytes (6). About 0.5–2% of HME will malignant into chondrosarcoma or osteosarcoma (7,8). When the cartilage cap continues to grow or the patient has persistent pain, it may indicate that the tumor has malignant transformation (9). The cases of HME with lung cancer are rare and only one case reported in Russia in 1981 was found (10). Herein, we present the following case in accordance with the CARE Guideline (11).

Case presentation

A 33-year-old male patient with a history of HME was admitted to local hospital due to cough and chest pain for almost half a year. The local hospital initially gave antitussive and anti-infective treatment, but the symptoms still recurred. Chest CT scan imaging showed that an occupying lesion in the right middle lobe and enlarged lymph nodes in the mediastinum of the right hilar lung. The endoscopic bronchoscopy indicated that there was stenosis

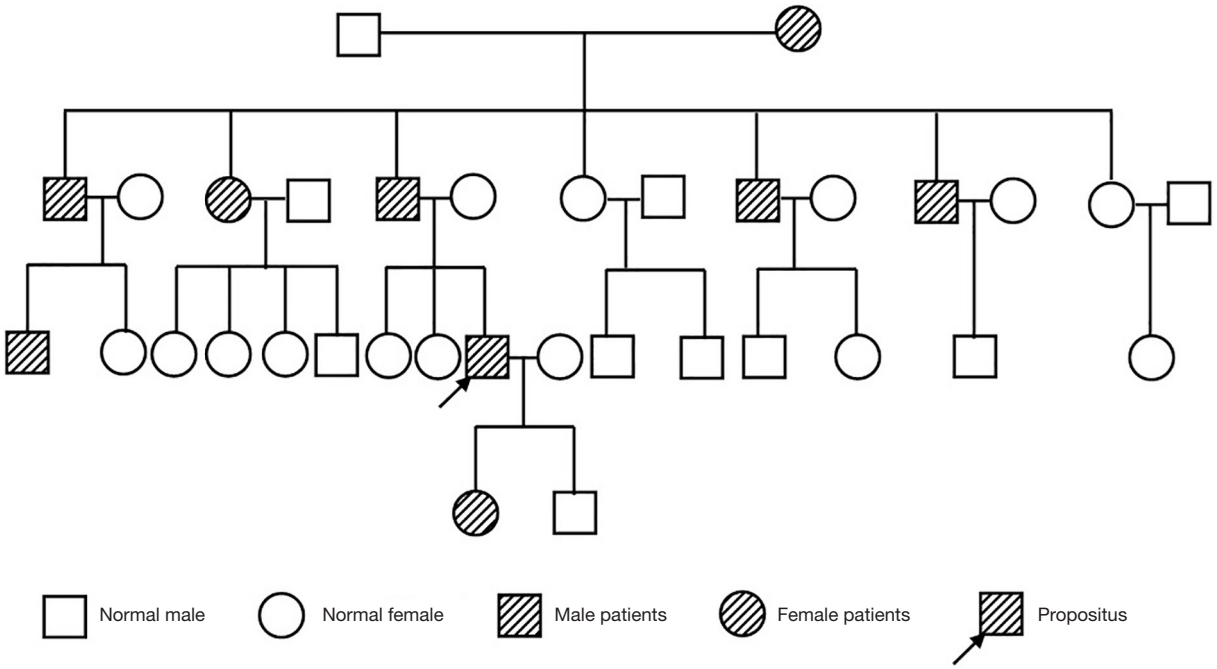

Figure 1 Pedigree of hereditary multiple exostoses.

of the right middle lobar bronchi under external pressure. The tumor marker suggested CA125 was 81.75 U/mL. Therefore, the patient was recommended to transfer for further diagnosis and admitted to our hospital on August 6, 2019. He was operated on in 2001 because of the compression by the exostoses of the lateral left knee. His paternal family had a history of HME (*Figure 1*). The patient denied other chronic diseases, smoking or drinking history.

The physical examination showed that the body temperature was 36.6 ℃, the heart rate was 70 beats/min, the respiratory rate was 14 breaths/min, and the blood pressure was 117/81 mmHg. The height of the patient was 156 cm, and the weight was 63 kg. Lung examination showed no thoracic deformity and no tenderness. The auscultation of both lungs was clear. The left acromioclavicular joint, the left shoulder joint, the right elbow joint, the bilateral knee joint and the left ankle joint could be seen with different sizes of protuberance. The fifth fingers and the fourth toes were slightly short. No obvious abnormality was found in the extremity movement and strength.

Laboratory data indicated that erythrocyte sedimentation rate (ESR) was 25 mm/h and the blood potassium level was 3.34 mmol/L. The tuberculosis antibody was weak positive and T-SPOT was negative. The rest of the laboratory data was unremarkable. CT of the thorax in our hospital was similar to that before. A 3.5×2.4 cm^2 irregular lesion showed a high density image in the middle lobe of the right lung and multiple patchy shadows scattered under the right lung pleura with local pleural thickness and adhesion, small amounts of pleural effusion. Multiple enlarged lymph nodes were found in mediastinum. There were multiple cauliflower-like exostosis on both ribs and scapula (*Figure 2*). The magnetic resonance imaging (MRI) result was consistent with CT result (*Figure 3*). In order to find out the occupying lesion in the right upper lobe, CT-guided percutaneous lung biopsy was performed. Pathology results showed that there were lung tissue arranged in cords with few allotypic cells (*Figure 4*). Immunohistochemistry results showed that few allotypic cells pointed out CK7(+), TTF-1(+), WT-1(–), Calretinin(–), CK5/6(–), D2-40(–). Combined with HE sections, this case was consistent with infiltrative adenocarcinoma. To determine the clinical stage of tumor, PET/CT examination was performed, which suggested that right lung cancer with right intrapulmonary and right pleura metastasis. The irregular edges of ribs and neck of femur on both sides were considered as multiple exostoses. Molecular pathologic analysis results showed no EGFR mutations. According to the results of PET/CT and pathology, the diagnosis of right lung adenocarcinoma,

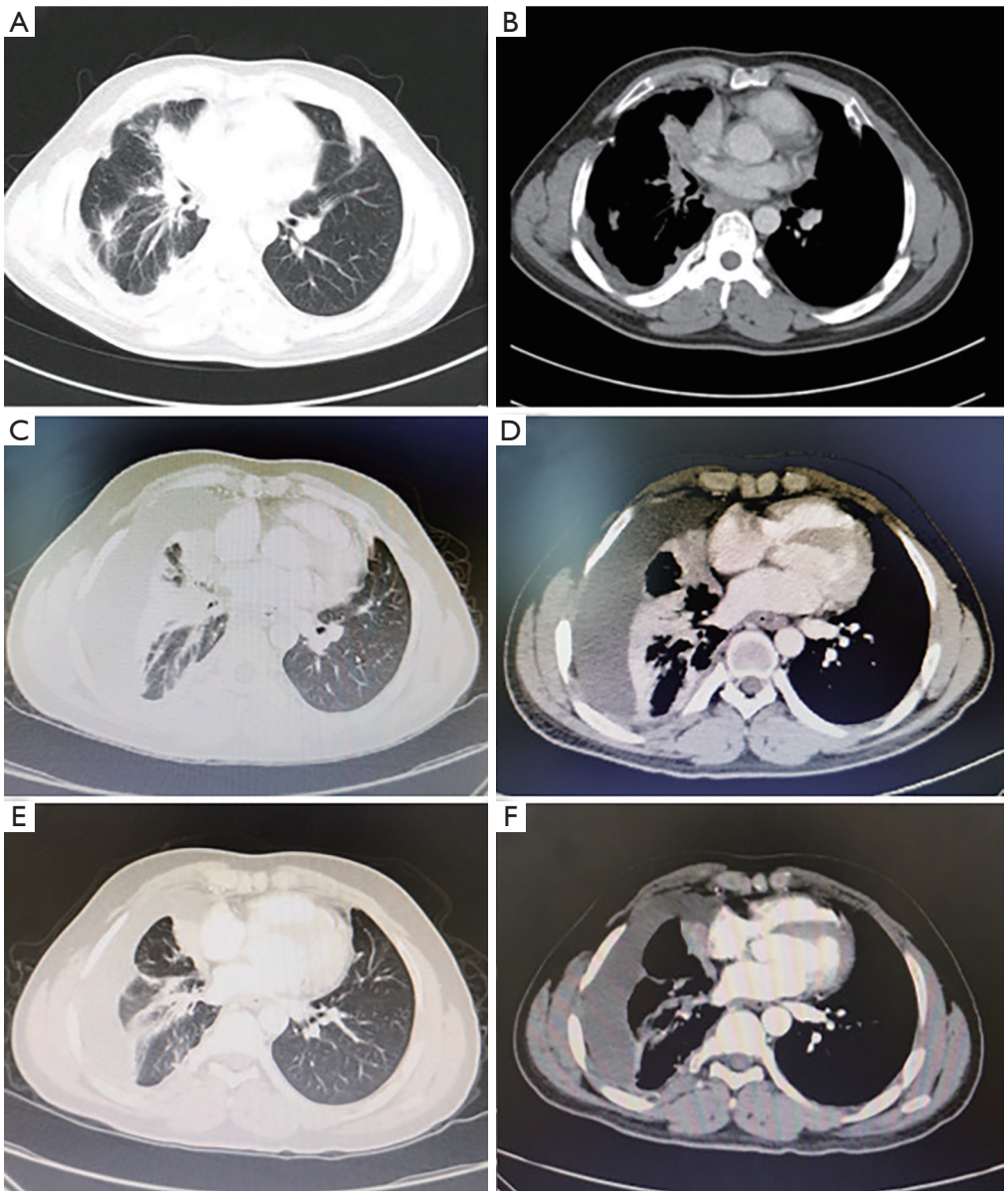

Figure 2 Changes in CT signs during the process of disease in the patient. (A) The right middle lobe lesion measuring about 3.5×2.4 cm^2 and multiple patchy shadows under the right lung pleura; (B) local pleural thickness and adhesion, small amounts of pleural effusion, multiple enlarged lymph nodes in mediastinum and multiple cauliflower-like exostosis on both ribs; (C) repeat chest CT after treatment for 6 weeks with the right lung lesions similar to the former; (D) the thickened right visceral pleura and the increased right pleural effusion; (E) repeat chest CT after treatment for 12 weeks with the right middle lobe lesion measuring about 3.0×1.7 cm^2; (F) pleural effusion slightly less than before.

T3N2M1a, stage IVA was considered.

The patient was started on pemetrexed 800 mg combined with nedaplatin 140 mg given every 3 weeks for 2 cycles on August 23 and September 17. After the second cycle, reexamination of chest CT showed that the right lung lesions were similar to the former, the right visceral pleura was thickened, and the right pleural effusion increased (*Figure 2*). Considering that the increase of pleural fluid was caused by pleural metastasis, we adjusted the treatment plan. The patient was added anlotinib 12 mg

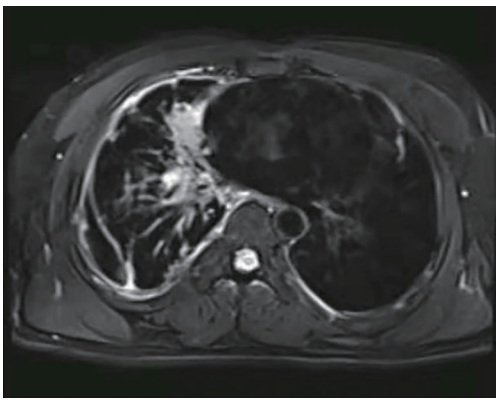

Figure 3 The magnetic resonance imaging. The occupying lesion in the right middle lobe.

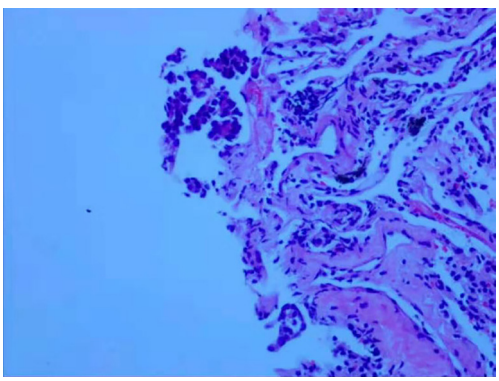

Figure 4 The pathology imaging. Lung tissue arranged in cords with few allotypic cells (IHC, ×100).

combined with pemetrexed 800 mg and nedaplatin 140 mg for additional 2 cycles on October 11 and November 6. A subsequent chest CT showed that the right middle lobe lesion measuring about 3.0×1.7 cm^2 had a slight decrease in size than that before (*Figure 2*). As a result, an additional 1 cycle of treatment was given on December 2 (for details see *Figure 5*). The patient is still under active treatment and further follow-up is in progress.

Discussion

HME with primary lung cancer is rare. After searching the related researches, only one case reported in Russia in 1981 was found (10). This case admitted in our hospital was a young man with cough as the first symptom. He had a paternal family history of HME. The main clinical symptoms of HME in the rest of the family were mostly caused by tumor compression, most of which did not cause dysfunction. The family history of malignant tumor was denied. According to the results of PET/CT, pathology and immunohistochemistry, right lung adenocarcinoma, T3N2M1a, stage IVA could be diagnosed finally. Due to the limited economic conditions of patients, we were not able to complete all molecular pathologic analysis. However, this case provides new thinking for our future diagnosis. When we meet patients with such multiple exostoses and lung occupying lesions, we need to think about many possibilities of the disease from various perspectives, such as multiple exostoses with primary lung cancer, malignant transformation of osteochondroma into chondrosarcoma complicated with lung metastasis, primary lung cancer with bone metastasis and hypertrophic pulmonary osteoarthropathy (HPOA), etc.

In the case of multiple exostoses with primary lung cancer, the diagnosis of primary lung cancer can be determined by combining imaging examination, pathological analysis, molecular pathologic analysis and other methods. In terms of the choice of treatment plan, this patient chose the conventional chemotherapy plan for non-small cell lung cancer, namely pemetrexed combined with platinum complexes. At present, the clinical treatment of HME is mainly surgery, including exostoses resections and orthopedic surgery for patients with obvious compression symptoms. The patient had no obvious symptoms this hospitalization, so multiple exostoses were not treated. Some researches have shown that estrogen is related to the occurrence, development and prognosis of lung cancer. β-estradiol can be detected in high concentration in non-small cell lung cancer tissues (12), which can stimulate tumor growth (13) and induce malignant transformation of normal tissues (14). Because chondrosarcoma has estrogen receptor, it has been proved to be sensitive to estrogen (15,16). The use of antiestrogen drugs may stimulate the growth of chondrosarcoma, thus increasing the risk of malignant transformation of HME into chondrosarcoma (17). Therefore, this kind of patients are not suitable for anti-estrogen treatment. Whether estrogen is the correlation point between these two diseases, and whether HME can increase the risk of lung cancer, many mysteries still need to be further explored.

About 0.5–2% of HME will turn into low-grade and highly differentiated peripheral chondrosarcoma (18). Compared with primary chondrosarcoma, secondary chondrosarcoma has less metastasis and better prognosis. After successful surgical treatment, patients may

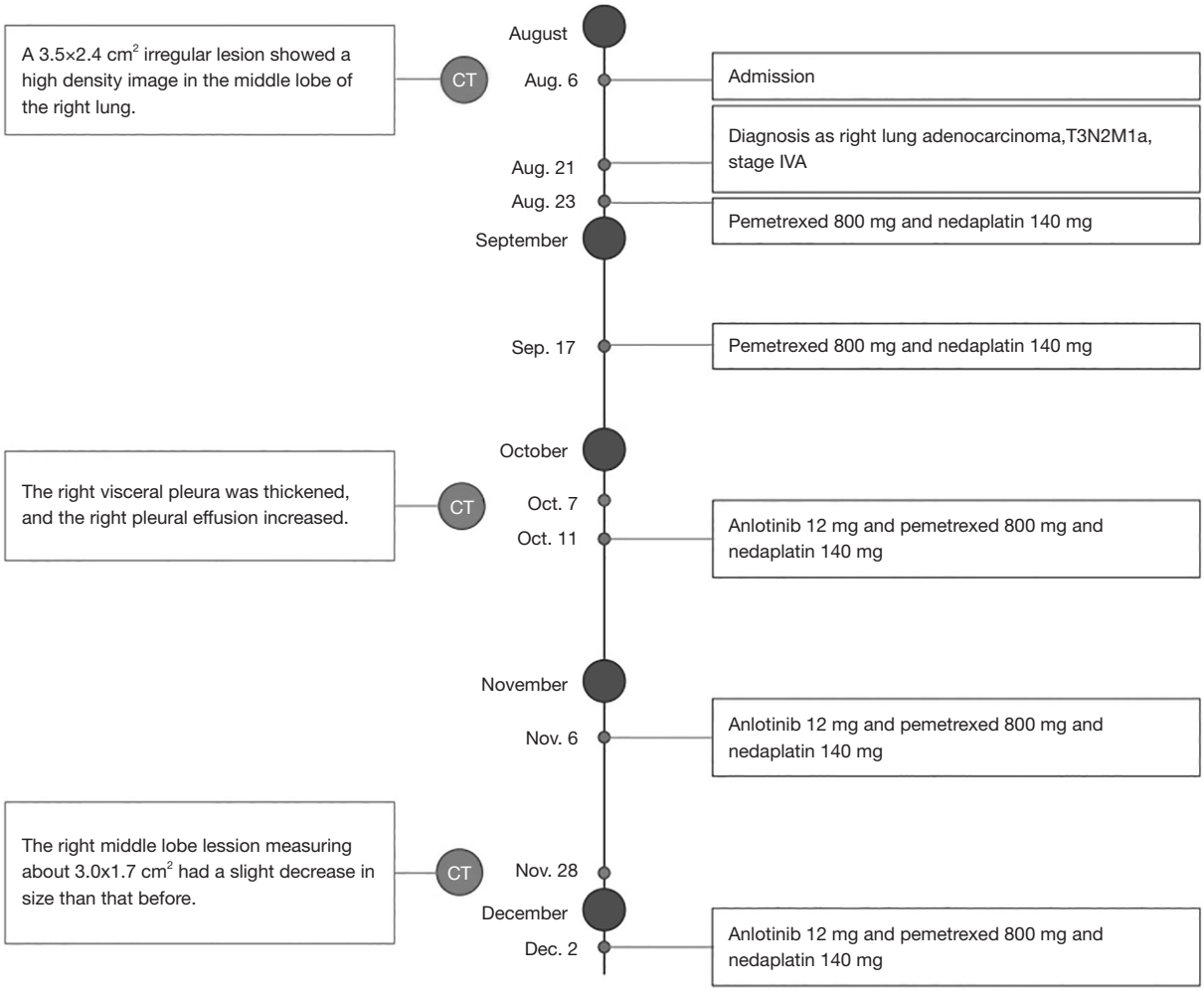

Figure 5 The timeline of the patient with right lung adenocarcinoma, T3N2M1a, stage IVA.

achieve long-term disease-free survival (19). About 10% of chondrosarcomas are dedifferentiated (18). It has been shown that peripheral dedifferentiated chondrosarcoma accounts for 3.86% (20) and 5.5% (21) of all dedifferentiated chondrosarcomas. It can be secondary to benign osteochondroma, with strong invasion, poor prognosis and low survival rate (22), in which the lung is the most common site of metastasis (19). If considering the malignant transformation of osteochondroma into chondrosarcoma complicated with pulmonary metastasis, the clinical manifestations are usually sudden swelling and persistent pain of the focus of osteochondroma, and the pulmonary symptoms generally appear later. In this case, cough was the first manifestation, and there was no symptom of bone compression. Therefore, the possibility could be excluded.

Bone metastasis is one of the main metastasis sites of lung cancer (23), the incidence is about 10–15% (24), most of which are osteolytic lesions (25). It often accompanied by bone pain and bone related events, such as pathological fracture, spinal cord compression (25), Bone metastasis is the first symptom in many patients. At present, radionuclide bone scan and PET/CT are the main screening methods. The PET/CT findings of this patient showed that the edges of ribs and the femoral neck at both sides were irregular, and there was no increase in FDG metabolism. Multiple chondroma may be considered. So, bone metastasis of lung cancer was excluded. However, for the high-risk patients who have a history of osteochondroma complicated with lung cancer and have new symptoms of bone pain, we still need to be aware of the possibility of bone metastasis.

HPOA is a syndrome characterized by digital clubbing, arthritis, and periostitis, which caused by lung disease (26). Its clinical characteristics are bilateral symmetric periosteal hyperplasia and new bone formation, which mainly affects long bone. Adenocarcinoma is common. The main pathogenesis may be related to abnormal secretion of growth hormone, autoimmune response, blood circulation disorders and so on (27). Joint pains usually precede pulmonary symptoms, so it is easy to missed diagnosis and misdiagnosis. When the primary tumor is treated with radiotherapy (28), chemotherapy (29) and surgical resection (30), the symptoms of bones and joints will be improved accordingly. The patient had no new symptoms of bone and joint, so it was excluded.

To sum up, the clinical cases of HME with primary lung cancer are rare. The diagnosis depends on the comprehensive judgment of clinical manifestations, imaging means and pathological examination. In the process of clinical diagnosis and treatment, it is possible to make more accurate diagnosis and targeted treatment by considering various clinical aspects. Whether HME is a risk factor for lung cancer and its related pathogenesis remains to be further studied.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.02.22). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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