CLINICAL VIGNETTE

Crushing It: A Rare Cause of Hypercalcemia

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Introduction

Rhabdomyolysis is a clinical syndrome resulting from muscle breakdown due to a range of conditions including trauma, burn injuries, toxins or heavy exertion.[1] The release of intracellular contents including calcium, potassium, and phosphorus can lead to life threatening electrolyte abnormalities. Hypocalcemia is the most common electrolyte abnormality, caused by calcium phosphate deposition into necrosed muscle cells.[2] We present an unusual case of rhabdomyolysis complicated by renal failure and hypercalcemia.

Case Report

A 20-year-old man with no past medical history was referred to the emergency department by his primary care physician after laboratory exam revealed acute renal failure. Three weeks prior to presentation he reported falling asleep on his right arm for over 12 hours and was admitted to an outside hospital with rhabdomyolysis. His hospital course was complicated by renal failure requiring three days of hemodialysis. He recovered renal function and was discharged with close follow up. Since discharge, he reported excessive urination and noted improvement in his arm pain and mobility. He denied abdominal pain, nausea, vomiting, constipation, bone pain, or change in mental status. His physical exam was only notable for blood pressure of 145/89mm/Hg and decreased flexion and extension in his right elbow. His labs were notable for BUN 21 mg/dL and creatinine of 2.0 mg/dL, Calcium 14.9 mg/dL (reference range: 8.9-10.3mg/dL), PTH 6 pg/mL (15-65pg/mL), Vitamin D 25-OH 32 pg/mL(30-100pg/mL), Vitamin D 1-25 11pg/mL (18-72 pg/mL), and PTH-related peptide 15pg/mL (14-27pg/mL). His albumin, TSH, creatinine kinase and angiotensin converting enzyme level were normal. Peripheral smear was normal and serum and urine protein electrophoresis did not reveal monoclonal proteins. Renal ultrasound was negative for nephrolithiasis, hydronephrosis or masses. He was admitted and started on intravenous fluids at 150cc/hr to maintain urine output with improvement in his renal function and calcium level. After two days of intravenous fluids he was given one 40 mg intravenous furosemide. On the day of discharge his calcium was 9.9 mg/dL and Cr was 1.5 mg/dL.

Discussion

Rhabdomyolysis can result from any form of muscle damage, such as the crush injury in our patient. Other causes of localized muscle ischemia that can result in rhabdomyolysis include thromboses, emboli, compartment syndrome, carboxyhemoglobinemia, or sickle cell disease.[1-3] The prolonged oxygen deprivation to the muscle precipitates muscle breakdown. The final common steps, regardless of initial insult, involve either direct myocyte injury or decreased energy supply within the cell. Acute renal failure (ARF) is one of the most serious complications of rhabdomyolysis and occurs in up to 33% of patients.[3] ARF occurs as a result of decreased plasma volume causing hypoperfusion of the kidneys and the toxic effect of myoglobin on the renal tubulars that can cause obstruction or precipitate obstructive casts.

At rest, a normally functioning muscle cell requires adenosine triphosphate (ATP) dependent ion channels (namely Na+/K+ pumps and Na+/Ca2+ exchangers) to maintain low concentrations of intracellular sodium and calcium and high intracellular potassium. Direct injury to the muscle or a decreased ATP supply through the mechanisms mentioned above disrupts proper cell functioning. In an injured muscle cell or with decreased ATP availability, there is an influx of extracellular socium and calcium into the cell. The prolonged high intracellular level of calcium leads to sustained myofibrillar contraction further depleting ATP and activating calcium dependent proteases and phospholipases promoting lysis of the cellular membrane. The end result of these alterations is an inflammatory, self-propagating myolytic cascade that causes necrosis of the muscle fiber and release of potassium, phosphorus and calcium into the extracellular space and blood stream.[1-4] The phosphorus binds to calcium forming a complex that deposits into necrosed muscle cells and results in the hypocalcemia typically seen in rhabdomyolysis.

During renal recovery, our patient began to develop hypercalcemia. This has been reported in only a handful of cases that hypercalcemia may be seen as a complication of the diuretic phase of rhabdomyolysis induced renal failure. This is thought to be the result of mobilization of the calcium phosphorus deposits in the severely injured muscles and soft tissues during recovery and is further potentiated by excessive diuresis.[5-8] Overdiuresis causes relative hypovolemia which

leads to renal vasoconstriction, reducing the GFR and calcium excretion.[7] Our patient reported both improvement in his arm mobility and excessive diuresis which support the mechanisms by which hypercalcemia can develop in the renal recovery phase.

It was essential to rule out other causes of hypercalcemia particularly in this young, previously healthy patient. The most common cause of hypercalcemia is primary hyperparathyroidism with a single adenoma responsible for about 85% of cases.[8] Other causes of hypercalcemia include hypervitaminosis D, Milk-alkali syndrome, hyperthyroidism, hypothyroidism, Addison's disease, sarcoidosis, granulomatous disease, and usage of thiazide diuretics. Serum calcium is regulated by an intricate series of interactions between parathyroid hormone (PTH), 1,25- dihydroxy vitamin D (calcitriol) and calcitonin. These hormones act on the bone, kidney and small intestine.[9] Our patient's PTH and calcitriol levels were appropriately suppressed and thus were unlikely to contribute to his condition. Additionally, evaluation for malignancy and granuloma forming infections were negative.

Rhabdomyolysis induced hypercalcemia is treated in a similar manner as other causes of hypercalcemia. Patients are typically hypovolemic and require large volume of fluid resuscitation. Our patient was started on maintenance crystalloid fluids at 150cc/hr for several days. After sufficient volume repletion, a loop diuretic was used to help further augment reduction in calcium levels.

Conclusion

Hypercalcemia is a rare late stage complication of rhabdomyolysis and can develop during the diuretic phase of renal recovery. Early identification is essential as untreated hypercalcemia can lead to further complications. This condition is transient and resolves spontaneously, and therefore treatment is largely supportive.

REFERENCES

1. **Giannoglou GD, Chatzizisis YS, Misirli G**. The syndrome of rhabdomyolysis: Pathophysiology and diagnosis. *Eur J Intern Med*. 2007 Mar;18(2):90-100. PubMed PMID: 17338959.
2. **Hechanova LA, Sadjadi SA**. Severe hypercalcemia complicating recovery of acute kidney injury due to rhabdomyolysis. *Am J Case Rep*. 2014 Sep 14;15:393-6. doi: 10.12659/AJCR.891046. PubMed PMID: 25218143; PubMed Central PMCID: PMC4172091.
3. **Torres PA, Helmstetter JA, Kaye AM, Kaye AD**. Rhabdomyolysis: pathogenesis, diagnosis, and treatment. *Ochsner J*. 2015 Spring;15(1):58-69. Review. PubMed PMID: 25829882; PubMed Central PMCID: PMC4365849.
4. **Khan FY**. Rhabdomyolysis: a review of the literature. *Neth J Med*. 2009 Oct;67(9):272-83. Review. PubMed PMID: 19841484.
5. **Sperling LS, Tumlin JA**. Case report: delayed hypercalcemia after rhabdomyolysis-induced acute renal failure. *Am J Med Sci*. 1996 Apr;311(4):186-8. PubMed PMID: 8602649.
6. **Olazo E, Sánchez-de la Nieta MD, Rivera F, Anaya S, Arambarri M, Ferreras I**. Massive hypercalcaemia in rhabdomyolysis associated with acute renal failure. *Nefrologia*. 2012;32(5):690-2. doi: 10.3265/Nefrologia.pre2012.Jun.11577. English, Spanish. PubMed PMID: 23013966.
7. **Mitrogianni Z, Tsimihodimos V, Tzavella E, Elisaf M**. Hypercalcemia and acute renal failure associated with calcium carbonate consumption in a patient with hypoparathyroidism. *Arch Med Sci*. 2014 Dec 22;10(6): 1255-7. doi: 10.5114/aoms.2014.47835. PubMed PMID: 25624866; PubMed Central PMCID: PMC4296081.
8. **Stojceva-Taneva O, Taneva B, Selim G**. Hypercalcemia as a Cause of Kidney Failure: Case Report. *Open Access Maced J Med Sci*. 2016 Jun 15;4(2):283-6. doi: 10.3889/oamjms.2016.044. Epub 2016 Mar 18. PubMed PMID: 27335601; PubMed Central PMCID: PMC4908746.
9. **Basok AB, Rogachev B, Haviv YS, Vorobiov M**. Treatment of extreme hypercalcaemia: the role of haemodialysis. *BMJ Case Rep*. 2018 Jun 4;2018. pii: bcr-2017-223772. doi: 10.1136/bcr-2017-223772. PubMed PMID: 29866671; PubMed Central PMCID: PMC5990060.