Urology Case Reports 30 (2020) 101042

Contents lists available at ScienceDirect

Urology Case Reports

journal homepage: http://www.elsevier.com/locate/eucr

Inflammation and infection

Alum irrigation for the treatment of adenovirus induced hemorrhagic cystitis in a kidney transplant recipient

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A B S T R A C T

Adenovirus is a rare cause of hemorrhagic cystitis in the transplant population. We present a case of a forty-one-year-old man with end-stage renal disease who underwent living unrelated donor kidney transplant in 2016. In 2018 he presented with acute onset gross hematuria and dysuria, with serologic testing and immunohistochemical stains of biopsy specimens positive for adenovirus. He was treated with reduction in immunosuppression, cystoscopy with evacuation of clots, and alum bladder irrigation. His hematuria resolved almost immediately with no recurrence to date. This case demonstrates the efficacy and safety of alum irrigation in patients with adenovirus hemorrhagic cystitis.

Introduction

Adenovirus is a common culprit in respiratory and gastrointestinal illness, usually affecting children and military recruits. It is also an important cause of morbidity and mortality in the immunosuppressed. Acute hemorrhage cystitis from adenovirus has been reported following bone marrow transplant but is rarely reported following solid organ transplant. It typically presents with fever, dysuria, urinary frequency, and gross hematuria. Treatment strategies have included adjustments of immunosuppression, treatment with antivirals, and continuous bladder irrigation with varying degrees of success. We present a case report of a renal transplant recipient with hemorrhagic cystitis secondary to adenovirus which resolved completely with alum irrigation.

Case presentation

A forty-one-year-old man with end stage renal disease from IgA nephropathy underwent living unrelated donor kidney transplant. Induction with alemtuzumab was followed by maintenance immunosuppression with tacrolimus and mycophenolate mofetil (MMF). Twenty-two months after transplant he presented with acute onset of dysuria and gross hematuria with clots. Renal function was at baseline with a serum creatinine of 1.1–1.2 mg/dL. Urinalysis and microscopy showed >50 WBC and >50 RBC per high power field and trace leukocyte esterase with no bacteria. Bacterial urine culture had no growth. Cystoscopy demonstrated a diffusely erythematous bladder with areas of hemorrhage without any discrete bladder tumors(Fig. 1). Random biopsies were taken. He was started on continuous bladder irrigation with 1% alum. Hematuria resolved within 24 h.

Pathology revealed totally denuded bladder mucosa, markedly engorged capillaries in the superficial submucosa and focal hemorrhage. Viral immunohistochemistry revealed stromal cells and vascular endothelial cells positive for adenovirus (Fig. 2). Serum quantitative DNA by PCR for adenovirus was highly positive (53,208 copies/mL) and negative for cytomegalovirus (CMV), BK virus, and herpes simplex virus (HSV). Foley catheter removed and patient discharged on post-operative day two. His MMF was discontinued, low dose prednisone was started, and tacrolimus was continued to target 12-h trough levels of 5–8 ng/mL. Adenovirus was detectable (32,086 copies/mL) 6 weeks after treatment and undetectable at 8 weeks and on all subsequent serum PCR assays. Low dose MMF at 250 mg orally twice daily was restarted three months after diagnosis. Renal function remained stable with serum creatinine of 1.1 mg/dL and no recurrence of hematuria at 18 months.

Discussion

Adenovirus is a non-enveloped, double-stranded DNA virus. It is endemic in the population and 80% of children have antibody to one or more serotypes by age 5. It has been known to cause respiratory illness, gastroenteritis, and conjunctivitis but disease is typically mild in immunocompetent hosts. In immunosuppressed populations illness can be prolonged, severe, and sometimes fatal. In these patients, infection can be related to reactivation of the virus as well as primary infection. One unusual sequelae is hemorrhagic cystitis which was first reported in

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https://doi.org/10.1016/j.eucr.2019.101042
Received 19 September 2019; Received in revised form 7 October 2019; Accepted 8 October 2019
Available online 10 October 2019

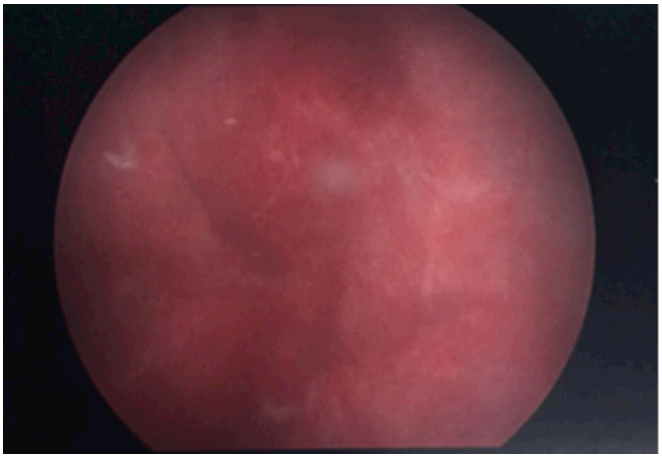

Fig. 1. Cystoscopy demonstrating diffusely erythematous bladder mucosa.

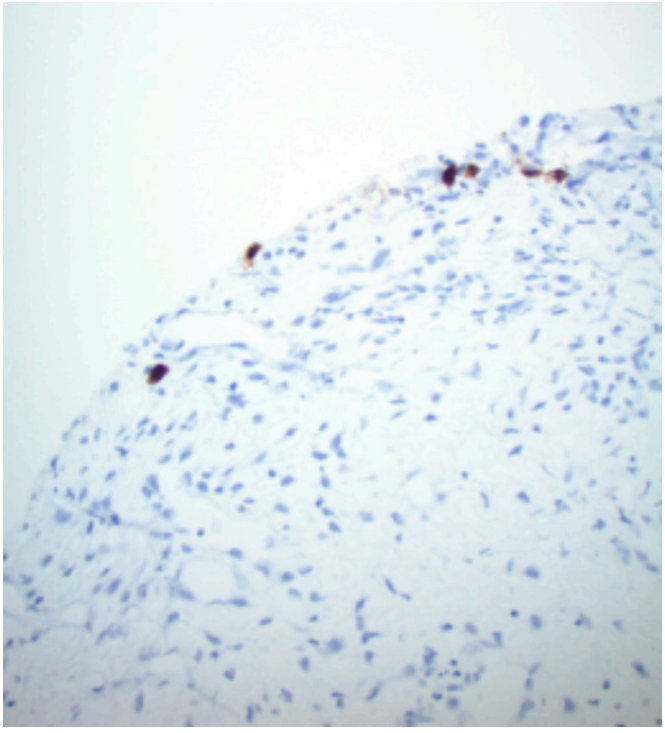

Fig. 2. Immunohistochemistry stain of bladder biopsy specimen revealing adenovirus positive cells.

1968 in children.[1] Typically, it presents with fever, gross hematuria, and dysuria and can be associated with acute kidney injury in the setting of negative bacterial urine cultures.

Adenoviral hemorrhagic cystitis is well reported in stem cell transplant but infrequently reported in solid organ transplants, specifically kidney transplants. The incidence of adenovirus infection in kidney transplant recipients has been reported as 6.5%[2] but the incidence of hemorrhagic cystitis from adenovirus is much lower. Mechanisms of spread to the bladder are unknown. Hypotheses include viral particles from the kidney travelling to the bladder in urine, retrograde spread through the urethra, pelvic lymphatic spread from the gastrointestinal tract, or direct hematogenous spread.[1]

The differential diagnosis for gross hematuria following transplant is broad and adenoviral infection is difficult to diagnose. Viral urine cultures have low sensitivity and therefore a negative viral culture does not exclude the possibility of adenovirus infection. Serologic tests should be performed with PCR.[3] On cystoscopy, bladder mucosa appears diffusely erythematous and hyperemic. Pathologic analysis shows cystitis, usually with an erosive component. If performed, immunohistochemical evaluation demonstrates large nuclei with basophilic inclusion bodies consistent with adenovirus.[3]

Reduction in pharmacologic immunosuppression permits T cell recovery allowing the immune system to mount an appropriate response to adenovirus.[3] Antiviral agents such as ribavirin and cidofovir[1] have been used. Treatment with cidofovir can be limited by nephrotoxicity. Intractable hematuria warrants aggressive intervention and cystoscopy with clot evacuation and fulguration with continuous bladder irrigation are sometimes necessary. Irrigation can be performed with normal saline, aminocaproic acid, alum, and formalin. Sparse literature is available on the use of alum in these patients.[1]

Alum irrigation was first reported in 1982 in the treatment of six patients with hemorrhagic cystitis of different etiologies. A 1% alum solution is created by mixing 50g of aluminum potassium sulfate with 5L of sterile water which is instilled as continuous bladder irrigation at a rate of 300 cc/hr. Alum is well tolerated and unlike formalin instillation, which requires instillation in the operating room under general anesthesia, can be delivered bedside. Alum is renally excreted and caution should be used in patients with impaired renal function as aluminum toxicity resulting in neurologic symptoms has been reported with inappropriate use.[4] The mechanism of action is proposed to be the induction of protein precipitation at the cell surface, decreased capillary permeability, vasoconstriction, hardening of the capillary endothelium, and a reduction in edema and inflammation.[4] Studies have shown the preservation of the mucosal integrity after alum irrigation, which is why alum can be delivered safely in the setting of vesicoureteral reflux.[5] Therefore, no cystogram is needed. This is important in kidney transplant patients because many have some degree of reflux.

Westerman et al. reported on the efficacy and safety of alum irrigation in the general population. In their series alum irrigation was successful in 60% of patients with mild adverse effects. Of those who responded to alum irrigation, response was durable in 54%, requiring no further hospitalizations for hemorrhagic cystitis at a median follow up of 16 months.[4] To our knowledge, this is the first report of its use in adenovirus associated hemorrhagic cystitis after renal transplant.

Conclusion

Our case report suggests alum irrigation is a safe and effective management strategy for gross hematuria secondary to adenovirus hemorrhagic cystitis.

References

1. Londergan TA, Walzak MP. Hemorrhagic cystitis due to adenovirus infection following bone marrow transplantation. *J Urol.* 1994. https://doi.org/10.1016/S0022-5347(17)35153-4.
2. Ortiz M, Ulloa C, Troncoso P, Rabagliati R, Jara A. Hemorrhagic cystitis secondary to adenovirus infection in a kidney transplant recipient: case report. *Transplant Proc.* 2009. https://doi.org/10.1016/j.transproceed.2009.06.074.
3. Majorant D, Qiu F, Kalil AC, Wilson N, Florescu DF. Adenovirus—a deadly disease in the solid organ transplant population: risk factors and outcomes. *Transplant Proc.* 2018. https://doi.org/10.1016/j.transproceed.2018.07.004.
4. Westerman ME, Boorjian SA, Linder BJ. Safety and efficacy of intravesical alum for intractable hemorrhagic cystitis: a contemporary evaluation. *Int Braz J Urol.* 2016. https://doi.org/10.1590/S1677-5538.IBJU.2015.0588.
5. Goel AK, Rao MS, Bhagwat AG, Vaidyanathan S, Goswami AK, Sen TK. Intravesical irrigation with alum for the control of massive bladder hemorrhage. *J Urol.* 1985. https://doi.org/10.1016/S0022-5347(17)49330-X.