

CASE REPORT

DRUG - INDUCED RHABDOMYOLYSIS SECONDARY TO LENALIDOMIDE

¹Himanshu Rathore, ²Sananjay Singh

¹OSF SAINT Francis Medical Center, Peoria IL, USA

²Faculty of Internal Medicine, University of Illinois, Peoria IL, USA

Corresponding Author: Himanshu Rathore, OSF SAINT Francis Medical Center, Peoria IL, USAZ

Email: himanshurathore.1357@gmail.com

ABSTRACT

Lenalidomide is an immunomodulator imide compound that works through its antitumor, anti-angiogenic and anti-osteoclastogenic effects. It is increasingly used for a multitude of inflammatory disorders and cancers. Diarrhea, thrombocytopenia, neutropenia, and blood clots are well established severe side effects of Lenalidomide, but rhabdomyolysis is a rare side effect of the drug. It is difficult to reach this diagnosis because it needs a detailed history of the evolution of symptoms and carefully ruling out other etiologies especially other drugs. Here we present the case of a 75-year-old female who developed rhabdomyolysis and, subsequently, acute kidney injury after receiving Lenalidomide therapy for multiple myeloma. Discontinuation of the diuretics and the use of isotonic fluids led to a gradual improvement in her condition. Physicians should be aware of this potential rare complication and keep it on the differential when treating patients on Lenalidomide.

KEYWORDS: Rhabdomyolysis; Lenalidomide; Creatine Kinase; Immunomodulatory drugs.

INTRODUCTION

Rhabdomyolysis is a severe medical condition that is caused by the breakdown and necrosis of muscle tissue and release of intracellular content into the bloodstream [1]. It can result from trauma and compression, exertion, infections, certain autoimmune diseases, endocrine abnormalities, electrolyte disturbances and body temperature changes, genetic disorders such as glycogen storage diseases, muscular dystrophies, disorders of fatty acid metabolism and mitochondrial diseases. Clinically, muscle injury can be asymptomatic or present as local or diffuse pain, tenderness, or weakness and may be associated with nonspecific symptoms including fatigue, nausea, vomiting and fever [2]. In addition, patients may report red or brown urine [2]. The most specific laboratory marker of rhabdomyolysis is elevated plasma creatine kinase level, with values at least five times the upper limit of normal (Normal 30-145U/L females and 55-170U/L in males) or creatine kinase level >1000. U/L [1]. Other markers of rhabdomyolysis are

elevated lactate dehydrogenase, serum transaminase, aldolase, myoglobin, troponin and carbonic anhydrase [3].

Lenalidomide is an immunomodulator interacting with ubiquitin E3 ligase cereblon to degrade Ikaros transcription factors IKZF1 and IKZF3 [4]. Rare adverse effects of Lenalidomide include an increased risk of death in people with chronic lymphocytic leukemia, increased risk of new cancers, tumor lysis syndrome, and severe liver and thyroid problems [5,6]. Here we present an interesting case of rhabdomyolysis while on Lenalidomide, where the diagnosis was finalized after carefully excluding other possible etiologies.

CASE PRESENTATION

Our patient is a 75-year-old African American female with IgG Kappa multiple myeloma diagnosed in 2014 who presented to the hospital with concerns of generalized muscle pains and weakness. The patient gave a history of diarrhea for the past two to three days. She

was on diuretics for congestive heart failure and reported compliance.

She was initially started on Bortezomib, dexamethasone, and Lenalidomide for her multiple myeloma. Unfortunately, she had a high IgG Kappa M spike in 2015 and was considered for a bone marrow transplant in the same year. However, in view of toxicities from standard therapy, overall clinical stability, and no high-risk cytogenetics, the patient and her oncologist it did not pursue it. Multiple myeloma became an issue again around late 2021 when the patient had an abnormal MRI lesion in the right supra-acetabular ileum concerning for metastatic disease. She received palliative radiation therapy to the right hip on 12/21/21 and was initiated on maintenance therapy with Lenalidomide, daratumumab and dexamethasone. Other medical problems include a history of pulmonary embolism for which she was on apixaban, chronic paroxysmal atrial fibrillation, and heart failure with preserved ejection fraction both of which were managed conservatively.

In the emergency room patient's initial blood work showed that she had acute renal failure and rhabdomyolysis. Her creatine kinase level was 4489U/L. Volume resuscitation was performed with isotonic fluids, which led to a gradual improvement in renal failure. At this stage, medications such as lisinopril, lasix and spironolactone were stopped in view of acute renal failure. Her oncologist was consulted, and therapy for multiple myeloma was also stopped. At the time of discharge from inpatient ward, the patient was doing better, her renal dysfunction had resolved, and her total creatine kinase levels were back to normal (100U/L). In addition, she reported no muscle aches or pains. Her repeat labs were scheduled after one week which also came back normal.

During evaluation for the cause of rhabdomyolysis, she denied any trauma or excessive exertional activity. She denied any infection or history of excessive alcohol use. She was not on any other medication commonly implicated in drug induced rhabdomyolysis. Therefore, we suspect her rhabdomyolysis and subsequent renal failure is secondary to Lenalidomide in the setting of acute dehydration with few reports suggesting the association [7,8].

DISCUSSION

Lenalidomide can synergize with dexamethasone to augment anti myeloma activity [10]. In addition, it exhibits immunomodulatory properties by increasing the number of T cells, NK cells, and NKT cells and inhibiting pro inflammatory cytokines by monocytes [5]. It inhibits cell proliferation and induces apoptosis of tumor cells in vitro, and inhibits tumor growth in vivo, leading to a decrease in tumor burden [5]. It also inhibits angiogenesis by reducing levels of VEGF, TNF-alpha, and IL-6 [5]. In 2006, Lenalidomide combined with dexamethasone, was indicated for treating adult patients with multiple myeloma [10]. In 2015 it was also approved for use with dexamethasone in newly diagnosed patients who are not candidates for an autologous stem cell transplant [10]. As of 2017, it is indicated as maintenance therapy in adult patients suffering from multiple myeloma following autologous hematopoietic stem cell transplant [10].

Lenalidomide is also used to treat anemia in patients with specific myelodysplastic syndrome known as 5q MDS [5]. In addition, it is used to treat mantle cell lymphoma in patients previously treated with Bortezomib and one additional medicine that was not successful. It is also used in combination with rituximab to treat previously treated follicular lymphoma and marginal zone lymphoma. Lenalidomide is available only under a restricted distribution program called the Lenalidomide REMS (Risk Evaluation and Mitigation Strategy) [5].

Commonly used drugs such as statins, HIV medications like zidovudine, gout medications like colchicine, Central Nervous System depressants, neuromuscular blocking agents, cocaine and other recreational substances induce rhabdomyolysis. Like all other causes of rhabdomyolysis, these medications increase calcium inside a muscle cell, which starts a cascade of muscle breakdown.

Treatment of rhabdomyolysis secondary to Lenalidomide is the same as treatment for rhabdomyolysis secondary to other factors. The drug in question should be discontinued. The patient should be given fluids and remain hydrated. Usually, patients have complete remission within days. Our patient's Lenalidomide was discontinued on discharge after discussion with her oncologist.

CONCLUSION

With increasing indications for Lenalidomide and other immunomodulatory drugs, it is essential to be aware of rhabdomyolysis as a rare complication. As mentioned previously, this can be an extremely difficult diagnosis to make. However, with increasing indications the complication will likely increase in frequency. About half of rhabdomyolysis occurs within a month of starting a new medication. Potential high-risk factors include age group younger than 10 years old and body weight less than 50 Kg. Physicians should be aware of this possible complication and keep it on their differential.

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