

Treatment of recurrent renal transplant lithiasis: analysis of our experience and review of the relevant literature

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Abstract

Background:Renal transplant lithiasis is a rather unusual disease, and the recurrence of lithiasis presents a challenging situation. **Methods:** We retrospectively analyzed medical history of the patient who suffered renal transplant lithiasis for two times, reviewed the relevant literature, and summarized the characteristics of this disease. **Results:** We retrieved 29 relevant studies with an incidence of 0.34% to 3.26% for renal transplant lithiasis. The summarized incidence is 0.52%, and the recurrent rate is 0.082%. The mean interval after transplantation is 33.43 ± 56.70 m. Most of the patients (28.90%) are asymptomatic. The management included percutaneous nephrolithotripsy (PCNL, 22.10%), ureteroscopy (URS, 22.65%), extracorporeal shockwave lithotripsy (ESWL, 18.60%) and conservative treatment (17.13%). In our case the patient suffered from renal transplant lithiasis at 6 years post transplantation, and the lithiasis recurred 16 months later. He presented oliguria, infection or ARF during the two attacks, but without pain. PCNL along with URS and holmium laser lithotripsy were performed. The patient had even recoveries after surgeries, except for a 3mm residual stone in the calyx after the second surgery. He had normal renal function without any symptom, and was allowed to discharge with oral anti-calculus drugs and strict follow-up at clinic. Fortunately, the calculus passed spontaneously about 1 month later. **Conclusions:** Due to lack of specific symptom in early stage, patients with renal transplant lithiasis may be delayed for diagnosis and present ARF. Minimally invasive treatment method was optimal, and combined usage of two or more procedures are beneficial for patients. After surgery taking anti-calculus drugs, correcting metabolic disorders and avoiding UIT are key measures to prevent the recurrence of lithiasis.

Background

Although renal transplant lithiasis is a rather unusual complication with the incidence of 0.2%-1.7% [1], we should not underestimate its severity since it can lead to disastrous consequence such as the loss of allograft without timely treatment [2]. Renal transplant recipients usually need to attend regular follow-up after transplantation for vigilant monitoring of allograft function. Therefore, part of the renal transplant lithiasis may be diagnosed during their follow-up without symptom. Early stage renal transplant lithiasis has less influence on allograft function. Unlike common kidney lithiasis, renal transplant lithiasis patient may not present obvious pain due to denervation of the allograft kidney [3]. Consequently, some severe renal transplant lithiasis patients without regular follow-up may not be diagnosed until they present hydronephrosis, fever, or ARF. In this situation, an emergent treat is necessary to avoid the loss of allograft.

Early diagnosis and appropriate therapy are essential to prevent aggravation for renal transplant lithiasis. If the renal calculus grows larger in size, even filling the inner hollow space of the kidney, or removes to the constriction site of ureter, ureteral obstruction and hydronephrosis will occur, and allograft function may deteriorate. As allograft compensatory function is weaker, ureteral obstruction can quickly lead to ARF, even loss of allograft, which is associated with high complication and mortality. Although some articles have been published on renal transplant lithiasis, few of them reported the treatment of recurrent renal transplant lithiasis.

In this study, we described a patient experiencing renal transplant lithiasis for two times, and the detailed process of attack, diagnosis and treatment. We also reviewed the relevant literature, analyzed the patient's characteristics, predisposing factors, symptoms, therapy, complications and outcome, and compared them with our case, so that we can have a full knowledge of this disease. As the renal transplant recipients have a relatively lower level of immunity, delay in diagnosis and treatment may result in severe infection. All physicians in this field should be alert to this rare but potential mortal disease to provide patients with the optimal management.

Methods

We collected the detailed data of our case with renal transplant lithiasis, including date of transplantation, anti-rejective medication, clinical presentation, laboratory test, imaging examination, therapy, and another process of diagnosis and treatment after recurrence. The electronic databases (Pubmed and Web of Science) were searched for relevant literature of clinical studies and case series excluding case reports and reviews published in English available from 2000 to 2019. The following keywords were used for the literature search: "renal transplant lithiasis / calculus" or "kidney transplant lithiasis / calculus" or "ureteral calculus / stone" or "urinary tract calculus" or "recurrence of lithiasis" or "recurrent lithiasis," in combination with "kidney / renal transplantation". The reference lists of these articles retrieved online were reviewed for potentially eligible studies. We extracted the data from all the relevant articles, summarized the patients' demography and symptoms, analyzed stone characteristics, treatment strategies, complications and outcomes, and then compared them with our case. So we can detailedly sum up the experience of management.

Results

Case presentation

A 35-year-old male with end-stage renal disease of unknown cause underwent cadaveric renal transplantation in our department 6 years ago. Both his parents and grandparents were healthy, and free of kidney disease. But his aunt received renal transplantation in another hospital when she was over forty. For lack of the kidney biopsy, we also did not know the exact etiology causing her to develop an end-stage renal disease. During the transplantation, we anastomosed the renal vein and artery to the right external iliac vein and artery, using 5-0 polypropylene in an end-to-side running anastomosis, and ureterocystostomy was performed in an end-to-side interrupted anastomosis with resorbable suture. The postoperative immunosuppression regimen consisted of tacrolimus, mycophenolate mofetil and prednisolone. The patient was followed at another clinic at about 8 months interval. There was no obvious abnormality except for medium microscopic hematuria for his latest follow-up. Unfortunately, the doctor in that clinic did not recommend further examination for him, so we had no idea about the source and morphology of red blood cells in urine. The patient did not have the history of hypertension, diabetes or hyperparathyroidism. Due to desk job he might lack adequate movements. He did not have bad lifestyle such as drinking alcohol or smoking, except for drinking Coca Cola (1 can per day) for 3-4 years. On the

6th year after transplantation the patient suddenly febrile with temperature 38.8°C and shiver, accompanied by oliguria with 400–500 ml urine/d and little gross hematuria. He was admitted to our hospital in emergency. Physical examination indicated that HR 92 bpm, Bp 131/88 mmHg, BMI 27.5 kg/m², and there was mild tenderness in the graft area. Blood chemical test presented that white blood cell (WBC) $7.37 \times 10^9/L$, lymphocyte 11%, neutrophil 79%, serum creatinine 4.04 mg/dl; Blood glucose 109.8 mg/dl; Serum uric acid 6.4 mg/dl; The blood calcium level 8.90 mg/dl. The pH value of the urine is 6.2. Computed tomography showed that there was a stone with the size of 18 mm in the ureteropelvic junction, which caused mild hypernephrosis (Fig. 1). An emergent operation was arranged, and in combination with efficient antimicrobial therapy. Ureteroscopy (URS) was performed in the lithotomy position and general anesthesia. Although we saw the new ureteral orifice in the dome of bladder, we could not insert the guide wire into the new orifice with 70° lens ureteroscopy due to the sharp angle of the new orifice and high resistance. We still failed although we switched to semirigid ureteroscopy. Therefore, we had to perform percutaneous nephrolithotripsy (PCNL) to remove the stones. The anterior calyx in the upper pole was chosen for puncture with an 18 G needle under guide of ultrasonography. When urine was aspirated, a 0.09 mm hydrophilic guidewire was inserted into the pelvicalyceal system. Then a 1.0-cm skin incision was made before the percutaneous tract was dilated over the guidewire to 18 Fr with a fascial dilator. After dilation a 18 Fr sheath was inserted as the percutaneous access port. Then a 18 Fr nephroscope was inserted through the sheath to inspect the pelvicalyceal system, and a 9.5–10 Fr flexible URS was used to inspect the ureter. Under direct vision a brown stone of 18 mm was located in the ureteropelvic junction. The stone can be fragmented by graspers. Larger fragments were extracted by forceps and smaller ones were flushed out with an endoscopic pulsed perfusion pump. After stone free was confirmed by the intraoperative ultrasonography, an 4.8 Fr double-pigtail stent was introduced. And a 14 Fr nephrostomy tube was placed. After operation the patient condition improved quickly, with normal temperature and gradually increased urine (2300 ml urine/day), and serum creatinine decreased to 1.65 mg/dl. The nephrostomy tube was clamped 3 days later when the drainage was clear, and then it was removed after clamping for 24 hours. The patient was discharged on 10 days postoperation with normal urine and serum creatinine, and stone free condition was confirmed by the ultrasonography. Double-pigtail stent was removed with the aid of cystoscope 4 weeks later. After discharged the patient was followed up every three months, and then every six months 1 year later. Besides no microscopic hematuria, there was no other abnormalities during follow-up. Unexpectedly, the patient admitted to hospital again on 16 months after operation for the similar symptom, including fever (39°C), shiver, anuria, but without pain. Blood chemical test indicated severe infection and ARF (WBC $8.14 \times 10^9/L$, lymphocyte 11.2%, neutrophil 84.2%, and serum creatinine 6.68 mg/dl; Blood glucose 113.4 mg/dl; Serum uric acid 6.6 mg/dl; The blood calcium level 8.82 mg/dl; The pH value of the urine is 5.7. CT demonstrated a 12 mm calculus in the proximal ureter with severe extension of ureter and hydronephrosis (Fig. 2). A 14 Fr percutaneous nephrostomy tube was firstly placed in emergency in order to promptly decompress and relieve the symptoms, in this time an interpolar middle calyx was accessed. Also the patient was treated in combination with efficient antimicrobial. Then the patient gradually restored, with normal temperature and about 1800 ml urine/day by through the nephrostomy tube, and serum creatinine decreased to 3.58 mg/dl. After the improvement of allograft

function, PCNL was performed. The nephroscope and flexible URS were advanced into the pelvicalyceal system or ureter through existing access tract. When a yellow-brown solid calculus was located in the ureter, holmium laser lithotripsy was performed and fragments of the calculus were completely removed using a stone basket, forceps or graspers. After confirming all stones were taken out, a 16 Fr nephrostomy tube was placed, but double-pigtail stent was not introduced. After operation allograft function was further improved with urine 1500 ml/day and serum creatine of 1.33 mg/dl. Percutaneous nephrostomy tube was removed 4 days later as mentioned above. Analysis of stone composition indicated uric acid calculus, so potassium sodium hydrogen citrate was recommended for the patient. Two point five grams 3 times a day, and take each dose after a meal. On 19th day postoperation, serum creatine decreased to 1.07 mg/dl. Ultrasonography indicated a hyperechogenic in the kidney. So a CT was performed again and indicated that there was a small residual stone with the size of 3 mm in the calyx (Fig. 3). The patient had a normal urine and renal function without pain and hematuria, and he was discharged with strict follow-up in clinic every one month, and then every three months 1 year later. Urinalysis was performed per month, and renal ultrasonography and renal function were performed every 3 months. The pH value of the urine was within the range of 6.0 to 7.0. As BMI of the patient was a little higher, we recommended he should lose some weight, do some exercise, and drink more water instead of Coca-Cola. Fortunately, the calculus passed through the urine tract spontaneously about 1 month later. Now the patient was healthy with normal allograft function and free of renal transplant lithiasis.

Twenty nine relevant studies were retrieved and analyzed [4–32], and the characteristics of these studies were listed in Additional 1. The incidence of the renal transplant lithiasis are between 0.34–3.26%. There are 551 cases with renal calculus except for 29 cases of bladder calculus and 1 case of urethra calculus. The number of renal transplant recipients included in these studies are ranged between 125 to 42096. After excluding the studies with missing number of recipients [5, 12, 13, 17, 18, 21, 24, 30], the summarized renal transplant lithiasis incidence is 0.52%. A total of 25 patients with recurrent renal transplant lithiasis after operation were reported in 13 studies [6, 8–10, 14, 15, 17, 20–22, 24, 26, 30], and the recurrent rate is 0.082%. The mean interval after transplantation is 33.43 ± 56.70 m. Figure 4A shows the distribution of stones locations. The patients with renal transplant lithiasis can present many kinds of clinical manifestations (Fig. 4B), but asymptomatic ones accounted for the largest proportion (28.90%). Except for donor-gifted stone (7.5%), the common etiologies of calculus are metabolic disorder (48.5%), infection (15%) and urinary obstruction (12.5%) (Fig. 4C). The management included PCNL (22.10%), URS (22.65%), Extracorporeal shockwave lithotripsy (ESWL, 18.60%) and conservative treatment (17.13%), et al. We also noted that stones passed spontaneously in 5.16% of patients, and open surgeries were performed only in 4.42% of patients. Twelve studies reported the stones composition were analysed (Fig. 4D). The most common calculi are calcium-based [54.54%, calcium oxalate stone (38.46%), calcium phosphate stone (16.08%)], followed by uric acid stone (14.69%), struvite stone (14.69%), mixed stone (12.59%). Fifty five patients with complications after transplantation were reported in 24 studies (Fig. 4E), the most frequent complication is residual stones (52.73%), followed by urinary tract infection (UTI, 21.82%), hematuria (7.27%) and sepsis (3.64%). Only one patient (1.82%) had to receive transplanted nephrectomy due to the serious illness caused by the renal calculus.

Discussion

According to the relevant studies retrieved in the database, the incidence of renal transplant lithiasis is lower (0.52%), and it is the least described urologic complication of renal transplantation. However, urinary obstruction caused by renal transplant lithiasis can even lead to a devastating loss of allograft without timely and appropriate therapy. We should pay more attention to this complication.

The etiology of renal transplant lithiasis includes donor-grafted, metabolic abnormality and mechanical factor. Renal transplant lithiasis identified within 6 weeks after transplantation are usually accepted as native to the donor kidney [33]. The increasing use of CT imaging in living donor assessment has given rise to an increased detection of asymptomatic renal calculus [34]. Nevertheless, the British Transplantation Society guidelines indicate that potential donors with a small renal calculus on imaging should be considered potential kidney donors if they do not have significant metabolic abnormality [35]. It is generally considered that renal calculus less than 4 mm could not be contraindication to donation even they are left in situ [15]. Therefore, in this case the donated kidney can be transplanted without removal of the stone. Ganpule thought that introduce of a ureteral stent can be useful to make the stone pass spontaneously [36]. For the donors after brain death, CT is not universally performed before operation due to the serious illness of donors. Therefore, the incidental renal calculus was found more often in deceased donors than that in living donors during procuring the donated kidney. Larger stones should be removed on the bench prior to transplantation. Both ESWL and nephrotomy can be performed to remove the stones prior to transplantation [37]. Nevertheless, Ex vivo ureteroscopy as a convenient procedure is recommended to retrieve the stones after kidney procurement [38]. The most common metabolic abnormalities contributing to renal calculus are hyperparathyroidism and hyperuricemia. Hyperparathyroidism usually exists in the patients with urimia due to the systemic metabolic abnormality. It leads to hypercalcemia which is one predisposing factor of renal calculus. Many of patients with urimia even suffer from native kidney stone before transplantation, although they are usually asymptomatic. Most of recipients present with hyperuricemia after kidney transplantation, which is one of side effects of immunosuppressive drugs. Norlen et al. considered that cyclosporin A produced hyperuricosuria in about 50–60% of patients receiving this medication for immunosuppression [39]. Also, ureteral stricture or obstruction due to unskilled surgical technique can lead to renal transplant lithiasis. Additionally, patients with UTI are more likely to suffer from renal stone, vice-versa, renal stone can lead to UTI. Unexpectedly, our case did not have any predisposing factors mentioned above. Moreover, he was even burdened by renal stone for two times. Based on the constituent of his calculus, we deduced that the level of uric acid in the urine maybe higher although it was normal in the blood. It's a pity that we did not detect the uric acid in urine.

The patient with renal transplant lithiasis usually has no specific symptom. They can present with oliguria, anuria, hematuria, urinary frequency, UTI, allograft dysfunction or even ARF, but seldom with graft pain. As we mentioned above, this can be attributed to denervation of the allograft kidney. Our data also demonstrated that only 3.18% of patients presented pain, and 28.90% of them were asymptomatic. Therefore, the patient usually would have a high propensity to be delayed for diagnosis. Our

case presented oliguria, anuria, UTI and ARF during the two attacks, but without pain. Due to lack of early manifestations, he was not diagnosed until the advanced stages of the disease. This also brought a huge impairment of the allograft, and the impairment would not be reversed if it was delayed for a few more days. Therefore, we recommend ultrasonography as routine examination during the recipients' follow-up, in order to detect the renal calculus in the early stage.

Management of renal calculus includes conservative treatment, ESWL, PCNL, URS and open surgery, and the choice of treatments depends on patient's symptom, the etiology, position and size of the stone. Challacombe et al. considered that treatment protocols for calculus in the transplanted kidney could mimic those for a solitary kidney [6]. Nevertheless, the management of transplant kidney lithiasis is more challenging and complicated. The renal transplantation recipients have lower immunological activity than general patients due to immunosuppressive drugs. They are more susceptible to all kinds of infection. Therefore, all the operation including surgery and anesthesia for the recipients should be performed with more caution. For patients with stone less than 4 mm and no presenting any symptom or urinary obstruction, it is more possible for stone to pass spontaneously, and conservative treatment can be chosen with close follow-up [16]. An alkalinizer drug can be recommended for patients with radiolucent stone and lower pH value of urine during the follow-up.

ESWL, as a non-operative treatment modality, is recommended for patients with stone less than 15 mm [40], and its most distinct advantage is that it can avoid risk of infection and impaired wound healing caused by surgery [32]. Nevertheless, some drawbacks of this treatment need to be noted. Firstly, the iliac bone adjacent to the transplanted kidney may potentially decrease the effectiveness of the shock waves. Secondly, it usually requires multiple sessions of operation to completely disintegrate the calculus, meaning possible impairment to the allograft. Thirdly, stone debris which are left in the kidney may potentially cause ureteral obstruction. Combination of ESWL and other auxiliary managements such as PCNL or URS can significantly decrease the disadvantages.

PCNL, as the most common operation, is used widely for the renal transplant lithiasis patients with stone size more than 2 cm or when ESWL failed [27]. PCNL is usually performed under general anesthesia in the supine position due to the special location of transplanted kidney. For the renal transplant recipients, the access to the pelvicaliceal system is usually punctured through an anterior calyx in the upper pole with the guide of ultrasonography. The serious perinephric fibrosis caused by immunosuppressive drugs increases the difficulty for puncturing and risks of bleeding [21]. And also the puncture location would become more fibrotic after the procedure. Therefore, we chose two different accesses to puncture for our case. Although the superficial location of the allograft is more easier to be accessed, it also increases the risk of bowel injury. This complication was reported by one of our retrieved studies [11]. This risk can be avoided with assistance of ultrasonography. During the surgery for our case, we employed both nephroscope and flexible URS, and in combination with laser lithiasis. Comparing with nephroscope, flexible URS can reach more far distance and has more advantages in treating ureteral stones. In fact, many kinds of other methods such as ESWL, scour, basket extraction and grasp can be performed as auxiliary procedures based on the position, component and size of the stone. In regarding to the impaired

renal function for this case, we chose laser lithiasis instead of ESWL to fragment the stone, since the former is more effective and less impact on the allograft function. Due to the proficiency in endourological technique, a modified mini-PCNL proposed by some authors provides an excellent treatment alternative [12, 41]. This technique should be recommended in well equipped centers with experienced surgeons since it can minimize the injury risk of the interlobar arteries of the transplanted kidney [42].

URS is another minimally invasive operation, which can be completed without any incision in the body. It is pretty appropriate for ureteral stone. As there is no exact anatomic position of bladder for ureteroneocystostomy, it is really difficult to locate new orifice by retrograde URS. Although orifice can be found sometimes, guide wire can not be inserted into transplanted ureter through the anastomosis. It was just like our case. In this situation, semirigid ureteroscope or with 70° lens can be tried to facilitate the process. If it still failed after several tries, switching into PCNL promptly to avoid unexpected injury to ureter due to repeated insertions. As the lack of connective tissue support of the allograft ureter can increase the risk of perforation when performing ureteroscopy, especially with a rigid scope [27]. Some articles reported 60%-67% success rate for extracting a ureteral stone by ureteroscopic management [29, 43]. URS along with holmium laser lithotripsy or basket extraction can increase the possibility of complete calculus removal. Ureteral stent is usually placed at the end of the ureteroscopic management [34]. It was considered that the stent can hold ureter open and conduce to pass of the residual stones. Although Branchereau et al. considered that stent is not a risk factor for early stone formation [5], we still suggest that patients with stent have a higher propensity to develop renal stone than ones without stent. So we did not place the stent after the second operation.

As the development of endoscopic techniques for management of urological lithiasis, the importance of open surgery is decreasing gradually. From the retrieved literature, we can see that the rate of open surgery is very lower (4.35%). Now very few patients with renal transplant lithiasis need an open surgery. Only when patients burdened by ureteral stricture or giant staghorn calculi can not be cured by other management methods, open surgery will be considered.

Every management has its own characteristics, and we should choose the optimal one for patients based on characteristics of stones and patients' general state. As the patients with renal transplant lithiasis are characterized by lower immunological activity, unusual anatomical position, and severe perirenal fibrosis, we should treat these patients with more caution and choose minimally invasive management. The combined usage of two or more procedures can raise the efficiency and decrease the negative impact on allograft. Based on our data, the most frequent complication is residual stones (52.73%). Therefore, we should try our best to remove all the calculi and avoid residual stones during the operation. Whether the stones were cleared should be verified by nephroscope or URS in combination with intraoperative ultrasonography. If it is impossible to remove all the stones, the small stone less than 4 mm can be left with close follow-up after operation. After removal of the stones, component of the stones should be tested to guide the medicine treatment to avoid recurrence of lithiasis. We think the most common reason for recurrence of lithiasis is exposure to predisposing factors

did not be reduced or eliminated after surgery. Repeated UTI after surgery and retained foreign body, such as stent and prolene suture, also contribute to the recurrence of lithiasis. Therefore, correcting metabolic disorders, treating UTI and removing the stent timely after surgery are pivotal to prevent the recurrence of lithiasis.

To our best knowledge, few articles reported the treatment protocols for recurrence of lithiasis in the transplanted kidney. We think it should mimic the protocol that was performed for them during their first attack. Minimally invasive surgery is optimal therapy if conserved treatment is not effective. We should choose a location different from the first one for puncturing when the second PCNL would be performed, and pay more attention to the operation since both surgery and anesthesia pose a potential threat to allograft function. Try best to remove all the stones and preventive drug therapy after operation is suggested according to the component of the stone. A close follow-up composed of renal ultrasonography, urinalysis and renal function is necessary, in this way the patients with lithiasis in the early stage can be detected timely. We would collect more cases in order to statistically analyze the risks for recurrence of renal transplant lithiasis in future.

Conclusions

Renal transplant lithiasis is unusual and special, as recipients taking immunosuppressive drugs are liable to infect. We should notice that these patients may be delayed for diagnosis and even present ARF as initial symptom since they usually do not have a symptom of graft pain. Based on the patients' characteristics combined usage of two or more minimal invasive procedures are beneficial to improve the efficiency and promote recovery after surgery. Patients should be rendered stone free at the end of the procedure. After surgery taking anti-calculus drugs, correcting metabolic disorders and avoiding UIT are key measures to prevent the recurrence of lithiasis. The patients are recommended to join the close follow-up and develop a healthy lifestyle with enough water intake and moderate exercise, especially for those with predisposing factors.

Abbreviations

ARF

acute renal failure; UTI: urinary tract infection; ESWL: extracorporeal shockwave lithotripsy;

PCNL: percutaneous nephrolithotomy; URS: ureteroscopy; PCN: percutaneous nephrostomy; BPH: benign prostate hyperplasia

Declarations

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Availability of data and materials

All data generated or analysed during this study are available from the corresponding author on reasonable request.

Authors' contributions

XL and JZ conceptualized and designed the study. XL wrote the manuscript. BL collected the data of the patient. YM and LY reviewed the literature and interpreted the data. GW analyzed the clinical data. HJ and JB critically revised the manuscript. JZ are corresponding author and organized the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethical Committee of First Affiliated Hospital, China Medical University(AF-SOP-2019-1.2-08). Written informed consent was obtained from the patient.

Consent for publication

Consent to publish from the patient was provided. A copy of the written consent is available for review by the editor of this journal.

Competing interests

The authors declare that they have no competing interests

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Figures

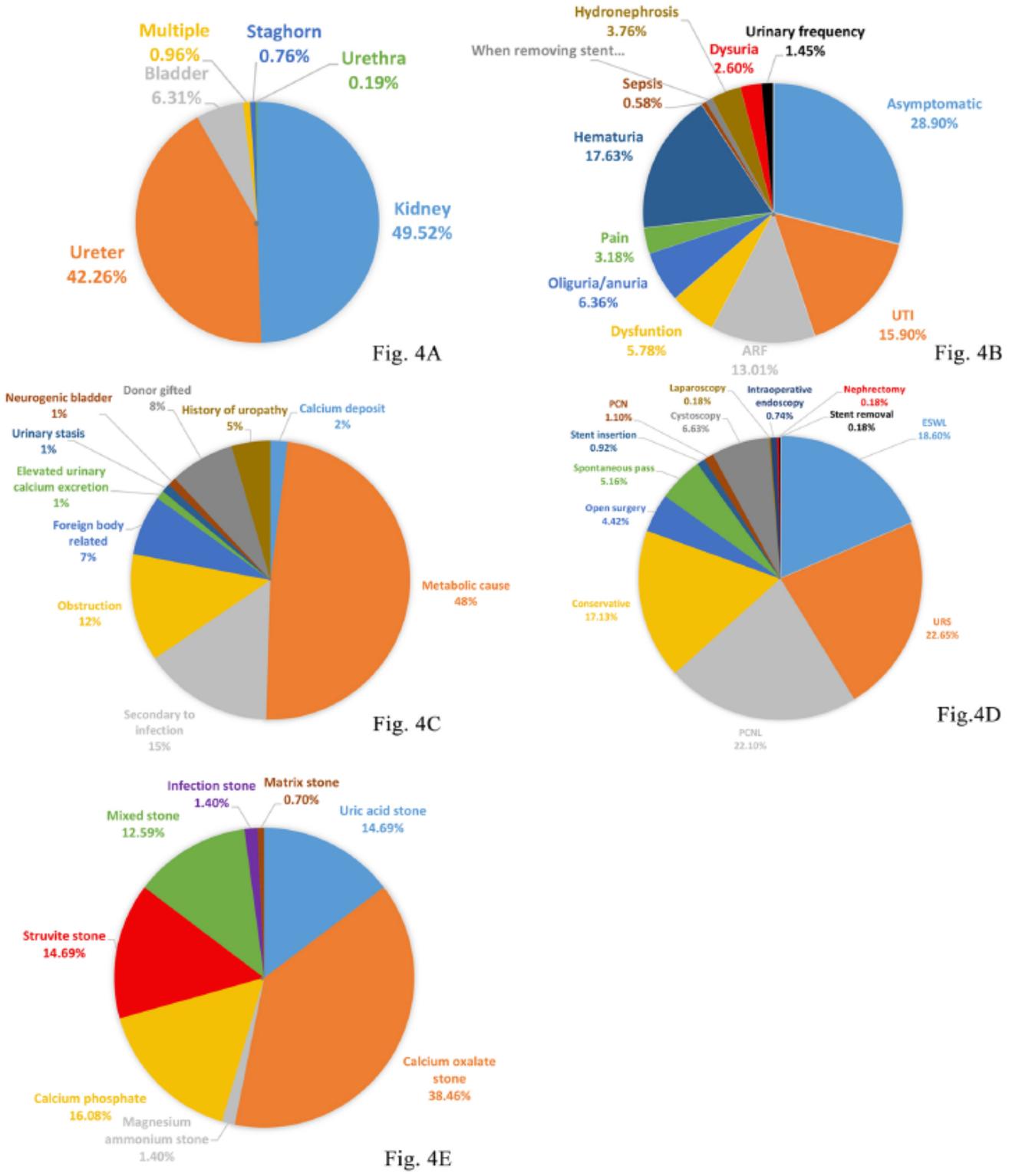


Figure 1

Characteristics of renal transplantation lithiasis and managements. (A) the distributin of stones locations, (B) the clinical presentation of patients with renal transplant lithiasis,(C) the etiologies of renal transplant lithiasis,(D) the managements of patients with renal transplant lithiasis, (E) the composition of transplanted kidney stones.