Pediatric cystectomy for refractory cystitis post-bone marrow transplant in dyskeratosis congenita: A case report

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ABSTRACT

We present a case of refractory cystitis after BK-virus associated hemorrhagic cystitis following bone marrow transplantation requiring cystectomy in a 17-year-old female with genetically confirmed dyskeratosis congenita, a telomere disorder characterized by early bone marrow failure. She presented with a contracted, small bladder with intense urinary symptoms non-responsive to conservative therapy and requiring opioids for pain control. Cystectomy is a rare, final surgical treatment for benign bladder conditions, especially among younger patients, and she experienced successful resolution of symptoms and cessation of chronic opioids post-intervention.

1. Introduction

We present a case of refractory cystitis after BK-virus associated hemorrhagic cystitis in a 17-year-old female with genetically-confirmed dyskeratosis congenita (DC), which failed conservative therapy and required cystectomy. DC is a rare congenital disorder caused by mutations in telomere maintenance genes. It’s characterized by bone marrow failure at a young age requiring bone marrow transplantation (BMT), and DC patients have high sensitivity to transplant-related damage due to cell senescence or delayed turnover. BK-virus associated hemorrhagic cystitis with gross hematuria, bladder pain, and spasms is common after BMT immunosuppression, though most patients fully recover. Patients with refractory cystitis symptoms can progress to end-stage bladder disease, characterized by a limited capacity, fibrotic bladder requiring urinary diversion as a treatment of last resort.

2. Case presentation

The patient underwent a reduced-intensity BMT from a 7/8-matched unrelated donor for DC-associated myelodysplasia and was admitted for hemorrhagic cystitis symptoms one month post-transplant. Her conditioning included alemtuzumab and fludarabine only, without radiation or cyclophosphamide. Prior to transplant, she reported normal bladder function. On admission, her BK titers were weakly positive in serum with >5 billion viral copies per mL in urine, and she was treated with cidofovir. During treatment, the patient developed worsening dysuria and bladder spasms, controlled with oxycodone and oxybutynin. She remained on scheduled immunosuppression with tacrolimus and mycophenolate until 6 months post-transplant.

Five months later she presented to the Emergency Department for worsening bladder pain. She reported severe dysuria, urgency, urinary incontinence, and frequency (20–30 voids per day). Computed tomography of the pelvis revealed a markedly thickened, 1cm bladder wall with enhanced urothelium (Fig. 1). Urinalysis revealed microhematuria, with BK virus weakly positive at 22,000 viral copies/ml in urine and undetectable in serum, suggesting symptoms were not due to BK virus. Cystoscopy under general anesthesia revealed a diffuse, severely inflamed bladder with edema and hypervascularity that bled easily with distension. Bladder biopsies displayed urothelial mucosa with chronic inflammation and granulation-type tissue (Fig. 2). Viral stains for CMV, HSV, Adenovirus, and SV-40 (BK/JC virus) were negative.

Conservative therapy was initiated with anti-cholinergic medication, though she required 32 morphine milligram equivalents (MME) daily for pain control. Systemic steroids were initially held during post-transplant management, and intravesical steroids were offered. For six weeks she received weekly intravesical treatments of 100mg hydrocortisone and 80mg lidocaine buffered with 2mEq of bicarbonate. At first instillation bladder capacity was 74ml under anesthesia and on final instillation biopsy showed repeat results of denuded urothelial mucosa. After unsuccessful intravesical treatments she received a 25mg/day course of...
The patient underwent a vaginal-sparing robotic-assisted simple cystectomy with ileal conduit urinary diversion. Intraoperatively the bladder was notably small with significant fibrosis around the distal cystectomy with ileal conduit urinary diversion. Intraoperatively the normal-appearing ureter and fibrotic changes near the bladder. Pain and incontinence diversion. Thus, it was decided to proceed with cystectomy and catheterize and therefore not a candidate for continent diversion or a neobladder. Gabapentin, but remained 52–132 MME/day. She was unwilling to catheterize and therefore not a candidate for continent diversion or a neobladder. Thus, it was decided to proceed with cystectomy and incontinent diversion.

The patient underwent a vaginal-sparing robotic-assisted simple cystectomy with ileal conduit urinary diversion. Intraoperatively the bladder was notably small with significant fibrosis around the distal right ureter. The ureter was dilated with a clear transition between normal-appearing ureter and fibrotic changes near the bladder. Pathology showed near complete loss of the bladder urothelium with chronic inflammation and granulation tissue not involving detrusor muscle, consistent with prior biopsy. After surgery her opioid use decreased to 20 MMEs per day with 300mg gabapentin, and she was without pain at 3 week follow up. At 3-month follow up she remained pain free and weaned from opioids, using only acetaminophen as needed. Her conduit was well-managed at initial follow up, though could be converted to a pouch if continence is desired.

3. Discussion

In DC abnormally short telomeres lose their self-renewing capability, leading to early cell senescence and pleiotropic effects including early bone marrow failure and poor wound healing. We hypothesize that the combination of BK virus damage during transplant immunosuppression, predisposition to early senescence, and poor healing led to scar tissue formation with the near complete loss of functional urothelium found on bladder biopsy. The scarred, non-functional, and spastic bladder resulted in permanent loss of capacity and function. Future strategies to prevent BK hemorrhagic cystitis could hopefully prevent such potential sequelae.

Cystectomy is a rare, final surgical treatment for benign bladder conditions, especially among younger patients. It has been performed successfully for pediatric patients with severely reduced bladder capacity due to intrinsic bladder disease, and only rarely in post-BMT hemorrhagic cystitis patients receiving full-dose cyclophosphamide with total body irradiation or busulfan. Documented cases of cystectomy for refractory cystitis after radiation therapy are generally in older patients with slower progression of symptoms. One case series of 21 patients was 81% male with median age of 77 and median 91 months from onset of symptoms to cystectomy. These patients had significant comorbidities and 43% experienced severe perioperative complications. In a study of cystectomies for 9 neurogenic bladder patients who were younger and less comorbid (mean age 43.6), only one patient experienced a perioperative complication.

Patients with debilitating bladder conditions refractory to conservative management may undergo partial, simple, or radical cystectomy for quality-of-life preservation. After thorough evaluation and failure of conservative methods, our patient’s low perioperative risk and debilitating symptoms made cystectomy reasonable for quality-of-life improvement. There is risk of pain persisting post-cystectomy if symptoms are due to a systemic condition. However, minimal bladder capacity under anesthesia and persistent cystoscopic findings suggest a bladder-centric pain phenotype amenable to cystectomy, further evidenced by resolution of symptoms and cessation of chronic opioids post-intervention.

4. Conclusion

We report a case of refractory cystitis in a patient with DC following BMT leading to a contracted, small bladder with severe urinary symptoms and pain which resolved after cystectomy.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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