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Lazertinib-Induced Rhabdomyolysis in a Patient With Non-Small Cell Lung Cancer: A Case Report

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Received: 21 October 2024 | **Revised:** 31 December 2024 | **Accepted:** 17 January 2025

Associate Editor: David Lam

Funding: This work was supported by the Korea University Guro Hospital convergence research support program in collaboration with the College of Pharmacy, Seoul National University (Project No. K2115711).

Keywords: case report | lazertinib | non-small cell lung cancer | rhabdomyolysis

ABSTRACT

Lazertinib is a third-generation epidermal growth factor receptor tyrosine kinase inhibitor effective in patients with non-small cell lung cancer. Although generally well tolerated, this case report presents a rare occurrence of common terminology criteria for adverse events grade 3 rhabdomyolysis in a 69-year-old Korean woman after taking lazertinib. The patient exhibited general weakness and tea-coloured urine with elevated levels of creatine phosphokinase (CPK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), serum myoglobin and hyperkalemia. Lazertinib was temporarily discontinued, and urine alkalization was initiated. After the patient's condition improved, lazertinib was restarted at a reduced dose (80 mg) without any adverse effects. This case highlights the importance of assessing CPK and LDH levels in patients undergoing treatment with lazertinib, particularly in those with myalgia and elevated AST levels. Further studies are required to clarify the mechanisms underlying lazertinib-induced rhabdomyolysis.

1 | Introduction

Lazertinib is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) used to treat non-small cell lung cancer (NSCLC). Lazertinib has been approved as the 2nd line treatment for patients with EGFR T790M-mutated advanced or metastatic NSCLC. The LASER301 randomised study demonstrated that lazertinib could extend the median progression-free survival in the first-line treatment for advanced NSCLC patients with exon 19 deletion(E19del) and L858R mutations [1]. Based on the findings of the LASER301 study, the Ministry of Food and Drug Safety in South Korea approved lazertinib as a first-line treatment for EGFR-mutated (L858R mutation or exon 19 deletion) advanced or metastatic NSCLC in 2023.

Adverse events were observed in 96% of patients undergoing treatment with 240 mg lazertinib once daily [1]. Only 20% of patients experienced adverse events of grade 3 or higher, indicating that lazertinib was generally well-tolerated. However, 21% of patients undergoing treatment with lazertinib had their dosage reduced owing to treatment-emergent adverse events, and only 10% discontinued the medication [1].

Rhabdomyolysis, characterised by the breakdown of skeletal muscle tissue, is a rare but serious complication. No cases

of rhabdomyolysis have been reported in patients treated with lazertinib. This report presents the first case of rhabdomyolysis after lazertinib administration.

2 | Case Report

The 69-year-old woman was diagnosed with NSCLC, adenocarcinoma with liver and iliac bone metastasis (cT2aN2M1c). The tissue was confirmed to contain an exon 21 mutation that activated the L858R mutation. The patient experienced underlying diseases including hypertension, diabetes mellitus, cerebral infarction, and stage 3 chronic kidney disease. The patient was administered lazertinib (240 mg daily) as the first-line treatment. Approximately 20 days after administration, the patient exhibited general weakness and tea-coloured urine.

Figure 1 displays the initial elevation in the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Initially, the increasing trend of AST level was more pronounced, and this raised the suspicion that it may be due to causes other than liver damage. Laboratory results of elevated levels of creatine phosphokinase (CPK), serum myoglobin, lactate dehydrogenase (LDH), and urine myoglobin and hyperkalemia indicated rhabdomyolysis. Figure 2 displays the initial elevations in the levels of CPK and LDH and continuous changes in their levels. The bone scan indicated diffuse and mild uptake of the radiotracer throughout the body (Figure 3). The patient was diagnosed with rhabdomyolysis based on elevated CPK levels and other typical symptoms. She had not experienced any recent physical stress or used any medications other than lazertinib. Urine alkalization was initiated, and lazertinib was discontinued. The patient's symptoms were mild, and steroids were not administered.

After 10 days of treatment, CPK levels decreased to below 1000 IU/L. After 18 days of treatment, the patient resumed lazertinib at a dose of 80 mg daily without any reported adverse effects. We subsequently increased the daily lazertinib dose to 160 mg 5 days after resuming at 80 mg daily. At the 1-month follow-up, the patient continued a maintenance dose of 160 mg, and no abnormalities were reported. Approximately 2-months after the initiation of lazertinib therapy, a computed tomography scan

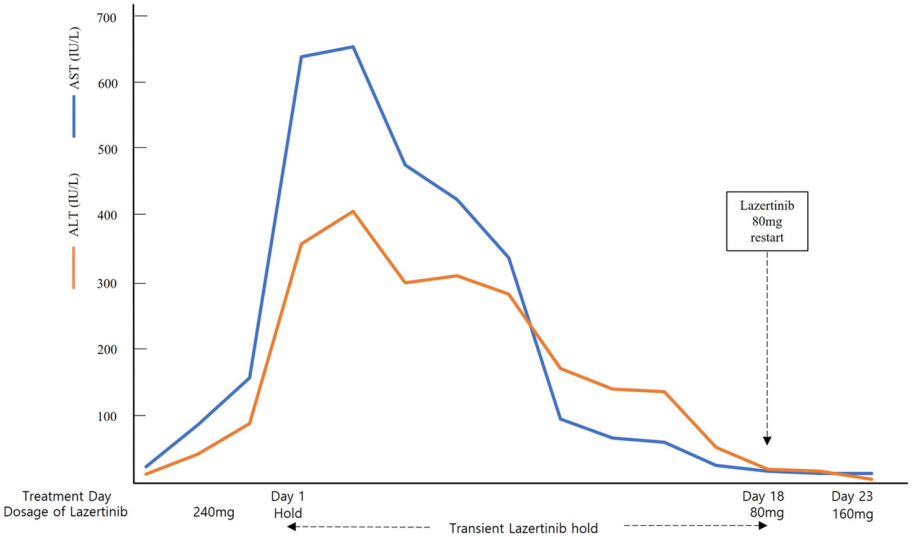

FIGURE 1 | Elevated progression of AST and ALT levels. Initially, the increase in AST was more pronounced than that in ALT. AST, aspartate aminotransferase; ALT, alanine aminotransferase.

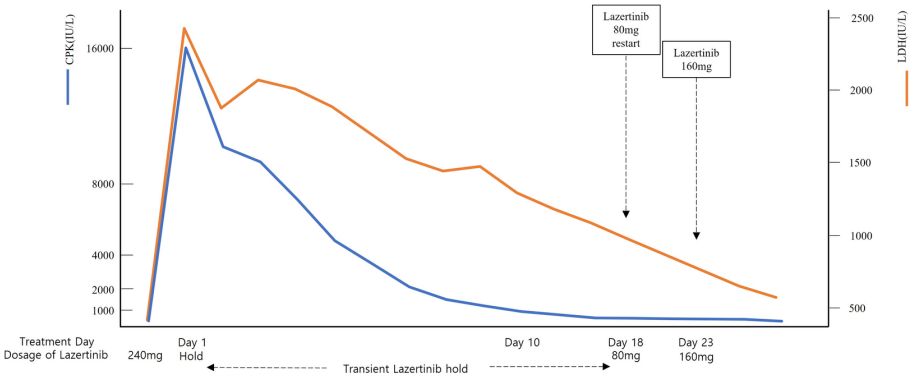

FIGURE 2 | Elevated progression of CPK and LDH levels. CPK and LDH levels decreased after discontinuation of lazertinib. After 18 days of discontinuation, lazertinib administration was resumed at a reduced dose (80 mg). After 23 days, the dosage of lazertinib was increased to 160 mg; however, CPK and LDH levels did not increase and remained stable. CPK, creatine phosphokinase; LDH, lactate dehydrogenase.

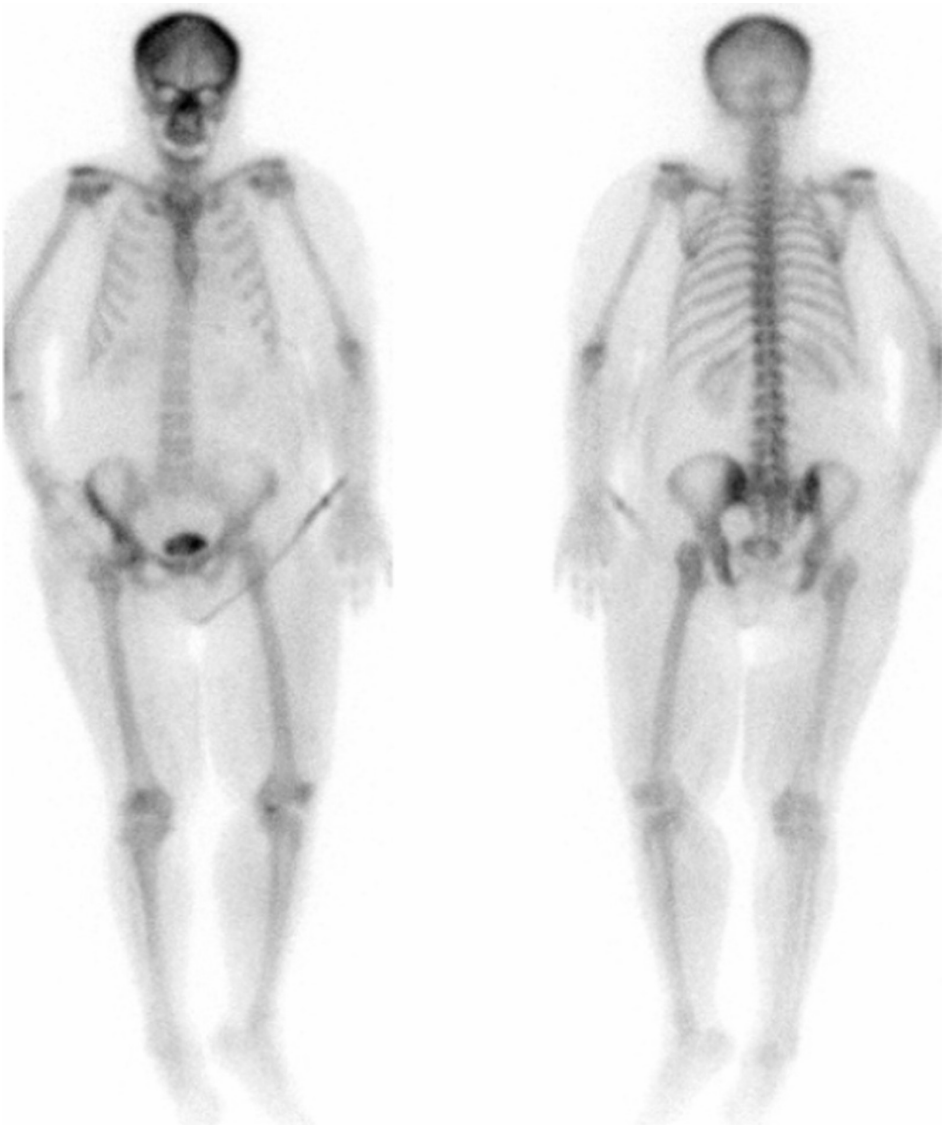

FIGURE 3 | Bone scan. A bone scan of the patient after diagnosis revealed diffuse and mild uptake of the radiotracer throughout the body.

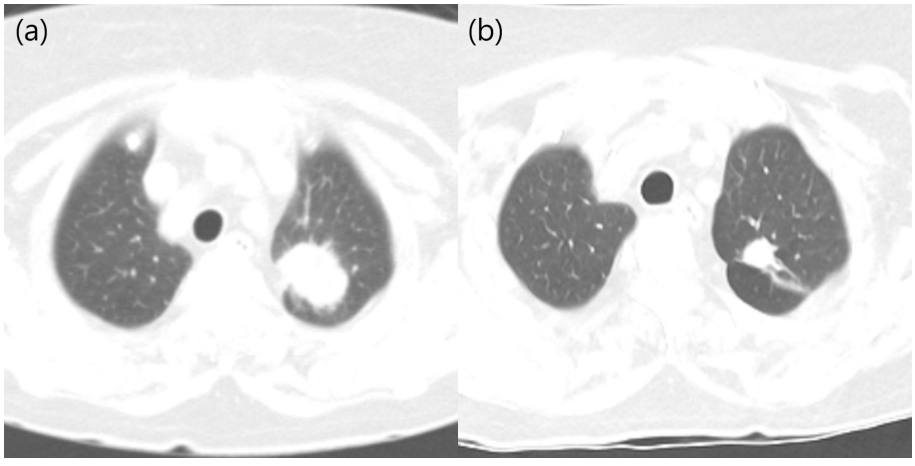

FIGURE 4 | CT scans taken before and after the treatment. (a) Baseline CT scan of the patient. (b) CT scan approximately 2 months after the initiation of lazertinib. CT, computed tomography.

revealed a partial response (PR) compared to the baseline scan, based on the RECIST 1.1 criteria (Figure 4). The best overall response was PR, and the patient remains on lazertinib therapy with no evidence of disease progression to date.

3 | Discussion

Patients with rhabdomyolysis exhibit a triad of symptoms, including myalgia, weakness, and myoglobinuria. The gold standard laboratory diagnosis is the plasma CPK concentration five times the upper limit of the normal reference range [2]. Rhabdomyolysis may be asymptomatic or evolve into a life-threatening condition with complications including disseminated intravascular coagulation and acute renal failure. The early diagnosis and appropriate treatment of rhabdomyolysis-induced acute kidney injury are crucial for maintaining kidney function.

Although rare, the occurrence of elevated serum CPK levels and rhabdomyolysis following EGFR TKI therapy highlights the necessity of monitoring serum CPK levels in patients undergoing these treatments. Lazertinib has not been associated with reported cases of rhabdomyolysis in real-world data, and no studies have investigated the elevation in serum CPK levels after its administration. However, post-marketing surveillance for erlotinib identified eight cases (0.08%) of elevated serum CK levels, while four cases (0.17%) were noted during the international phase III trial of afatinib, and four cases (0.7%) were observed during the international phase III trial of osimertinib, according to pharmaceutical interview data [3]. Furthermore, to the best of our knowledge, rhabdomyolysis has been reported with other EGFR TKIs, including two cases with afatinib, one with erlotinib, one with gefitinib, and one with osimertinib, among which the case involving gefitinib attributed to an overdose rather than standard use [3, 4].

However, the mechanisms underlying lazertinib-induced rhabdomyolysis remain unclear. According to an in vitro study, EGFR is a key regulator of the differentiation of myoblasts [5]. Myoblasts differentiate during skeletal muscle regeneration. Downregulation of EGFR activity is observed during the early stages of human myoblast differentiation [5]. Lazertinib may more selectively bind to EGFR expressed in skeletal muscle compared to other EGFR-TKIs. Further studies are required to investigate the association between rhabdomyolysis and lazertinib use.

In conclusion, we recommend assessing serum CPK levels in patients undergoing lazertinib, particularly those presenting with myalgia and elevated AST levels, to exclude rhabdomyolysis. Based on our case report, dose reduction in patients with rhabdomyolysis allows the reuse of lazertinib without additional side effects.

Author Contributions

Seunghun Lee contributed to data curation, conducted the investigation, performed the formal analysis, and was responsible for the visualisation and writing the original draft of the manuscript. Juwhan Choi was responsible for the project administration, contributed to the development of the methodology, and validated the findings. Sung Yong Lee provided the conceptual framework, supervised the overall project, contributed resources, and reviewed and edited the manuscript.

Acknowledgements

This study was supported by the Korea University and Korea University Guro Hospital.

Ethics Statement

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and the accompanying images.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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