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Obstruction from Deflux leading to significant kidney function loss and chemotherapeutic challenges in pediatric Ewing sarcoma

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ABSTRACT

This report presents the case of an 8-year-old female with a history of vesicoureteral reflux (VUR) treated with Deflux injections, who developed Ewing sarcoma metastasized to the lungs. Despite the initial resolution of VUR following Deflux procedures, recurrent urinary tract infections prompted further evaluation revealing significant ureteral obstruction. Pre-chemotherapy workup included renal ultrasonography, nuclear medicine renal scan, and cystogram, identifying obstructive uropathy necessitating bilateral ureteral stent placement. This discussion encompasses the challenges of managing VUR, Deflux complications, and the importance of tailored follow-up protocols.

1. Introduction

Vesicoureteral reflux (VUR), the retrograde flow of urine from the bladder into the ureters and kidneys, poses significant challenges in pediatric urology.[1] The management of VUR has evolved from conservative approaches to minimally invasive interventions such as endoscopic injection therapies.[1] Among these, dextranomer/hyaluronic acid copolymer (Deflux®) has emerged as a popular choice for its efficacy and low-risk profile.[1] However, despite its widespread use, concerns persist regarding potential complications, including ureteral obstruction, emphasizing the importance of comprehensive preoperative evaluation and meticulous postoperative monitoring. This report discusses the case of an 8-year-old female with a history of VUR treated with Deflux, who subsequently presented with Ewing Sarcoma, necessitating careful urologic evaluation before initiating chemotherapy.

2. Case presentation

The patient's urologic history began with a febrile UTI at 6 months old caused by Klebsiella and Pseudomonas, which led to a renal ultrasound (US) and voiding cystourethrogram (VCUG), revealing bilateral SFU grade 2 hydronephrosis and bilateral grade 4 VUR. She was started on daily Bactrim prophylaxis. At one year old, she underwent bilateral Deflux injections, and a subsequent VCUG two years later was normal, allowing discontinuation of prophylaxis. At six years old, she experienced two UTIs (one was febrile). Repeat renal US showed SFU grade 3 hydronephrosis on the left, and VCUG indicated grade 2 VUR on the right. A second bilateral Deflux injection was performed without subsequent follow up. Her last UTI, E. coli positive, occurred at eight years old in October 2023. All treatments and care were at a separate institution.

In December 2023, this 8-year-old female presented with worsening right thigh pain and a limp. Initially attributed to growing pains, her symptoms were refractory to Tylenol and NSAIDs. Examination revealed tenderness in the superior thigh with elevated ESR (72 mm/hr) and CRP (12.194 mg/L). X-ray revealed an aggressive-appearing, expansile lytic lesion with periosteal reaction in the right femoral mid-diaphysis. Chest X-ray identified a 4 mm nodule at the medial right lung base. MRI and chest CT confirmed Ewing sarcoma with lung metastasis. Before initiating chemotherapy, a thorough review of her urological medical history was conducted.

Pre-chemotherapy evealuation included a renal ultrasound, revealing right grade 2 hydronephrosis and left grade 4 hydronephrosis. Nuclear medicine renal MAG3 scan demonstrated high-grade obstruction of the left kidney, partial to moderate obstruction of the right, and renal function of 4 % from the left kidney and 96 % from the right. The right side had a T ½ of 30–40 minutes, while the T ½ could not be calculated on the left side. VCUG was normal. A PIC cystogram revealed no reflux, but bilateral cystourethroscopy showed right ureter with proximal and distal Deflux blebs, and a left ureteral orifice (UO)

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displaced laterally by Deflux (Fig. 1). Right retrograde pyelogram showed dilation of the right UO with intramural narrowing distal ureter while left RPG showed dilation of the entire ureter. Bilateral double J stents (4.7 × 16 cm) were placed to address the obstructions with a 5 week follow up ultrasound revealing reduction to right-sided grade 1 and left-sided grade 3 hydronephrosis. She was subsequently started on COG protocol AEWS1221 Regimen A on January 2024, which consists of cycles of vincristine/doxorubicin/cyclophosphamide (VDC) and ifosfamide/etoposide (IE) and is the standard treatment for localized and metastatic Ewing Sarcoma in pediatric populations.[2]

This case highlights the complexity of managing pediatric Ewing sarcoma in the presence of Deflux-related ureteral obstruction and significant renal function impairment, emphasizing the need for careful pre-chemotherapy evaluation and intervention.

3. Discussion

The management of VUR involves various approaches, including spontaneous resolution with prophylactic antibiotics, surgical intervention, and endoscopic treatments like Deflux injections.[3] Spontaneous resolution is more likely in lower grades of VUR (I–III) in younger children, with an annual resolution rate of 5 % for grades IV–V.[4] The VUR Index (VURx) was a simple scoring tool designed to identify factors associated with VUR resolution in children under 2 years old and predict improvement and resolution (Fig. 2.).[5] VURx 1 to 5–6 had improvement/resolution rates of 89 %, 69 %, 53 %, 16 % and 11 %, respectively.[5] In our patient, initially diagnosed with grade 4 VUR before the first Deflux procedure, the condition persisted and later recurred. Early repair of higher-grade VUR (IV–V) should be considered after 18 months of age.[4]

Deflux, a minimally invasive alternative approved by the FDA in 2001, has become a preferred treatment due to its low risk and ease of administration. However, it is most effective in children with low-grade reflux and normal bowel and bladder function. Complications, although rare, include VUR recurrence, ureteral obstruction, dysuria, urgency, and frequency. Literature suggests an obstruction incidence of 0.7 %–7.6 % after Deflux, with some cases requiring stent placement and others resolving spontaneously.[6–9] Delayed diagnosis of ureteral obstruction

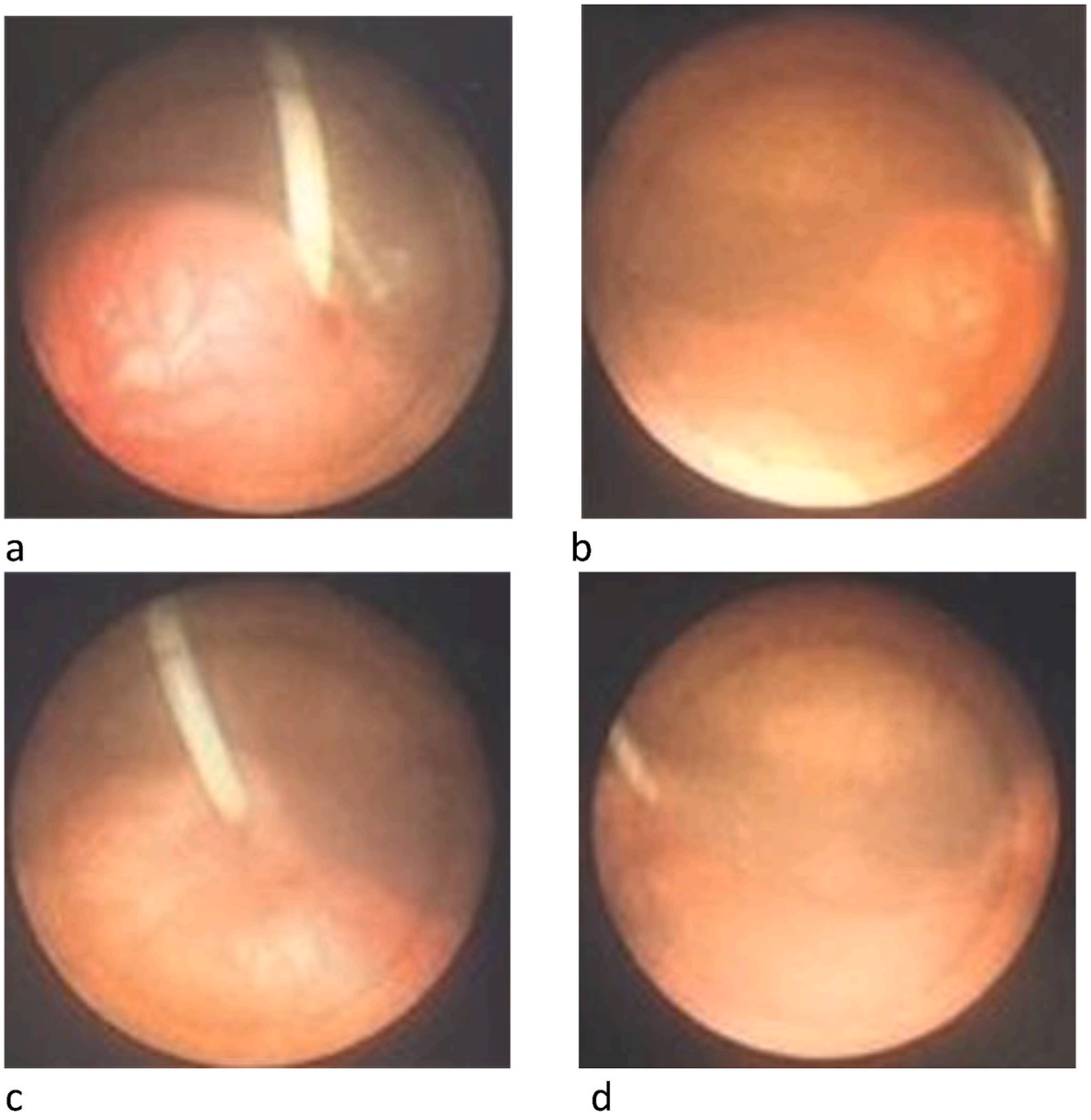

Fig. 1. (a) Left ureteral orifice with stent. (b) Left ureteral orifice with stent. (c) Right ureteral orifice with stent. (d) Trigone.

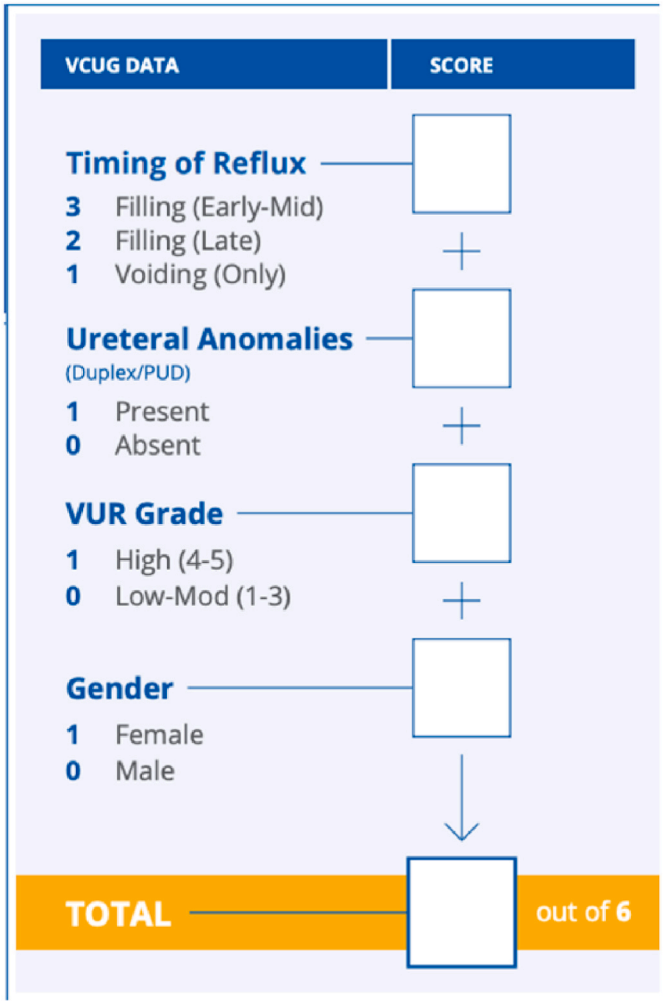

Fig. 2. VUR Index (VURx).

can occur, underscoring the need for close monitoring post-treatment.

The management of VUR refractory to endoscopic treatments often necessitates ureteral reimplantation. This surgical procedure corrects the anatomy and has a high success rate (97–99 %). Despite its effectiveness, improvements in endoscopic techniques have reduced the frequency of reimplantation surgeries.

Previous literature highlights the importance of tailored follow-up protocols. Studies indicate that children with higher preoperative VUR grades and renal scarring are at increased risk of VUR recurrence, even if initial post-operative imaging is negative.[10] Follow-up imaging, such as direct isotope cystography or voiding cystourethrogram, is recommended in cases of subsequent febrile UTIs to detect recurrent VUR. Current guidelines on post-Deflux monitoring are inconsistent, with some suggesting extended follow-up while others argue for reduced surveillance if no VUR is detected at one-year post-procedure.[11] Further research is needed to establish definitive guidelines for post-Deflux monitoring to improve patient outcomes and minimize adverse effects.

This case demonstrates the complications associated with Deflux, including significant ureteral obstruction leading to impaired renal function, which affected considerations for chemotherapy treatment. For this patient, a combination therapy of VDC and IE was administered. All of these drugs have been shown to have some nephrotoxic effect.[12] Ifosfamide most prominently features risk of nephrotoxicity particularly in the pediatric context, where this drug is very effective at curing childhood sarcomas and is being incorporated increasingly into treatments.[13,14] For this reason, careful monitoring and follow-up with regard to kidney function is highly recommended, especially in patients with pre-existing urologic dysfunction. If the renal function remains severely impaired (<10 %), nephrectomy would be considered to prevent recurrent infections. Conversely, if there is partial recovery, continued surveillance is recommended to monitor for obstruction or function improvement.[15] The complexity of this patient's urologic and oncologic management underscores the necessity for multidisciplinary coordination and vigilant follow-up to prevent and promptly address complications.

4. Conclusion

This case illuminates the intricate interplay between oncological and urological considerations in pediatric patients, particularly those with a history of VUR managed with Deflux injections. Despite the success of Deflux procedures in resolving reflux initially, the potential for complications such as ureteral obstruction underscores the importance of vigilant postoperative monitoring, especially in the context of oncologic patients. In this rare instance, the obstruction necessitated bilateral ureteral stent placement, highlighting the need for close surveillance and prompt intervention in similar cases. Additionally, lack of consensus on follow-up protocols for patients treated for VUR underscores the need for further research to establish clear guidelines.

CRediT authorship contribution statement

Luke Martin: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Dipen Mehta:** Writing – review & editing, Writing – original draft. **Bradley Morganstern:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Data availability statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Statement of ethics

Informed consent was obtained from patient involved in the study. Written informed consent was obtained from the patient for the publication of this paper.

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Declaration of competing interest

Authors have no conflicts of interest to declare.

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