CME

Management of Erectile Dysfunction in Patients with Sickle Cell Disease

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Introduction

Treating erectile dysfunction (ED) in a patient with an increased risk of priapism can create a dilemma. In this article, we discuss two patients with sickle cell disease (SCD) with different presentations: one with no history of priapism and one with post-priapism ED.

Case Study 1

A 27-year-old man with a history of heterozygous sickle cell trait was referred with ED. Other than hypertension, he had no other significant medical history and, in particular, no history of priapism. He took amlodipine for his hypertension and had a smoking history of 15 cigarettes per day for 10 years. He was a migrant from an African nation 10 years ago and was found to have the sickle cell trait after arriving in North America. He was generally asymptomatic from the sickle cell trait. His hematologist's instructions to him were to avoid severe exertion, especially dehydration, so as to prevent a sickle cell crisis. He described a gradual worsening of his ED in the last 6 months. He had been married for 5 years and was in a stable relationship. There was no history of premature ejaculation and his libido had been normal. Blood work, including bioavailable testosterone levels, was normal, and the cause of his ED was thought to be multifactorial (vasculogenic, medication related, and possibly psychogenic). We were concerned about his increased risks of priapism because there had been case reports of that even in sickle cell trait patients. He was given a trial dose of sildenafil (50 mg, on-demand), which was successful in treating his ED without causing priapism.

Case Study 2

A 32-year-old man with known homozygous sickle cell anemia was referred with post-priapism ED. He had a history of recurrent, stuttering erections of 2–3 hours duration, but never an acute or major episode until about 8 months ago. During that episode, his priapism went on for 16 hours before he presented to the emergency department. Irrigation, aspiration, and then intracavernosal injection of phenylephrine failed to treat it. The patient subsequently had a Winter shunt done with a large bore biopsy needle, which gradually caused detumescence over a period of about 1 week. Since then, he could only achieve partial erections of poor quality and was unable to achieve sexual penetration. On examination, there was palpable fibrosis mainly on the proximal half of his penile shaft. After informed consent, we tried him on the vacuum device and intracavernosal injections. He had acceptable results with the vacuum device, but found it to be ill-fitting despite having seen the device representative, who checked his technique. He was researching on some other manufacturers' vacuum device products. He had tried intracavernosal alprostadil injections with poor results. During his most recent clinic appointment, we reinjected him and found that the penile fibrosis caused increased resistance during the injection. We managed to inject him slowly and could only get a partial erection. He was going to keep practicing at a higher dose at home. We had discussed

with him about the option of a penile prosthesis and he was still considering it.

Discussion

Sickle Cell Anemia (HbSS) and Sickle Cell Trait (HbAS)

SCD is an autosomal codominant blood disorder characterized by erythrocytes that have an abnormal, inflexible, sickle shape. This occurs because of a mutation in the hemoglobin gene (HbS). In the United States, it affects approximately one in 5,000, mostly in Americans of Sub-Saharan African descent. Sickle cell anemia is a type of SCD in which patients exhibit homozygosity for the mutated HbS gene (i.e., possess two HbS chains or HbSS). The reported prevalence rate of priapism in this group ranges between 29 and 42% of males [1–4].

Sickle cell trait describes a condition in which a person has only one abnormal allele of the hemoglobin gene (heterozygous). This person produces both normal and abnormal hemoglobin (the two alleles are codominant). Individuals with this trait have a genetic advantage by having some malarial resistance in endemic environments. Sickle cell trait is typically a benign condition, which is spared of the major complications of a homozygous SCD, and is generally not believed to be associated with priapism. However, there have been case reports and small series describing this association in the literature from the 1960s and 1970s [5–9] to more recent ones [10,11].

SCD and Priapism

Before treating a SCD patient with ED, it is important to understand the risks of priapism and its management. The most important mechanism for priapism in SCD is microvascular occlusion. Deoxygenated, sickled red blood cells have increased viscosity and endothelial adherence, and clump together to form hemoglobin polymers that have a veno-occlusive effect. Ischemic priapism may result from low penile venous nitric oxide concentration causing vasoconstriction, blood stasis, deoxygenation, and sickling [12]. Sickling promotes a vicious cycle, resulting in reduced blood flow and worsening deoxygenation. This explains why the vacuum device is contraindicated in SCD patients, as the constriction ring would result in deoxygenation of the blood and encourage sickling and priapism. Sickling can also occur in sickle cell trait patients under extreme, stressful conditions (dehydration, hypoxia, infection).

SCD patients can present with acute, major episodes of ischemic priapism and also with recurrent, "stuttering" forms. The acute major episodes can last from a few days to several weeks and, if left untreated, would usually result in some degree of ED. Stuttering attacks are typically self-limited and last less than 3 hours. They are generally not associated with severe ED in contrast with the acute or major episodes [13]. However, Adeyoju et al. reported a 25% ED rate among SCD patients with only stuttering attacks [4]. Rarely, high-flow priapism has been described in patients following surgical treatments for previous episodes of ischemic priapism [14].

All episodes of stuttering priapism should be treated according to recommendations for ischemic priapism [15]. For SCD patients, systemic medical therapies, such as analgesia, hydration, oxygenation, alkalinization, transfusion, and plasmapheresis, may be performed; however, these interventions should not lead to delays in intracavernosal treatment [16]. The success rates of systemic medical treatments are less than 37%, and higher resolution rates can be achieved with therapies directed at the penis [15]. Patients should first try conservative methods like a cold shower, taking pseudoephedrine tablets, or ice packs. Definitive intracavernosal treatments consist of evacuation of blood and irrigation of the corpora cavernosa, along with injection of an alpha-adrenergic sympathomimetic agent in conjunction with monitoring vital signs. The creation of surgical shunts may also be necessary, especially to those with prolonged priapism of more than 48 hours.

Preventative strategies may be implemented in patients with stuttering priapism. These include hormonal therapies, intracavernosal self-injection of sympathomimetic agents, penile prosthesis surgery, and other more experimental treatments. The most reliable hormonal therapy is a trial of gonadotropin-releasing hormone agonist or androgen receptor antagonist therapy. Intracavernosal self-injection of phenylephrine may be taught with proper instructions given to patients with regard to injection site, dosing, and side effects, especially the risk of priapism and when to seek medical help. Phenylephrine should be mixed to a concentration of 500 μg/cc, and a dose of 100 μg (or 0.2 cc) can be injected into the cavern-

ous body every 3–5 minutes until detumescence. Of all the sympathomimetic agents, phenylephrine has the least cardiovascular side effects. At this concentration, little impact on systemic blood pressure is seen in most men. Patients should seek medical help if they develop headaches or palpitations or after 1 hour of failed self-injections. Self-injection of phenylephrine is not recommended in patients with high cardiovascular risks. Early penile prosthesis implantation has been advocated to spare the patient of the pain and psychological trauma of recurrent priapism and to reduce the technical difficulties and complications associated with dense fibrosis [17]. However, the implication of the young patient "outliving" his prosthesis and needing future revisions cannot be ignored.

Based on the hypothesis that phosphodiesterase type 5 (PDE5) dysregulation plays a pathogenic role for priapism, long-term PDE5 inhibitor therapy has been used for prevention of stuttering priapism. Burnett et al. reported an improvement in priapism recurrences in six of seven patients treated with daily PDE5 inhibitor with a follow-up period of 2 years [18]. This therapy was well tolerated and did not cause adverse effects. However, additional evaluation in the form of a controlled clinical trial is still needed. More recently, increased adenosine levels were found to contribute to priapism in animal models. Polyethylene glycol-modified adenosine deaminase (PEG-ADA) drug therapy was found to reduce priapism in SCD transgenic mice by decreasing adenosine levels [19]. PEG-ADA is already being used in humans with a deficiency of the adenosine deaminase enzyme who have a condition called severe combined immunodeficiency disease (or the "bubble boy" syndrome) and certainly shows some promise in the treatment of priapism.

Patient 1: PDE5 Inhibitor Use in SCD Patients

Patient 1, who has sickle cell trait, does not have the same risks of treatment induced priapism as a homozygous SCD patient. What if he had been a homozygous SCD patient with no prior history of priapism? Is a PDE5 inhibitor medication safe for him? We can infer the answer from the information on oral PDE5 inhibitors in the treatment of pulmonary arterial hypertension (PAH), which SCD patients can also develop. PDE5 inhibitors are shown to be beneficial in patients with PAH by potentiating the effects of endogenous nitric oxide, leading to smooth muscle cell relaxation and reductions in pulmonary arterial pressures and pulmonary vascular resistance [20]. In June 2005, the Food and Drug Administration (FDA) approved the use of sildenafil (20 mg) three times a day (Revatio, Pfizer Labs) for PAH. What about the use of PDE5 inhibitor in PAH *secondary* to SCD? Initial data were encouraging; in a pilot study in 2005, Machado et al. described the safety and efficacy of sildenafil in 12 SCD patients with PAH, and none of the three male patients developed priapism [21]. However, a later multicenter trial in 2009 involving 134 patients showed that sildenafil may cause more vaso-occlusive crisis compared with placebo (38% vs. 8%), and the trial was stopped prematurely. Hence, sildenafil is not approved by the FDA in PAH caused by SCD. Although this information was based on a daily dosing of PDE5 inhibitor, we can still infer that on-demand usage of PDE5 inhibitors in homozygous SCD patients still has significant risks. As sickle cell trait patients do not generally get sickle cell crisis, PDE5 inhibitors should be safe in them. There are only very rare reports of patients with sickle cell trait who developed priapism after using sildenafil [22]. There are no data regarding which PDE5 inhibitor is safest.

In sickle cell trait, the red blood cells can also undergo sickling in intense, stressful conditions such as hypoxia, infection, and exhaustion. The vacuum device, which induces hypoxia, is contraindicated in both homozygous and heterozygous SCD patients, as explained above.

The use of intracavernosal injections and intraurethral alprostadil in SCD patients is controversial. Alprostadil binds to a membrane receptor, activates adenylate cyclase, and increases intracellular cyclic adenosine monophosphate, resulting in relaxation of trabecular smooth muscle and dilatation of cavernosal arteries. This induces an erection by entrapment of blood by compressing the venules against the tunica albuginea. Therefore, there is an indirect hypoxic effect in the penile tissues, and this can cause sickling of red blood cells in SCD patients. The product information of Caverject (intracavernosal alprostadil, Pfizer Labs) and MUSE (intraurethral alprostadil, Meda Pharmaceuticals, Inc.) include both homozygous SCD and sickle cell trait as contraindications. However, in our practice, we prescribe them with caution and informed consent in SCD patients, if all else fails. Alprostadil has a lower incidence of priapism compared with papaverine (2% vs. 10%) and

should be the intracavernosal injection drug of choice. The key points are starting at a low dose, education of the patient, and having an action plan in case priapism occurs.

Patient 2: Post-Priapism ED and Treatment Options

Post-priapism ED occurs when corporal tissue is replaced with dense fibrosis, after a prolonged period of ischemia. The degree of ED differs in each individual. Patient 2 still has some residual erectile function left, and he should not be resigned to a penile prosthesis as his only option. After all, he has "nothing to lose" by trying the other options. He can be tried on oral PDE5 inhibitors, intraurethral alprostadil, the vacuum device, or intracavernosal injection therapy, cautiously with low starting doses. Again, he should be educated about the risk of priapism and given an action plan.

On the other hand, it can be argued that this patient would eventually need a penile prosthesis, and he should have it done before too much fibrosis occurs. Dense fibrosis would often require sharp dissection and dilatation to form a tunnel for the prosthesis [23]. Damage to the tunica is common and urethral damage can occur. The rate of subsequent migration of the prosthesis is significantly greater in the case of post-priapism ED [24].

The persistence of a shunt fistula, instead of corporal fibrosis, may also be a cause for ED. A Finnish study reported on this in 4 out of 26 patients with ED who previously had open shunt surgery [25]. Shunt closure has been reported to be successful in restoring erectile function [25,26]. If suspected, duplex ultrasound or infusion cavernosometry and cavernosography can be useful to diagnose the fistula.

Key Points

1. Heterozygous and homozygous forms of SCD should be distinguished as they have different risks of priapism.
2. Sickle cell trait (heterozygous) patients should also be warned of the risk of priapism, although it is rarer.
3. Each SCD patient should have a priapism action plan, along with preventative measures in those with stuttering priapism.
4. The vacuum device is contraindicated in both homozygous and heterozygous SCD patients because it can induce hypoxia and sickling.
5. PDE5 inhibitors may cause more vaso-occlusive crisis in homozygous SCD patients but should be safe in heterozygous patients.
6. ED treatments can be tried cautiously and at a lower starting dose as long as the patient has priapism treatment measures implemented.
7. In post-priapism ED, conservative options can be explored prior to proceeding directly to a penile prosthesis.

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References

1 Emond AM, Holman R, Hayes RJ, Serjeant GR. Priapism and impotence in homozygous sickle cell disease. Arch Intern Med 1980;140:1434–7.
2 Fowler JE Jr, Koshy M, Strub M, Chinn SK. Priapism associated with the sickle cell hemoglobinopathies: Prevalence, natural history and sequelae. J Urol 1991;145:65–8.
3 Mantadakis E, Cavender JD, Rogers ZR, Ewalt DH, Buchanan GR. Prevalence of priapism in children and adolescents with sickle cell anemia. J Pediatr Hematol Oncol 1999;21:518–22.
4 Adeyoju AB, Olujohungbe AB, Morris J, Yardumian A, Bareford D, Akenova A, Akinyanju O, Cinkotai K, O'Reilly PH. Priapism in sickle-cell disease; incidence, risk factors and complications—An international multicenter study. BJU Int 2002;90:898–902.
5 Farrer JF, Goodwin WE. Treatment of priapism: Comparison of methods in fifteen cases. J Urol 1961;86:768–75.
6 Duback RT, Ramey JA. Priapism in sickle cell trait: Case report utilizing hemovac suction as an adjunct to therapy. J Urol 1968;100:175–8.
7 Krauss L, Fitzpatrick T. The treatment of priapism by penile aspiration under controlled hypotension. J Urol 1961;85:595–8.
8 Grace DA, Winter CC. Priapism: An appraisal of management of twenty-three patients. J Urol 1968;99:301–8.
9 Larocque MA, Cosgrove MD. Priapism: A review of 46 cases. J Urol 1974;112:770–2.
10 Rehman JU, Kindi SS, Pathare AV, Jain R, Choudry A. Recurrent priapism in sickle cell trait with protein S deficiency. J Pak Med Assoc 2008;58:701–2.
11 Birnbaum BF, Pinzone JJ. Sickle cell trait and priapism: A case report and review of the literature. Cases J 2008;1:429.
12 Nolan VG, Wyszynski DF, Farrer LA, Steinberg MH. Hemolysis-associated priapism in sickle cell disease. Blood 2005;106:3264–7.
13 Fowler JJE, Koshy M, Strub M, Chinn SK. Priapism associated with the sickle cell hemoglobinopathies: Prevalence, natural history and sequelae. J Urol 1991;145:65–8.
14 Ramos CE, Park JS, Ritchey ML, Benson GS. High flow priapism associated with sickle cell disease. J Urol 1995;153:1619–21.
15 Montague DK, Jarow J, Broderick GA, Dmochowski RR, Heaton JP, Lue TF, Nehra A, Sharlip ID, Members of the

Erectile Dysfunction Guideline Update Panel, American Urological Association. American Urological Association guideline on the management of priapism. J Urol 2003;170: 1318–24.
16 Mantadakis E, Ewalt DH, Cavender JD, Rogers ZR, Buchanan GR. Outpatient penile aspiration and epinephrine irrigation for young patients with sickle cell anemia and prolonged priapism. Blood 2000;95:78–82.
17 Monga M, Broderick GA, Hellstrom WJ. Priapism in sickle cell disease: The case for early implantation of the penile prosthesis. Eur Urol 1996;30:54–9.
18 Burnett AL, Bivalacqua TJ, Champion HC, Musicki B. Feasibility of the use of phosphodiesterase type 5 inhibitors in a pharmacologic prevention program for recurrent priapism. J Sex Med 2006;3:1077–84.
19 Wen J, Jiang X, Dai Y, Zhang Y, Tang Y, Sun H, Mi T, Kellems RE, Blackburn MR, Xia Y. Adenosine deaminase enzyme therapy prevents and reverses the heightened cavernosal relaxation in priapism. J Sex Med 2010;7:3011–22.
20 Ramani GV, Park MH. Update on the clinical utility of sildenafil in the treatment of pulmonary arterial hypertension. Drug Des Devel Ther 2010;25:61–70.
21 Machado RF, Martyr S, Kato GJ, Barst RJ, Anthi A, Robinson MR, Hunter L, Coles W, Nichols J, Hunter C, Sachdev V, Castro O, Gladwin MT. Sildenafil therapy in patients with sickle cell disease and pulmonary hypertension. Br J Haematol 2005;130:445–53.
22 Kassim AA, Fabry ME, Nagel RL. Acute priapism associated with the use of sildenafil in a patient with sickle cell trait. Blood 2000;95:1878–9.
23 Douglas L, Fletcher H, Serjeant GR. Penile prostheses in the management of impotence in sickle cell disease. Br J Urol 1990;65:533–5.
24 Souillac I, Pignot G, Galiano M, Hastert V, Sibaud O, Virag R. Inflatable penile prostheses: Results, complications and prognostic factors. Prog Urol 2009;19:563–71. Epub May 14, 2009.
25 Kulmala RV, Lehtonen TA, Lindholm TS, Tammela TL. Permanent open shunt as a reason for impotence or reduced potency after surgical treatment of priapism in 26 patients. Int J Impot Res 1995;7:175–80.
26 Stein RJ, Patel AS, Benoit RM. Treatment of post-priapism erectile dysfunction by closure of persistent distal glans-cavernosum fistulas 5 years after shunt creation. Urology 2005;65:592.