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A Case of Tumor Lysis Syndrome Induced by Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor for Lung Adenocarcinoma

Yosuke Eguchi[1], Kohei Nishida[1], Masato Shinoki[1], Nobuyuki Uraoka[1], Yuko Nakatsuji[1], Yuzo Miki[2], and Kenichi Minami[1]

Department of Respiratory Medicine[1], Ishikiri-Seiki Hospital; and Department of Respiratory Medicine[2], Osaka City General Hospital

Abstract

A 73-year-old man who had complained of right chest pain was found to have a nodule, measuring 4×2 cm in a diameter at the base of the right lung. A bronchoscopic examination revealed adenocarcinoma. Metastasis to the right fourth rib rapidly manifested 2 weeks later. The patient was treated with the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) because of the harbouring mutation of EGFR. However, he rapidly developed renal dysfunction, and elevated levels of serum uric acid and serum lactate dehydrogenase without achieving any transient partial clinical response. The patient died 3 weeks after the initial administration of the EGFR-TKI. This is the first reported case of severe tumor lysis syndrome in a patient lung adenocarcinoma treated with EGFR-TKI.

Key Words: Primary lung adenocarcinoma; Gefitinib; Tumor lysis syndrome; Renal dysfunction

Introduction

Lung adenocarcinoma is often treated with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs)[1]. An improvement in survival has been described in a study of EGFR-TKI therapy[1]. First-line treatment with a EGFR-TKI (gefitinib[1], erlotinib[2], or afatinib[3]) is the preferred treatment of patients with tumors bearing an activating EGFR mutations[4]. Tumor lysis syndrome (TLS) has been reported to be induced by cytotoxic chemotherapy in malignancies including lung cancer[5]. However, it has not been reported that TLS is induced by EGFR-TKIs, and the treatment of this syndrome has not been established. Here, we report a case of rapid progression of renal dysfunction in a patient with lung adenocarcinoma with bone metastasis who was treated with gefitinib as the first-line chemotherapy.

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Correspondence to: Yosuke Eguchi, MD, PhD
Department of Respiratory Medicine, Ishikiri-Seiki Hospital,
18-28, Yayoi-cho, Higashi-Osaka, Osaka 579-8026, Japan
Tel: +81-72-988-3121; Fax: +81-72-988-3119
E-mail: m1293549@msic.med.osaka-cu.ac.jp

Case Report

A 76-year-old man presented at the outpatient clinic of Ishikiri-Seiki Hospital (Higashi-Osaka, Japan) with a complaint of right chest pain. Initial computed tomography (CT) of the chest demonstrated a nodule measuring 4×2 cm at the base of the right lung (Fig. 1). A bronchoscopic examination on the main lung tumor revealed adenocarcinoma, and the genetic test results were positive for EGFR mutation (exon 19 deletion). Thereafter, right chest pain had gradually aggravated, and CT performed 14 days after the initial consultation revealed enlargement of bone metastasis (Fig. 2). The patient's laboratory test results showed anemia and increased serum levels of C-reactive protein, and lactate dehydrogenase (Table 1).

The patient was treated with the EGFR-TKI; gefitinib (250 mg/day) as the first-line chemotherapy because positron emission tomography (PET) demonstrated metastasis to multiple bones as abnormal

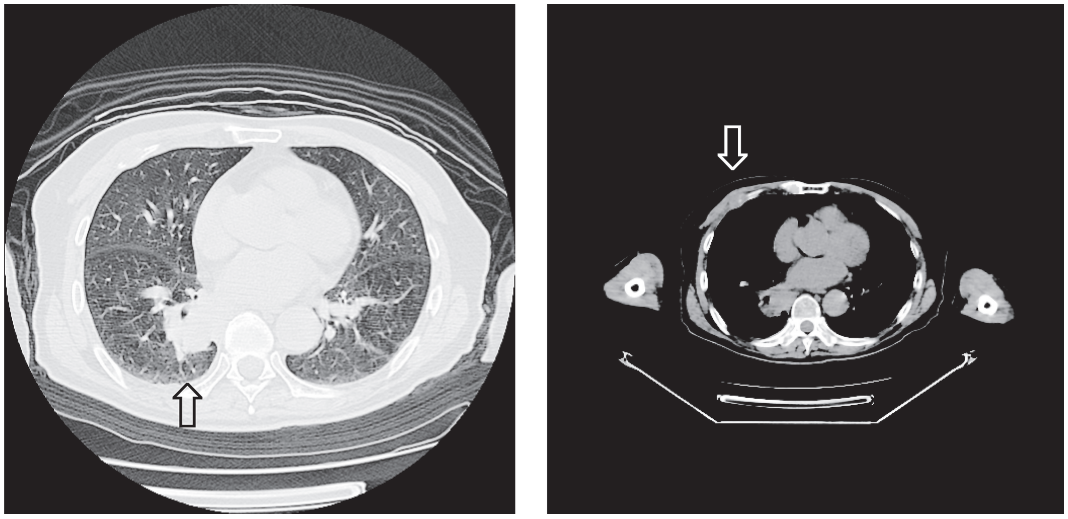


Figure 1. Initial computed tomography of the chest. A tumor measuring 4×2 cm was observed at the base of the right lung (left arrow). A metastatic tumor to the ribs (right arrow).

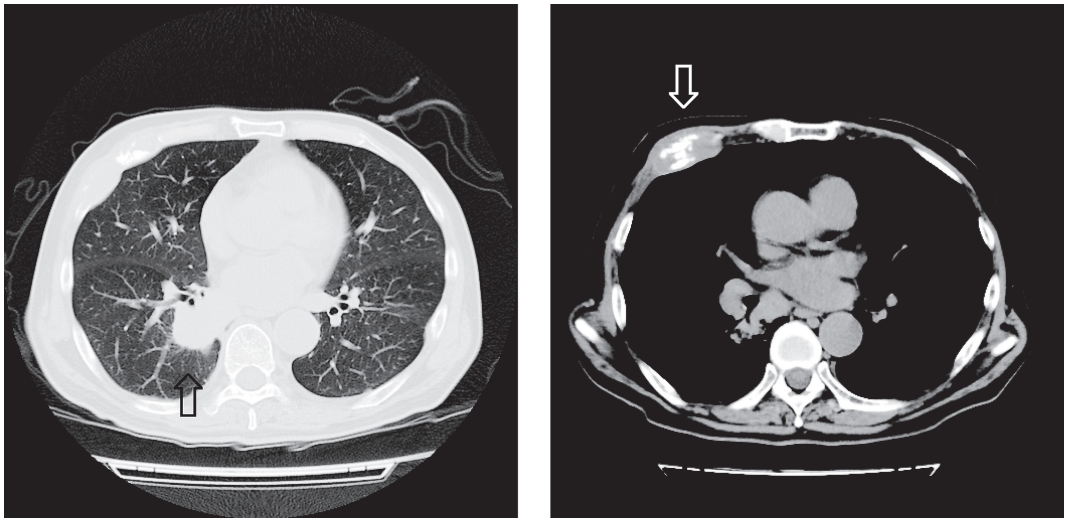


Figure 2. Enlargement of a metastatic tumor to the ribs (right arrow). No remarkable change of primary lesions (left arrow).

Table 1. Laboratory tests before the administration of epidermal growth factor receptor tyrosine kinase inhibitor

Hematology			Biochemistry		
WBC	7950	/μL	T-Bil	0.4	mg/dL
Neu	92.5	%	BUN	11.4	mg/dL
Ly	4.0	%	Cr	0.65	mg/dL
RBC	282×10^4	/μL	TP	6.8	g/dL
Hb	7.1	g/dL	ALB	2.4	g/dL
Ht	22.7	%	Na	136	mEq/L
PLT	22.8×10^4	/μL	K	4.0	mEq/L
			Cl	99	mEq/L
			UA	5.0	mg/dL
			eGFR	79.0	
Serology			AST	27.0	IU/L
CRP	23.4	mg/dL	ALT	15.0	IU/L
CEA	4.8	ng/mL	CK	21.0	IU/L
			LDH	252.0	IU/L

uptake before the initiation of therapy. Although the treatment did not lead to any transient change in the tumor size, increased serum levels of creatinine, uric acid, and lactate dehydrogenase were observed 5 days after the administration (Figs. 3 and 4). According to the Laboratory TLS and clinical TLS guideline[6], he was diagnosed with TLS. Despite of cessation of gefitinib, and the provision of dialysis, and palliative therapy, the patient's general condition continued to worsen until his death.

Discussion

For the treatment of patients with EGFR mutations in lung adenocarcinoma, EGFR-TKIs such as gefitinib[1], erlotinib[2], and afatinib[3] were approved in Japan. These drugs significantly prolonged progression-free survival compared with standard platinum-based chemotherapy and was also better tolerated and less toxic than combination chemotherapy[7,8].

The most common side effects are dermatological adverse reactions, which are occur in up to 50% of patients[8]. Other adverse effects include diarrhea, nausea, stomatitis, and asymptomatic elevation of liver enzymes[8].

However, to the best of our knowledge, there have been no reports of EGFR-TKI induced TLS, which is mainly associated with the treatment of cytotoxic chemotherapy[9]. According to the Laboratory TLS and Clinical TLS guideline[6], the laboratory definition for TLS includes a 25% change from the baseline values of uric acid, potassium, phosphorus, and calcium. In addition, abnormal values that occur within 3 days before and 7 days after the initiation of treatment are included. The clinical definition of TLS also requires the presence of 1 or more of the 3 most significant clinical complications of TLS: acute renal failure, cardiac arrhythmias/sudden death, and seizures. The typical symptoms of TLS are arrhythmia and dyspnea[10]. In some previous cases, TLS may have been incidentally identified based on blood examinations without presentation of any symptoms.

In our case, the serum levels of creatinine, uric acid, and lactate dehydrogenase had increased 5 days after gefitinib administration (Figs. 3 and 4). Finally we made a diagnosis of TLS according to the definition. Symptoms may have been absent because the laboratory findings were detected

Fig3

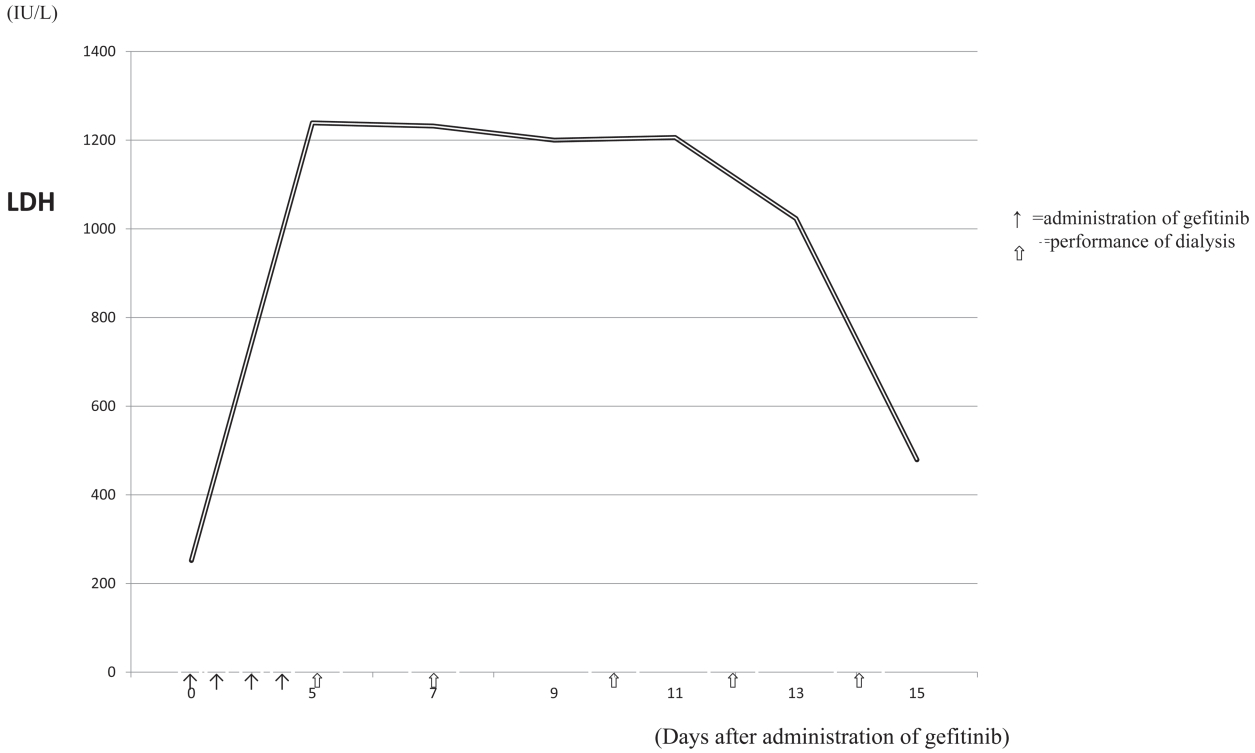
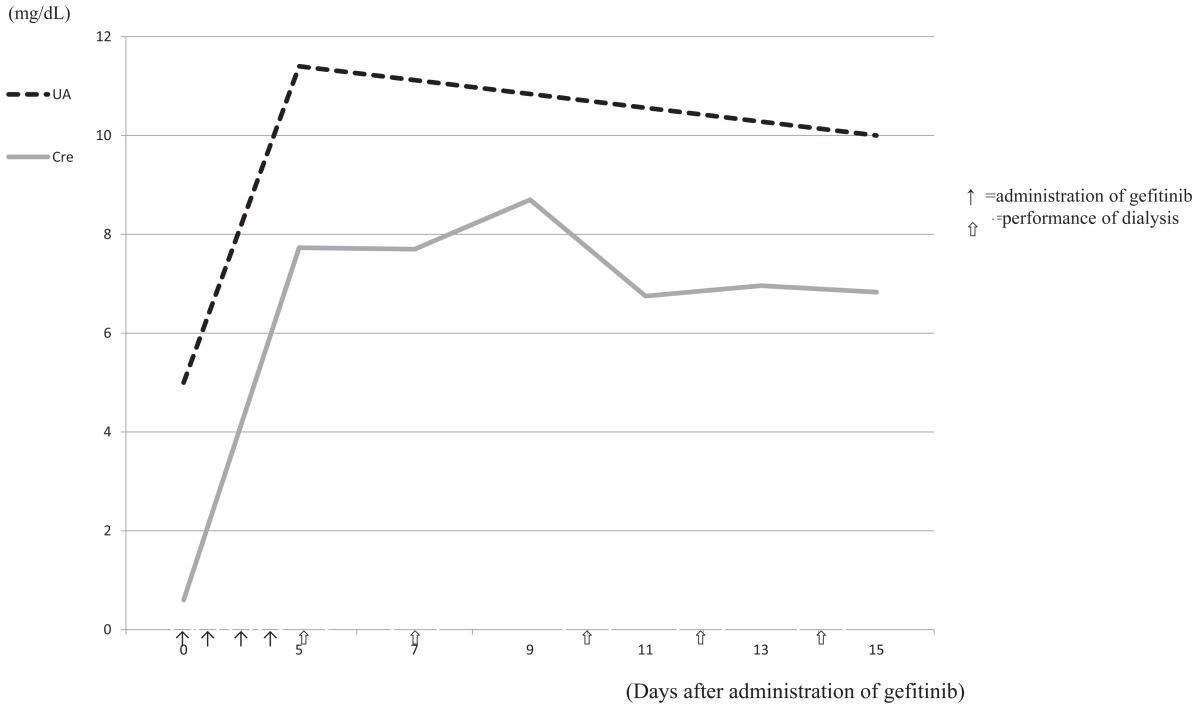


Fig4



Figures 3 and 4. Clinical course. First-line chemotherapy (gefitinib, an EGFR-TKI) was not followed by a partial response, and resulted in TLS with renal crisis. ↑, administration of gefitinib; ⇧, performance of dialysis; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; Cre, creatinine (mg/dL); LDH, lactate dehydrogenase (IU/L); and UA, uric acid (mg/dL).

Table 2. Characteristics of tumor lysis syndrome induced in patients with adenocarcinoma of lung cancer

	Age, sex	Chemotherapy	metastasis	Size of primary lesion	Size of metastatic lesion	period	Laboratory data of pre-medication	Laboratory data of post-medication	Outcome
Persons[11]	38,F	Irinotecan +Cisplatin	lymph nodes	NR	4 cm	13days	LDH 710 UA 5.4 Cre 0.8	LDH 3238 UA 19.0 Cr 7.2 P 11 Ca 6.5 K 5.3	Resolved
Feld[12]	72,M	Spontaneous	Liver	NR	NR	NA	LDH 863 UA NR Cre 1.05 P 4.5 Ca 9.5 K 4.4	LDH 1016 UA 12.8 Cre 1.28 P 8.6 Ca 8.2 K 7.0	Died
Kurt[13]	52,M	Zoledronic acid	Brain, Paraspinal, Liver, Bone, Small intestine	8 cm	Liver:7 cm	4 days	LDH NR UA 3.7 Cre 0.7 P 3.5 Ca 10.9 K4.5	LDH NR UA 14.25 Cre 2.45 P 6.8 Ca 6.53 K 6.5	Died
Ajzensztejn[14]	65,M	Docetaxel	Hepatic, adrenal, renal, pulmonary nodules with lymph-angitis carcino-mitosis	NR	NR	3days	WNL	LDH NR UA 21.7 Cre 2.7 P 12.2 Ca NR K 6.3	Died
Honda[15]	61,M	Carboplatin +Paclitaxel +Bevacizumab	Liver, Lymph nodes	3 cm	NR	NR	LDH NR UA 13.6 Cre 1.0 P 3.0 Ca 9.4 K 5.5	LDH NR UA 14 Cre NR P NR Ca NR K 7.0	Died
Our case	73,M	Gefitinib	Bone, Lymph nodes	4 cm	Bone:1.6 cm	5days	LDH 252 UA 5.0 Cre 0.65 K 4.0	LDH 1239 UA 11.4 Cre 7.73 P 5.6 K 5.0	Died

Ca, calcium (mg/dL); Cre, creatinine (mg/dL); K, potassium (mEq/L); LDH, lactate dehydrogenase (IU/L); NA, not applicable; NR, not reported; P, phosphorus (mg/dL); UA, uric acid (mg/dL); Period, period between initial administration of drug and manifestation of tumor lysis syndrome; and WNL, within normal limit.

early in the course of TLS. Rapid development (within 2 weeks) of metastasis to the bones was also observed in our case, and may sometimes occur in TLS.

There is no standard treatments for TLS induced by gefitinib. The treatment administered in the present case was based on that reported by other groups for leukemia, and lymphoma occurring at other sites[10], which included hydration, and other therapeutic approaches.

Several previous reports have described severe TLS induced by the administration of other anticancer drugs (Table 2)[11-15]. Renal crisis by TLS was considered, especially in patients with rapid progression of any lesions. Frequent blood tests can be useful to consider the disease in the patients with risk factors including old age, and rapid tumor growth.

Here, we report a case of severe TLS in a patient with lung adenocarcinoma treated with gefitinib. To further improve the outcome of lung cancer patients treated with EGFR-TKI, the accumulation of information on rare events like TLS is required.

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