

Vascular Necrosis of the Upper Extremity After Self-Treatment for Peyronie's Disease



David Yang, MD,¹ Joshua Savage, PA-C,² Tobias Köhler, MD, MPH,¹ Sevann Helo, MD,¹ Landon Trost, MD,² and Matthew Ziegelmann, MD¹

ABSTRACT

Peyronie's disease (PD) is associated with significant psychosocial distress, including anxiety, depression, and negative effects on interpersonal relationships. We report outcomes in a patient who researched an enzymatic supplement intended for oral administration for treatment of PD and subsequently self-injected it intravascularly. The enzyme, a combination of serrapeptase and nattokinase, resulted in vascular necrosis of the upper extremity. Despite attempts to salvage the limb, he ultimately required transhumeral amputation. Although extreme, this case illustrates the potential risks of non—Food and Drug Administration—approved therapies, the significant psychosocial impact that PD can have on patients' emotional well-being, and the extent to which some may go to seek treatment. **Yang D, Savage J, Kohler T, et al. Vascular Necrosis of the Upper Extremity After Self-Treatment for Peyronie's Disease. Sex Med 2021;9:100282.**

Copyright © 2020, The Authors. Published by Elsevier Inc. on behalf of the International Society for Sexual Medicine. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Key Words: Peyronie's Disease; Enzyme; Collagenase Clostridium Histolyticum; Xiaflex; Psychological; Depression

INTRODUCTION

Peyronie's disease (PD) is a fibrotic disorder involving the tunica albuginea of the penis. Although the physical aspects of the disease, including penile curvature, pain, shortening, and changes in sexual function, are well known to most providers, the significant impact that PD has on the psychosocial well-being of a patient and his partner may be overlooked.^{1,2} Men with PD commonly report emotional distress and relationship difficulties, including loss of sexual confidence, sexual performance anxiety, and social isolation as a result of their PD.^{2,3} Nelson et al⁴ demonstrated that nearly 50% of men with PD in their clinic met the definition for clinically meaningful depression that would warrant medical evaluation.

Although it is clear that PD significantly impacts patients' emotional well-being, the extent to which a patient is willing to go to improve his symptoms is often unrecognized. Similarly, the

combination of PD and pre-existing psychiatric disorders may lead to impaired judgment, increase higher risk behaviors, or reduce the ability to cope with adverse outcomes. Herein, we present one such example of a patient with a prior history of psychiatric conditions and high-risk behavior who attempted to self-treat his PD with disastrous consequences.

CASE REPORT

A 47-year-old male presented to our sexual health clinic with a 7-month history of stable dorsal penile curvature estimated at 80°. He reported concomitant erectile dysfunction that was responsive to sildenafil, with a current International Index of Erectile Function score of 3 because of the lack of a current sexual partner. He denied changes in libido, penile pain, or prior penile trauma and felt that the curvature was impacting his ability to have penetrative intercourse. He had previously trialed topical vitamin E without benefit and had not pursued further treatments with injections or surgery. The patient's past medical history was otherwise notable for polysubstance abuse including methamphetamine dependence, for which he was currently in remission for 15 months, as well as major depressive disorder treated with bupropion. He did not have any known history of IV drug use.

Physical examination demonstrated a 2 × 2 cm palpable plaque on the dorsal penile shaft, located 0.5 cm from the corona of the glans. Objective penile curvature measurement was performed with a goniometer after injection of a mixture of

Received August 8, 2020. Accepted October 22, 2020.

¹Department of Urology, Mayo Clinic, Rochester, MN, USA;

²Male Fertility and Peyronie's Clinic, Orem, UT, USA;

Patient Informed Consent: Consent was obtained from the patient for publication.

Copyright © 2020, The Authors. Published by Elsevier Inc. on behalf of the International Society for Sexual Medicine. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.esxm.2020.10.010>

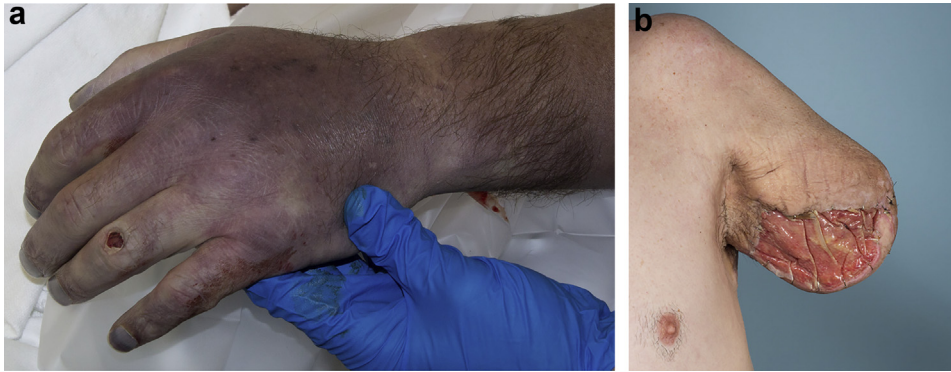


Figure 1. Photographs of the left upper extremity before amputation (A) and after transhumeral amputation with interval placement of a latissimus myocutaneous flap and split-thickness skin grafting of the area (B).

papaverine (30 mg/mL), alprostadil (10 mcg/mL), and phenolamine (1 mg/mL) to achieve a goal erection of 8/10. This revealed a 60° uniplanar dorsal curvature without indentation, hourglass deformity, or buckling. Penile duplex Doppler ultrasound revealed normal peak systolic and end diastolic cavernosal artery velocities and no calcification of the plaque. The patient was educated on his diagnosis and counseled as to treatment options including observation, intralesional therapy, or penile plication. After discussion, he elected to pursue intralesional collagenase clostridium histolyticum injections and scheduled his first injection 6 weeks later.

Approximately 5 weeks after his initial presentation, the patient presented to our emergency department with progressive discoloration, numbness, and pain in his left upper extremity. He reported injecting an enzyme, “Serracor-NK” (AST Enzymes; Chino, CA), into his left radial artery after researching online about its efficacy in treating PD. Although the therapy is sold as an oral capsule, he elected to inject it intravenously based on recommendations from a friend to augment the efficacy and enhance delivery of the medication to the penis. Unfortunately, owing to the patient’s inexperience with intravenous injection, the medication was injected intra-arterially.

The patient was subsequently evaluated by a vascular surgeon who noted stable vitals, with a swollen, dusky, and mottled upper extremity that lacked sensory and motor function. Laboratory evaluation was notable for hyponatremia, leukocytosis, acute kidney injury, and markedly elevated creatine kinase of 25,600 (normal range 52–336 U/L), suggesting severe ischemia and muscle necrosis. A computed tomography angiogram of the upper extremity revealed complete occlusion of the left brachial artery. He was emergently taken to the operating room for upper extremity revascularization and ultimately required left transhumeral amputation with interval placement of a latissimus myocutaneous flap and split-thickness skin graft (Figure 1). He was dismissed on hospital day 17 after a combined 6 days in the intensive care unit, 7 operative procedures, and prolonged antibiotic therapy for a wound infection.

One month after dismissal, the patient underwent his first course of collagenase clostridium histolyticum injections, with plans to continue for a total of 4 series.

DISCUSSION

Although extreme, the current case highlights the significant psychological burden of PD and the extent to which high-risk patients may go to achieve a satisfactory treatment. Several authors have identified associations between PD and overall psychosexual and social well-being. Gelbard et al⁵ found that nearly 80% of patients reported negative psychological effects from PD, which persisted in more than half of the men. Several other studies identified low self-esteem, depression, and reduced quality of life with PD, suggesting a clear link between sexual well-being and overall health.^{1,2} Patients may feel socially stigmatized and isolated from their peers, which further exacerbate the detrimental psychosocial consequences of this disease process.² These factors, combined with a prior history of depression and substance abuse, likely contributed to the poor decision-making in the case described.

Unfortunately, it is difficult to predict when a patient will take extraordinary attempts at self-treatment. Spending ample time with patients to explore their psychosocial burden is necessary along with discussing the rationale for using an evidence-based approach. While counseling patients with PD, we often focus on the proven therapies and gloss over unproven or debunked treatments as they are not a part of our treatment armamentarium. This patient had history of high-risk behaviors and had already attempted self-treatment with topical vitamin E. In our experience, roughly 20% of our patients with PD have attempted previous treatment with various oral therapies before presentation to our clinic.⁶ With the increase in direct-to-consumer advertising and the rise of online men’s health clinics, counseling patients on the risks of unproven therapies may protect patients from physical and financial harm. As seen here, even over-the-counter treatments, when not properly used, can lead to serious and unforeseen consequences.

Serracor-NK (AST Enzymes) is an over-the-counter supplement that consists of enteric-coated serrapeptase and nattokinase in a capsule form. Serrapeptase (also known as serratiopeptidase) is a proteolytic enzyme, derived from the *Serratia* bacterium, with anti-inflammatory and analgesic properties.⁷ It is delivered enterally and has been studied in multiple surgical specialties. Several small trials from the orthopedic, otorhinolaryngology, and dentistry literature have suggested improvements in pain and inflammation for conditions such as carpal tunnel syndrome, arthritis, and molar extraction.⁷ Although reports detailing adverse effects with this agent are few, pneumonitis, joint aches, and dermatitis have all been reported with the oral preparation.⁷ Nattokinase, a protease with fibrinolytic activity, was derived from *Bacillus subtilis*.⁸ It is being investigated as an alternative to currently available thrombolytic agents and has been suggested to protect the brain in the setting of an ischemic insult.⁹ Interestingly, the 2 agents together have been studied in a rat model for Alzheimer's disease.¹⁰

Although limited use of serrapeptase and nattokinase has been reported in other conditions, to date, no studies have evaluated its use for the treatment of PD. Despite this lack of evidence, an online search for "Serracor-NK and Peyronie's disease" reveals multiple distributors claiming efficacy when used for the treatment of penile curvature and pain. The therapy has not been submitted to the Food and Drug Administration for review and has not previously undergone phase I trials to assess for safety. In addition, to our knowledge, neither serrapeptase nor nattokinase has been evaluated for clinical safety with intravenous or intra-arterial administration in humans as was observed in the current case.

The case emphasizes the emotional toll that PD can take on patients and serves as reminder to consider addressing the psychosocial consequences of the disease concurrently with physical changes. It is our current practice to refer patients to a therapist specializing in sexual health concerns based on clinician judgment and the patient's reported level of distress. However, many patients are reticent to discuss their emotional hardships during their initial consultation, and there are likely many patients who would benefit from a collaborative model that integrates both care of the disease itself and the psychological impact.¹

Corresponding Author: Matthew Ziegelmann, MD, 200 First Street SW, Rochester, MN 55905, USA. Tel: # 507-266-3982; Fax: # 507-284-4951; E-mail: ziegelmann.matthew@mayo.edu

Conflicts of Interest: none.

Funding: None.

STATEMENT OF AUTHORSHIP

David Yang: Conceptualization, Methodology, Investigation, Writing - Original Draft, Formal Analysis, Writing - Review & Editing, Funding Acquisition; Joshua Savage: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition; Tobias Köhler: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition; Sevann Helo: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition; Landon Trost: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Funding Acquisition; Matthew Ziegelmann: Conceptualization, Methodology, Investigation, Resources, Writing - Original Draft, Formal Analysis, Writing - Review & Editing, Funding Acquisition.

REFERENCES

1. Nelson CJ, Mulhall JP. Psychological impact of Peyronie's disease: a review. *J Sex Med* 2013;10:653-660.
2. Rosen R, Catania J, Lue T, et al. Impact of Peyronie's disease on sexual and psychosocial functioning: qualitative findings in patients and controls. *J Sex Med* 2008;5:1977-1984.
3. Smith JF, Walsh TJ, Conti SL, et al. Risk factors for emotional and relationship problems in Peyronie's disease. *J Sex Med* 2008;5:2179-2184.
4. Nelson CJ, Diblasio C, Kendirci M, et al. The chronology of depression and distress in men with Peyronie's disease. *J Sex Med* 2008;5:1985-1990.
5. Gelbard MK, Dorey F, James K. The natural history of Peyronie's disease. *J Urol* 1990;144:1376-1379.
6. Ziegelmann M, Bole R, Avant R, et al. Conservatively managed Peyronie's disease-long-term survey results from patients undergoing nonsurgical and noninjection therapies. *Urology* 2018;113:99-104.
7. Bhagat S, Agarwal M, Roy V. Serratiopeptidase: a systematic review of the existing evidence. *Int J Surg* 2013;11:209-217.
8. Sumi H, Hamada H, Tsushima H, et al. A novel fibrinolytic enzyme (nattokinase) in the vegetable cheese Natto; a typical and popular soybean food in the Japanese diet. *Experientia* 1987;43:1110-1111.
9. Ji H, Yu L, Liu K, et al. Mechanisms of Nattokinase in protection of cerebral ischemia. *Eur J Pharmacol* 2014;745:144-151.
10. Fadl NN, Ahmed HH, Booles HF, et al. Serrapeptase and nattokinase intervention for relieving Alzheimer's disease pathophysiology in rat model. *Hum Exp Toxicol* 2013;32:721-735.