



Case Report

Localized Rhabdomyolysis Associated With Testosterone Enanthate for Gender-Affirming Hormonal Therapy

Rashmi Reddy, MD ¹, Sergio Lizama-Hernández, MD ², Ava M. Port, MD ^{1,*}

¹ Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine, Baltimore, Maryland

² Department of Endocrinology, Medstar Franklin Square Medical Center, Baltimore, Maryland

ARTICLE INFO

Article history:

Received 3 June 2022
 Received in revised form
 2 September 2022
 Accepted 26 September 2022
 Available online 30 September 2022

Key words:

rhabdomyolysis
 testosterone
 hormone therapy
 transgender

ABSTRACT

Background/Objective: Rhabdomyolysis is a condition characterized by the destruction of skeletal muscle tissue that leads to systemic complications. We present a case of gender-affirming intramuscular (IM) testosterone therapy precipitating localized deltoid rhabdomyolysis.

Case Report: A 34-year-old transgender man presented to the emergency department with dark-colored urine and pain in the left deltoid muscle where he had been injecting IM testosterone. He was found to have significant elevation in the level of creatinine kinase that was consistent with rhabdomyolysis and managed with intravenous fluids. He received trial therapy with IM testosterone again in the contralateral deltoid twice with recurrent rhabdomyolysis. He eventually transitioned to subcutaneous testosterone to achieve his masculinization goals without adverse effects.

Discussion: Localized anabolic steroid use has been associated with rhabdomyolysis. However, to the best of our knowledge, this is the first case report of rhabdomyolysis attributed to gender-affirming testosterone therapy. Our patient had been administering testosterone intramuscularly into larger muscles (thigh and gluteus) for many years without any issues, whereas recurrent focal rhabdomyolysis developed only in association with deltoid injections. We theorize that a relative increase in dose and volume of testosterone per gram of muscle after switching to the deltoid site precipitated rhabdomyolysis. Subcutaneous testosterone is an acceptable alternative to IM testosterone for patients desiring an injectable delivery route with minimal adverse effects.

Conclusion: This case report highlights the potential risk of rhabdomyolysis associated with IM testosterone administration in the deltoid region for gender-affirming care. Patients on IM testosterone should use the thigh or gluteal muscles rather than the deltoid.

© 2022 AAACE. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Rhabdomyolysis is a syndrome characterized by skeletal muscle destruction leading to intracellular enzymatic release and systemic complications such as renal failure.¹ Clinically, it manifests with myalgias, tea-colored urine, weakness, and elevations in the level of creatinine kinase (CK) typically >5 times the upper limit of the normal level.¹ Rhabdomyolysis has been linked to numerous precipitants, including stimulants, toxins, metabolic derangements,

primary muscle injury, trauma, infections, dehydration, and seizures. In the literature, anabolic-androgenic steroid (AAS) abuse has been linked to rhabdomyolysis and myositis dating back to as early as 1988.²⁻⁸ Although testosterone remains the primary management strategy for transmasculine care, it has not been linked to rhabdomyolysis. We describe a case of localized rhabdomyolysis with the use of intramuscular (IM) testosterone therapy in a transgender man that improved with cessation of the therapy and transition to subcutaneous (SC) administration.

Case Report

A 34-year-old transgender man began receiving gender-affirming hormonal therapy 9 years before the presentation and had been maintained on IM testosterone enanthate 60 mg weekly administered in the thigh and gluteal regions. In the previous year,

Abbreviations: AAS, anabolic-androgenic steroid; CK, creatinine kinase; IM, intramuscular; SC, subcutaneous.

* Address correspondence to Dr Ava M. Port, Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine, 800 Linden Ave, 8th Floor Diabetes Center, Baltimore, MD 21201.

E-mail address: aport@som.umaryland.edu (A.M. Port).

he elected to switch his injection site to the left deltoid muscle to allow his partner attending nursing school to practice the IM injection technique. He preferred using the left side because of his right-handedness. His medical history was notable for obstructive sleep apnea, polycystic ovary syndrome, cervical neoplasia, total abdominal hysterectomy with bilateral salpingo-oophorectomy for gender affirmation, and bilateral mastectomy for chest masculinization. He presented to the emergency department with dark-colored urine that was preceded by severe pain, swelling, and soreness near his left deltoid injection site. These symptoms began 2 days after his last testosterone injection. His baseline exercise regimen consisted of CrossFit exercise 3 to 5 times weekly and interval weight training for years, and he denied any new strenuous exercise. Baseline laboratory test results obtained 14 weeks before presenting included a total testosterone level of 490 ng/dL (normal range, 264–916 ng/dL), free testosterone level of 16.5 ng/dL (normal range, 8.7–25.1 ng/dL), hemoglobin A1C level of 4.9% (30 mmol/mol) (normal level, <5.7% [39 mmol/mol]), and creatinine level of 1.14 mg/dL (normal range, 0.76–1.27 mg/dL).

During his initial evaluation, the CK level was 9690 U/L (normal range, 24–204 U/L) and creatinine level was 1.1 mg/dL. An ultrasound scan of his left upper extremity ruled out deep vein thrombosis and showed changes in musculature echogenicity consistent with rhabdomyolysis. He was treated with intravenous fluid and recommended for close follow-up. Testosterone therapy was held, and the patient ceased participation in high-intensity exercise and weight training, believing that these factors contributed to his presentation. A repeat CK level test 11 days later showed a decrease to 243 U/L, and his symptoms subsided. One month later, the patient injected IM testosterone contralaterally into his right deltoid but again developed right upper extremity pain and tea-colored urine. Testosterone was discontinued and symptoms abated. The patient avoided exercise and held therapy for 8 weeks before attempting IM testosterone into his right deltoid again and sought medical attention after identical symptoms developed in him. Laboratory test values were notable for elevated CK level of 555 U/L, creatinine level of 1.09 mg/dL, microscopic hematuria with red blood cell count of >50 per high power field (normal range, 0–2 per high power field), total testosterone level of 272 ng/dL, free testosterone level of 13.5 ng/dL, hematocrit of 46.3% (normal range, 37.5%–51%), and thyroid stimulating hormone level of 2.1 mIU/L (normal range, 0.47–4.5 mIU/L).

At this point, the therapy with IM testosterone was stopped and he instead began transdermal testosterone 4 mg daily. He could not tolerate transdermal testosterone owing to skin irritation, thus he transitioned to SC testosterone enanthate 80 mg weekly instead. After 6 months, a total testosterone level of 500 ng/dL and free testosterone level of 23.4 ng/dL were at goal and the patient remained asymptomatic.

Discussion

Although AAS abuse has been linked to rhabdomyolysis, we found no published cases of rhabdomyolysis occurring with

Highlights

- Intramuscular testosterone usage may increase the risk of rhabdomyolysis
- Androgen-related rhabdomyolysis increases with smaller muscle sites of administration
- Subcutaneous administration is a safe alternative to intramuscular testosterone

Clinical Relevance

In this case report, to our knowledge, we present the first reported case of testosterone-associated rhabdomyolysis in a transgender man. This case serves to raise awareness among clinicians that rhabdomyolysis can occur as a complication of testosterone replacement, even when being used at physiologic dosing under medical supervision.

prescription testosterone or masculinizing hormonal therapy. AAS-associated rhabdomyolysis usually presents with diffuse multi-muscle group involvement; however, interestingly, the only case of focal rhabdomyolysis that we identified also occurred in deltoid muscle related to the AAS injection site (Table). The mechanism by which AAS causes localized rhabdomyolysis remains unclear. Testosterone increases skeletal muscle mass locally by augmenting muscle protein synthesis and promoting differentiation of mesenchymal pluripotent cells into myocytes.⁹ Studies conducted in animal have demonstrated that AAS can induce apoptosis in differentiated skeletal muscles.¹⁰ Furthermore, this cellular death could be attributed to a mismatch between muscle demand and energy supply. Additionally, by increasing muscle mass and decreasing elasticity, AAS injections can increase the pressure within the deltoid fascial compartment, potentially contributing to localized rhabdomyolysis.^{6,9} In our case, IM testosterone was tolerated for >8 years without any adverse events when administered in the thigh and gluteal regions and associated with localized rhabdomyolysis only after switching the injection site to the deltoid. By volume, gluteus and quadriceps muscles are approximately 2 to 3 times larger than deltoid muscle.¹¹ We hypothesize that by administering testosterone into a smaller muscle compartment, the relative increase in concentration and volume of testosterone per gram of muscle led to changes within the deltoid fascial compartment and focal skeletal muscle hypertrophy that precipitated rhabdomyolysis.

Testosterone is seen today as the cornerstone of transmasculine care with multiple delivery strategies, including oral, transdermal, IM, or SC. The choice of administration route varies depending on patient preference, affordability, and whether they are achieving their masculinization goals. Although the esters in various testosterone formulations (propionate, enanthate, undecanoate, and cypionate) were designed for IM use via the thigh, gluteal, and

Table
Reported Cases of Anabolic-Androgenic Steroid Related Rhabdomyolysis

Study	Anabolic agent	Route	Injection site	Rhabdomyolysis	Patient features
Hageloch et al ²	Not reported	IM	Not reported	Diffuse	31-y-old man, professional bodybuilder
Adamson et al ³	Stanozolol plus metenolone	IM	Thigh	Diffuse	25-y-old man, professional dancer
Braseth et al ⁴	Not reported	Oral	N/A	Diffuse	25-y-old man, amateur bodybuilder
Gnanapandithan et al ⁵	Trenbolone	IM	Not reported	Diffuse	Young adult man
Hughes and Ahmed ⁶	Not reported	IM	Not reported	Diffuse	23-y-old man, recreational user, died from complications
Farkash et al ⁷	Stanozolol	IM	Right deltoid	Deltoid/right upper extremity	39-y-old man, amateur bodybuilder
Daniels et al ⁸	Methyltestosterone	Oral	Thigh	Diffuse	34-y-old man, amateur bodybuilder
	Boldenone plus trenbolone	IM			

Abbreviations: IM = intramuscular; N/A = not applicable.

deltoid regions, some recent studies have explored the pharmacokinetics and safety of these agents via SC administration.¹² In 2018, Wilson et al¹³ published a prospective crossover study of 14 transgender men comparing SC versus IM administration of either testosterone cypionate or enanthate. In this study, there was no difference in the area under the time–concentration curve profiles of IM versus SC testosterone (1.9 ± 0.6 nmol·days/L/mg vs 1.7 ± 0.6 nmol·days/L/mg). Participants reported less anxiety and discomfort with SC injections, and there were no significant differences in mood, libido, acne, and sleep after switching from IM to SC injections.¹³ Kaminetsky et al¹⁴ compared the pharmacokinetics of testosterone enanthate 200 mg IM with 50 mg SC and 100 mg SC administered via a novel autoinjector system. One patient had injection site–related ecchymosis; however, the SC autoinjector system was overall tolerated well.¹⁴ Although IM testosterone was noted to result in supraphysiologic testosterone levels during the first week after dosing, SC testosterone was able to achieve the testosterone level goals with less variation.

A similar but larger retrospective cohort study followed up 63 adult transgender men using SC testosterone cypionate or enanthate weekly for 9 months.¹⁵ In this study, SC therapy was widely accepted and all participants achieved therapeutic testosterone level targets with a mean SC testosterone dose of 75 mg weekly. Only 14% of the patients reported minor, transient local reactions such as cellulitis, inflammation, small nodule, or urticaria at the injection site. On SC injections, 51 of 53 premenopausal transgender men with an intact uterus achieved amenorrhea. In addition, hematocrit and hepatic function remained within the normal limits during the course of therapy. Another study of 36 transgender young men demonstrated comparable findings with SC testosterone cypionate, with testosterone therapeutic level targets begin achieved by 91% of participants within 6 months of the treatment.¹⁶

Conclusion

In this case report, we describe a unique presentation of IM testosterone–induced localized rhabdomyolysis and the clinical utility of SC testosterone in transmasculine care. We recommend against using deltoid muscle as the primary site for IM testosterone administration because of the potential risk of rhabdomyolysis.

Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Chavez LO, Leon M, Einav S, Varon J. Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. *Crit Care*. 2016;20(1):135.
2. Hageloch W, Appell HJ, Weicker H. Rhabdomyolysis in a bodybuilder using anabolic steroids. Article in German. *Sportverletz Sportschaden*. 1988;2(3):122–125.
3. Adamson R, Rambaran C, D'Cruz DP. Anabolic steroid-induced rhabdomyolysis. *Hosp Med*. 2005;66(6):362.
4. Braseth NR, Allison Jr EJ, Gough JE. Exertional rhabdomyolysis in a body builder abusing anabolic androgenic steroids. *Eur J Emerg Med*. 2001;8(2):155–157.
5. Gnanapandithan K, Karthik N, Singh A. Rhabdomyolysis and acute kidney injury associated with anabolic steroid use. *Am J Med*. 2019;132(8):e652–e653.
6. Hughes M, Ahmed S. Anabolic androgenic steroid induced necrotising myopathy. *Rheumatol Int*. 2011;31(7):915–917.
7. Farkash U, Shabshin N, Pritsch Perry M. Rhabdomyolysis of the deltoid muscle in a bodybuilder using anabolic-androgenic steroids: a case report. *J Athl Train*. 2009;44(1):98–100.
8. Daniels JMA, van Westerloo DJ, de Hon OM, Frissen PHJ. Rhabdomyolysis in a bodybuilder using steroids. Article in Dutch. *Ned Tijdschr Geneesk*. 2006;150(19):1077–1080.
9. Herbst KL, Bhasin S. Testosterone action on skeletal muscle. *Curr Opin Clin Nutr Metab Care*. 2004;7(3):271–277.
10. Abu-Shakra S, Alhalabi MS, Nachtman FC, Schmidt RA, Brusilow WS. Anabolic steroids induce injury and apoptosis of differentiated skeletal muscle. *J Neurosci Res*. 1997;47(2):186–197.
11. Ribeiro AS, Schoenfeld BJ, Nunes JP. Large and small muscles in resistance training: is it time for a better definition? *Strength Cond J*. 2017;39(5):33–35.
12. Turner L, Ly LP, Desai R, et al. Pharmacokinetics and acceptability of subcutaneous injection of testosterone undecanoate. *J Endocr Soc*. 2019;3(8):1531–1540.
13. Wilson DM, Kiang TKL, Ensom MHH. Pharmacokinetics, safety, and patient acceptability of subcutaneous versus intramuscular testosterone injection for gender-affirming therapy: a pilot study. *Am J Health Syst Pharm*. 2018;75(6):351–358.
14. Kaminetsky J, Jaffe JS, Swerdloff RS. Pharmacokinetic profile of subcutaneous testosterone enanthate delivered via a novel, prefilled single-use autoinjector: a phase II study. *Sex Med*. 2015;3(4):269–279.
15. Spratt DJ, Stewart II, Savage C, et al. Subcutaneous injection of testosterone is an effective and preferred alternative to intramuscular injection: demonstration in female-to-male transgender patients. *J Clin Endocrinol Metab*. 2017;102(7):2349–2355.
16. Olson J, Schragger SM, Clark LF, Dunlap SL, Belzer M. Subcutaneous testosterone: an effective delivery mechanism for masculinizing young transgender men. *LGBT Health*. 2014;1(3):165–167.