



Rhabdomyolysis in a patient with advanced lung cancer treated with osimertinib: a case report

You Li^{1,3#}, Yu Liu^{1,2#}, Zichen Zhao^{1#}, Yan Zhang^{1,2}

¹Lung Cancer Center, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China; ²Department of Thoracic Oncology, Cancer Center, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China; ³Department of Respiratory, Dazhou Southern Hospital, Dazhou, China

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[#]These authors contributed equally to this work.

Correspondence to: Yan Zhang. Lung Cancer Center, West China Hospital, Chengdu, China. Email: zhang.yan@scu.edu.cn.

Background: As a third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), osimertinib is the standard treatment for patients with *EGFR* mutations. Diarrhea and rash are the most common side effects, and some rare adverse reactions have started appearing owing to their increased clinical application. Osimertinib-associated myositis was reported to be more common compared with previous studies; however, osimertinib-associated rhabdomyolysis (RM) has not yet been reported. This is the first report of osimertinib-associated RM during the treatment of a lung adenocarcinoma patient with *EGFR* exon 19 deletion and *T790M* mutation. Compared to myositis, RM could lead to much more serious consequences, such as acute renal failure (ARF), disseminated intravascular coagulation (DIC) and electrolyte disturbances. Our case exemplifies the symptoms, diagnosis and treatment of osimertinib-associated RM, meanwhile, the potential mechanisms and related therapeutic choices have been fully discussed.

Case Description: Herein, we present a 70-year-old non-smoking woman diagnosed with metastatic lung adenocarcinoma harboring an *EGFR* exon 19 deletion, who had received afatinib plus bevacizumab as the first-line therapy and almonertinib plus bevacizumab as the second-line therapy. Then the patient underwent osimertinib and bevacizumab as the third-line therapy. After 5-month treatment, the patient developed myalgia, muscular weakness, and tea-colored urine. The muscle strength grade of both the upper and lower limbs was III, and no other abnormalities were found. Serum creatine kinase (CK) and myoglobin (Mb) levels increased to 1,470 IU/L and 616.5 ng/mL. The patient also developed acute renal insufficiency, hyperuricemia, metabolic acidosis, and electrolyte disturbances. All symptoms were improved following the withdrawal of osimertinib. As a result, the patient was diagnosed with osimertinib-associated rhabdomyolysis.

Conclusions: This is the first report of osimertinib-associated RM during the treatment of a lung adenocarcinoma patient. Although osimertinib-associated RM is rare, it is worthy of clinical attention in clinical practice, especially in patients receiving osimertinib plus bevacizumab. Once developed myalgia, muscular weakness and tea-colored urine, laboratory tests including serum creatine kinase (CK) and myoglobin (Mb) levels must be done, also osimertinib should be timely withdrawn to identify the cause.

Keywords: Osimertinib; rhabdomyolysis; side effect; lung cancer; case report

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Introduction

At present, lung cancer is still the leading cause of cancer mortality, accounting for 18% of all cancer-related deaths (1). Activating mutations in epidermal growth factor receptor (*EGFR*) are observed in 15–50% of non-small cell lung cancer (NSCLC) patients (2). Osimertinib has been approved by the U.S. Food & Drug Administration (FDA) for the first-line treatment of patients with metastatic NSCLC and *EGFR* mutations and those with *T790M*-positive NSCLC who progressed on prior *EGFR* tyrosine kinase inhibitor (EGFR-TKI) treatment (3). Osimertinib was reported to have a better tolerability in patients with locally advanced and metastatic *EGFR*-positive NSCLC than the first and second generation EGFR-TKIs, the most common osimertinib-associated adverse events were rash, diarrhea, nausea, dry skin, paronychia and stomatitis (4–6). Previous clinical study has reported that the incidence of myositis associated with osimertinib is less than 1%, except for one retrospective study, which showed that symptomatic myositis or asymptomatic serum creatine kinase (CK) elevation occurred in over 10% (4/38) of patients treated with osimertinib (3).

Rhabdomyolysis (RM) involves acute destruction and dissolution of skeletal muscle, resulting in the release of large amounts of muscle cell components into the circulation. Apart from myalgia and weakness, its clinical manifestations, including dark-colored urine and systemic symptoms such as malaise, fever, abdominal pain, nausea, and vomiting, can also

occur in RM. These may be accompanied by intravascular volume depletion, metabolic acidosis, and various electrolyte abnormalities, and patients with severe disease could also develop acute renal failure (ARF) and disseminated intravascular coagulation (DIC) (4,5).

To date, osimertinib-associated RM has not been reported. Herein, we report the case of a patient with an *EGFR* exon 19 deletion and *T790M* mutations who developed RM, a rare adverse event, after treatment with osimertinib. In this case, bevacizumab was co-administrated with osimertinib, which may increase the risk of osimertinib-associated RM. We present this case to exemplify the symptoms, diagnosis and treatment of osimertinib-associated RM, meanwhile, the related therapeutic choice of osimertinib plus oxycodone and bevacizumab have been fully discussed. We present the following article in accordance with the CARE reporting checklist (available at <https://tldr.amegroups.com/article/view/10.21037/tlcr-22-916/rc>).

Case presentation

A 70-year-old Chinese woman presented with generalized pain with muscle weakness for 2 weeks and tea-colored urine. The patient was diagnosed with metastatic adenocarcinoma with *EGFR* exon 19 deletion and programmed cell death 1 ligand (PD-L1) expression of 5% 2 years previously (*Figure 1*). Imaging examinations showed primary cancer in the left lower lobe with metastasis to the bilateral hilar, mediastinal lymph nodes, right lung, and pleura. The patient subsequently underwent first-line combination treatment with afatinib and bevacizumab (7.5 mg/kg every three weeks) from September 2019. The best efficacy evaluation was a partial response (PR). However, progressive disease (PD) was detected in July 2020 due to the growth of the hilar, mediastinal lymph nodes, pleural lesions, and new brain metastases. Blood testing revealed a *T790M* mutation, and she received almonertinib (110 mg daily) plus bevacizumab in September 2020 as second-line treatment. The patient tolerated this treatment well and the best efficacy evaluation was PR. However, follow-up imaging showed disease progression after 5 months of treatment in June 2021. The patient declined chemotherapy, and osimertinib (80 mg daily) plus bevacizumab were administered as third-line treatment. The patient tolerated the treatment well initially, and imaging revealed stable disease of the primary and metastatic lesions.

Nevertheless, after 5 months of treatment, she

Highlight box

Key findings

- This is the first report of osimertinib-associated rhabdomyolysis (RM) during the treatment of a lung adenocarcinoma patient with *EGFR* exon 19 deletion and *T790M* mutation

What is known and what is new?

- Osimertinib-associated myositis was reported to be more common compared with previous studies.
- Regular testing of serum creatine kinase (CK) and myoglobin (Mb) levels and monitoring of relevant symptoms are highly recommended in clinical practice.

What is the implication, and what should change now?

- The manifestations associated with muscle injury should be considered with caution during osimertinib treatment, particularly in patients receiving osimertinib plus bevacizumab. The co-administration of bevacizumab may also increase the risk of rhabdomyolysis.

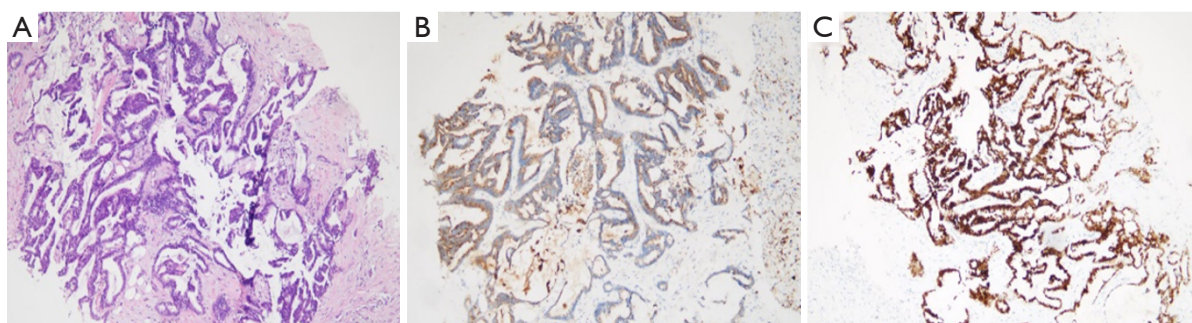


Figure 1 Histopathology and immunohistochemistry of tumor tissues in our patient. (A) The hematoxylin-eosin staining (H&E staining) under microscopy (100 \times); (B,C) Immunohistochemical staining for TTF1 and NapsinA (100 \times). H&E, hematoxylin-eosin.

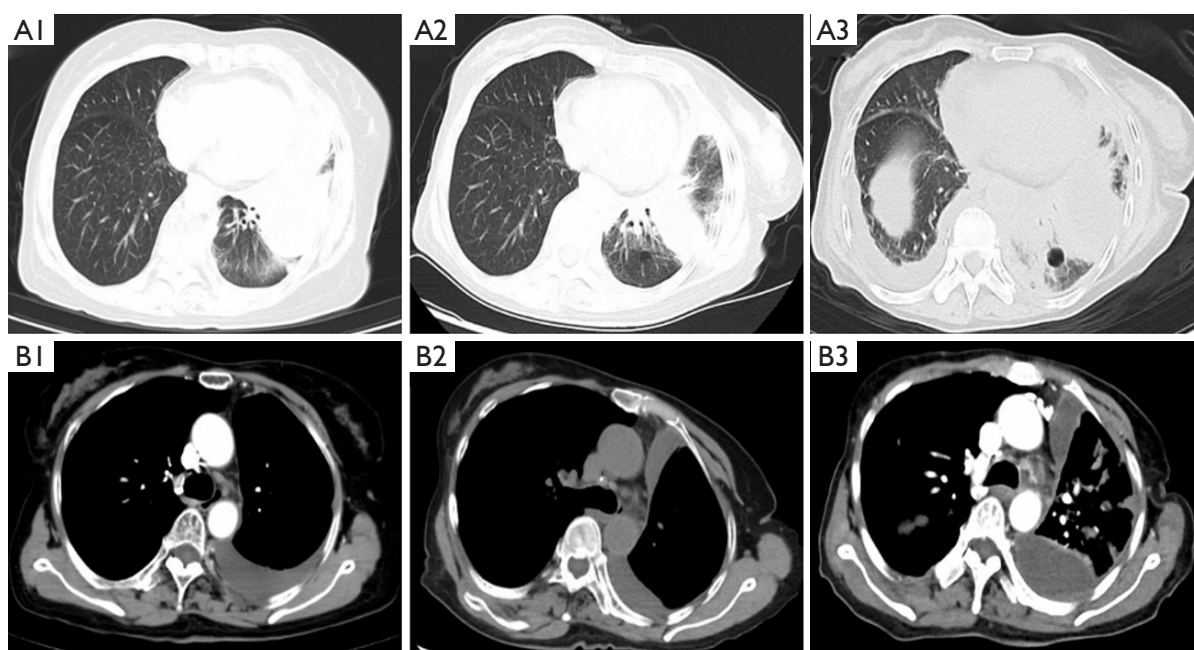


Figure 2 Chest CT showing the changes in lung lesions and mediastinal lymph nodes. The disease became stable after 3 months of osimertinib administration at 80 mg/day, and then disease progressed after 5 months. (A1,B1) Before the administration of osimertinib; (A2,B2) 3 months after the administration of osimertinib; (A3,B3) 5 months after the administration of osimertinib. CT, computed tomography.

experienced generalized pain with muscle weakness, mainly in the extremities. Oxycodone was then administered, and there were no changes of combined drugs (*Figure 2*). Approximately 2 weeks later, tea-colored urine appeared. The muscle strength grade of both the upper and lower limbs was III, and no other abnormalities were found. Serum creatine kinase (CK) and myoglobin (Mb) levels increased to 1,470 IU/L and 616.5 ng/mL, respectively, together with acute renal insufficiency, hyperuricemia,

metabolic acidosis, and electrolyte disturbances (such as hyperkalemia and hypocalcemia) (*Table 1*). Other possible causes of elevated CK levels, such as myocardial infarction, stroke, and combined medications, were excluded by auxiliary examinations.

Osimertinib was interrupted in November 2021. Due to her poor performance status score, the patient did not undergo further examinations, such as a muscle biopsy. Osimertinib-associated rhabdomyolysis was considered

Table 1 Routine blood and urine tests in the patient

Tests	Reference value	Baseline	Peak value	Follow-up value
Creatinine ($\mu\text{mol/L}$)	49–88	84	197	92
MCV (fL)	82–100	92	90.3	94
MCH (pg)	27–34	32	27.3	30.1
MCHC (g/L)	316–354	324	303	312
Leukocyte count ($\times 10^9/\text{L}$)	3.5–9.5	4.73	5.41	5.37
AKP (IU/L)	50–135	107	138	128
GGT (IU/L)	<45	37	60	47
Albumin (g/L)	40.0–55.0	38	28.6	32.5
Glomerular filtration rate ($\text{mL}/\text{min}/\text{m}^2$)	56–122	60.86	21.72	54.52
Uric acid ($\mu\text{mol/L}$)	160–380	225	558	233
Potassium (mmol/L)	3.5–5.5	4.03	2.93	3.59
Magnesium (mmol/L)	0.75–1.02	0.87	1.05	0.67
Calcium (mmol/L)	2.11–2.52	2.19	1.71	1.88
Color of urine	Clear	Clear	Clear	Clear
Urinary specific gravity	1.003–1.030	1.02	1.041	1.02
Protein in urine (g/L)	Negative: 0	0.15(-/+)	0.3(+)	(-)
Red blood cells in urine ($/\mu\text{L}$)	0–25	27	716	38
pH	7.35–7.45	–	7.296	7.409

The peak value was tested on 29th November 2021. The follow-up value was tested on 8th December 2021. MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; AKP, alkaline phosphatase; GGT, γ -glutamyl transpeptidase.

after a multidisciplinary discussion with nephrologists and pharmacologists. Osimertinib was discontinued thereafter, and after symptomatic treatments such as alkalization of urine and rehydration, the patient's myalgia was relieved, her serum CK and Mb levels decreased (*Figure 3*), myoglobinuria returned to normal, and her renal function also improved (*Table 1*, *Figure 4*).

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

It is commonly considered that the diagnosis of RM is

established when patients present with myalgia or muscle weakness, combined with a serum CK level $\geq 1,000$ U/L or \geq five times the upper limit (4,5). Serum CK levels are slightly elevated in myositis and notably in RM; lower serum CK levels may more appropriately be defined as osimertinib-associated myositis, which is accompanied by myalgia or muscle weakness, and usually without myoglobinemia or myoglobinuria (3). Neither myositis nor RM has been officially reported as a side effect of osimertinib in major studies; nevertheless, manifestations of muscle damage including fatigue, weakness, and increased liver enzymes were observed in the AURA2, AURA3, and FLAURA studies (3,6–8). In this case, after receiving the treatment of osimertinib plus bevacizumab, the patient demonstrated a satisfying treatment response in the beginning. All laboratory tests showed normal results. However, five months later, the patient began to develop muscular pain. Oxycodone was then administered and there was no change of other combined drugs. Moreover,

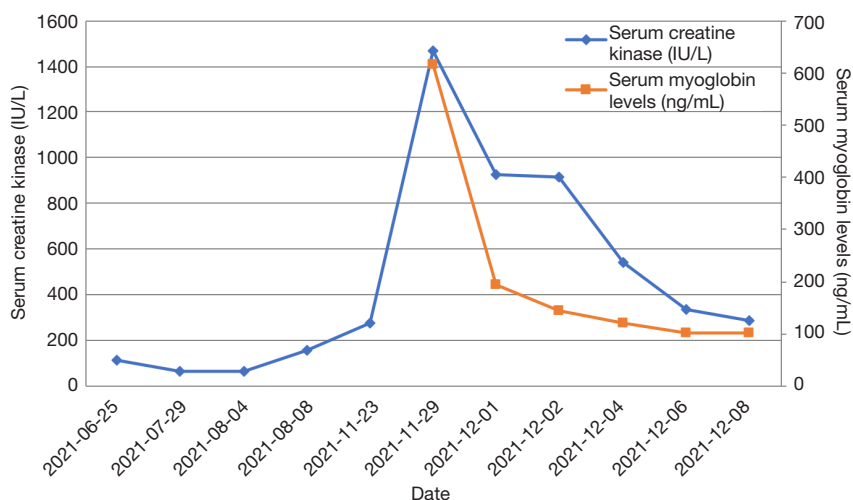


Figure 3 Changes in serum CK and Mb levels throughout the osimertinib treatment. Osimertinib was started in June 2021. Myalgia and muscle weakness appeared in November 2021, while myoglobinuria occurred after 2 weeks. Osimertinib treatment was discontinued on November 30, 2021. A remarkable decrease in both serum CK and Mb levels was observed after the withdrawal of osimertinib. CK, creatine kinase; Mb, myoglobin.

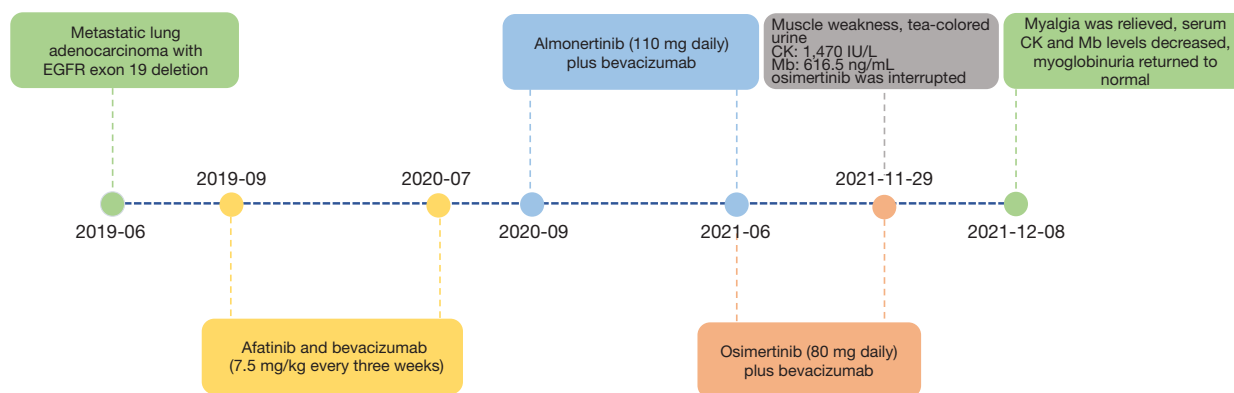


Figure 4 Timeline figure describe the whole disease process of the case. EGFR, epidermal growth factor receptor; CK, creatine kinase; Mb, myoglobin.

the patient received the treatment of bevacizumab since the first-line therapy and did not show any RM-related symptoms. Therefore, these symptoms were considered to be mainly related to osimertinib rather than oxycodone. Osimertinib-associated myositis was reported to be more common compared with previous studies; however, osimertinib-associated RM has not yet been reported (3,9,10) (Table 2).

As a rare side effect, the incidence of myositis associated with osimertinib was reported to be less than 1%, and serum CK elevation was reported in only one case in the AURA2 study (7). However, symptomatic myositis or asymptomatic

CK elevation has a significantly higher incidence in real-world practice (3,10). Although RM did not occur in patients receiving combined treatment with EGFR-TKI and bevacizumab, the combination therapy yielded increased adverse effects compared with monotherapy, including CK elevation, myalgia, muscle weakness, and proteinuria, which may indicate that combination therapy is more likely to trigger potential muscle injury (11-19) (Table 3). Thus, the manifestations associated with muscle injury should be considered with caution during osimertinib treatment, particularly in patients receiving osimertinib plus bevacizumab.

Table 2 Reported cases of elevated serum creatine kinase levels during osimertinib treatment for lung cancer

Case number	Age (years)	Sex	Type of EGFR mutation	Peak serum CK (U/L)	Muscular symptoms	Biopsy
1 (9)	68	Male	T790M	1,238	Myalgia	Present
2 (3)	72	Female	L858R	790	Cramps	None
3 (3)	66	Male	T790M	2,511	Cramps	None
4 (3)	68	Female	Exon 19 and T790	596	None	None
5 (3)	42	Male	Exon 19 deletion	298	None	None
6 (10)	56	Female	Exon 19 deletion	989	Cramps	None

EGFR, epidermal growth factor receptor; CK, creatine kinase.

Table 3 Reported adverse events associated with muscle injury during combined therapy of EGFR-TKIs and anti-angiogenic drugs

Study	Treatment	Phase	AE					
			CPK increased	Myoglobinemia or myoglobinuria	Myalgia	Muscle weakness	Proteinuria	Myositis
RELAY (13)	Erlotinib+ Ramucirumab	III	–	–	–	–	34% (75/221)	–
SWOG S0635 and S0636 Trials (14)	Erlotinib+ Bevacizumab	II	–	–	–	17% (28/161)	16% (26/161)	–
SAKK 19/05 (15)	Erlotinib+ Bevacizumab	II	–	–	–	–	42% (42/101)	–
OLCSG140 (16)	Afatinib+ Bevacizumab	I	–	–	–	–	58% (11/19)	–
WJOG8715L (17)	Osimertinib+ Bevacizumab	II	–	–	–	–	58% (47/81)	–
NCT02803203 (18)	Osimertinib+ Bevacizumab	I/II	4% (2/49)	–	20% (10/49)	4% (2/49)	43% (21/49)	4% (2/49)
NEJ026 (19)	Erlotinib+ Bevacizumab	III	–	–	–	–	32% (36/112)	–

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; AE, adverse event; CPK, creatinine phosphokinase.

The mechanism of osimertinib-induced myopathy remains unclear. One *in vitro* study reported that EGFR has a key role in the differentiation process of myoblast. Thus, osimertinib may affect myoblast differentiation and cause skeletal muscle injury through blocking EGFR pathway (20). Considering that osimertinib is almost not influenced by strong CYP3A4 inhibitor, it is not considered that the concentration of osimertinib changes by oxycodone (21,22). Furthermore, bevacizumab is both a recombinant humanized monoclonal antibody and an anti-angiogenesis drug. Only muscle weakness has been reported as one of the adverse effects of bevacizumab, and there is no reference to CK increase or RM (23). There is only one report of an 82-year-old man with RM due to bevacizumab, and RM was reported after treatment with monoclonal antibodies and anti-angiogenic drugs; the mechanism may be associated with complement activation and elevated tumor necrosis factor- α (24-27). Thus, the co-administration of

bevacizumab may also increase the risk of RM.

Conclusions

To our knowledge, this is the first report of osimertinib-associated RM during the treatment of a lung adenocarcinoma patient with an *EGFR* exon 19 deletion and *T790M* mutation. Regular testing of serum CK and Mb levels and monitoring for relevant symptoms are highly recommended in clinical practice, especially in patients receiving osimertinib plus bevacizumab.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://tldr.amegroups.com/article/view/10.21037/tldr-22-916/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tldr.amegroups.com/article/view/10.21037/tldr-22-916/coif>). 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. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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