# Case Report Sarcomatous transformation of EGFR and TP53 mutation-positive metastatic adenocarcinoma of the lungs, masquerading as a primary pleomorphic sarcoma of the proximal femur

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**Abstract:** We investigated a case of metastatic adenocarcinoma of the lungs at the left proximal femur, masquerading as a primary pleomorphic sarcoma. A 72-year-old woman presented with pain in her left thigh in conjunction with a mass that had been gradually growing over a few months. She was being treated with gefitinib for lung adenocarcinoma positive for the epidermal growth factor receptor (*EGFR*) mutation L858R, and had multiple bone metastases. The lung adenocarcinoma and metastases had stabilized with the treatment. The metastatic lesions in the bone had also received radiation; however, a tumor in the proximal femur kept growing despite treatment. A biopsy specimen from the proximal femur revealed the proliferation of spindle-shaped cells without an epithelial glandular component. The patient underwent en bloc resection of the proximal femur that was replaced by prosthesis. Histologically, the resected tumor was entirely composed of pleomorphic cells and tumor giant cells exhibiting no apparent glandular structures. Tumor cells were diffusely positive for p53 and focally positive for epithelial markers and EGFR, but were negative for thyroid transcription factor-1, suggesting an initial diagnosis of primary pleomorphic sarcoma. Genetic examination revealed mutations in *EGFR* and *p53* that were of the same type as the lung tumor, leading to the final diagnosis of the femoral mass as a sarcomatous transformation of metastatic lung adenocarcinoma. However, secondary genetic alterations that might explain the acquired resistance to gefitinib could not be found in the proximal femoral tumor. The patient remains alive and the remaining lesions are well controlled.

Keywords: Lung adenocarcinoma, EGFR, TP53, metastasis

#### Introduction

Non-small cell lung cancer (NSCLC) accounts for a significant number of cancer-related deaths in the world. Recently, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib, have provided a marked benefit for patients with NSCLC tumors harboring specific genetic alterations [1-3]. However, in spite of remarkable initial response, *EGFR*-mutated NSCLCs eventually acquire secondary resistance to these agents [4]. Several mechanisms of acquired resistance to EGFR-TKIs have been described, the most common of which is a secondary *EGFR* T790M point mutation in exon 20 [4, 5]. Other molecular mechanisms of resistance are the upregulation of MET/HGF, HER2 mutations, HER3 overexpression, persistent activation of IGF-1R, mutation of PIK3CA/AKT, loss or downregulation of PTEN, and abnormal dimerization of STAT3 [5-8]. Additionally, epithelial to mesenchymal transition (EMT) has been reported as a cause of acquired resistance to EGFR-TKIs [5, 9]. There were several studies and case reports describing changes in EMT status and transformation to small cell lung cancer (SCLC) [10-12]. However, we could not find a case that described a bone metastasis undergoing sarcomatous transformation after treatment with gefitinib. Herein, we describe a case of sarcomatous overgrowth of metastatic adenocarcinoma of the lungs at the left proximal femur, masquerading as a primary pleomorphic sarcoma.

Gene	Re-	Forward/	Primer sequence	Size
	gion	Reverse		(00)
EGFR	EX 18	F	5'-CAA GTG CCG TGT CCT GGC ACC CAA GC-3'	381
	F 40	к г		007
	EX 19	F	5'-GCA CCA TCT CAC AAT IGC CAG TTA-3'	207
	F 00	к г	5'-AAA AGG TGG GCC TGA GGT TCA-3'	270
	EX 20	F		3/9
	F. 01	R		074
	EXZI	Г		374
	Ev E	к г		011
922	EX D	Г		211
	Ev 6	r L		100
	EX 0	r D		197
	Ev 7	r. E		100
		Г		192
	Ev 0			12/
	EX O	Г D		134
	Ev Q			101
	EX 9	Г D		101
Kras	Ev O	F		166
		ı D		100
	Fv 3	F		121
	LAG	P		191
	Fy /	F		381
		P		501
Nras	Fy 2	F		301
		P		301
	Fx ٦	F	5'-GGT GAA ACC TGT TTG TTG GA-3'	272
	LAU	R		212
Hras	Fx 2	F		169
		R	5'-CGC TAG GCT CAC CTC TAT AGT G-3'	100
	Fx 3	F	5'-CTG CAG GAT TCC TAC CGG A-3'	160
		R	5'-ACT TGG TGT TGT TGA TGG CA-3'	100
PIK3CA	Fx 9	F	5'-GCT AGA GAC AAT GAA TTA AGG GAA A-3'	122
		R	5'-AGC ACT TAC CTG TGA CTC CA-3'	
	Fx 20	F	5'-AAC TGA GCA AGA GGC TTT GG-3'	122
		' R	5'-CTT TTC AGT TCA ATG CAT GCT G-3'	122

Table 1. Primer sequences used in this study

tion factor-1 (TTF-1) (DAKO, clonal; 8G7G3/1), p53 (Leica Biosystems, clonal; PAb 1801), CA-M5.2 (Becton, Dickinson and Company, clonal; CAM5.2), epithelial membrane antigen (EMA) (Leica Biosystems, clonal; GP1.4), AE1/3 (Leica Biosystems, clonal; AE1 and AE3, mixed to a ratio of 20:1), desmin (Leica Biosystems, clonal; DE-R-11), SMA (DAKO, clonal; 1A4), M-actin (DAKO, clonal; HHF35), and EGFR (DAKO, clonal; 2-18C9). Mutation analysis of

the EGFR, TP53, KRAS, NRAS, HRAS, and PIK3CA

Genome DNA was extracted from formalin-fixed, paraffin-embedded blocks from which the tumorbearing areas were dissected manually with a scalpel. DNA samples from the primary lung tumor as well as tumorous and non-tumorous tissue from the left femoral tumor were prepared for mutation analysis. Bidirectional sequencing of EGFR, TP53 KRAS, NRAS, HRAS, and PIK3CA were performed. The primer sequences used in this study are listed in Table 1. PCR cycling conditions were as follows: 94°C for 2 minutes fol-

Detection of the same mutations of *EGFR* and *TP53* in the both lung and femoral lesions led us to the final diagnosis of the latter as metastatic carcinoma.

#### Materials and methods

#### Immunohistochemistry

Immunohistochemical staining was performed with the following antibodies: thyroid transcrip-

lowed by 40 cycles of 94°C for 30 seconds, 55°C for 30 seconds, and 72°C for 30 seconds, and a final hold at 72°C for 2 minutes.

## **Case presentation**

A 72-year-old woman presented with pain in her left thigh that had persisted over a few months concomitant with a gradually growing mass. The patient was receiving gefitinib to treat lung



**Figure 1.** Presurgical imaging of the primary tumor and femoral metastasis. (A) Computed tomography (CT) of the chest showed a high-density nodular mass before gefitinib treatment. (B) Plain radiography revealed an osteolytic lesion in the left proximal femur before gefitinib treatment. (C, D) Contrast enhanced CT of the femurs and pelvis showed a thin cortex in the left femur with no soft tissue mass before gefitinib treatment. (E) Chest CT taken during gefitinib treatment and irradiation revealed marked shrinkage of the tumor. (F) Plain radiograph taken before surgery showed an osteosclerotic lesion with osteolytic change in the left proximal femur and decreased permeability into the surrounding soft tissue. (G, H) Enhanced CT taken before surgery revealed an isodense mass within the bone marrow and surrounding soft tissue. (I, J) Magnetic resonance imaging performed before surgery revealed a mass with isointensity on T2-weighted images (I) and with heterogenous intensity on fat-suppressed T2-weighted images (J) around the left femur.



**Figure 2.** Histologies of the primary lung adenocarcinoma and femoral tumor. (A) Biopsy specimen shows adenocarcinoma without an apparent sarcomatous component. (B, C) Tumor cells in the lung adenocarcinoma are negative for EGFR staining (B), but positive for thyroid transcription factor-1 (TTF-1) staining (C). (D) Tumor cells show diffuse expression of p53. (E) The resected femoral tumor shows a proliferation of spindle-shaped pleomorphic cells. (F) The tumor contains myxoid area with lower cellularity. (G) The tumor includes a necrotic area. (H) Mitoses are frequently observed.

adenocarcinoma that had multiple bone metastases and was positive for the EGFR mutation L858R (Figure 1A-D). The patient had no respiratory symptoms, and she had never smoked. The primary lung adenocarcinoma and all metastatic lesions except one on the left proximal femur had remained staduring ble treatment (Figure 1E). The bone metastatic lesions had also received radiation: however, the proximal femoral tumor continued to grow despite treatment. A physical examination revealed swelling and pain at the left proximal thigh. Laboratory tests detected high levels of carcinoembryonic antigen, although gefitinib treatment decreased the levels from 446.2 ng/mL to 23.5 ng/ mL prior to surgery. Radiography revealed an osteosclerotic lesion with osteolytic change in the left proximal femur (Figure 1F). Computed tomography revealed that the tumor inside of the left femur gradually enlarged, penetrated the cortex, and invaded the surrounding soft tissue (Figure 1G, 1H). Magnetic resonance imaging uncovered a mass with isointensity on T2weighted images and with heterogenous intensity on fat-suppressed T2-weight-



**Figure 3.** Immunohistochemistry of the left proximal femoral tumor. (A) The tumor cells show focal expression of EGFR. (B) The tumor cells are negative for TTF-1. (C) The tumor cells show diffuse expression of p53. (D-F) The tumor cells show focal expressions of CAM5.2 (D), epithelial membrane antigen (E), and AE1/AE3 (F).

ed images (**Figure 1I**, **1J**). A biopsy specimen from the proximal femur revealed the proliferation of spindle-shaped cells without an epithelial glandular component. With an initial diagnosis of pleomorphic sarcoma, the patient underwent en bloc resection of the left proximal femur where tumorous tissue was replaced with an artificial joint.

## Pathological examination

The biopsy specimen from the lung tumor revealed adenocarcinoma without a sarcomatous component (Figure 2A). Immunohistochemically, EGFR was not detected (Figure 2B) but diffuse TTF-1 (Figure 2C) and focal p53 (Figure 2D) staining were observed. The resect-



**Figure 4.** Genomic analysis of the primary lung adenocarcinoma and femoral tumor. Both the primary lung adenocarcinoma and the left femoral tumor contained the *EGFR* variant at codon 858 (CTG>CGG; L858R), and this was confirmed to be a tumor-specific mutation. (A) DNA sample from non-tumorous tissue, (B) DNA from the left femoral tumor, (C) DNA from the lung adenocarcinoma. Furthermore, both the primary lung adenocarcinoma and the left femoral tumor contained a *TP53* variant at codon 181 (CGC>CCC; R181P), and this was confirmed to be tumor-specific mutation. (D) DNA sample from non-tumorous tissue, (E) DNA from the left femoral tumor, (F) DNA from the lung adenocarcinoma.

ed tumor was also entirely composed of spindleshaped pleomorphic cells and tumor giant cells without glandular structures (Figure 2E, 2F). Focally, necrosis was observed (Figure 2G). Mitosis was also frequently detected (Figure 2H). Immunohistochemically, EGFR was expressed focally on the cell membrane (Figure 3A), but TTF-1 expression was not observed (Figure 3B). In addition, tumor cells were diffusely positive for p53 (Figure 3C), and focally positive for the epithelial markers CAM-5.2, EMA, and AE1/AE3 (Figure 3D-F). Based on these findings, a diagnosis of primary pleomorphic sarcoma with epithelial differentiation was tentatively made; however, genetic testing for EGFR was performed to confirm the diagnosis. TP53. KRAS. HRAS. NRAS, and PIK3CA mutations were screened in both the lung and femoral tumors to identify any possible genetic alterations responsible for the acquired resistance to TKIs in the femoral tumor. Genetic testing revealed that the same types of mutationsin EGFR (L85-8R) and TP53 (R181P) were present in both the tumors (Figure 4A-F), confirming a common clonal origin of the two tumors and leading to the final diagnosis of sarcomatous overgrowth of metastatic lung adenocarcinoma. However, KR-AS, NRAS, HRAS, and

*PIK3CA* mutations were not detected. The patient remains alive and walks with the assistance of crutches; the remaining lesions are well controlled.

# Discussion

When the patient was first admitted, two possibilities were considered regarding the femoral tumor. One was that it was a metastasis from the primary lung adenocarcinoma. A primary bone tumor was the other differential diagnosis because it was puzzling that only the femoral tumor grew progressively among the multiple metastatic lesions that were being identically treated. Biopsy from the proximal femur revealed that the tumor was entirely composed of a proliferation of sarcomatous pleomorphic cells without glandular structure, thus supporting the diagnosis of a primary bone tumor. Furthermore, histological examination of the surgical specimen showed features consistent with a diagnosis of primary pleomorphic sarcoma of the proximal femur. However, genetic testing of EGFR and TP53 was performed for further confirmation, and this analysis led us to revise the diagnosis to that of a metastasis due to identical genetic patterns in both the lung and femoral tumors. TTF-1 is used as a sensitive marker for lung adenocarcinoma, although loss of its expression has been reported to correlate with increased tumor aggressiveness [13]. In this case, TTF-1 expression was absent in the metastatic tumor despite its strong expression in the lung biopsy specimen. Hence, this patient illustrates the importance of genetic testing for resolving ambiguous cases.

As the patient had received radiation therapy (24 Gy) for metastases in the lumbar vertebrae and left femur 1 year previously, radiationinduced sarcoma or dedifferentiation of metastatic lung adenocarcinoma could also explain the femoral tumor. Several studies describe that radiation-related sarcoma commonly occurs after radiation therapy, although the interval between irradiation and detection of the second malignancy is at least 3-5 years [14-18]. Thus, the possibility of the radiationrelated sarcoma was disregarded. Nakanishi et al. reported that TP53 mutations were one of the causative factors of radiation-induced sarcoma [18]. In the present case, the TP53 mutation R181P was detected in both the lung biopsy specimen and the left femoral tumor; thus, this alteration in TP53 was deemed not related to the radiation.

Various studies show that almost all EGFRmutation-positive NSCLCs acquire resistance to EGFR-TKIs despite remarkably good responses initially. Recently, several mechanisms of acquired resistance to EGFR-TKIs in NSCLC have been described, the most common of which is a secondary EGFR T790M mutation [4, 5]. Other molecular mechanisms of resistance include upregulation of HGF/MET, HER2 mutations, HER3 overexpression, persistent activation of IGF-1R, mutations of PIK3CA/AKT, loss or downregulation of PTEN, and abnormal dimerization of STAT3 [5-8]. Some secondary genetic alterations or histological changes occurred in all 11 cases of lung adenocarcinoma with acquired resistance to EGFR-TKIs in a study by Uramoto et al. [10]. Sequist et al. described that histological change were observed in 8 of 37 cases with drug-resistant NSCLCs carrying EGFR mutations, and EMT was described as the cause of drug resistance in 3 of these 8 cases [11]. The molecular mechanisms and the associated mesenchymal phenotypes underlying drug resistance to TKIs remain unknown, although it has been shown that cell lines undergoing EMT are intrinsically resistant to EGFR inhibitors [19-21]. In our case, secondary genetic alterations such as T790M in EGFR, or additional mutations in Kras, Nras, Hras, and PIK3CA, were not found. The femoral tumor in this case was entirely composed of pleomorphic cells and tumor giant cells with bizarre nuclei, and no apparent glandular structures were observed. It is not clear whether the lung tumor was pure adenocarcinoma or pleomorphic carcinoma from the small biopsy specimen. According to the WHO classification, a carcinoma is defined as pleomorphic if the sarcomatous component is greater than 10% [22, 23]. EGFR mutation was reported to occur in 15-20% of pleomorphic carcinomas of the lungs, and EGFR-TKIs such as gefitinib and erlotinib have high efficiency against EGFRmutated tumors including pleomorphic carcinoma [24-26]. Furthermore, metastases often arise from poorly differentiated components of tumors with pleomorphic features. However, the fact that the primary tumor as well as the remaining metastatic lesions remained stable due to TKI treatment suggests that the lung

adenocarcinoma was a pure adenocarcinoma while EMT occurred only in the proximal femoral tumor. Thus, EMT could be the cause of acquired drug resistance to TKI in this case.

In conclusion, we investigated a metastatic adenocarcinoma of the lungs on the left proximal femur, masquerading as a primary pleomorphic sarcoma. Our results show that genetic testing is highly recommended in such cases when the histologic features of suspected metastases are markedly different from the primary lesion.

After acceptance of the manuscript, a new lesion of the right lung was noticed by the chest-CT and it has been gradually enlarged. The biopsy from this lesion revealed sarcomatous feature without apparent glandular structures. Because the original lesion of the right lung remained stable, the newly established lesion was considered to be metastasized from the femoral lesion.

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# Disclosure of conflict of interest

## None.

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