CASE REPORT

Life-Threatening Myositis in a Patient With *EGFR*-Mutated NSCLC on Osimertinib: Case Report

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ABSTRACT

Osimertinib is the standard of care for the first-line treatment of *EGFR*-mutated NSCLC. We report a case of a 52-year-old woman who developed life-threatening myopathy because of treatment with osimertinib. Limited instances of myositis have been previously reported in the literature; however, none have resulted in life-threatening oropharyngeal and respiratory muscle weakness as seen in this case. Care should be taken in administering osimertinib concurrently with other medications metabolized by the CYP3A4 system, and ongoing work to identify patients at risk for severe reactions is necessary. The use of routine creatinine phosphokinase monitoring should be considered as part of oncologic management.

Keywords: Osimertinib; Myositis; NSCLC; EGFR; Case report

Introduction

Osimertinib has become the standard first-line treatment for *EGFR* exon 19 or 21–mutated advanced NSCLC in the United States. Osimertinib is generally very well tolerated. In the four major studies of osimertinib in NSCLC, creatinine phosphokinase (CPK) elevation has only been reported in the osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2) trial (two patients).[1] However a small number of case reports of mild myositis have been published.[2,3] Here, we discuss a case of fulminant and life-threatening myositis, which progressed to respiratory compromise and was refractory to conservative supportive management.

Case Presentation

A 52-year-old woman with recently diagnosed stage IV NSCLC was referred to our outpatient clinic for a second opinion.

She was diagnosed 1 month before with primary lung adenocarcinoma with diffuse osseous metastases and several small enhancing intracranial lesions. Molecular testing revealed an *EGFR* L858R mutation; the programmed death-ligand 1 tumor proportional score was 10%. She was prescribed osimertinib 80 mg orally daily.

At the time of diagnosis, she enjoyed an excellent performance status and no functional limits in exercise tolerance. She took apixaban for an incidentally noted small pulmonary embolism and did not use supplements. After 4 days of starting osimertinib, she experienced mild fatigue and muscle soreness. Over the next week, she noted increasing weakness. At the time of initial presentation to our clinic, 12 days after starting osimertinib, she needed assistance to walk short distances and her arm strength was decreased. Laboratory

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Drs. Crowley and Fitzgerald contributed equally to this work.

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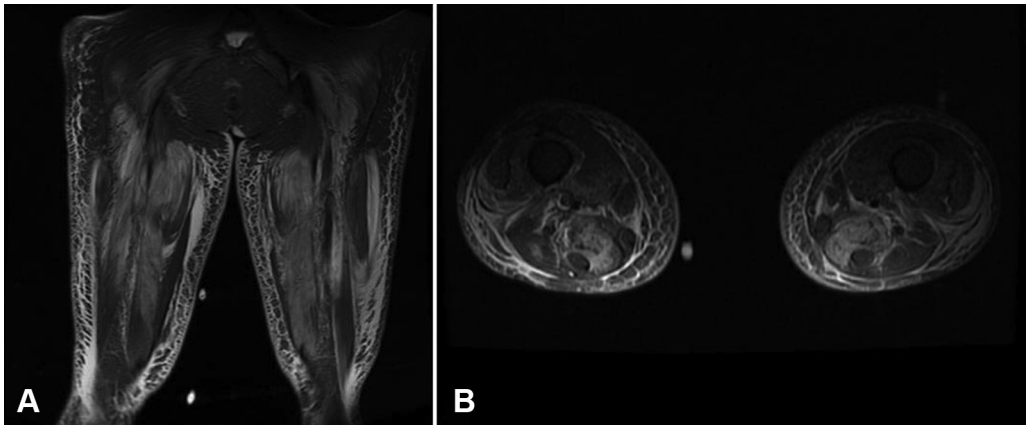

Figure 1. STIR-weighted (A) coronal and (B) axial MRI imaging of the lower extremities illustrating hyperintense signal throughout the posterior and adductor compartments consistent with diffuse bilateral lower extremity intramuscular edema. MRI, magnetic resonance imaging; STIR, short tau inversion recovery.

testing was notable for elevation in transaminases, with aspartate aminotransferase (AST) of 942 U/liter and alanine aminotransferase (ALT) of 433 U/liter.

Osimertinib was immediately discontinued, however, liver function tests continued to rise with AST being greater than 1000, and she was admitted to the hospital. The CPK level was 29,680 U/liter. Magnetic resonance imaging of the spine and lower extremities revealed muscle edema (Fig. 1*A* and *B*). Prednisone (40 mg orally daily) was started for the treatment of hepatitis; CPK levels began to trend downward. Muscle biopsy was deferred to avoid further injury to the already damaged muscle. As she had already started steroids, it was felt this would not change management. Similarly, electromyography was not completed as this would unlikely impact clinical management. Evaluation for other contributions to liver disease with hepatitis serologies, antimitochondrial antibodies, Epstein-Barr virus, and cytomegalovirus was unrevealing. Rheumatologic workup including the following autoimmune myositis antibodies were negative: anti-Jo, anti–SS-A, anti–PL-7, anti–PL-12, anti-EJ, anti-OJ, anti-SRP, anti-MI-2, anti–TIF-1gamma, anti–MDA-5, anti–NXP-2, anti-SAE1, anti–PM/SCL-100, anti-KU, anti-U1 RNP, anti-U2 RNP, anti-U3 RNP, anti-LRP4, and anti-SRP. Serum antinuclear antibodies were nondiagnostic. Anti–SS-A 52 kD U antibody was slightly elevated at 50 (normal <20). The patient was also strongly positive for HMGCR antibody (U) with a reported level of 154 (reference <20). Neuro-oncologic testing for antineuronal nuclear antibodies, anti-GAD antibodies, antiglial nuclear antibodies, Purkinje cell cytoplasmic antibodies (type 1, 2, and Tr), amphiphysin antibodies, CRMP-5 IGG, calcium channel antibodies, acetylcholine receptor ganglionic neuronal antibodies, and neuronal voltage-gated potassium channel antibodies were negative.

Her lower, then upper extremity weakness intensified. Deep tendon reflexes were preserved on physical examination consistent with weakness secondary to myopathy. She developed dysphagia, and oropharyngeal muscle weakness was observed on direct laryngoscopy. Frank aspiration of thin liquids on modified barium swallow (Fig. 2*A-C*) prompted nasogastric tube placement.

Given the concern for inflammatory myositis, she was started empirically on pulse-dose steroids solumedrol 60 mg intravenous (IV) daily and IV immunoglobulin 1g/kg daily for 2 days. CPK and liver function tests continued to improve, however, her strength deteriorated. She began to experience difficulty completing sentences and the work of breathing increased. Two weeks after admission, her negative inspiratory force dropped to a nadir of -12 cm H_2O and she developed hypoxia, necessitating admission to the intensive care unit for close respiratory monitoring. In consultation with neuromuscular neurology, she was diagnosed with presynaptic muscle fiber damage caused by profound muscle necrosis. She was started on empirical pyridostigmine 2 mg IV every 3 hours to prolong acetylcholine action in the neuromuscular junction to compensate for synaptic dysfunction. Despite negative serum acetylcholine receptor antibodies, her strength increased, and negative inspiratory force improved to -30 cm H_2O. With an ongoing slow steroid taper and prolonged taper of pyridostigmine, she recovered some distal strength, which is currently 4+ out of 5 power in all extremities. She continued to have proximal muscle weakness, but she was able to eat a regular diet and did not require supplemental oxygen. At the time of submission (2 months after admission), she has been transferred to acute rehabilitation. She has not received any cancer-directed treatment in 2 months. Imaging done a month

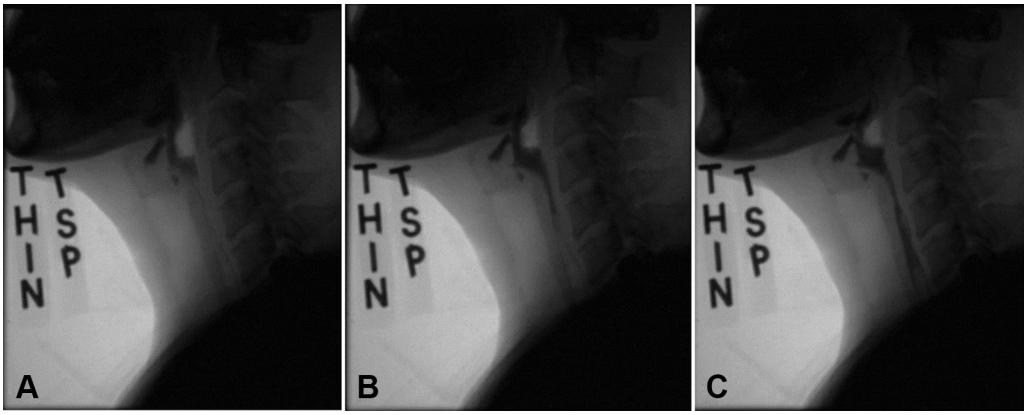

Figure 2. Modified barium swallow. Representative stills from videofluoroscopy from the earliest time point (A), mid-swallow (B), and latest time point (C). Laryngeal contrast penetration can be observed during speech. THIN

after admission revealed a stable disease. The plan when she recovers is to start chemotherapy and stereotactic brain radiation (Fig. 3).

Discussion

Serious adverse reactions to osimertinib are rare. The osimertinib in untreated *EGFR*-mutated advanced non–small-cell lung cancer authors reported grade 3 or 4 adverse events in 42% of patients, with diarrhea being the most common any-grade adverse effect (60%).[1] Musculoskeletal pain was reported in 10% of patients with 10% experiencing an increase in AST and 7% in ALT. Within the four major studies of osimertinib (AURA phase 2 extension, AURA 2, AURA 3, and osimertinib in untreated *EGFR*-mutated advanced non–small-cell lung cancer), CPK elevation was only reported in AURA2. In this trial, increased blood CPK was reported in two patients (1%); both were grade 2 in severity with no mention of rhabdomyolysis.[2] Increased AST and ALT were seen in 12 (<6%) and 13 patients (6%), respectively.[2]

The relationship between high CPK and transaminitis is unclear in this case but several reports have described the strong correlation between CPK levels and serum transaminases.[3] We are aware of five reported cases of osimertinib related myositis, all comparatively mild. One 2020 case series described four cases of myositis in patients treated with osimertinib.[4] Two of these patients had mild symptoms, two were identified after CPK monitoring was implemented as screening. All cases were initially Common Terminology Criteria for Adverse Event grade 1 to 2, with one patient later developing grade 4 elevation in CPK (2511 U/liter) without associated symptoms. In two of the patients affected, myositis resolved within 1 month of drug cessation. Two other patients continued treatment with close monitoring. A literature search yielded only one further case of myositis secondary to osimertinib with a CPK of 1238 U/liter (Common Terminology Criteria for Adverse Events grade 3).[5] In this case, osimertinib was successfully restarted at a reduced dose after discontinuation for 1 month, although CPK remained elevated. In none of the reported cases was myositis associated with respiratory or oropharyngeal muscle weakness. As far as we are aware, none of the cases necessitated an intensive care unit admission.

It is unclear why our patient's reaction was so much more severe than those previously reported or why the condition progressed despite stopping osimertinib. Anti–SS-A 52 kD U, which was elevated, is one of the "myositis-associated" antibodies, not myositis-specific antibodies. It is typically seen in the setting of myositis as part of another systemic autoimmune disease like Sjogren's or systemic lupus erythematous and is generally not severe. Our patient had moderate range antibodies and no signs of systemic autoimmune disease. HMGCR antibody (U) is associated with statin-induced immune-mediated necrotizing myopathy, which is associated with high CPK and proximal weakness, which endures despite statin withdrawal.[6] Our patient was not taking a statin. It has been postulated that statins may change the conformation of the HMGCR protein and trigger autoimmunity by exposing cryptic epitopes.[6] In addition, regenerating muscle cells express high levels of HMGCR, which may provide a continuous source of antigen to drive the immune response.[6] There are no data on EGFR inhibitors and HMGCR antibodies. This lack of remittance after withdrawal of the drug contrasts with cancer-associated myositis, which, in general, improves with treatment of underlying cancer.

Tyrosine kinase inhibitors are known to interact with a number of other medications. These interactions are mediated by a number of processes: effects on

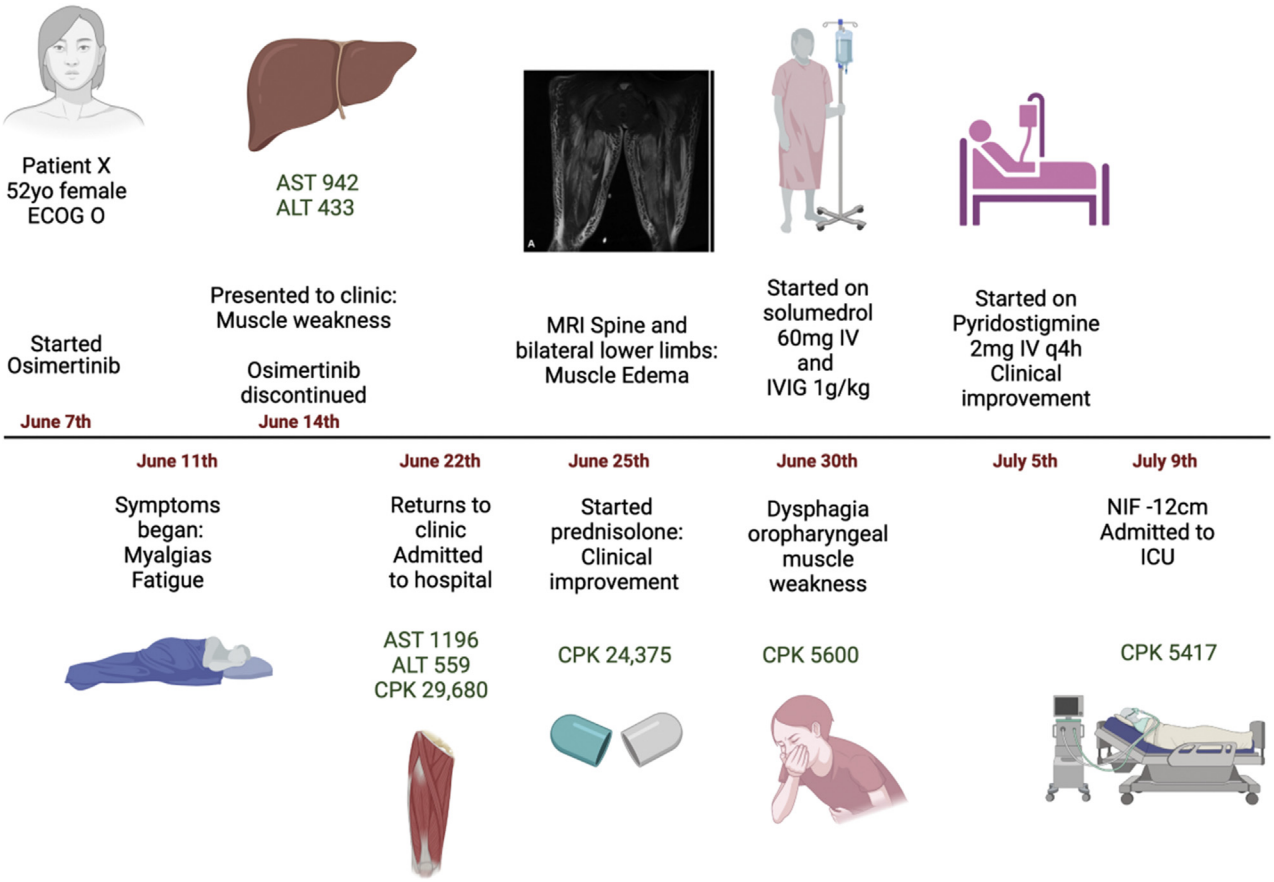

Figure 3. Timeline of events. Made with BioRender.com. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatinine phosphokinase; ECOG, Eastern Cooperative Oncology Group; IVIG, intravenous immunoglobulin; IV, intravenous; MRI, magnetic resonance imaging; NIF, negative inspiratory force; q4h, every 4 hours; yo, years old.

gastrointestinal pH, cytochrome P450–dependent metabolism, uridine diphosphate glucuronosyltransferase, and transporter proteins.5 In vitro studies indicate that osimertinib is predominantly metabolized by CYP3A4 or CYP3A5 and is a weak inducer of CYP3A4.[7] This patient was taking apixaban when she started osimertinib, which is also metabolized by CYP3A4 and might be hypothesized to have contributed to poor metabolism. However, with in vitro and modeled pharmacokinetic data, no dose adjustment for administration with strong CYP3A4 inhibitors was necessary.[5]

Our patient still has a long recovery ahead and has not received any cancer treatment in over 2 months. Her reaction to osimertinib has not only interrupted her cancer care but also limited future treatment options. It remains to be seen what consequence this will have on her long-term survival.

Conclusions

Although rare, this case illustrates that myositis and ensuing muscle weakness precipitated by treatment with osimertinib can be life-threatening. We believe that patients should, therefore, be educated on signs and symptoms of impending myopathies, and clinicians should have a low threshold to check CPK levels and hold the medication when these signs develop. Care should be taken in administering osimertinib concurrently with other medications metabolized by the CYP3A4 system, and ongoing work to identify patients at risk for severe reactions is necessary.

CRediT Authorship Contribution Statement

Fionnuala Crowley: Conceptualization, Visualization, Writing - original draft; Writing - review & editing.

Bailey G. Fitzgerald: Conceptualization, Writing - original draft; Writing - review & editing.

Aarti S. Bhardwaj, Cardinale Smith: Conceptualization, Writing - review & editing.

Irine Siraj: Investigation.

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Written informed consent for publication was obtained from the patient.

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