Difficult Management of a Patient with Complicated Bilateral Duplication of Renal Collecting Systems and Associated Pathology

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Abstract

A 31-year-old female with a 19-year history of chronic urinary tract infections, intermittent hematuria, and associated flank pain was referred to our service for evaluation and treatment. Increasing frequency and severity of the infections prompted the following diagnostic studies to elucidate the etiology of the patient’s condition: abdominal and pelvic computed tomography scans, intravenous pyelography, voiding cystourethrography, kidney ureter and bladder x-rays, flexible cystoscopy, bilateral renal ultrasonographies, cystourethroscopy with sounding, bilateral retrograde pyelographies with fluoroscopy, and ureteroscopy. Our studies revealed an uncommon, bilateral duplication of the urinary collecting systems. Upper and lower pole collecting systems, each with their own ureter, were discovered bilaterally. Chronic changes of the upper pole collecting system of the left kidney were observed, including hydroureter, caliectasis, and renal calculi. Furthermore, a large ureterocele, measuring 4 cm in length × 2 cm maximum transverse diameter, was observed in the distal portion of the left upper pole ureter. This ureter inserted into the proximal portion of the external sphincter muscle of the female urethra. These findings are consistent with an obstructive process that resulted in chronic damage to the left upper pole collecting system, and presents a difficult clinical scenario to manage. The duplicated collecting system on the right showed normal function despite its anatomical variation. Based on this finding, we believe that the location where the duplicated ureter inserts into the bladder is more predictive of chronic renal insult and associated pathology versus the presence of the variant alone causing problems.

INTRODUCTION

Anatomic variation is generally part of the differential diagnosis when a healthcare professional sets out to diagnose and manage chronic urologic problems, such as chronic Urinary Tract Infections (UTI) or chronic pyelonephritis. These conditions can be caused by anatomic variations that create backward pressure on the renal collecting system. Concrete figures detailing prevalence of ureter duplication are elusive; however, some studies suggest that unilateral and bilateral duplication occur in approximately 1.5% and 0.3% of the population, respectively. All forms of renal duplication have a 2:1 predominance for females to males. Ureteroceles are commonly linked with renal duplication, but only in unilateral duplications, and only on the non-duplicated side. Renal duplications are found to have a significantly increased incidence in chronic pyelonephritis and UTIs [1].

One group of investigators looked into a set of complicated renal duplications and found that most cases were unilateral. Furthermore, among those unilateral duplications, a predominance of upper pole duplications were found in a 3:1 ratio, with lower pole duplications comprising the smaller group. They also demonstrated that the most common comorbid condition present with a duplicated urinary collecting system was hydronephrosis [2]. Hydronephrosis is the condition resulting from the constant reflux of urine back into the kidney. Blunting of the renal calyces and swelling of the renal pelvices can provide evidence of reflux on IVP or retrograde pyelography.

One particular case study revealed a total obstruction of both duplicated lower pole moieties in a case of bilateral duplication of the urinary collecting system. The patient was a 22-year-old primagravid who experienced sepsis and flank mass two days after a normal vaginal delivery. Angiography and retrograde pyelography were used to observe significant bilateral occlusion of the lower pole moieties and subsequent hydronephrosis in those areas [3]. The group described a spherical mass that contained a curved segment of thickened calcification that blocked flow from lower aspect of the left kidney, and a significantly large inflammatory mass that blocked the lower portion of the right inferior renal fossa.

The treatment of vesicoureteral reflux and/or hydronephrosis in patients with some form of obstruction as a result of complications secondary to partial duplication of the urinary collecting system has been controversial. The standard operative procedure for such conditions has traditionally been heminephrectomy, in which case the dysfunctional pole of the kidney is removed, along with its associated ureter. The duplication of the ureter and the associated renal pelvis is the most common upper urinary tract variation in childhood. When heminephrectomy has been undertaken, in most cases the defunctionalized segment is often left in situ. In such cases, long-term follow-up has shown that leaving behind the problematic segment causes little to no problem. One study showed that later resection of the defunctionalized segment was unnecessary [4].

Another study analyzed the effectiveness of nonsurgical management of vesicoureteral reflux and/or hydronephrosis restricted to segments of kidney associated with duplication of the urinary collecting system. In that study, the group included unilateral and bilateral duplications, all of which were experiencing some form of reflux and dysfunction. Reflux was graded on a scale of I-V, and all groups were included in the analysis. The patients were divided into three groups: no treatment, antibiotics, and surgical intervention. Outcomes were shown to be statistically equal across the three groups, with the antibiotic group having less UTIs. These findings caused the investigators to conclude that conservative management of vesicoureteral reflux is preferred over surgical intervention [5].

Despite the obvious lean away from surgical intervention in the case of duplicated urinary collecting systems, a group of urologists showed that a new technique known as the modified psoas hitch with Lich-Gregorionlay is an effective technique for ureteral reconstruction. The group conducted a retrospective analysis of 20 patients that had undergone modified psoas hitch with Lich-Gregorionlay during reconstruction of the ureter. The group showed resolution of symptoms and no long-term sequelae such as chronic flank pain, recurrent pyelonephritis, hydronephrosis, or compromised renal function [6]. The technique was limited to ureteral reconstruction; however, the technique could be utilized in some cases of renal reconstruction in which a segment of kidney is defunctionalized while attempting to utilize the segment of ureter for the purpose of lengthening an existing ureter.

Our case study provides an uncommon anatomic variation and its associated pathology, which we utilized to illustrate the delicate and often controversial aspects of managing a patient with complicated duplication of urinary collecting systems with concomitant chronic pyelonephritis and persistent flank pain. Furthermore, the unusual nature of the variant in our case presents a unique clinical dilemma, and requires a thorough understanding of the condition, the associated complications, and the available treatment modalities to successfully manage the patient.

**MATERIALS AND METHODS**

In the routine evaluation of a 31-year-old Caucasian American female for chronic UTI and chronic flank pain, an anatomic variant was discovered on imaging studies. Multiple diagnostic tools were utilized in the study of this patient. Studies included abdominal and pelvic CT scans, Intravenous Pyelography (IVP), Voiding Cystourethrography (VCUG), Kidney Ureter and Bladder X-Rays (KUB), flexible cystoscopy, Bilateral Renal Ultrasonographies (RUS), cystourethroscopy with sounding, bilateral retrograde pyelographies with fluoroscopy, and ureteroscopy. Images used in this report (Figure 1-3) were obtained with screen capture during real-time fluoroscopy, which were printed off the machine. These images were scanned into a computer with an Epsom 420xi scanner. Subsequently, the images were imported into Microsoft PowerPoint and black boxes were used to obscure patient identifiers in respect to HIPAA laws and patient privacy. The images were not modified or altered in any other respect.

**RESULTS**

The aforementioned studies revealed an uncommon, bilateral duplication of the urinary collecting systems. Upper and lower pole collecting systems, each with their own ureter, were discovered in both kidneys (Figure 1-2). Chronic changes of the upper pole collecting system of the left kidney including hydroureter, caliectasis, and renal calculi were also observed. Furthermore, a large ureterocele, measuring 4 cm in length x 2 cm maximum transverse diameter, was observed in the distal portion of the left upper pole ureter (Figure 3). This ureter inserted into the proximal portion of the external sphincter muscle of the female urethra. Both left ureters were observed to be dilated (Figure 1).

**DISCUSSION**

Chronic UTI, chronic pyelonephritis, ureteroceles, hydroureter, caliectasis, chronic flank pain, and renal calculi are important conditions that each alone poses a threat to the kidneys. When they occur in concert, the threat is magnified, and the management complicated. Such a case has potentially devastating effects on the well-being of the patient. A treatment plan must be carefully constructed to include consideration for the best result with the least amount of invasive management as possible. The diagnosis of the anatomical variant in this case required a great deal of moderately invasive procedures, each with their own set of risks. Fortunately, the information gleaned was essential to rescuing the kidneys from the detrimental cycle that had already begun to damage them.

Ureteral duplication is the result of abnormal development of the Ureteric Bud (UB). For this discussion, we will focus on the processes behind complete ureteral duplication as opposed to partial duplication. The ureteric bud, induced by the metanephric...
mesenchyme, arises from the distal portion of the mesonephric duct around the 5th week of gestation. The UB further branches and elongates, developing into the ureter, renal pelvis, calyces, and collecting ducts. A wide array of genes is involved in the formation of the UB. The embryological basis of complete ureteral duplication may be explained by the development of two separate ureteral buds from a single mesonephric duct, either by increased induction stimulus or inadequate suppression of induction. Studies have shown that normal renal development depends on reciprocal interactions between the UB and metanephric mesenchyme. The metanephric mesenchyme stimulates outgrowth of the UB primarily through production of glial-derived neurotrophic factor (GDNF) [7]. GDNF, acts on its receptor c-RET, inducing proliferation and branching of UB cells. A GDNF-independent pathway has also been described; however, the exact mechanism has not been elucidated.

Individuals possessing Wilms tumor-1 (WT1) mutations show that induction of the UB fails despite GDNF presence [8]. Studies involving Six1-knockout mice have also demonstrated the failure of UB development despite normal expression of GDNF and WT1 [8]. These findings suggest an alternative induction mechanism that is independent of GDNF. Many genes play a role in this inductive process and abnormal increases in inductive stimulus is a possible explanation for formation of multiple ureteric buds. Another aspect associated with inductive signaling relates to the proper positioning of the UB and regulation of inductive stimuli. Several factors have been implicated in this process and will be discussed independently.

Separate negative regulators of UB formation include Bone Morphogenetic Protein 4 (BMP-4) and Sprouty1. BMP-4 expressed in the mesenchyme surrounding the mesonephric duct acts locally to inhibit ectopic budding by antagonizing GDNF [9]. Embryos lacking BMP-4 have been shown to have duplicated ureters [8]. Gremlin 1 is a suspected inhibitor of BMP-4. Studies show that development arrests at the UB stage in Gremlin 1-deficient mice embryos, and, when cultured with Gremlin 1 ureteric epithelial outgrowth is restored and several supernumerary buds result [10]. Sprouty1 is a negative regulator of a downstream signaling cascade activated by GDNF. Studies show that embryos lacking Sprouty1 have supernumerary UB formation [8]. FoxC1 is produced by the metanephric mesenchyme adjacent to the mesonephric duct and acts to restrict the activity of GDNF. Loss of FoxC1 is associated with ectopic ureteric buds and formation of duplicated ureters [8]. Similar proteins regulating location of bud growth include ROBO2 and Slit2. Slit2 is a factor secreted from the mesonephric duct which acts on its receptor ROBO2 in the metanephric mesenchyme. Similarly, deficiencies in Slit2 or ROBO2 are associated with ectopic UB formation [8]. However, studies show that, unlike cases with FoxC1 deficiencies, ectopic ureters resulting from ROBO2 or Slit2 deficiencies failed to undergo normal development, and insertion into the bladder [8]. Fibroblast growth factors also appear to play an important role in ureter development. The loss of fibroblast growth factor receptor 2 (Fgfr2) in animal models often leads to multiple ureteric buds and anomalies, including duplicated ureters [11]. Normally, Fgfr2 is expressed in stromal cells adjacent to the mesonephric duct and main ureteric bud trunks and is important in ensuring that there is a single, properly positioned ureteric bud [11]. In one particular study involving mice with Fgfr2 deletions, 67% of the embryos had two ureteric buds from one mesonephric duct [11]. Deletion of Fgfr2 did not change expression of GDNF, BMP-4, or other major regulators of ureteric bud formation suggesting an alternative pathway in the process of appropriate development of UB and eventual ureter formation and insertion [11]. Many different genes are involved with proper ureteral development, and an alteration in any step of the process could result in duplication of the urinary collecting system.

Our patient had learned to cope with most of her symptoms and only sought treatment when the pain was unbearable or when she developed systemic symptoms, such as the hyperthermia associated with her chronic pyelonephritis. This behavior is typical of a patient dealing with a life-long illness, but it presents the possibility that while she sought treatment for significant illness, she was not seeking treatment for minor and moderate symptoms. Mild and moderate renal diseases are significant with respect to the health of the kidneys, as well as the problems associated with damage to the renal system, and should be investigated whenever possible. The kidneys have an amazing amount of reserve capacity that allows them to perform their function in the face of constant chemical and mechanical insults. The downside to the fantastic renal reserve is that kidney disease is often not detected until significant damage has already occurred. We were compelled to obtain the full picture of what was troubling our patient as she had already experienced at least two decades of chronic insult to her renal system.

Complete metabolic profiling of the patient’s blood revealed good renal function, which was encouraging to the patient and our team. However, the process does not end there. The difficult decisions remained, as any of the potential treatments could fail to resolve the chronic pain and dysfunction despite invasive and irreversible surgical methods, such as nephrectomy. Removing the kidney of an overall healthy young woman, in order to relieve pain, is never an easy choice, and should not be undertaken without scrupulous examination of all the clinical data. Likewise, the potential for extensive surgical interventions to fail to correct the presenting symptoms provide reasons for additional pause before initiating such therapies. Two of the most important goals of medicine are to relieve suffering and to do no harm. Nephrectomy, or heminephrectomy, would undoubtedly predispose the patient to future complications with only one functional kidney. However, many people live a full life of normal longevity with one healthy kidney, but the potential exists for future insults to the renal system to put the patient in a dangerous clinical state. Therefore, such a serious therapy should ideally have a high probability of success in order to give the patient a favorable prognosis. Removal of the dysfunctional segment of kidney would correct the mechanical problem creating chronic infection in the urinary tract. This could likely reduce the chronic pain syndrome affecting the patient’s life. Unfortunately, chronic pain syndromes can persist after removal of the perceived offending agent.

Education of the patient and informed consent are equally important aspects of the management of a surgical candidate. The patient has a right to have their disease explained in understandable terms. The discussion of treatments available...
to them, as well as the possible complications associated with the treatments, is also required. In the case of our patient, after several evaluations and multiple discussions with the medical director of urological surgery, a conservative method of treatment was agreed upon. Six months of antibiotic therapy and opioid analgesia were initiated in the hope that clearing the chronic infection would alleviate the stress on the system, and subsequently alleviate the debilitating pain afflicting the patient. Follow up at six months for reevaluation of the disease process would provide the opportunity to discuss the future direction of therapy. Unfortunately, the patient experienced reinfection and significant pain refractory to opioid therapy only one month after agreeing to conservative management. While she refused surgical intervention at that time, it is unlikely that she will be able to avoid the operating room altogether. These events highlight the difficult nature of such a clinical presentation involving complicated duplication of urinary collecting systems.

ETHICAL STANDARDS

All experiments and endeavors related to this investigation were conducted in accordance with the laws of the State of Texas, United States of America.

REFERENCES


