Case Report

Hyperbaric Oxygen for Refractory Dystrophic Calcifications of the Prostate: A Case Series and Review of the Literature

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Abstract

Dystrophic calcifications have been detected in the prostatic fossa, especially after de-obstructing procedures or radiotherapy for prostate cancer. These calcifications can be recalcitrant in patients with poor tissue healing. Hyperbaric Oxygen (HBO) therapy has multiple applications in urology but has not been reported as a treatment of recalcitrant dystrophic calcifications of the prostatic fossa or prostatic urethra. This article reviews the literature about HBO therapy and describes its successful use in 2 men with extensive, recalcitrant dystrophic calcifications of the prostatic fossa. The improvement in our patients may indicate a role for HBO therapy in these challenging cases.

ABBREVIATIONS

CT: Computed Tomography; FDA: US Food and Drug Administration; HBO: Hyperbaric Oxygen; HoLEP: Holmium Laser Enucleation of the Prostate; MGP: Matrix Gla Protein

INTRODUCTION

Dystrophic calcifications commonly occur in sites of previous inflammation or damage, even without a generalized disturbance in calcium or phosphorus metabolism [1]. Tissue injury can lead to calcification in 2 ways: 1) damaged cell membranes leak calcium ions, which concentrate to levels high enough to form crystals, and 2) necrosis can create an acidic environment that lacks inhibitors of calcification [1]. Dystrophic calcifications have been described after transurethral intervention for bladder outlet obstruction or lower urinary tract symptoms [1], but there is scant literature regarding treatment options. Treatment with laser lithotripsy has been described; however, little has been written about post treatment follow-up. Although not approved by the US Food and Drug Administration (FDA) for any urologic indication, hyperbaric oxygen (HBO) therapy has multiple recorded uses within urology, including for Fournier gangrene, radiotherapy cystitis, interstitial cystitis, cyclophosphamide-induced hemorrhagic cystitis, fistula, and, historically, urothelial carcinoma [2-4].

The mechanisms of action of HBO therapy are based on Henry’s law and the multiple effects of hyperoxia. Ultimately, HBO increases the dissolved oxygen concentration in arterial blood and enhances the diffusion rate of oxygen into poorly perfused tissues, as well as induces secondary growth of healthy tissue and neovascularization by promoting collagen matrix formation [3,4]. Hyperoxia causes a transient diffusion gradient between the circulating blood and surrounding tissue. As a result, oxygen delivery to poorly oxygenated tissues aids in healing [4]. Because dystrophic calcifications occur in places of poor tissue healing, HBO therapy could theoretically bring oxygen to these tissues, which rely on diffusion rather than on adequacy of the vascular supply, and could therefore be a potential therapeutic solution to these challenging clinical scenarios.

CASE PRESENTATION

Patient 1

A 71-year-old man had recurrent dystrophic calcifications of the prostatic fossa after a holmium laser enucleation of the prostate (HoLEP). He had a history of recurrent prostatitis that had been treated with ciprofloxacin on numerous occasions and a history of urinary retention that was secondary to benign prostatic hypertrophy. He required intermittent self-catheterization for a year before his surgical procedure. On preoperative transrectal ultrasonography the prostate measured 155 mL, and cystoscopy showed a 4.5-cm prostatic urethra with massive bilobar benign prostatic hypertrophy. He required intermittent self-catheterization for a year before his surgical procedure. On preoperative transrectal ultrasonography the prostate measured 155 mL, and cystoscopy showed a 4.5-cm prostatic urethra with massive bilobar benign prostatic hypertrophy. His preoperative maximum flow rate (Qmax) was 10 mL/s, and his post-void residual was more than 1 L. In December 2011, the patient underwent HoLEP, which required 61 minutes of enucleation time, 41 minutes of morcellation time, and a total energy use of 112.45 kJ. The final
pathological findings showed prostate tissue with glandular stromal hyperplasia (weight, 86 g). Postoperatively, the patient’s voiding was vastly improved; he had a maximum flow rate of 51 mL/s and a post-void residual of only 56 mL. In May 2013, he began spontaneously passing stone material. Computed tomography (CT) showed extensive calcifications in the prostatic fossa in the area of prior resection (Figure 1), which were confirmed with cystoscopy (Figure 2). In July 2013, he underwent cystoscopy and holmium-laser lithotripsy of the calcifications. After discharge he was treated with HBO at an outside facility (37 sessions either at 2.0 atm or 2.4 atm). Follow-up cystoscopy showed substantial improvement, although there was some recurrence of the dystrophic calcifications; therefore, in May 2014, he underwent another laser lithotripsy. He then completed an additional 20 sessions of HBO treatments at 2.0 atm, after which cystoscopy showed a well-healed prostatic fossa with healthy urothelium and only a few, small calcifications (less than 2 mm) that were easily dislodged with the cystoscope (Figure 3).

**Patient 2**

In 2011, an 81-year-old man was evaluated at our institution for recurrent urethral calcifications. In 1991, he had undergone brachy therapy and external beam radiotherapy for prostate cancer. In 1994, biochemical recurrence was diagnosed, and he underwent salvage cryotherapy. After cryotherapy, he had clinically significant urinary retention that required intermittent self-catheterization. In 1995, he underwent a transurethral resection of the prostate followed by placement of an artificial genitourinary sphincter for post-prostatectomy urinary incontinence. In 2007, the sphincter malfunctioned and was replaced; however, he continued to have a poor functional result. Extensive calcifications developed secondary to the multiple interventions and, likely, to devascularized tissue of the prostatic urethra, which required multiple laser ablations. When he came to our clinic, he had a suprapubic catheter in place, and cystoscopy showed diffuse calcifications of the prostatic urethra (Figure 4). In 2011 and 2012, he underwent 3 additional procedures, including laser ablation of the prostatic calcifications and explant and reimplant of the artificial sphincter. After the explant of the sphincter, he underwent a series of 20 HBO treatments. All follow-up cystoscopic procedures showed well-healed epithelium, no recurrence of the dystrophic calcifications, and a well-functioning artificial urinary sphincter (Figure 5).

**DISCUSSION**

During HBO therapy, patients breathe nearly 100% oxygen in a chamber with an atmospheric pressure greater than that at sea level [4]. HBO therapy is based on Henry’s Law, that is, the amount of an ideal gas that is dissolved in solution is directly proportional to its partial pressure. At sea level (1 atm), the dissolved plasma oxygen concentration is 3 mL/L. With the delivery of 100% HBO at 3 atm, this dissolved oxygen content increases to 60 mL/L of blood [5]. The amount of oxygen in solution compared with the
Oxygen in solution, rather than attached to hemoglobin, can reach physically obstructed areas that red blood cells cannot reach [5]. In addition, oxygen tension is substantially increased. For example, when a person breathes air at sea level, oxygen tension is reportedly 100 mm Hg, and tissue oxygen tension is around 55 mm Hg [5]. At 100% oxygen at 3 atm, such as in an HBO chamber, arterial oxygen tensions can increase to 2,000 mm Hg and tissue oxygen tensions to 500 mm Hg, thus delivering a significantly higher amount of oxygen per liter of blood. The hyperoxia allows for transient diffusion of the circulating oxygen from the blood supply to surrounding hypoxic, damaged tissue.

The oxygen delivery also facilitates fibroblast proliferation, angiogenesis, and wound healing [4]. HBO therapy is available at major medical centers around the country and, in general, is well tolerated and safe; only minor risks have been described [5]. Untreated pneumothorax is the only absolute contraindication. Relative contraindications include emphysema, sinus infections, severe seizure disorders or a history of tympanic membrane perforation.

HBO therapy was first described in the 1660s by an English physician who attempted to control climate by creating a sealed room and changing atmospheric pressure through manipulation of a series of valves [6]. In the 1770s, oxygen was officially discovered and reported in the scientific literature. In the 1830s, a French physician reported the health benefits of atmospheric oxygen after treating various conditions, mostly respiratory, with this therapy. In the late 1880s a New York neurologist, J. Leonard Cornings, introduced “compressed air baths” in the United States for decompression sickness in tunnel workers, and eventually the US Navy adopted the therapy for divers, which is perhaps the most well-known historical use of HBO [6]. The gas bubbles that accumulate from decompression sickness obstruct capillary circulation, which results in ischemic injury. At 5 atm, such as in an HBO chamber, a gas bubble decreases to 20% of its original volume and 60% of its original diameter. Ultimately, the hyperoxia decreases the obstruction from those gas bubbles and helps to re-oxygenate damaged tissues [4]. In the mid-1900s, HBO therapy gained popularity for numerous conditions, especially myocardial infarction, bacterial infection, and wound healing [7].

The use of HBO therapy in urology was first described in the 1960s in conjunction with radiotherapy for bladder tumors, although that practice was eventually abandoned because of poor outcomes. In the 1980s, HBO therapy again gained favor in urology. An article published in 1985 in the Journal of Urology described HBO treatment of 3 patients with radiotherapy-induced hemorrhagic cystitis refractory to conventional therapy. The urothelium eventually healed in all 3 patients, as documented by cystoscopy [7]. In 1986, several articles were published about the utility of HBO in treating both vesicocutaneous fistula and Fournier gangrene. The treatment of Fournier gangrene is aided by hyperoxia-induced neovascularization and tissue healing and by increased antimicrobial activity from HBO-induced activity of polymorphonuclear leukocytes, which require oxygen to aid in phagocytosis [4]. Almost 2 decades later, HBO was found to be useful for treating interstitial cystitis. One prospective study showed that HBO was a well-tolerated treatment of interstitial cystitis patients’ pain symptoms improved for at least 12 months [8]. Another study showed that HBO improved the effects of intravesical dimethyl sulfoxide in patients with interstitial cystitis [9].

Dystrophic calcifications occur when damaged cell membranes leak calcium ions, which ultimately form crystals. Extracellular fluids are physiologically supersaturated with calcium phosphate, but inhibitors such as osteopontin and matrix protein prevent calcium deposition under normal physiological conditions [1]. Areas of necrosis and tissue damage lack these inhibitors and create an acidic environment in which calcium ions leak into cells in high enough concentrations to form crystals [1]. Dystrophic calcifications rarely resolve spontaneously and often become recalcitrant. Patients may be treated with medical therapy, such as sodium warfarin, diltiazem, aluminum hydroxide, intrallesional corticosteroid injections, and etidronate disodium, although medical therapy is often ineffective [1]. The mechanisms of action of these therapies are varied, and most literature describes their use in the treatment of cutaneous calcification disorders. Increased levels of matrix Gla protein [MGP] have been documented in areas of calcification. Sodium warfarin suppresses the vitamin K dependent γ-carboxylation of MGP and minimizes the form of MGP that prevents calcification. It seems counterintuitive, but warfarin has been used successfully to treat mixed calcification disorders, including small calcified deposits in calcinosis cutis [10]. The calcium channel blocker diltiazem decreases calcium influx into cells. Aluminum hydroxide decreases the intestinal absorption of phosphate, which leads to decreased hydroxyapatite and amorphous calcium phosphate, both of which are often components of dystrophic calcifications [10]. Intrallesional corticosteroid injections have been used for decades, including for the plaques caused by Peyronie disease.

Prostate tissue that has been irradiated is at high risk for formation of dystrophic calcifications, as is the prostatic urethra after tissue resection. The formation of dystrophic calcifications after radiotherapy may depend on the method of resection, energy source, and hemostasis. Dystrophic calcifications have been described in patients after photoselective vaporization with...
a potassium-titanyl-phosphate laser [1,11]. Patients who have vascular disease may be at higher risk after these procedures. The effects of pelvic radiotherapy on the bladder include mucosal edema and inflammation acutely and submucosal hemorrhage and scarring often occur in these treatment areas, which makes them prone to the tissue imbalance that leads to dystrophic calcifications. These calcifications can often be recalcitrant, as described in our case studies. HBO treatment can deliver high levels of oxygen to the damaged tissues, aid in tissue healing, and prevent recurrence of the tissue imbalance that results in the dystrophic calcifications.

As discussed above, the specific use of HBO for recalcitrant dystrophic calcifications has not yet been described in the literature. No prospective randomized trials have been done regarding HBO’s use for any urologic indication, and HBO has not been approved for use in urology by the FDA. The number of treatments needed for urologic indications is also not known, however, 20 to 30 sessions is most often cited in published reports although the reports are very limited [2]. In addition, the exact mechanism of action of HBO therapy on urothelium is not fully understood. However, the success of HBO therapy in our patients shows that it may have important clinical value for the treatment of recalcitrant calcifications of the prostatic urethra. The topic deserves more research and exploration.

CONCLUSION

HBO for recalcitrant dystrophic calcifications of the prostate is a valid treatment option that worked well in our 2 patients. The objective improvement in our patients’ conditions may indicate a role for HBO therapy in this disease.

REFERENCES