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Case Report

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Proximal Femoral Metastasis From Epidermal Growth Factor Receptor-Mutated Lung Adenocarcinoma Mimicking Osteosarcoma on Magnetic Resonance Imaging

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Abstract

The aggressive nature of lung cancer is frequently accompanied by a high incidence of bone metastasis; however, proximal femoral metastasis from lung cancer is comparatively uncommon when compared to other malignancies. In this report, we present the case of a 53-year-old Asian male who presented with pain in the left thigh and back. Magnetic resonance imaging revealed severe bone destruction with involvement of adjacent soft tissue mass at the left thigh, exhibiting imaging findings that mimic osteosarcoma. Subsequent bone biopsy confirmed the diagnosis of epidermal growth factor receptor (*EGFR*)-mutated lung adenocarcinoma with bone metastasis. The patient achieved survival following administration of osimertinib and underwent surgery for femoral metastases without palliative surgery for lung cancer. Therefore, proximal femoral metastasis from *EGFR*-mutated lung adenocarcinoma should be considered as a differential diagnosis in patients suspected to have osteosarcoma. The imaging findings of proximal femoral metastasis from *EGFR*-mutated lung adenocarcinoma were presented, and their therapeutic management was discussed.

Keywords: Proximal femoral metastasis; *EGFR* mutation; Lung adenocarcinoma; Osteosarcoma

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Introduction

Lung cancer, especially lung adenocarcinomas, is a commonly diagnosed malignancy in the world and is associated with high frequencies of bone metastases [1, 2]. As metastasis becomes the leading cause of cancer-related deaths, emerging studies have been focusing on revealing the mechanism of metastasis to control this adverse process. Studies have found that manipulating immune cells, such as pro-metastatic macrophages and reprogrammed $CD8^+$ T lymphocytes, can significantly inhibit lung metastases via their antitumor activity [3-6]. For example, Celus et al have found that macrophage caveolin-1 signaling is critical for metastasis, whose inhibition may drive lung metastatic growth via promoting angiogenesis [7]. The bone metastasis of lung cancer is commonly located in the spine, with a lesser extent in the ribs, pelvis and proximal femur [8]. Unlike the common site of osteosarcoma, such as distal femur, proximal tibia, and proximal humerus, proximal femur was an uncommon site of osteosarcoma [9]. Here, we describe an interesting case of epidermal growth factor receptor (*EGFR*) mutant lung adenocarcinoma with proximal femoral metastasis, whose imaging findings (severe cortical bone destruction and a large soft tissue mass) mimic osteosarcoma.

Case Report

Investigations

We admitted a 53-year-old smoking Asian male. He has a 1-month history of persistent swelling pain in his left thigh and back. The pain was more severe at night. His laboratory studies of arrival showed (normal reference ranges are given in parenthesis) white blood cell count of 8.38×10^9/L (3.5 - 9.5 $\times 10^9$/L); neutrophil percentage 51.9% (40-75%); hemoglobin 152 g/L (130 - 175 g/L); albumin 40.5 g/L (40 - 55 g/L); calcium 2.35 mmol/L(2.09 - 2.54 mmol/L); carcinoembryonic antigen 137.61 ng/mL (0 - 5 ng/mL); carbohydrate antigen 125 167.5 U/mL (0 - 35 U/mL); carbohydrate antigen 19-9 10.94 U/mL (0 - 27 U/mL); ferritin 531.78 ng/mL (21.8 - 274.66 ng/mL); neuron specific enolase 26.63 ng/mL (0 - 16.3 ng/mL);

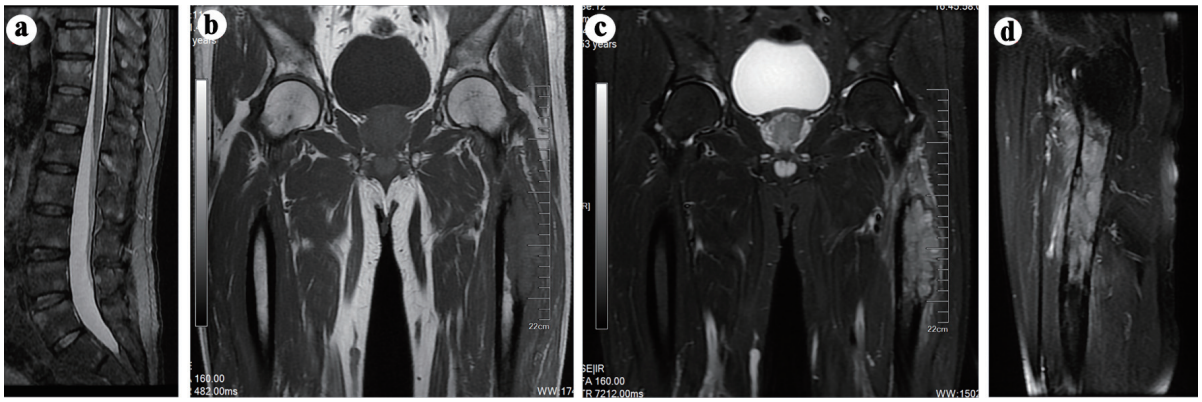

Figure 1. (a-c) MRI scans indicating potential multiple metastatic lesions in bilateral proximal femur, ilium, ischium, pubis, and spine. (b) T1-weighted sagittal spin-echo sequence of the thigh and hip joint displaying a hypointense lesion in the left proximal femur. (c, d) T2-weighted sagittal spin-echo sequence with fat-suppression demonstrating a hyperintense lesion involving intraosseous and extraosseous soft tissue in the left proximal femur. MRI: magnetic resonance imaging.

and cytokeratin 19 fragment 3.53 ng/mL (0.1 - 3.3 ng/mL). The rest of the results of the laboratory studies were almost normal. On physical examination, a lump was found on his left lower extremity, which was tough and lacks mobility, causing pain when pressed.

Diagnosis and treatment

Then we arranged a magnetic resonance imaging (MRI) to examine the thigh, hip joint, and the spine. The results of thigh and hip joint revealed aggressive cortical destruction of left proximal femur, with an adjacent extraosseous soft tissue mass. MRI results also showed possible multiple bone metastases to the right proximal femur, bilateral ilium, bilateral ischium, bilateral pubis, and spine (Fig. 1a-d). Accidentally, the patient develops spontaneous fracture of left proximal femur, which could not enable a computed tomography (CT) scan due to unbearable pain. Therefore, an ultrasound-guided needle biopsy of the mass was conducted, and lung adenocarcinoma was diagnosed based on pathologic examination. In order to facilitate further examination and treatment, we applied external fixation to temporarily fix the displaced pathological fracture. Then, we conducted chest CT, with results showing a lesion at the left upper lobe (Fig. 2a, b), which is finally revealed as stage IV adenocarcinoma (Fig. 3a-c). Then the patient was transferred to the oncology department for further management, where mutational analysis of the tumor revealed an *EGFR* exon 19 deletions mutation, and the patient then received osimertinib, an EGFR-tyrosine kinase inhibitor (TKI).

Follow-up and outcomes

At the 3-month follow-up, he exhibited a favorable response to osimertinib without any further deterioration of his condition (Fig. 2c). Additionally, he underwent left proximal femoral replacement at a local hospital. At the 6-month follow-up, he achieved disease stability and regained the ability to ambulate freely.

Discussion

Bone metastasis frequently occurs in lung cancer, including lung adenocarcinomas [1]. According to a retrospective study, the mean age of patients with lung cancer and bone metastases is 61.5 years, and most of the patients were presented between 50 and 59 or 60 and 69 years old [10]. Among the oncogenic mutations, *EGFR* mutations are the most commonly identified

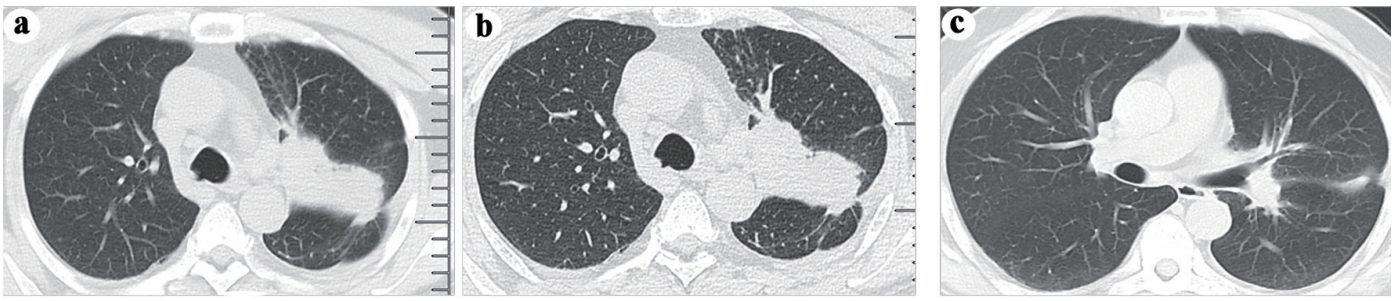

Figure 2. (a) A neoplasm in the left upper lobe was observed on a computed tomography (CT) scan. (b) The presence of a neoplasm in the left lung was confirmed through an enhanced CT scan. (c) A follow-up CT scan at 3 months after osimertinib administration revealed shrinkage of the neoplasm in the left upper lobe.

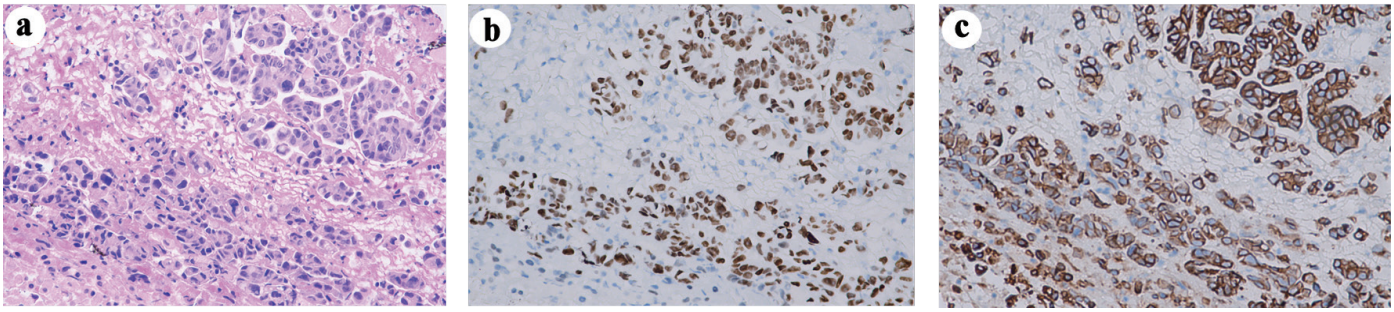

Figure 3. (a) H&E staining (original magnification, × 400) depicting tumor cell morphology. Immunohistochemical analysis revealed expressions of CK7 ((b) original magnification, × 400) and TTF1 ((c) original magnification, × 400), confirming the diagnosis of lung adenocarcinoma. H&E: hematoxylin and eosin; CK7: cytokeratin 7; TTF1: thyroid transcription factor 1.

mutation in non-small cell lung cancer, including squamous cell carcinoma, lung adenocarcinoma, and large cell carcinoma; Of which, *EGFR* exon 21 L858R mutations are the most common mutation in *EGFR* followed by *EGFR* exon 19 deletions and *EGFR* exon 20 insertion mutations (exon20ins) [11]. The presence of *EGFR* mutation in lung cancer can induce the upregulation of the EGFR signaling pathway, consequently resulting in an increase in vascular endothelial growth factor (VEGF) expression to promote angiogenesis and facilitate tumor invasion and metastasis [12, 13]. Additionally, exosomes derived from lung cancer cells have been shown to activate the EGFR pathway, resulting in increased receptor activator of nuclear factor kappa B ligand (RANKL) expression and subsequent induction of osteoclastogenesis, ultimately facilitating osteolytic bone metastasis [14, 15]. Therefore, numerous mechanisms may underlie the promotion of rare bone metastasis in *EGFR*-mutated lung adenocarcinoma.

And *EGFR*-mutant lung adenocarcinoma shared a similar bone metastatic features with overall lung cancer. According to a retrospective study, spine remains the most common site of bone metastasis for those patients, followed by ribs, pelvis, scapula, femur, humerus, and skull, whose finding was mostly in consistent with previous reports [8, 16]. Among them, femur metastasis only occurs in approximately 7.7% patients of lung adenocarcinomas with bone metastasis [16]. Moreover, studies have found that the prognosis was poor in patients with metastasis to the femur [8]. For patients with *EGFR* exon 19 deletions, osteolytic bone metastasis is commonly observed, and these patients can benefit from the administration of bisphosphonate at least six times for a duration exceeding 1 year to effectively reduce the occurrence of skeletal-related events [16]. In our case, the patient develops spontaneous fracture of his left femur during the hospitalization, which highlights the importance of protecting affected limb after admission to hospital.

Osteosarcoma is the most common primary malignant bone tumor, which primarily attacks younger patients, especially patients with an age of 10 to 30 years. The tumors usually involve extremities, including distal femur, proximal tibia, and proximal humerus and show high frequencies of lung metastases [9, 17, 18]. However, the proximal femur is a rare site of osteosarcoma, where they may have some unusual manifestations and pose diagnostic and therapeutic mistakes [9]. According to a retrospective study, no patients with proximal femoral osteosarcoma reported typical symptoms of pain with a soft tissue swelling; on imaging, 92% lesions were osteolytic and had immature osteoid matrix, 58% lesions involved soft tissue, and 8% lesions had a periosteal reaction [9]. Imageology examination is important for the evaluation of osteosarcoma. Of which, radiography of osteosarcoma can vary from osteolytic to osteoblastic depending on the amount of mineralized matrix. CT can be used to early detect metastases in the lung, while MRI can be used to evaluate the intraosseous and extraosseous tumor extent [19]. In our case, his initial MRI showed osteolytic lesions with extensive intraosseous and extraosseous involving, whose manifestations favored the diagnosis of atypical osteosarcoma. However, the pathological diagnosis of the mass after needle biopsy was lung adenocarcinomas, which is far from our initial diagnosis. Thus, we highlighted the importance of making final diagnosis based on not only imaging tests but also histopathological studies.

Most of the lung cancers are detected at an advanced stage. As for the management of cancer, studies have recommended to conduct comprehensive treatment for disease control, such as pain management, immunotherapy and chemotherapy and surgery [1]. Among them, antiresorptive drug, such as zoledronic acid and denosumab, was recommended to initiate as soon as possible when bone metastases appear or when it became symptomatic [20]. Palliative surgery, such as performing lobectomy plus lymph node resection, of the primary site of stage IV non-small cell lung cancer, was also recommended for patients that can tolerate the surgery [21, 22]. For patients with advanced-stage *EGFR* mutated lung adenocarcinoma, TKIs, such as osimertinib, are the primary therapeutic option. Studies have shown that TKI with lung cancer salvage surgery may prolong the overall survival of these patients by removing TKI-resistant subclones [23, 24]. However, for proximal femoral metastasis derived from lung adenocarcinoma, the data of clinical management and surgical treatment of metastasis are scarce. A retrospective study included 148 consecutive patients of femoral metastases demonstrated that internal fixation, which is a less invasive and time-saving procedure, is beneficial for patients with short-term expected survival, and that endoprosthetic replacement may offer favorable long-term results [25]. In our case, the patient underwent immunotherapy and received external fixation for a spontaneous fracture of his left femur. Following improvement in his condition, he subsequently underwent surgical intervention for femoral metastases at a local hospital; however, no surgical procedure was per-

formed for lung cancer. After a follow-up period of 6 months, the patient showed positive response to TKIs, and there was no further deterioration of his condition. Therefore, surgery for femoral metastases would be beneficial if the patient can tolerate the surgery; however, studies with a high level of evidence are needed to verify our recommendations.

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Conflict of Interest

The authors declared no conflict of interest.

Informed Consent

Written informed consent was obtained from the patient.

Author Contributions

CJC and JFY participated in the drafting, writing, and revising of the manuscript. HXZ, QWM, XZ, MC and DYP participated in the data selection and analysis. CJC and DYP contributed to the study concept and acquired and analyzed the data. All authors contributed to the drafting of the manuscript and figure preparation.

Data Availability

The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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