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Long-Term Clean Intermittent Catheterization, Chronic Inflammation and Cancer: A Case Report and Review

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Case Report

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Abstract

In areas not endemic for schistosomiasis, the development of squamous cell carcinoma of the bladder (bSCC) is commonly associated with long-term indwelling catheterization (LTIC) and its associated bladder inflammation. Today, many patients unable to void use clean intermittent catheterization (CIC), a practice which gained popularity over the last 2-3 decades. Historically, CIC has not been perceived as a potential risk factor for bSCC; yet we believe that for many of the same reasons LTIC creates a hostile inflammatory environment potentially resulting in bSCC, CIC may also lead to bSCC, albeit at a slower pace. Using our interesting case as a starting point, we reviewed LTIC-related inflammatory mechanisms and drew connections between these mechanisms and CIC in an effort to raise awareness of the possible link to bSCC as the number of patients practicing CIC over multiple decades continues to grow.

Keywords: Clean intermittent catheterization; Indwelling catheter; Inflammation; Long-term indwelling catheterization; Squamous cell carcinoma of the bladder

Introduction

Squamous cell carcinoma of the bladder (bSCC) arises in the setting of chronic bladder inflammation and is thus the most common bladder malignancy in areas endemic for Schistosomiasis [1]. Elsewhere, bSCC comprises less than 5% of all bladder cancer, most frequently in patients with spinal cord injuries [SCI] dependent on long-term indwelling catheterization (LTIC) [2]. This connection has been well established in the literature for almost 40 years [3].

Today, however, the gold standard for the management of neurogenic bladders is clean intermittent catheterization (CIC). Following its inception in 1972, usage in managing newly neurogenic bladders grew in popularity from 12% to around 50% from 1991 onward [4]. Time and research have demonstrated that practicing CIC, in many ways, results in better outcomes than those practicing LTIC; however, CIC does not come without its own risks, especially to those performing self-

catheterization long-term. These risks include increased rates of urinary tract infections (UTI), traumatic catheterization and increased time of bladder exposure to irritants in the urine [5]. But rarely, if ever, listed amongst those maladies is an increased risk for bSCC.

We report a unique and informative case highlighting this potential link in a patient who had performed CIC for 35 years in the absence of other risk factors commonly present in cases of bSCC.

Case Report

A 49-year-old female was seen in clinic for a symptomatic UTI and new onset hematuria when passing a catheter. The patient was diagnosed at birth with spina bifida, but suffered from no weakness or orthopedic abnormalities, walking into our clinic without the stigmata commonly associated with the condition. In fact, she had no functional impairment at all until she underwent back surgery at the age of 14 for spina bifida-associated chronic lower back pain. It was at this time the patient developed a neurogenic bladder which was drained by CIC up to three times per day without incident over the next 35 years.

In the hematuria work-up, cystoscopy discovered a large, isolated bladder mass on the posterior wall which was found to be squamous cell carcinoma invading into the muscular layer of the bladder.

The patient underwent a radical cystectomy, hysterectomy and bilateral salpingo-oophorectomy with an ideal conduit urinary diversion and bilateral pelvic lymph node dissection (Figure1). The patient tolerated the procedure well, but one lymph node on the left and one on the right were found to contain metastatic SCC. The patient was referred to an oncologist for chemotherapy.

Discussion

Chronic inflammation is associated with multiple cancers all over the body including skin, esophageal, gastric, pancreatic, liver, colon and bladder cancer. Although the exact mechanisms behind inflammatory tumorigenesis are yet to be elucidated, it has become evident that chronic inflammation creates an environment, rich in cytokines and growth factors, that favors cell proliferation, migration, angiogenesis and the suppression of apoptosis [6]. This inflammatory microenvironment potentially contributes to tumor development through induction of oncogenic mutations and genomic instability, all while acting in every step of tumor development-from initiation to metastasis [7]. Given this premise, the conclusion follows that LTIC may lead to bSCC as these patients are setups for chronic bladder inflammation due to both mechanical trauma and chronic UTIs.

Local mechanical trauma and chronic irritation of the bladder epithelium from indwelling catheters, like schistosomiasis, are believed to promote the development of bladder cancer due to the induction of epithelial hyperplasia [8]. This trauma can be due to pressure damage from the catheter tip as the bladder drains and collapses around the catheter or from suction damage as the bladder wall is aspirated into the drainage eyelets [9-11]. Not only does this constant irritation promote a much localized chronic inflammatory response, but the mechanical trauma associated with long-term catheterization has been demonstrated to create alterations in histological architecture hypothesized to provide a route for both local spread and distant metastasis [8,12].

Likewise, chronic UTIs have been associated with both chronic catheterization and bladder cancer and corroborate the connection between the two. In a recent case-control study using the data found in the Nijmegen Bladder Cancer Study, Vermeulen, et al found recurrent UTIs to have an odds ratio of developing bladder cancer of 6.6 in men and 2.7 in women [13]. Possible explanations for this link include the carcinogenic N-nitrosamines formed in the presence of nitrate-reducing bacteria and the up regulation of local nitric oxide production by the activation of inducible nitric oxide synthase which may promote tumor growth and proliferation [14,15]

Undoubtedly, local mechanical trauma and recurrent UTIs create perpetually inflamed bladders primed for tumorigenesis, yet these factors are not unique to LTIC—our patient presented with a symptomatic UTI and had performed CIC approximately 30,000 times over a 35-year span. Each catheterization provided not only an opportunity for infection but also for direct catheter trauma to the bladder, as evidenced by the tumor's location directly opposite the urethral orifice through which catheters were passed (Figure 1).

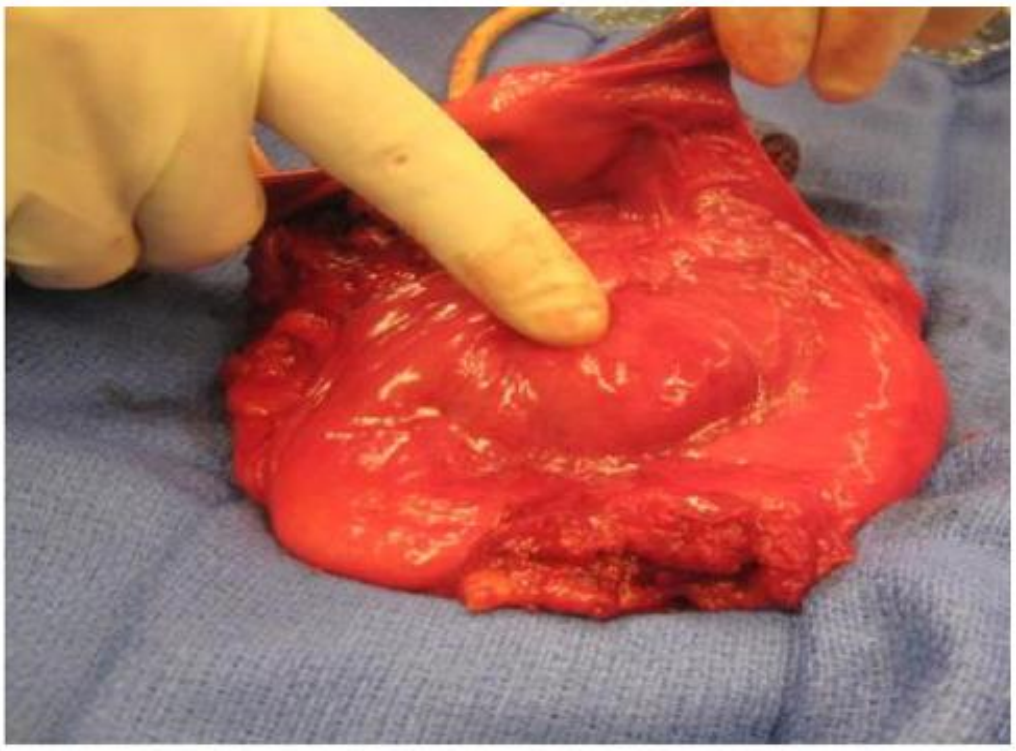

Figure 1: The large, isolated mass located on the posterior wall of the bladder found to be squamous cell carcinoma invading into the muscular layer.

Also implicating the role of direct mechanical trauma in our patient was the fact that epithelial tissue distant from the tumor remained urothelial. This observation has been made in other cases of CIC leading to bSCC, and other authors have proposed this to be evidence of local trauma's role in bSCC [16-20]. Similarly, UTIs are the most common complication in patients practicing CIC and increase over time the longer a patient practices CIC [5,21].

Distinct from LTIC, a third setup for chronic inflammation exists for long-term practitioners of CIC. Depending upon the duration between and effectiveness of each catheterization, urinary stasis similar to that which exists in bladder outlet obstruction, can be present. Bladder outlet obstruction has also been implicated in bladder cancer, as urinary stasis leads to a theoretical increase in contact between urinary irritants, potential carcinogens and the bladder epithelium leading to chronic inflammation [14].

Despite all of these inflammatory factors coalescing in this particular method of neurogenic bladder management, bSCC in the setting of CIC is difficult to find outside of case reports. One possible reason for this fact is that the inflammatory onslaught in the setting of LTIC is much more unrelenting than the frequent, punctuated insults of CIC. Because of this, the average time to tumorigenesis may be much greater in CIC than in LTIC. It took our patient 35 years of self-catheterization, so a timeline of multiple decades may be more likely. Considering that the use of CIC for bladder management in newly neurogenic bladders only began to approach 50% in 1991, some authors propose—and we agree—that we may just now begin to see more cases of bSCC related to CIC in our clinics and operating rooms [4,19].

Conclusion

Most patients diagnosed with bSCC will die within 1 to 3 years of diagnosis [2]. The poor prognosis of this disease is in large part due to its late presentation, so awareness of a potential link to those practicing CIC over multiple decades could be lifesaving. As was the case with our patient, up to 95% of patients present at an advanced stage with invasion to local organs or spread to pelvic

lymph nodes; [22] thus in order to arrive at the earliest possible diagnosis, it is imperative to be aware of all patient populations with chronically inflamed bladders at risk of developing bSCC—especially those practicing LTIC and long-term CIC. This has proven to be easier said than done. Despite the known connection between bSCC and patients practicing LTIC, annual urine cytology alone has demonstrated to be ineffective for adequate surveillance and a healthy debate continues in the literature regarding the use of surveillance cystoscopies for bladder cancer in at risk populations [23-27]. If cystoscopy is the answer, effective surveillance cystoscopy guidelines will likely be decided by our ability to successfully risk-stratify LTIC and CIC patients according to inflammatory risk factors such as duration of LTIC, duration and frequency of CIC, chronicity of UTIs, presence of bladder calculi and urinary retention along with carcinogenic risk factors such as cigarette smoking.

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