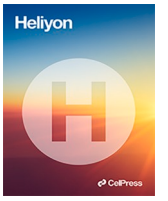
Heliyon 10 (2024) e30294

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Case report

Vesicoureteral reflux postoperative radical nephroureterectomy for upper urinary tract urothelial carcinoma: A case report

Mueataz A. Mahyoub [a,b,c,1,*], Bassam Musleh Yousef [d,1], Radman A.M. Ghaleb [e], Saleh Obad [f], Abdullatif Mothanna [g], Fayed Al-Yousofy [h], Mohamed Elhoumed [i,j], Mustafa Abbas [c], Mohammed Alnaggar [k,l], Mudan Ren [a,b], Shuixiang He [a,b,**]

[a] *Department of Gastroenterology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China*
[b] *Clinical Medical Research Center for Digestive Diseases (Oncology) of Shaanxi Province, Xi'an, China*
[c] *Department of Internal Medicine, Faculty of Medicine, Thamar University, Thamar, Yemen*
[d] *Department of Urology, Al- Ameen Typical Hospital, Ibb, Yemen*
[e] *Department of Urology, Faculty of Medicine, Taiz University, Taiz, Yemen*
[f] *Department of Anesthesiology, Al- Ameen Typical Hospital, Ibb, Yemen*
[g] *Department of Radiology, Ibb Scan Center, Ibb, Yemen*
[h] *Department of Pathology, Faculty of Medicine, Taiz University, Taiz, Yemen*
[i] *Department of Epidemiology and Biostatistics, School of Public Health, Xi'an Jiaotong University Health Science Center, Xi'an, Shaanxi, 710061, China*
[j] *National Institute of Public Health Research (INRSP), BP. 695, Nouakchott, Mauritania*
[k] *Department of Internal Medicine, Clinic Medical College, Hubei University of Science and Technology, Xianning, Hubei, China*
[l] *Department of Oncology, South Hubei Cancer Hospital, Xianning, Hubei, China*

ARTICLE INFO

Keywords:
Upper urinary tract urothelial carcinoma
Vesicoureteral reflux
Ascending cystography
Radical nephroureterectomy

ABSTRACT

Introduction: Primary Upper tract urothelial carcinoma (UTUC) is a rare subtype of urothelial carcinoma and has an unknown incidence and prevalence in Yemen. Radical nephroureterectomy (RNU) with bladder cuff removal is the standard treatment for UTUC.

Case presentation: We present a 67-year-old male patient who developed grade II vesicoureteral reflux (VUR) on the left side of the urinary tract after undergoing right-sided RNU for non-invasive UTUC. Follow-up examinations at one-, three-, and six-month post-surgery revealed no evidence of kidney diseases. The patient's recovery has been satisfactory, and ongoing regular follow-ups are being maintained.

Conclusion: Vigilant monitoring of VUR presence and effective management following RNU is crucial to minimize complications and preserve renal function. The underlying mechanisms linking VUR development and RNU remain unclear, necessitating further research.

* Corresponding author. Department of Gastroenterology, First Affiliated Hospital of Xi'an Jiaotong University, Clinical Medical Research Center for Digestive Diseases (Oncology) of Shaanxi Province, Xi'an 710061, China and Department of Internal Medicine, Faculty of Medicine and Health Sciences, Thamar University, Thamar, Yemen.

** Corresponding author. Department of Gastroenterology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China, and Clinical Medical Research Center for Digestive Diseases (Oncology) of Shaanxi Province, Xi'an 710061, China.

E-mail addresses: mz.abbas1989@qq.com (M.A. Mahyoub), dyyyjxk@mail.xjtu.edu.cn (S. He).

[1] They have contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e30294
Received 8 June 2023; Received in revised form 21 April 2024; Accepted 23 April 2024
Available online 26 April 2024

1. Introduction

Primary upper tract urothelial carcinoma (UTUC) is a rare subtype of urothelial carcinoma that arises in the upper urinary tract lined with urothelium. While the estimated incidence and prevalence of UTUC in Yemen are unknown, Western nations report approximately two cases per 100,000 people annually, with a peak incidence between the ages of 70 and 90, and men are affected at a rate twice as high as women [1]. The standard treatment for UTUC is radical nephroureterectomy (RNU) with the removal of the bladder cuff [2,3]. In addition to RNU, endoscopic management (EM) has been recognized as a beneficial approach in certain patient populations with low-risk UTUC. This includes patients with normal renal function, as well as those with isolated and/or impaired renal function. In cases of low-grade UTUC, the overall survival rates observed in patients receiving EM have been found to be comparable to those undergoing RNU. However, it is crucial to note that EM is associated with higher local recurrence rates. This necessitates long-term, strict surveillance, and potentially repeated interventions to manage these recurrences. The choice between EM and RNU should be made considering the patient's overall health, renal function, and the specific characteristics of the tumor [4]. However, the occurrence of vesicoureteral reflux (VUR) postoperative RNU has not been reported. This case report presents a patient who developed grade II VUR postoperative RNU, highlighting an uncommon complication of this procedure.

2. Case presentation

A 67-year-old male patient who was referred to Al- Ameen Typical Hospital, Ibb, Yemen, with a history of hypertension (HTN), diabetes mellitus (DM), myocardial infarction with percutaneous coronary intervention, and right inguinal herniorrhaphy presented with a ten-day history of painless gross hematuria with the passage of clots, which progressed to urinary retention. The patient had experienced hematuria for six months and was initially misdiagnosed with cystitis and prostatitis at a rural primary healthcare facility.

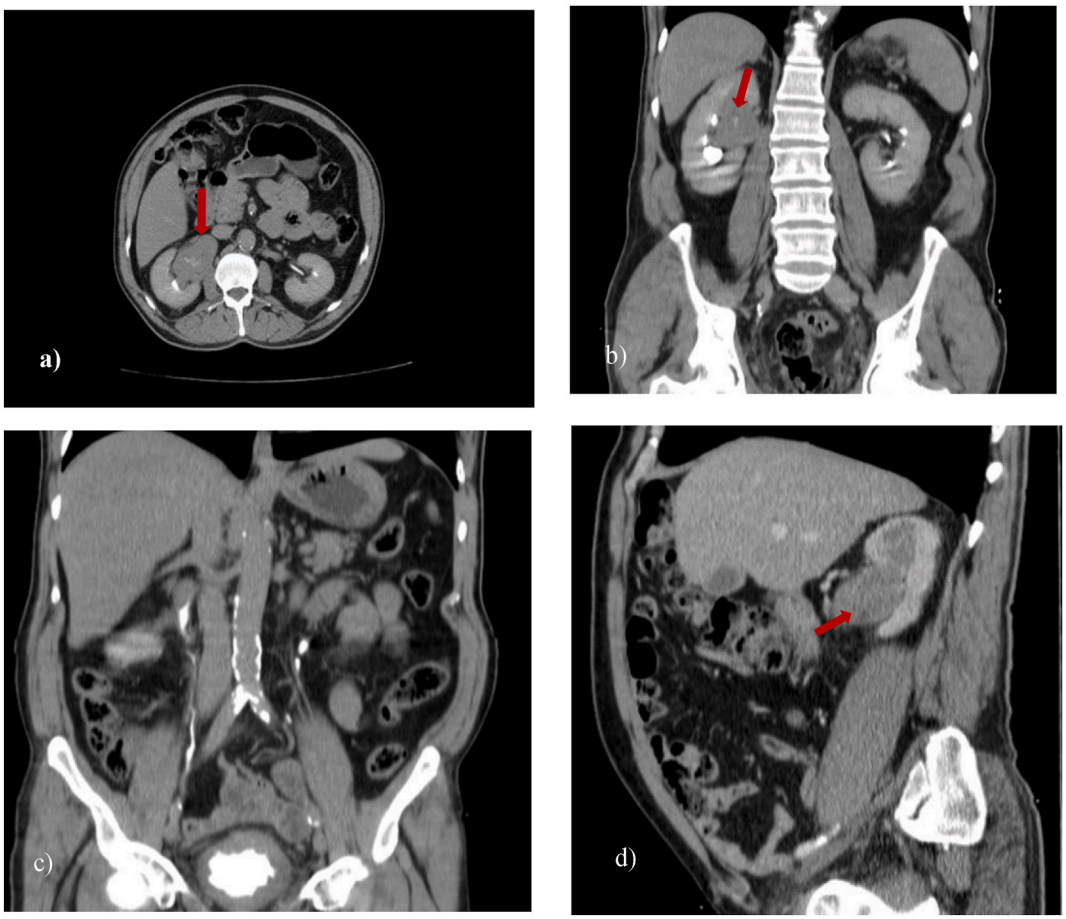


Fig. 1. (a–d) CT scans of the abdomen and pelvis delineating a renal lesion. (a) An axial CT scan of the abdomen revealed mild hydronephrosis of the right kidney resulting from a substantial focal lesion (arrow) in the renal pelvis extending from the proximal calyxes to the pelviureteric junction (PUJ). (b, c) A coronal sections CT scan of the abdomen and pelvis with contrast, the lesion appeared hypodense (arrow) and exhibited mild enhancement during the delayed phase of the contrast study. The lesion caused significant constriction, resulting in the lumen appearing as a large filling defect. (d) A sagittal section from a CT scan. No enlarged lymph nodes were observed.

The patient was a heavy smoker and chewed khat daily.

Physical examination revealed mild pallor with normal vital signs, and laboratory results showed a hemoglobin level of 10 mg/dl (normal range 13–17 mg/dl), serum creatinine of 1.2 mg/dl (normal range 0.6–1.2 mg/dl), and serum urea of 38 U/L (normal range up to 42 U/L). Abdominal ultrasound showed mild dilatation of the right renal pelvis with hypoechoic content, and abdominal CT imaging revealed a large focal lesion in the renal pelvis extending from the proximal calyx to the pelviureteric junction, causing mild hydronephrosis of the right kidney. The lesion appeared hypodense on non-contrast imaging and showed mild enhancement on the delayed contrast-enhanced phase. The lumen of the renal pelvis appeared significantly narrowed, with a large filling defect present. The absence of enlarged lymph nodes was noted (Fig. 1(a–d)).

Initially, a ureteroscopy with biopsy was recommended, but the family preferred to avoid multiple procedures and wait for the biopsy results. However, a radical nephroureterectomy (RNU) with bladder cuff excision was performed due to the urgent nature of the patient's condition. An 18-Fr Foley catheter was inserted into the bladder and was removed on the fifth day after the RNU procedure (Fig. 2 (a, b)).

Histopathological examination of the tumor involved microscopic examination of the complete specimen. The examination revealed that a papillary tumor measuring 6 × 6 cm filled the renal pelvis completely. A 13 cm long attached ureter was also identified, but no gross abnormalities were observed. The tumor was diagnosed as a low-grade papillary urothelial carcinoma, which was found to be confined to the renal pelvis without any evidence of invasion to the muscular layer of the pelvis, renal sinus, perinephric fat, or the ureter (Fig. 3(a and b)).

Following the RNU, chemotherapy was not administered to the patient following the oncologist's recommendation (B.A.M). On the first day post-RNU, the laboratory analysis showed serum creatinine of 2.2 mg/dl (normal range 0.6–1.2 mg/dl) and serum urea of 64 U/L (normal range up to 42 U/L). On the second day post-RNU, the laboratory results showed serum creatinine decreased to 0.8 mg/dl (normal range: 0.6–1.2 mg/dl), and serum urea decreased to 28 U/L (normal range: up to 42 U/L). Two weeks following the right-sided RNU, ascending cystography was performed, revealing grade II vesicoureteral reflux (VUR) on the left side of the urinary tract (Fig. 4 a, b). Renal function tests remained within the upper normal range at this time and subsequent intervals of one, three, and six months post-RNU. The patient's current health status is stable, and a follow-up CT scan is scheduled six months after the RNU procedure.

3. Discussion

UTUC is a rare urological condition that affects the renal pelvis and the ureter. UTUC differs from bladder urothelial carcinoma (UCB) in that more than half of patients present with the invasive disease at the time of diagnosis, compared to bladder tumors, where the proportion is only 20 %. RNU with excision of the ureteral orifice and the bladder cuff is the standard therapy for high-risk UTUC patients with a tumor in the pelvis or proximal ureter while kidney-sparing surgery is an option for Low-risk UTUC patients with a mid or distal ureteral tumor [5]. The spectrum of kidney-sparing surgical options, including ureteroscopic and percutaneous treatments, as well as segmental ureterectomy. These are often supplemented with adjuvant topical and intracavitary chemo-immunotherapies [4,6,7]. Notably, kidney-sparing surgery is a challenging procedure associated with higher rates of unfavorable outcomes than RNU [8].

Treatment for UTUC is selected based on the anatomical location, extent, pathological stage, and tumor grade, and kidney-sparing therapy is determined. According to the European Association of Urology (EAU) criteria based on clinical, endoscopic, radiological, and histopathologic considerations, UTUC patients are classified into low-risk and high-risk groups. Low-risk indicators include unifocal disease, tumors smaller than 2 cm, low-grade cytology and/or ureteroscopy biopsy, and non-invasive disease on imaging. High-risk conditions include hydronephrosis, multifocal disease, tumors measuring more than 2 cm in diameter, high-grade cytology and/or ureteroscopy biopsies, invasive disease on imaging, and a history of radical cystectomy [2,9].

Several intrinsic kidney risk factors and systemic comorbidities may influence UTUC. Baseline demographics, including age, sex, race, environmental factors such as nutrition, smoking status, and lifestyle, and genetic factors such as APOL1 variants, may all contribute to its development [10]. One of the most significant risk factors is tobacco smoking. Smoking increases the relative risk of

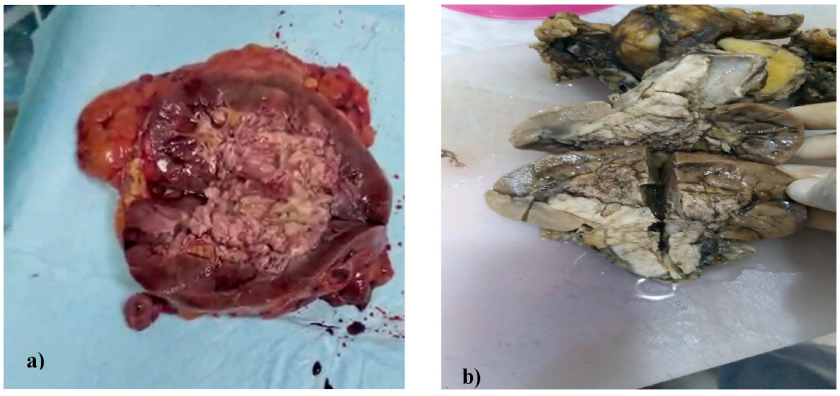


Fig. 2. (a, b) A Post-operative right-sided radical nephroureterectomy with bladder cuff. The tumor was filling the renal pelvis, and the surrounding renal tissue was free.

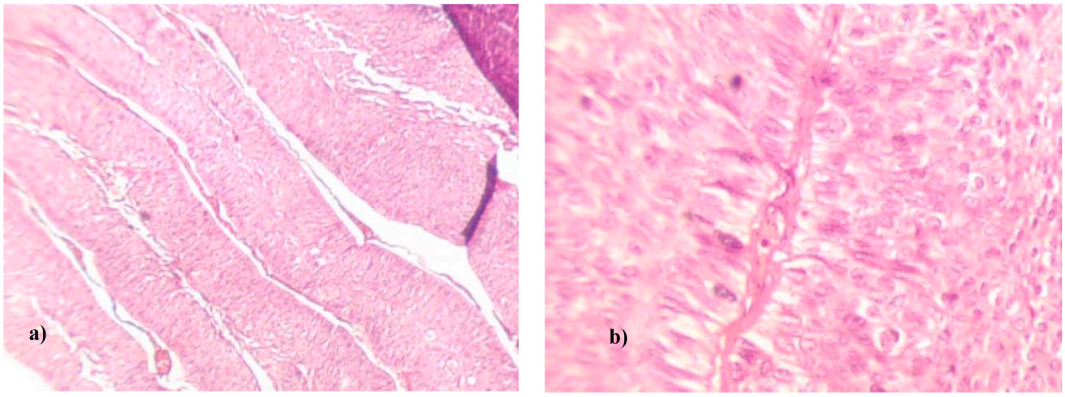


Fig. 3. Histopathology appearance of the tumor. a) Thin papillary structures with thin vascular connective tissue cores lined by multiple layers of urothelial cells. b) High power view of urothelial cells. Note the low-grade dysplasia.

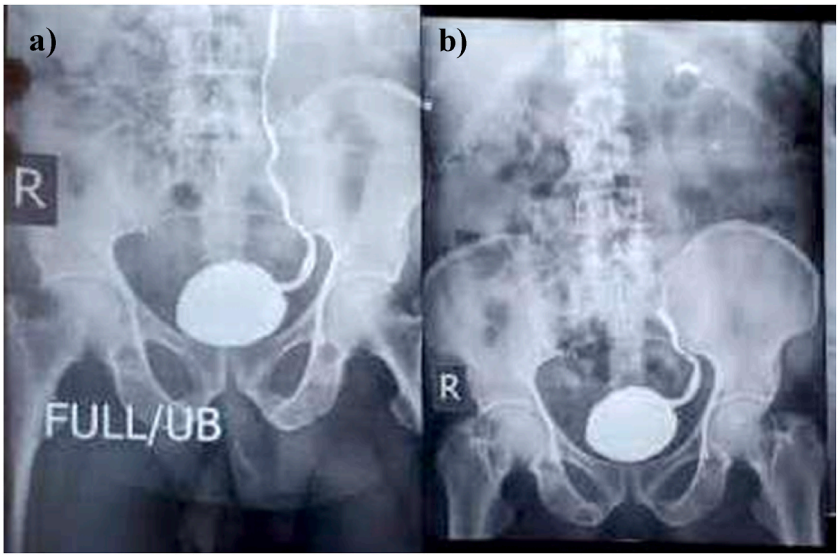


Fig. 4. Per-voiding cystography two weeks after a right-sided radical nephroureterectomy showed a second-degree left vesicoureteral reflux. a) Full blader. b) Post-voiding residue. R: right, UB: urinary bladder.

developing UTUC by 2.5–7 times, influenced by factors like the duration of smoking, the number of cigarettes consumed daily, and individual susceptibility to oxidative damage. Heavy smokers, those who smoke $\geq$40 cigarettes per day, are at twice the risk compared to lighter smokers. There's a notable reduction in risk for former smokers, with a 60–70 % decrease in relative risk after a decade of being smoke-free. Smoking not only advances the onset of UTUC by approximately five years compared to non-smokers but also escalates the risk of disease recurrence and cancer-specific mortality following RNU treatment. This risk is particularly pronounced in female heavy smokers, who exhibit worse survival outcomes than their male counterparts. Another significant risk factor is occupational exposure to diesel fumes and aromatic amines, such as Benzidine and β-naphthylamine, commonly used in dye, textile, rubber, and chemical industries, which is another major risk factor. The relative risk of developing UTUC after exposure to these substances is estimated at 8.3, with an average exposure duration of 7 years and a latency period of around 20 years. A critical discovery in recent years is the causative link between aristolochic acid and UTUC. This compound, derived from plants like Aristolochia fangchi and Aristolochia clematis, is endemic in the Balkans and was commonly ingested in traditional herbal remedies or through contaminated food. It's the primary agent causing Balkan endemic nephropathy and Chinese herbs nephropathy, leading to specific mutations in the p53 gene. Hereditary factors also play a crucial role, with familial or hereditary UTUC accounting for 10–20 % of cases. These are closely linked to hereditary non-polyposis colorectal carcinoma (HNPCC) or Lynch syndrome. Individuals with HNPCC are at a significantly increased risk, approximately 22 times higher than the general population, of developing UTUC [11]. Additionally, comorbid conditions like metabolic syndrome (including components like visceral obesity, glucose intolerance, hypertension, and hyperlipidemia) and DM can elevate the risk of UTUC [12,13]. These factors may lead to chronic kidney disease (CKD) in the non-neoplastic kidney parenchyma following RNU. Patients who have undergone RNU may have a higher incidence of CKD than the

general population [14,15].

VUR is characterized by the abnormal flow of urine from the urinary bladder back into the upper urinary tract [16]. The classification of VUR is based on the anti-reflux mechanism and function of the ureterovesical junction (UVJ) and can be categorized as primary or secondary VUR. Primary VUR is due to an inherent deficiency in the UVJ, while secondary VUR occurs due to increased bladder pressure despite a structurally normal UVJ. Primary VUR is commonly observed in infancy and childhood, whereas secondary VUR is typically seen in adults with neurogenic bladder dysfunction or bladder outlet obstruction, both of which increase the back pressure on the anti-reflux mechanism of the UVJ [17]. Cystourethrography is used to grade VUR severity into four grades. Low-grade reflux (grade I-II) usually resolves spontaneously [16]. Previous studies have reported the occurrence of VUR after kidney transplantation, with varying rates ranging from 40.7 % to 86 % and a significant reduction in estimated GFR (eGFR) levels at 1-year post-transplantation [18–20]. However, to our knowledge, no studies have reported the incidence of VUR following RNU. The exact mechanisms underlying the development of VUR following RNU remain elusive and may be multifactorial. Factors such as postoperative changes in bladder dynamics, including altered bladder capacity and compliance, could increase the likelihood of reflux. Inflammation and scarring resulting from the surgery can interfere with the normal function of the ureter.

Additionally, pre-existing, undetected VUR may become apparent after RNU. Neurological effects on bladder function due to surgical intervention, accidental damage during the procedure, and the patient's unique anatomical features might also play a role in the onset of VUR following RNU. It is unclear whether the reflux will naturally resolve or persist after recovery from RNU. Previous research suggests that VUR may change over time following kidney transplantation [21]. VUR and the development of CKD after RNU may be associated, but further studies are needed to elucidate this relationship.

Although specific guidelines for managing VUR following RNU are lacking, the literature suggests a personalized management approach. This approach considers factors such as the severity of VUR, the patient's overall health status, and any accompanying symptoms or complications.

For mild VUR exhibiting minimal symptoms and no significant renal function impairment, conservative management is appropriate. This strategy encompasses vigilant monitoring of renal health, periodic imaging to observe VUR progression, and potentially using prophylactic antibiotics to avert urinary tract infections [22].

For VUR cases that are symptomatic or threaten renal health, medical therapy is recommended. This involves using medications such as anticholinergics or alpha-blockers, which are aimed at improving bladder function and reducing bladder pressure, thereby potentially reducing the occurrence of reflux [23].

Surgical intervention is recommended for advanced cases (grade III VUR or higher), patients with recurrent episodes of pyelonephritis, or those showing signs of renal impairment or scarring. Surgical options include ureteral reimplantation to reposition the ureter and prevent reflux and endoscopic approaches involving the injection of bulking agents near the ureteral orifice [24,25].

Urodynamic evaluations are essential in the management of VUR. They assess bladder function and pressure, providing critical insights into VUR's underlying causes. This information is pivotal in guiding the choice of treatment and developing effective intervention plans tailored to the patient's specific condition [26].

Patient education and lifestyle changes are important in managing VUR. This approach involves educating patients about their condition and its potential impacts, emphasizing the importance of regular medical follow-ups. Advising lifestyle modifications, such as avoiding constipation and maintaining a healthy weight, can also help in reducing bladder pressure, contributing to the overall management strategy for VUR [27].

Ongoing monitoring and Follow-up are essential for evaluating VUR progression and renal health, necessitating regular medical check-ups, imaging tests like renal ultrasounds or voiding cystourethrograms, and urinalysis. For complex cases of VUR, especially those associated with recurrent UTIs or renal dysfunction, more intensive management strategies are often necessary. These may include a combination of medical and surgical treatments. In these challenging situations, a collaborative, multidisciplinary approach is crucial. Involving specialists such as urologists and nephrologists, along with other healthcare professionals, ensures comprehensive and effective patient care [16].

4. Conclusion

Histopathological analysis remains the gold standard for diagnosing upper urinary tract tumors. It is imperative to monitor patients who have undergone RNU for the development of VUR and manage it appropriately to minimize complications and preserve renal function. Further investigation is required to understand the relationship between VUR and RNU. Future research in this area may help to identify effective management strategies and improve patient outcomes.

Availability of data and materials

The clinical data utilized in this report are described in this article. For further details, the corresponding author can be contacted.

Consent for publication

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images.

Funding

Funding statement This work was supported by the Key Research and Development Plan in Shaanxi Province of China (2021ZDLSF02-06).

CRediT authorship contribution statement

Mueataz A. Mahyoub: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Data curation, Conceptualization. **Bassam Musleh Yousef:** Writing – review & editing, Writing – original draft, Resources, Investigation, Conceptualization. **Radman A.M. Ghaleb:** Writing – review & editing. **Saleh Obad:** Writing – review & editing, Visualization. **Abdullatif Mothanna:** Writing – review & editing, Resources. **Fayed Al-Yousofy:** Writing – review & editing, Resources, Investigation. **Mohamed Elhoumed:** Writing – review & editing. **Mustafa Abbas:** Writing – review & editing. **Mohammed Alnaggar:** Writing – review & editing. **Mudan Ren:** Writing – review & editing, Supervision. **Shuixiang He:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors extend their sincere gratitude to Abdu Ahmed Al-Hadad, the General Manager of AL- Ameen Typical Hospital in Ibb, Yemen for his support towards this work.

References

[1] D.H. Bagley, R. Tanimoto, K.A. Healy, Upper tract urothelial carcinoma: ureteroscopic biopsy and specimen preparation, in: Upper Urinary Tract Urothelial Carcinoma, Springer, 2015, pp. 1–15.
[2] M. Rouprêt, et al., European Association of Urology guidelines on upper urinary tract urothelial carcinoma: 2020 update, Eur. Urol. 79 (1) (2021) 62–79.
[3] J.J. Munoz, L.M. Ellison, Upper tract urothelial neoplasms: incidence and survival during the last 2 decades, J. Urol. 164 (5) (2000) 1523–1525.
[4] T. Kawada, et al., Oncologic and safety outcomes for endoscopic surgery versus radical nephroureterectomy for upper tract urothelial carcinoma: an updated systematic review and meta-analysis, Eur. Urol. Focus 9 (2) (2023) 236–240.
[5] J. Baard, et al., Diagnostic dilemmas in patients with upper tract urothelial carcinoma, Nat. Rev. Urol. 14 (3) (2017) 181–191.
[6] F. Esperto, et al., New technologies for kidney surgery planning 3D, impression, augmented reality 3D, reconstruction: current realities and expectations, Curr. Urol. Rep. 22 (2021) 1–9.
[7] K. Ni, et al., Immunotherapy with or without targeted therapy for metastatic upper tract urothelial carcinoma: case report and literature review, Heliyon 9 (5) (2023) e15813.
[8] H. Van Poppel, et al., A prospective randomized EORTC intergroup phase 3 study comparing the complications of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma, Eur. Urol. 51 (6) (2007) 1606–1615.
[9] M. Azizi, et al., Optimal management of upper tract urothelial carcinoma: an unmet need, Curr. Treat. Options Oncol. 20 (5) (2019) 1–11.
[10] M.G.K. Cumberbatch, et al., Epidemiology of bladder cancer: a systematic review and contemporary update of risk factors in 2018, Eur. Urol. 74 (6) (2018) 784–795.
[11] F. Soria, et al., Epidemiology, diagnosis, preoperative evaluation and prognostic assessment of upper-tract urothelial carcinoma (UTUC), World J. Urol. 35 (2017) 379–387.
[12] F. Cantiello, et al., Association between metabolic syndrome, obesity, diabetes mellitus and oncological outcomes of bladder cancer: a systematic review, Int. J. Urol. 22 (1) (2015) 22–32.
[13] M.A. Mahyoub, et al., Fatty infiltration of the pancreas: a systematic concept analysis, Front. Med. 10 (2023).
[14] L. Li, et al., Risk of chronic kidney disease after cancer nephrectomy, Nat. Rev. Nephrol. 10 (3) (2014) 135–145.
[15] J.D. Hunt, et al., Renal cell carcinoma in relation to cigarette smoking: meta-analysis of 24 studies, Int. J. Cancer 114 (1) (2005) 101–108.
[16] A. Salib, B. Rudnick, A.J.C.U.R. Murphy, Vesicoureteral reflux in adults with urinary tract infections: is there a role for treatment? Curr. Urol. Rep. 21 (10) (2020) 1–5.
[17] A. Khoury, D.J.C.-W.U. Bagli, Reflux and megaureter, Campbell-Walsh Urol. 4 (2007) 3423–3481.
[18] E. Favi, et al., Long-term clinical impact of vesicoureteral reflux in kidney transplantation, in: Transplantation Proceedings, Elsevier, 2009.
[19] G. Jung, et al., Clinical significance of posttransplantation vesicoureteral reflux during short-term period after kidney transplantation, in: Transplantation Proceedings, Elsevier, 2008.
[20] M. Margreiter, et al., Value of routine voiding cystourethrography after renal transplantation, Am. J. Transplant. 13 (1) (2013) 130–135.
[21] B. Ranchin, et al., Vesicoureteral reflux after kidney transplantation in children, Nephrol. Dial. Transplant. 15 (11) (2000) 1852–1858.
[22] J.C. Routh, et al., Vesicoureteral reflux: current trends in diagnosis, screening, and treatment, Eur. Urol. 61 (4) (2012) 773–782.
[23] J.C. Clothier, A.J.J.P.N. Wright, Dysfunctional voiding: the importance of non-invasive urodynamics in diagnosis and treatment, Pediatr. Nephrol. 33 (2018) 381–394.
[24] A.A. Friedman, M.K.J.T. Hanna, L.C.i.C. Urology, Vesicoureteral reflux and the adult, Trans. Lifelong Care Congenit. Urol. (2015) 173–205.
[25] A. Dinckan, et al., Surgical correction of vesico-ureteric reflux for recurrent febrile urinary tract infections after kidney transplantation, BJU Int. 112 (4) (2013) E366–E371.
[26] E. Altobelli, et al., Urodynamics investigation on children with vesicoureteral reflux identifies overactive bladder and poor compliance in those with voiding dysfunction, Pediatr. Surg. Int. 27 (2011) 517–522.
[27] D.L. Johnston, et al., Contemporary management of vesicoureteral reflux, Curr. Treat. Opt. Pediatr. 2 (2016) 82–93.