Adalimumab-associated hypokalemia and rhabdomyolysis in a patient with Crohn's disease: A case report

So Young (Regina) Jung, PharmD Candidate 2021[1,2]; Seohyun (Claudia) Choi, PharmD, BCCCP[1,2]

[1]Saint Barnabas Medical Center, Livingston, New Jersey, [2]Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey

Background

- Crohn's disease (CD) is a chronic inflammatory condition of the gastrointestinal (GI) tract. It is a progressive disease with relapsing and remitting phases; symptoms include chronic diarrhea, abdominal pain and weight loss.[1,2]
- Patients may develop strictures, fistulas, or abscesses that inhibit intestinal function, which often require surgical interventions.[2]
- CD may have extra-intestinal manifestations due to chronic inflammation including arthritis, cutaneous lesions, ocular disorders, and hepatobiliary diseases.[2,3]
- Mucosal inflammation in CD may impair electrolyte secretion and absorption, resulting in significant electrolyte imbalance. Deficiencies of potassium, calcium, and magnesium either alone or in combination have been reported in patients even in disease remission.[4]
- Potassium plays a major role in increasing blood flow to contracting muscles. In animal models, hypokalemia has been shown to cause ischemia and muscle necrosis after prolonged and intense physical activity. In general, potassium depletion caused minor abnormalities to the muscle and elevated serum creatine phosphokinase (CK), indicating muscle loss.[5]
- Treatment for CD is based on severity of disease and risk of progression, with the goal of achieving and maintaining remission. Common classes of drugs are 5-aminosalicylates, antibiotics, corticosteroids, immunomodulators, and biologics.[2]
- Adalimumab is a tumor necrosis factor alpha (TNFα) monoclonal antibody indicated for the induction and maintenance of remission for moderate to severe CD. The recommended dosage is 160 mg on day 1, followed by 80 mg on day 15, followed by a 40 mg maintenance dose every other week beginning day 29.[6,7]
- Common adverse effects include headache, infections, and dermatologic complications. Serious adverse effects include risk of serious infections, congestive heart failure, lupus-like syndrome, and demyelinating disorders.[7,8]

Introduction

- Patients with CD may experience extra-intestinal complications such as electrolyte disorders, yet cases of severe hypokalemia resulting in elevated CK and rhabdomyolysis have rarely been reported.
- Severe electrolyte deficiencies or rhabdomyolysis are not known adverse effects of adalimumab listed in the FDA-approved prescribing information.[7]
- We present a unique case of a patient with CD who developed hypokalemia and rhabdomyolysis following administration of adalimumab.

Patient Case

- **Patient Background Information**
  - A 59-year-old male presented to the emergency department with complaints of muscle pain and weakness in the extremities beginning 2 days prior to admission.

Past medical history	• 20-year history of CD
History of present illness	• CD symptoms had been well-controlled with oral budesonide and mesalamine • He experienced an exacerbation 1.5 weeks prior to admission, which resolved after receiving a loading dose of adalimumab • Patient denied recent fevers, strenuous activity, or changes in bowel movements
Chronic medications for CD	• **Adalimumab, loading dose administered 10 days prior to admission** • Oral budesonide, dose unknown • Mesalamine, dose unknown
Initial laboratory values	• Serum K^+ 2.0 mEq/L • Serum Ca^{2+} 5.5 mg/dL • CK 10,118 U/L
Initial electrocardiogram (EKG)	• Normal sinus rhythm (NSR), prolonged QTc 501 ms

- **Emergency Department Course and Treatment**

Initial treatment	Repeat laboratory values
• 40 mEq oral potassium chloride • 40 mEq IV potassium chloride • 2 g IV calcium gluconate • 3 L normal saline IV fluids	• Serum K^+ 1.7 mEq/L • Serum Ca^{2+} 5.3 mg/dL • Serum PO_4^{3-} 2.0 mg/dL • Serum Mg^{2+} 0.48 mEq/L

  - The patient was admitted to the intensive care unit (ICU) for close monitoring and aggressive electrolyte replacement.
- **ICU Course and Treatment**
  - All CD medications were held until further evaluation. The patient's outpatient GI physician confirmed that laboratory values were unremarkable before administering the loading dose of adalimumab.

	Day 1	Day 2	Day 3
Treatment			
Potassium chloride ER oral (mEq/day)	40	160	--
Potassium chloride IV (mEq/day)	--	260	100
Potassium phosphate IV (mmol/day)	--	--	8
Magnesium oxide oral (g/day)	--	2.4	--
Magnesium sulfate IV (g/day)	1	13	--
Calcium gluconate IV (g/day)	--	1	4
Calcitriol IV (mcg/day)	--	3	2
Daily Laboratory Values			
Serum K^+ (mEq/L)	1.9	3.4	4.1
Serum Ca^{2+} (mg/dL)	5.7	5.9	7.4
Serum PO_4^{3-} (mg/dL)	2.0	2.6	2.5
Serum Mg^{2+} (mEq/L)	1.00	3.14	2.17
CK (U/L)	--	7,246	6,508
EKG	--	NSR, QTc 493 ms	--

Patient Case, *cont.*

- On day 4, the patient was transferred to a non-ICU unit.
- No active GI losses such as vomiting or diarrhea were noted during the hospitalization.

Discussion

- Hyperkalemia, hyperphosphatemia, and late hypercalcemia are common laboratory abnormalities due to rhabdomyolysis.[9] However, our patient uniquely presented with severe electrolyte deficiencies, which led us to hypothesize that these deficits were the causative factors of rhabdomyolysis.
- In 2007, a case report described a 40-year-old woman with a history of CD requiring surgical resection of the bowel who experienced rhabdomyolysis and increased CK (7,316 U/L) due to hypokalemia (1.8 mEq/L) after disease relapse.[10]
- Although electrolyte abnormalities have been linked to uncontrolled CD, our patient did not report any recent GI losses or strenuous activity that could have triggered severe electrolyte abnormalities.
- It is possible that our patient's long history of CD, while well-controlled, caused an underlying impairment of electrolyte absorption. However, without evidence of other triggers, it can be postulated that adalimumab contributed to this patient's presentation.

Conclusions

- Hypokalemia and rhabdomyolysis are potential adverse effects of adalimumab. There are no previous reports of severe symptomatic cases.
- Prescribers should be aware of these complications of adalimumab therapy since patients with CD are at a higher risk for electrolyte disturbances.
- Further evaluation should be done to determine the incidence and severity of electrolyte abnormalities and rhabdomyolysis due to adalimumab, with the potential for including these events to the adverse effect profile.

Disclosures

Authors do not have any conflict of interest.

References

1. Adegbola SO, Sahnan K, Warusavitarne J, et al. Anti-TNF therapy in Crohn's disease. *Int J Mol Sci.* 2018;19(8):2244.
2. Lichtenstein GR, Loftus EV Jr, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol.* 2018;113:481–517.
3. Colia R, Corrado A, Cantatore FP. Rheumatologic and extraintestinal manifestations of inflammatory bowel diseases. *Ann. Med.* 2016;48(8):577-585.
4. Barkas F, Liberopoulos E, Kei A, et al. Electrolyte and acid-base disorders in inflammatory bowel disease. *Ann Gastroenterol.* 2013;26(1):23-28.
5. Knochel JP, Schlein EM. On the mechanism of rhabdomyolysis in potassium depletion. *J Clin Invest.* 1972;51:1750-1758.
6. Cassinotti A, Ardizzone S, Porro GB. Adalimumab for the treatment of Crohn's disease. *Biologics.* 2008; 2(4): 763-777.
7. Humira (adalimumab) [prescribing information]. Ludwigshafen, Germany: AbbVie Deutschland GmbH & Co. KG; 2020.
8. Asgharpour A, Cheng J, Bickston SJ. Adalimumab treatment in Crohn's disease: an overview of long-term efficacy and safety in light of the EXTEND trial. *Clin Exp Gastroenterol.* 2013;6:153-160.
9. Zhang M. Rhabdomyolysis and its pathogenesis. *World J Emerg Med.* 2012;3(1):11-15.
10. Mangone M, Spagnolo A, Capurso G, et al. Rhabdomyolysis due to severe hypokaliemia in a Crohn's disease patient after budesonide treatment. *Digest Liver Dis.* 2007;39:776-779.