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A Patient with Vesicoureteral Reflux Due to Neurogenic Bladder with Complications of Chronic Kidney Disease

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Abstract: Vesicoureteral reflux (VUR) is the backward flow of urine from the bladder into the upper urinary tract and is more commonly observed in children compared to adults. Adult-onset VUR is relatively rare and often linked to secondary causes such as neurogenic bladder or post-surgical complications. This case report presents a 56-year-old male patient with secondary VUR due to neurogenic bladder, complicated by chronic kidney disease (CKD) stage V. The patient exhibited symptoms including increased urinary frequency, difficulty controlling urination, and pubic pain. Diagnostic findings included severe hydronephrosis, detrusor overactivity with small bladder capacity, and lumbar spondylosis with nerve root compression. Management involved medical therapy with antimuscarinic agents and preoperative hemodialysis to optimize renal function. Surgical intervention was recommended, but the patient opted for continued regular hemodialysis. This case underscores the importance of early diagnosis and integrated. management of VUR and its complications to prevent CKD progression. **Case report:** A 56-year-old male presented with chronic urinary frequency and discomfort, significantly disrupting daily activities. Medical history revealed recurrent episodes over three years, worsening recently. Imaging and diagnostic evaluations showed severe hydronephrosis and evidence of neurogenic bladder due to lumbar nerve compression. Laboratory tests indicated CKD stage V, with anemia, elevated creatinine, and proteinuria. Treatment included solifenacin and preoperative hemodialysis, but the patient declined surgery. Regular dialysis was initiated as the primary management. **Discussion:** The etiology of adult-onset VUR is often secondary to structural or neurological abnormalities. In this case, lumbar spondylosis led to neurogenic detrusor overactivity, causing reflux and subsequent renal damage. Pathophysiology involves bladder dysfunction and intrarenal reflux, which aggravates kidney scarring. Integrated care, combining medical and potential surgical management, remains critical in mitigating disease progression. **Conclusion:** This case highlights the complexity of secondary VUR in adults, emphasizing the need for a multidisciplinary approach to management. Early identification and tailored treatment are pivotal in preventing severe complications like CKD.

Keywords: Vesicoureteral Reflux, Neurogenic Bladder, Chronic Kidney Disease, Hydronephrosis, Lumbar Spondylosis

INTRODUCTION

Vesicoureteral reflux (VUR) is much more commonly encountered in children compared to the number of adult patients. The incidence of vesicoureteral reflux decreases with age (1). A study described the incidence rate as 49% in the group of children under 1 year of age, then 26% in children under 12 years old, and only 4.4% in adults with vesicoureteral reflux (2). Although the incidence of vesicoureteral reflux is relatively low, the fact remains that 10% of this group eventually develops chronic kidney disease. Other complications of vesicoureteral reflux include hypertension, proteinuria, urinary tract infections, and kidney stones (3).

In other adult patients who are vulnerable to vesicoureteral reflux, the groups include those who have undergone cystectomy with the formation of urostomy, post-kidney transplant patients, and patients with neurogenic bladder due to spina bifida, as well as pregnant women (4). Among the various risk factors mentioned above, the most common are pregnancy and patients with a predisposition to infections. In women, most complaints are related to urinary tract infections, while in men, the common complaints are associated with chronic kidney disease such as hypertension and proteinuria. Patients with acute onset vesicoureteral reflux in childhood mostly do not experience spontaneous recovery as they grow older. Therefore, early detection and proper treatment of vesicoureteral reflux can prevent secondary complications such as chronic kidney disease (5).

The following is a case report of a patient with vesicoureteral reflux complicated by chronic kidney disease, reviewed from the aspects of diagnosis, therapy, and progression prior to surgery. This report aims to enhance our understanding of the diagnostic aspects, etiology, and pathophysiology of vesicoureteral reflux in relation to chronic kidney disease, as well as the connection between the neurological aspects of the disease and urinary disorders (reflux).

METHOD

A 56-year-old man, a Hindu of Balinese ethnicity, married and working as a lecturer, came to Sanglah Central General Hospital with complaints of increased frequency of urination, to the point that the patient felt disturbed. In Balinese, this condition is commonly referred to as "anyang-anyangan." The patient had been experiencing these symptoms for quite some time, estimated to be over six months with intermittent episodes, and they worsened three months before hospital admission. In addition to the frequent urge to urinate, the patient reported difficulty controlling the onset of urination, with the urge becoming more frequent than normal, sometimes up to three times within a 30-minute period at its worst. The patient felt very disturbed and frequently attempted to hold in the urge to urinate, which eventually led to painful urination, pain in the pubic area, and intermittent fever within the week before being admitted to the hospital.

The patient has a past medical history of similar complaints, which have been occurring frequently for the past three years and were noted to worsen during the most recent hospital admission. Two years ago, the patient was diagnosed with kidney stones, which spontaneously passed after treatment. Additionally, the patient has undergone DJ stent surgery twice, but neither of these procedures successfully alleviated the main symptoms that persist to this day. The patient denies any history of similar complaints during childhood. The patient also denies any accompanying conditions such as hypertension, heart disease, or diabetes. Additionally, the patient denies any family history of similar conditions.

On physical examination, the patient appeared to be in moderate pain, with a compos mentis level of consciousness. Blood pressure was 150/90 mmHg, pulse was 88 beats per minute, respiratory rate was 20 breaths per minute, and axillary temperature was 36.7°C. The visual analogue scale (VAS) for pain was 3 out of 10, and the patient's weight was 60 kg. General physical examinations of the heart, lungs, and abdomen were within normal limits, but tenderness over the symphysis pubis was noted.

Laboratory tests revealed the following results: hemoglobin level was 8.72 g/dL, platelet count was 254 x 10^3/µL, and leukocyte count was 9.24 x 10^3/µL. The HBsAg and Anti-HCV tests were non-reactive. The cholesterol panel showed total cholesterol at 133.9 mg/dL, HDL at 33 mg/dL, LDL direct at 68 mg/dL, and triglycerides at 88 mg/dL. Uric acid levels were elevated at 8.5 mg/dL. Serum iron was 133.9 µg/dL, and the total iron-binding capacity (TIBC) was 191 µg/dL. Urinalysis indicated a specific gravity of 1.015, pH of 5, leukocytes at 500 (+3), negative nitrites, protein at 75 (+2), negative glucose, negative ketones, negative urobilin, negative bilirubin, with many leukocyte and erythrocyte sediments noted. Blood chemistry tests showed an INR of 1.1, APTT of 33.7, GOT (AST) at 17 U/L, GPT (ALT) at 13 U/L, total bilirubin at 0.3 mg/dL, direct bilirubin at 0.1 mg/dL, total protein at 8.5 g/dL, albumin at 4.0 g/dL, fasting blood glucose at 80 mg/dL, BUN at 91 mg/dL, serum creatinine at 8.4 mg/dL, uric acid at 8.6 mg/dL, sodium at 140 mEq/L, and potassium at 4.6 mEq/L.

On the posteroanterior chest X-ray, no abnormalities were detected. The MRI results showed lumbar spondylosis with posterior disc bulging at levels L1, L3-4, and L4-5, causing mild compression of the anterior thecal sac, narrowing of the neural foramina on both the right and left sides, and compression of the exiting nerve roots at L1, L3, and L4 on both sides.

The contrast-enhanced CT scan revealed severe hydronephrosis of the left kidney with partial non-function in the upper and middle poles, while the lower pole remains functional. The right kidney shows mild hydronephrosis without stones, along with kinking in the proximal third of the right ureter. Additionally, aortic atherosclerosis and lumbar spondylosis were noted. The ultrasound confirmed severe hydronephrosis in the left kidney.

The voiding cystometry examination resulted in a diagnosis of neurogenic bladder with detrusor overactivity and small bladder capacity. Based on these findings, the use of antimuscarinic agents or intravesical botulinum toxin was suggested. Additionally, a bladder biopsy indicated chronic non-specific cystitis.

Based on the history, physical examination, and supporting tests, the patient was diagnosed with chronic kidney disease (CKD) stage V due to reflux nephropathy, mild normochromic normocytic anemia related to CKD, controlled hypertension, vesicoureteral reflux with spastic-type neurogenic bladder, and suspected urinary tract infection (UTI).

The latest therapy provided included 0.9% NaCl at 12 drops per minute, a diet of 35 kcal/kg body weight per day, and protein intake of 0.8 grams/kg body weight per day plus additional protein to compensate for losses. The patient was also given oral candesartan 8 mg once daily. Previously, the patient had been prescribed solifenacin succinate 5 mg once daily, but since the main symptoms did not improve with this antimuscarinic agent, a urological surgical procedure was planned. Preoperative hemodialysis was to be performed until serum creatinine levels dropped below 7 mg/dL. However, during the course of treatment, the patient ultimately refused the surgery and proceeded with regular hemodialysis.

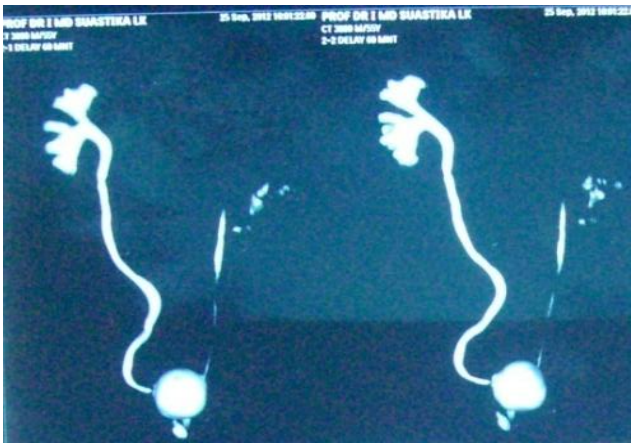

Figure 1. Kinking of the right ureter (proximal 1/3) from the RPG examination.

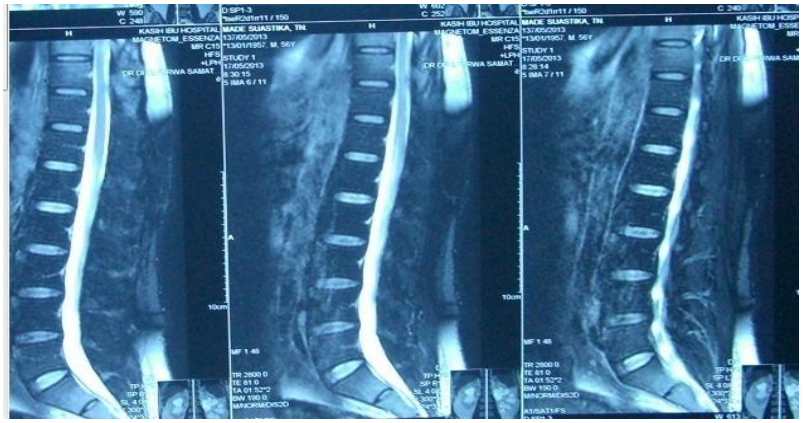

Figure 2. Illustration of lumbar compression from the MRI.

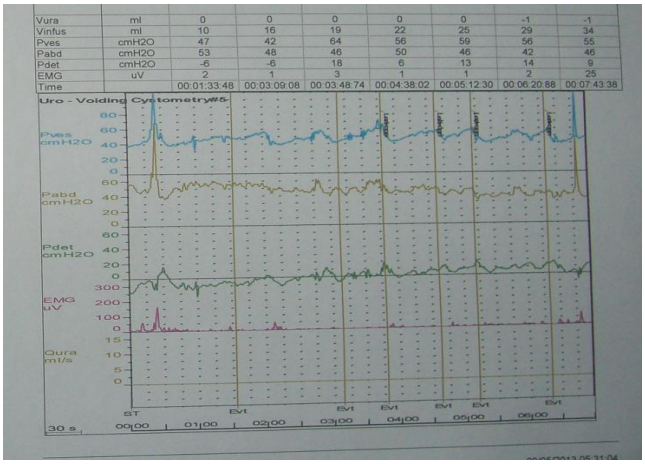

Figure 3. Illustration of voiding cystometry showing overactive bladder and small bladder.

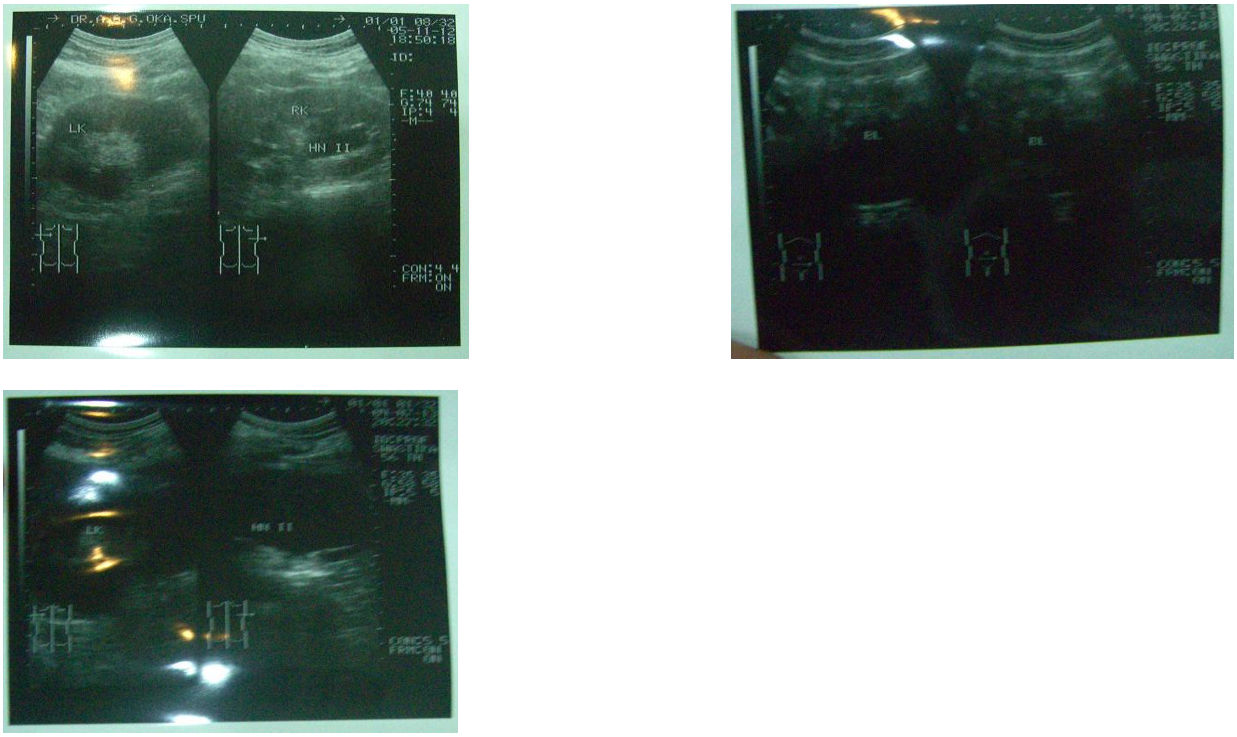

Figure 4. Urological ultrasound of the patient.

RESULT AND DISCUSSION

Vesicoureteral reflux (VUR) is defined as the backward flow of urine from the bladder into the kidneys. It is classified into two types: primary and secondary. The primary type is the more dominant form. Primary vesicoureteral reflux occurs without any underlying disease. On the other hand, secondary vesicoureteral reflux occurs as a result of another ongoing condition, such as obstruction, surgical interventions, or neurological abnormalities in adults (6). In this case, based on a more detailed history and heteroanamnesis, there was no history of obstruction or operative procedures like transplantation, making it likely that this case is a form of secondary VUR with a suspected neurological cause.

VUR occurs in approximately 1–2% of the general population, with an increased incidence among siblings. In patients with congenital VUR, the majority experience resolution before reaching adolescence. Differentiating between VUR with adult onset and VUR with childhood onset is often challenging. As a result, many adults with VUR may not clearly recall a history of urinary tract infections (UTIs) during childhood and only recognize those episodes as acute during adulthood. In this case, the patient reported no history of incontinence or recurrent UTIs during childhood, with all symptoms appearing in adulthood. There is limited data available regarding VUR symptoms during childhood in this case (6, 7).

There is an estimate in a study by El Khathib (1990), where the ratio of female to male VUR patients is 5:1 (8). Meanwhile, in the group of VUR patients aged 60-70 years, there is an increase in the incidence rate of VUR, which is likely caused by the rise in bladder obstruction cases in men of that age group (9, 10). Renal transplant recipients may suffer from both primary and secondary types of VUR (11, 12).

A normal micturition process requires coordination and function of the bladder and urethra, including the detrusor muscle and the urethral sphincter. The micturition process is regulated by the central nervous system, with coordination from the sympathetic, parasympathetic, and somatic nervous systems. Urinary dysfunction in relation to VUR continues to be studied, with various causes

including structural or mechanical causes or structural abnormalities of the urinary tract that lead to sphincter instability in the effort to regulate bladder pressure. Damage or disease affecting the central nervous system and/or the peripheral autonomic nervous system can result in dysfunction known as Neurogenic Bladder. This dysfunction is found in 40% to 90% of patients in the United States with Multiple Sclerosis, 37% to 72% of patients with Parkinson's, and 15% of stroke patients (21).

Neurogenic bladder also occurs in patients with diabetes mellitus with autonomic neuropathy, as a side effect of pelvic surgery, and Cauda Equina Syndrome due to pathological causes of the spine (21). Most patients with multiple sclerosis, cerebrovascular trauma, and spinal cord injury experience involuntary bladder contractions, with various complaints ranging from urinary incontinence, increased urinary frequency, and urgency in urination (22). Inadequate management increases the risk of infections, vesicoureteral reflux (VUR), and ultimately leads to chronic inflammation and progression to chronic kidney disease (CKD).

In this case, the MRI examination results showed lumbar spondylosis with posterior disc bulging at levels 1, 3–4, and 4–5, causing mild compression of the anterior thecal sac, narrowing of the right and left neural foramina, and compression of the exiting nerve roots 1, 3, and 4 on both sides. In the neurogenic bladder review, this is considered a supra-sacral lesion. The lesion causes detrusor overactivity, leading to complaints of incontinence. It also results in detrusor external sphincter dyssynergia, causing varying complaints such as urinary overactivity, urinary obstruction, and incomplete bladder emptying. The sensation of bladder filling may be reduced or remain normal, while lesions above thoracolumbar 6 will cause autonomic hyperreflexia (23). In this case, the predominant complaint is urinary overactivity, as shown in the voiding cystometry image..

Family history in cases of Vesicoureteral Reflux (VUR) is very important to investigate, as theoretically, the prevalence in family history ranges from 4.7% to 51% (13, 14). However, in this case, family history was denied, especially by the patient's siblings. The mechanism of primary VUR is thought to involve a weakness in the trigone muscle of the bladder, which results in the urethral orifice being positioned abnormally (15). The ectopic position of the ureter leads to a shortening of the detrusor muscle cycle. The valve becomes incompetent, ultimately causing urine to flow backward when intravesical pressure increases during bladder filling and during urination or bladder emptying.

The pathophysiology of primary Vesicoureteral Reflux (VUR) in pediatric patients compared to adult patients has not yet been fully explained. About 35% of adult patients with VUR have a history of recurrent urinary tract infections (UTIs) during childhood, accompanied by various complaints during the acute onset (7, 14). Adult VUR patients differ from pediatric VUR, as the chances of recovery being a self-limiting disease are very low (5). In adults, complications persist due to the existing reflux mechanism. Meanwhile, in pediatric patients, the reflux can also cause scarring in the kidneys, but over time, the scarring tends to disappear as the child grows (9).

his process is also not fully understood. It is suspected that the growth and maturation of the kidneys may still protect them from scar tissue formation. In adult patients with VUR, the onset and duration of primary VUR are often unclear, and secondary complications such as scarring and nephropathy only become evident at a very late stage in the disease course. In secondary adult VUR, the pathophysiology is explained as a result of damage to the ureteral orifice valve due to surgical interventions or neurological issues. In kidney transplant recipients, secondary VUR can arise due to poor implantation techniques (16).

In this case, it is a type of VUR with adult onset, consistent with the literature, where there is no history of surgical interventions or transplantation, but there is suspicion of a neurological lesion. Based on the anamnesis, it is concluded that the patient has secondary VUR. Pathologically, as previously explained, this case represents adult-onset VUR with the complication of end-stage chronic kidney disease, which was only discovered at an advanced stage.

In clinical presentation, VUR can occur asymptomatically. Broadly, there are two types of clinical manifestations. The first involves patients with VUR that has been present since childhood, asymptomatic and undetected, with complaints only emerging in adulthood after complications have developed. The second involves patients who develop VUR in adulthood without a history of urinary tract infections (UTIs) (8). In this case, it is still difficult to determine the onset of VUR in the patient, given the lack of a history of VUR during childhood. Most VUR complaints, such as UTI symptoms accompanied by frequent urination, began to be felt approximately three years before hospitalization and worsened in the three months prior to admission.

There are differences in the clinical manifestations of VUR in male and female patients. Most women are diagnosed with VUR primarily due to UTI-related symptoms, while other manifestations may include asymptomatic bacteriuria incidentally found during routine urine examinations, or some female patients may show no symptoms at all. Bacteriuria in women can be explained by the tendency due to the shorter urethra in females compared to males (17). Male patients with VUR tend to exhibit more complications, such as VUR-related nephropathy symptoms, including hypertension and proteinuria (18, 19, 20).

In this case, the patient experiences both types of symptoms previously described. Both male and female symptoms are present, as the patient shows UTI symptoms accompanied by nephropathy symptoms, evidenced by +2 proteinuria, incidentally found through urinalysis. However, in terms of onset, it is not possible to differentiate the patient's case.

In pregnant women with reflux nephropathy, both conditions greatly influence each other. More than half of pregnant women with VUR will experience complications during their pregnancy. Physiological dilation of the urinary tract and increased glomerular filtration cause pregnant women with VUR to be highly susceptible to UTIs, eclampsia, and kidney complications. Therefore, detecting VUR during pregnancy can also initiate screening for neonatal VUR, allowing for early therapy through early screening (4).

The study of the occurrence of VUR (Vesicoureteral Reflux) cannot be separated from the causality of the disease, especially secondary VUR, which is an acquired condition. In this case, it is secondary VUR with neurological causality in the form of structural abnormalities, specifically compression of the exiting nerve roots 1, 3, and 4 on both the right and left sides, involving compression of more than two exiting roots. Disorders from the rostral to the lumbosacral region will eliminate voluntary control and supraspinal control of urination, leading to the emergence of autonomic micturition and ultimately resulting in neurogenic detrusor overactivity. This is mediated by the spinal reflex pathway. Urination becomes inefficient due to the simultaneous contraction between the bladder and the urethral sphincter, known as detrusor-sphincter dyssynergia. (24).

In this case, detrusor overactivity can be clearly observed during the urodynamic cystometry examination, where the filling phase is not optimal due to overactive bladder contractions, as evidenced by the presence of unwanted contractions during the bladder filling phase, represented by recurring contraction graphs. Meanwhile, detrusor-sphincter dyssynergia in this case is indicated by EMG sphincter activity that is not synergistic with Pdet contractions, with both excessively contracting simultaneously. This leads to urinary retention, urine backflow, and the occurrence of VUR (Vesicoureteral Reflux).

The gold standard for diagnosing VUR (Vesicoureteral Reflux) should ideally be done using MCUG (Micturating Cystourethrography), where the contrast will clearly show the backflow of urine from the bladder to the kidneys. However, due to limitations in supporting tools in this case, VUR can still be diagnosed by analyzing the results of urodynamic cystometry. The recorded results in this case show that the excessive contractions are accompanied by leakage when the detrusor pressure exceeds 20 cmHg. The patient's detrusor pressure is suboptimal, ranging only between 12-20 cmHg, with an overactive contraction pattern. This is further supported by the evaluation of the

patient's total urine storage capacity, which only reaches 80 ml, or just a quarter of the normal capacity, referred to as Small Bladder Capacity.

The mechanism leading to end-stage kidney disease in VUR (Vesicoureteral Reflux) is highly complex. In animal models, when urinary flow obstruction occurs, the following developments in the kidneys can take place: impaired glomerular maturation, glomerulosclerosis, ischemia and necrosis of tubular cells, apoptosis of tubular cells and ductus coleductus, interstitial inflammation, proliferation and fibrosis, as well as tubular dilation and atrophy. Numerous studies have shown the occurrence of scarring on the papillae in individuals who experience intrarenal reflux (25).

In an abnormal intramural ureter (too short), the valve malfunctions, leading to VUR (Vesicoureteral Reflux). When the intramural segment is too short, urine flow tends to reflux back into the ureter. The kidney has two types of papillae: simple papillae (convex papillae) and compound papillae (concave papillae). Compound papillae dominate the kidney poles, while the rest are simple papillae. It is estimated that 66% of the papillae are convex, and 33% are concave. Structurally, simple papillae can prevent intrarenal urine reflux. In patients with uncorrected VUR, renal scarring will develop, ultimately accelerating the progression of renal damage. Renal scarring, which develops step by step, is worsened by persistent intrarenal reflux, eventually leading to kidney function impairment, hypertension, and proteinuria (25).

In this case, reflux nephropathy has caused a form of chronic inflammation, as shown in the patient's ultrasound image. The findings include an asymmetrical appearance, with grade II hydronephrosis in the right kidney, thinning of the right kidney cortex, and damage to the pelvicalyceal system, while the left kidney still shows a relatively thick cortex.

The principle of managing VUR (Vesicoureteral Reflux) in this case is an integrated approach that addresses both the underlying cause and the management of reflux nephropathy, along with treatment for complications related to chronic kidney disease (CKD) and urinary tract infections. Broadly, this includes both medical and surgical management. The causality of VUR in this case is neurogenic bladder (26).

In this case, overactive bladder is managed with the administration of antimuscarinic agents, one of which is Solifenacin. Medical management of neurogenic bladder is considered first-line therapy, aiming to reduce detrusor activity, increase bladder capacity, and either increase or decrease bladder outlet resistance. However, no studies have clearly demonstrated the effectiveness of these agents in resolving detrusor-sphincter dyssynergia. Monotherapy has been reported to be effective only for mild cases of neurogenic bladder, while in severe cases, intermittent catheterization and/or surgical intervention are recommended (26).

Surgical management includes ureteral reimplantation or the injection of synthetic polytetraethylene paste. Medical treatment involves antimicrobial therapy or prophylaxis for urinary tract infections (UTIs), as well as the use of antihypertensive agents. The choice of therapy can be adjusted based on the severity and indications. Long-term antibiotic use is not ideal, especially in young patients, where definitive surgical intervention is more recommended. In young patients who are pregnant, surgical intervention is also preferable to avoid various complications associated with medical therapy. Neves and Weton et al. in their study indicated that once renal scarring has formed, surgical intervention no longer provides significant benefits (27, 28, 29, 30).

To date, there is no definitive guideline for the management of VUR (Vesicoureteral Reflux) in adults. However, the American Academy of Pediatrics has recommended that MCUG and ultrasound be performed on all children who experience their first episode of a UTI as a form of screening. Improved understanding of VUR among medical professionals will facilitate early detection and prevention of various complications associated with VUR (31, 32, 33, 34).

CONCLUSION

A case has been reported of a 56-year-old patient suffering from VUR (Vesicoureteral Reflux) with advanced secondary complications, namely stage five chronic kidney disease. The diagnosis of VUR was made despite not using MCUG, as recommended by pediatric VUR guidelines. However, other supporting results, such as MRI and voiding cystometry, indicated the presence of VUR accompanied by a secondary cause, such as neurological abnormalities. These findings were further supported by clinical observations, all of which pointed to VUR in this case. Management was carried out in an integrated manner, addressing the underlying cause, definitive VUR therapy, and treatment of complications, including CKD and UTIs.

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