NU Rounds
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Dear Doctor,

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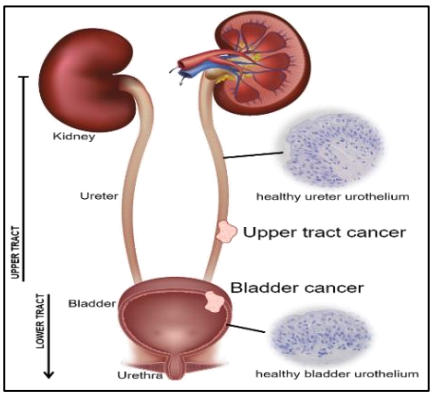
Relationship between pre-existing renal impairment and oncological outcomes in upper tract urothelial carcinoma

Introduction



Upper tract urothelial carcinoma (UTUC) is a rare yet aggressive cancer, representing about 5-10% of all urothelial cancers.[1] Bladder cuff excision combined with radical nephroureterectomy (RNU) is the gold standard treatment for localized UTUC offering a survival benefit regardless of a patient's age or comorbidities.[2] Studies have shown that several factors, such as prior cancer, tumor features like stage, grade, and lymph node involvement, and patient characteristics like age and body mass index, are predictive of a poorer oncological outcome.[3] Chronic kidney disease, or CKD, has recently been suggested as a predictor of poorer postoperative results and there was an association between renal insufficiency and other urological cancers. Studies have also indicated that CKD may be linked to a higher risk of bladder and prostate cancer recurrence. Additionally, in cases of renal cell carcinoma, it has been linked to an increased risk of papillary histology. CKD patients are at an increased risk of postoperative complications, including acute kidney injury and cardiopulmonary events, which may also have an impact on the patient's subsequent recovery.[3,4] So, this study investigated the relationship between pre-existing renal impairment and oncological outcomes in UTUC patients treated with radical nephroureterectomy (RNU).

Methods

This retrospective study comprised consecutive patients over the age of 18 who were diagnosed with non-metastatic UTUC and eventually received RNU treatment. Cases with inadequate follow-up results or those without documentation of renal function prior to surgery were excluded. Individuals who had previously developed bladder cancer were not excluded. Patient baseline characteristics, follow-up data and disease details were documented. Follow-up data, including check cystoscopy and imaging results up to 30 months after surgery, were recorded and analysed. Based on the evaluation of the specimen, the staging was reported. A patient was categorized as having chronic kidney disease (CKD) if their estimated glomerular filtration rate (eGFR) was less than 60 mL/min/1.73 m² and as non-CKD if it was greater than that. This dichotomous classification was based on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. The primary endpoints were overall survival and disease-free survival.

Results

Of the participated individuals, 528 (37.2%) were found to have chronic kidney disease, while 875 patients (62.4%) had a normal renal function, with a median follow-up of 9.2 months. Preoperative eGFR was 43.9 mL/min/1.73 m² in the CKD group and 78.6 mL/min/1.73 m² in the non-CKD group. The non-CKD group was younger, had slightly lower Charlson comorbidity scores, and showed comparable tumour characteristics, predominantly in the renal pelvis. Grade 3 histology was found in 57.4% of CKD and 49.7% of non-CKD patients. Most underwent robot-assisted or laparoscopic RNU (64.0% in the non-CKD group and 67.6% in the CKD group, p=0.505). Non-CKD patients had better 30-month disease-free survival (HR = 1.419; 95% CI = 1.060–1.898; p = 0.019) (Figure 1). Univariate analysis identified smoking history (HR=1.373, p=0.033), advanced tumour stage (HR=2.121, p=0.002), grade 3 histology (HR=2.340, p=0.003), prior renal impairment (HR=1.419, p=0.019), and adjuvant chemotherapy use (HR=2.274, p<0.001) as predictors of poorer outcomes. In UTUC patients, overall survival after RNU was significantly associated with tumour staging (HR=4.631; 95%CI=1.924–11.065; p=0.007) and cardiovascular disease (HR=1.892; 95%CI=1.971–3.340; p=0.028).

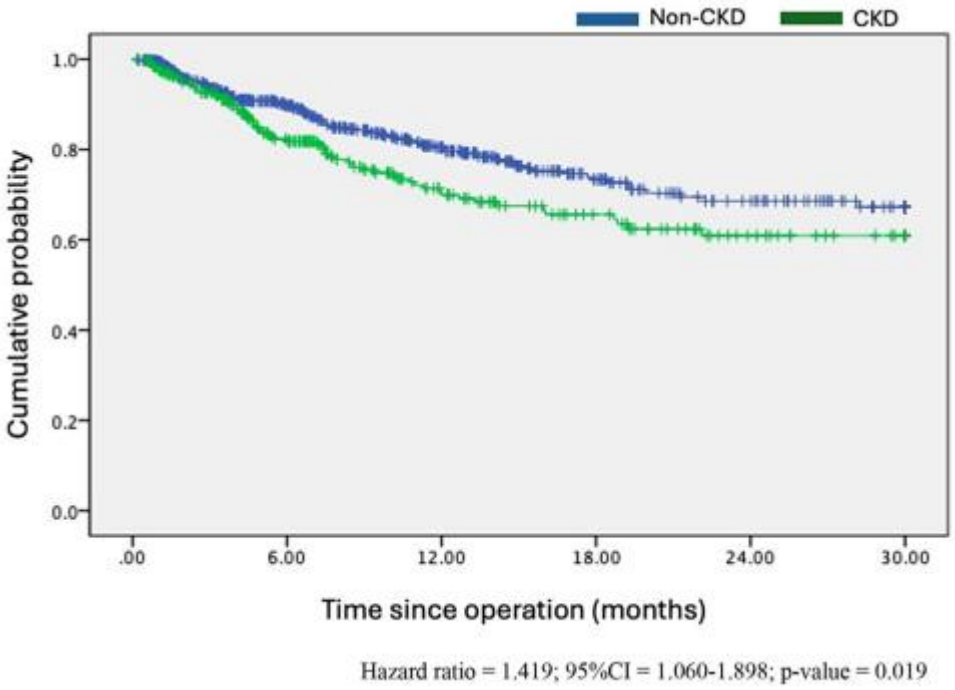


Figure 1: Kaplan Meier Survival Curves on disease-free survival of CKD and non-CKD cohorts

Discussion

According to this study, CKD was identified as an independent predictor of disease-free survival after adjusting for potential confounders and this was consistent with findings from existing cohorts.[4] CKD is associated with the worst prognosis in RNU patients, highlighting its

clinical significance. One of the reasons for poorer DFS may be treatment restrictions due to renal impairment that contributes to worsened outcomes. In the current study, 37.6% of patients had renal insufficiency before surgery, which was a significant proportion of CKD patients. Also, a variety of risk factors for renal impairment were present in UTUC patients, in that, the main contributing factors were age, comorbidities, and obstruction of the urinary tract.[5]

Conclusion

In UTUC patients, a worse prognosis after RNU is predicted by a pre-existing renal impairment of eGFR < 60 mL/min/1.73 m². The study emphasizes the effect of CKD on the management of UTUC in real-life scenarios. Physicians should be aware that CKD prior to surgery may be a predictor of poorer oncological outcomes.

In patients with upper tract urothelial carcinoma undergoing radical nephrouretectomy, preoperative CKD is a predictor of poorer disease-free survival.

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Impact of Erythrocyte Indices on the response to hypoxia-inducible factor prolyl hydroxylase inhibitors in CKD Patients with Renal Anaemia

Introduction

Renal anaemia is the most frequent complication of chronic kidney disease (CKD), affecting 40-60% of individuals with a glomerular filtration rate below 30 ml/min.[1,2] Anaemia in CKD patients is linked to increased cardiovascular risk and CKD progression. The administration of recombinant erythropoietin and erythropoiesis-stimulating agents (ESAs) has long been the standard treatment for improving Hb levels in CKD patients. However, concerns persist regarding the use of ESAs, including ESA hyporesponsiveness and the risk of cardiovascular damage at higher doses. Hypoxia-inducible factor Prolyl hydroxylase inhibitors (HIF-PHIs), a

new class of oral agents, have been indicated for renal anaemia. By inhibiting hypoxia-inducible factors (HIF), these drugs stimulate erythropoiesis. Studies suggest that low mean corpuscular volume (MCV) levels, even within the normal range, are linked with increased CKD progression risk.[3] So, this study aimed to evaluate whether erythrocyte indices and their changes in response to treatment are associated with the effectiveness of ESAs and HIF-PHIs in CKD patients with renal anaemia.

Methods

In this retrospective study, the non-dialysis-dependent CKD patients with eGFR <60 ml/min/1.73 m2 who had started ESA (darbepoetin) or HIF-PHI for the treatment of anaemia were included. Patients with active bleeding and those who shifted from ESA to HIF-PHIs were excluded. Demographic data (age, sex, height, weight, life history, and medical history) and clinical parameters (hemoglobin (Hb), erythrocyte indices, iron (Fe), ferritin, and C-reactive protein (CRP)) were obtained through medical record abstraction. The number of missing values for each variable was reported. Clinical values were gathered and evaluated. The Mann-Whitney U test and Fisher's exact test compared patient characteristics between ESA and HIF-PHI groups, the Paired t-test analysed values between two-time points, and Spearman's correlation assessed the relationship between parameters. Subgroup analysis compared anemia improvement by stratifying patients by MCV. Graph Pad Prism software, version 7.05, and JMP version 14.3.0 (SAS institute, USA) were used for all analyses.

Results

The study included 233 patients with anemia with a median age of 77 [interquartile range (IQR), 68–85] years, 39% of whom were female. The baseline Hb level was 9.7 [9.0-10.3] g/dL which was similar between HIF-PHI and ESA groups (P=0.44). Both ESA and HIF-PHIs treatments significantly increased Hb levels after three months of treatment. While MCV remained unchanged in the ESA group following treatment, it significantly increased in the HIF-PHI group. In the HIF-PHI group, there was a significant positive correlation between changes in Hb and MCV (r=0.24; P=0.02) indicating that anemia improvement was accompanied by an increase in MCV, but not in the ESA group. A subgroup analysis based on the mean reference range for MCV (90.9 fL) showed a significant difference between ESA and HIF-PHIs in proportion of patients with improved anemia among those with lower MCV values. Multivariable logistic regression confirmed a significant interaction between anti-anemic treatment and baseline MCV levels, HIF-PHI were more effective than ESAs for anemia improvement, whereas no significant difference was observed in patients with higher MCV values (P=0.23) (Figure 1). Interaction analysis further validated a statistically significant interaction between the anti-anemic treatment and MCV values (P=0.038).

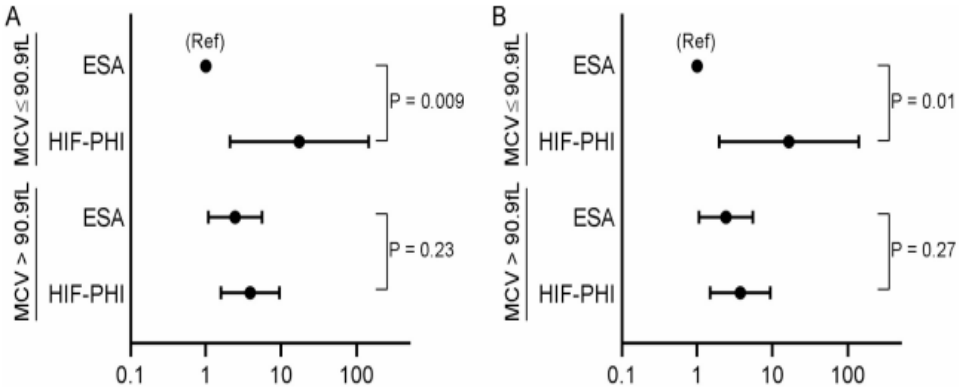

Figure 1: Logistic regression analysis in the study participants based on anti-anemic treatments and baseline MCV values

Discussion

In the HIF-PHI group, Hb levels increased by 1.1 g/dL after three months among the trial participants with the NDD-CKD study. An increase in Hb levels of 0.5 to 2.0 g/dL was observed 12 to 16 weeks following the initiation of HIF-PHIs, and the study participants' eGFR levels were generally comparable to those in the current trial (around 20 ml/min/1.73 m^2).[4] The multivariable analysis and the interaction analysis indicated that the effectiveness of anti-anemic drugs in improving anemia was influenced by pre-treatment MCV values. Although the underlying cause is not entirely clear, one possible explanation is that lower MCV values, even within normal range, may indicate impaired or inadequate iron uptake by erythrocytes in anemic conditions.[5]

Conclusion

In patients receiving HIF-PHI treatment, an increase in haemoglobin levels is linked to an increase in MCV. Baseline MCV values may affect the anti-anaemic effects of ESA and HIF-PHIs. However, further studies are required to determine the long-term outcomes.

HIF-PH inhibitors are more effective in treating anaemia in CKD patients with lower baseline MCV.

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Relationship between preoperative iron metabolism and acute kidney injury following cardiac surgery

Introduction

Each year, between 1 and 1.25 million cardiac surgeries are performed,[1] with 30 to 50 percent of patients developing acute kidney injury as a complication of the procedure. The aetiology of cardiac surgery-related acute kidney injury (CSA-AKI) is complex and multifactorial. Among the various detrimental mechanisms of CSA-AKI, ischemia-reperfusion injury (I-RI), inflammation, and oxidative stress have been identified as the primary research hotspots. Ferroptosis, a controlled necrotic cell death mechanism, is characterised by an iron-dependent accumulation of lipid peroxides.[2,3] Although recent studies shown that dysregulation of iron metabolism may play a significant role in CSA-AKI pathophysiology, it was constrained by small sample sizes, limited available biochemistry makers, and inconsistent findings. So, this study aimed to investigate the linear and nonlinear association between preoperative iron metabolism and CSA-AKI in patients undergoing cardiac surgery with cardiopulmonary bypass.

Methods

This single-centre retrospective study included 2420 patients who underwent CPB-assisted cardiac surgery, ranging in age from 18 to 70. In that 1676 of the 2420 participants were excluded due to a history of chronic renal disease, the need for immediate surgery, and the dearth of information on iron metabolism. Finally, this study included 744 patients. Complex techniques such as total circulatory arrest was also not included. Additionally, patients who underwent cardiac surgery were analysed using the Medical Information Mart for Intensive Care dataset (MIMIC-IV). An electronic medical recording system was used to gather information for the study on the patient's demographics, medical history, prescription drugs,

lab test results, and intraoperative factors. Iron metabolism, including ferritin, transferrin (TRF), total serum iron-binding capacity (TIBC), and serum iron (SI), was analysed to understand the patient's state and difficulties before surgery. Kidney Disease Improving Global Outcomes (KDIGO) criteria, which include a 0.3 mg/dL increase in serum creatine within 48 hours or 1.5 times higher than baseline, were used to define AKI following surgery; urine output criteria were not used. Data were analysed using SPSS software version 26.0 and R Foundation for Statistical Computing (R) software version 4.3.1.

Results

About 1488 eligible patients (Fuwai Hospital: n=744, MIMIC-IV: n=744) were enrolled for the final analysis out of 10,639 screened patients (2420 in the Fuwai Hospital and 8219 in the MIMIC-IV dataset). AKI had occurred in 25.7% and 56.5% of cases, respectively. The TIBC (OR=1.05, 95% CI:1.02–1.07, p<0.001) and TRF (OR=1.53, 95% CI:1.01–2.14, p=0.012) were positively correlated with AKI, while transferrin saturation (TS) was negatively correlated (OR=0.989, 95% CI: 0.96–0.99, p=0.002). In the MIMICIV dataset, SF and AKI were also found to be positively correlated, with an OR of 1.001 (95% CI: 1.00-1.001, p<0.001). The relationship between iron metabolism and CSA-AKI can be flexibly modelled using RCS. It revealed a non-linear relationship for SI (p=0.0015), SF (p=0.0291), TRF (p=0.0339), TS (p=0.0195), TIBC (p=0.0326), and AKI. The U-shaped relationship between preoperative SI and AKI shows that as SI rose, the risk reached its lowest point at 16.5 µmol/L and then experiencing a notable increase at 26.68 µmol/L (Figure 1). SI below 16.5 µmol/L had an OR of 1.62 (95% CI: 1.12 to 2.33, p=0.011) per SD when compared to SI between 16.5 and 26.68 µmol/L. With an OR of 1.71 (95% CI: 1.21 to 2.43, p=0.003) per SD, there is a significant risk increase in TRF above 2.43 g/L. The odds ratio for TS below 31% was 1.87 (95% CI: 1.32 to 2.65, p<0.001) per SD, according to the U-shaped relationship between TS and AKI and there is a J-shaped relationship between TIBC and AKI; after 54 µmol/L, there is a significant increase in risk with TIBC after 54 µmol/L (OR=2.01, 95% CI:1.48–2.96, p<0.001).

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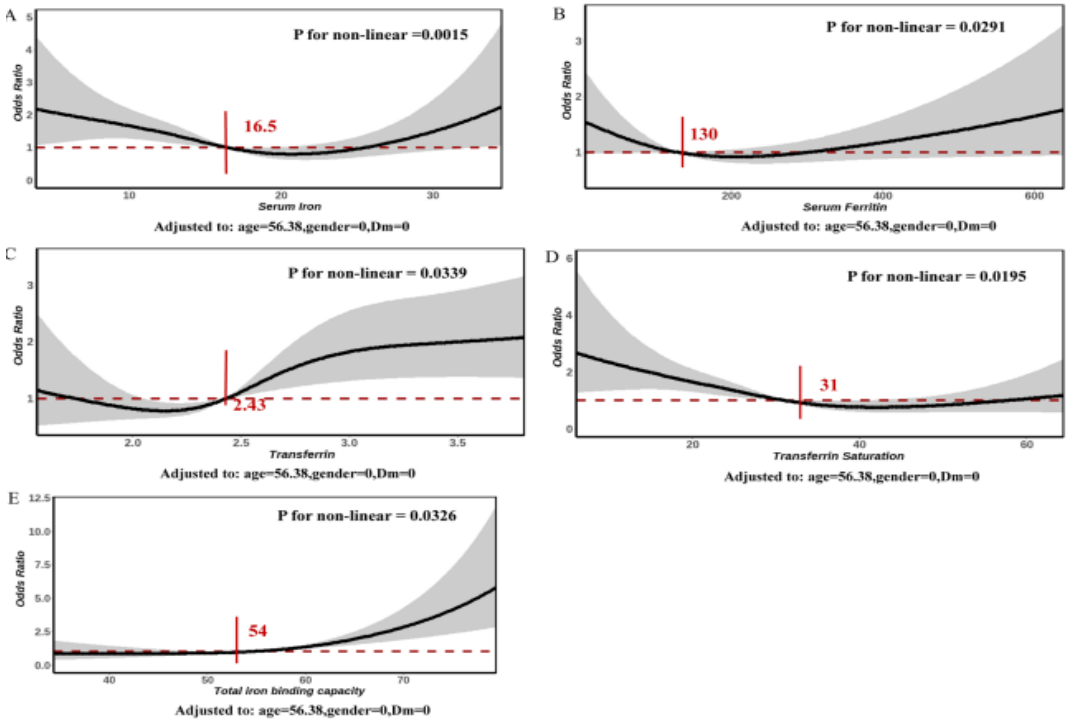

Figure 1: Multivariable-adjusted odds ratios for AKI (A) Serum Iron, (B) Serum ferritin (C) Transferrin, (D) Transferrin saturation, (E) Total iron binding capacity

Discussion

The primary outcome of the study revealed a non-linear relationship between SI and SF and AKI.A non-linear relationship was found between TRF, TS, TIBC, and CSA-AKI in the dataset, but the RCS model (adjusted by age, gender, and diabetes history) did not find any significant relationships in the MIMIC-IV dataset. The U-shaped curve relationship between iron metabolism and the risk of AKI following cardiac surgery was accurately depicted by RCS analysis. The older age in MIMIC-IV (68.3 years) and 56.4 years in the dataset and the physiological changes and multiple chronic diseases can impact iron metabolism. TRF, TS, and TIBC are involved in iron transport and exhibit sensitivity to such changes compared to SI and SF.[3] In the MIMIC-IV dataset, patients who had preoperative SF levels higher than 143 umol/L were at a higher risk of developing post-cardiac AKI. The non-linear relationship between SF and AKI was also validated by the J-shaped result.[4]

Conclusion

Iron metabolism markers (SI, SF, TS, TRF, and TIBC) exhibited a nonlinear relationship with AKI. The MIMIC-IV dataset demonstrated a nonlinear relationship between SF and AKI in

elderly patients. These findings highlight the potential of targeting iron metabolism to manage AKI in cardiac surgery patients.

Preoperative iron metabolism testing can help identify individuals at risk for acute kidney injury after cardiac surgery.

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Co-occurrence of Hydronephrosis and pyelonephritis with Renal pelvic urothelial carcinoma

Introduction

Urothelial carcinomas (UCs) of the renal pelvis and ureters are uncommon cancers that make up just 5–10% of all UCs.[1] Histologically variable renal pelvic UCs are uncommon; very few patients report histological changes like squamous or sarcomatoid differentiation. Hydronephrosis and pyelonephritis can further complicate the cases by masking clinical and radiological signs of upper urinary tract urothelial carcinoma (UUTUCs), making diagnosis more challenging and delaying the detection of renal pelvic UC.[2] This rare case is reported in order to share the experience for understanding similar cases and prevent UC from misdiagnosing or delaying in detecting UCS.[3]

Case presentation

A 56-year-old female patient arrived at the hospital with distension in her right waist. A computed tomography (CT) revealed significant hydronephrosis (Fig. 1A) resulting from a solitary ureteral stone (Fig. 1B). The glomerular filtration rate (GFR) of the right kidney was 20 millilitres per minute, according to renal nuclear scintigraphy. The waist distension resolved following a percutaneous renal puncture drainage technique. After two months of drainage, flexible ureteroscopic lithotripsy was performed, and a subsequent CT scan demonstrated improvement in the hydronephrosis (Fig. 1C, D). Flexible ureteroscopy revealed no tumours

or other suspected lesions in the kidney's calyces or pelvis. Both lower calyx and right ureter stones were removed. For a year, the patient did not return to the hospital for follow-up because of a satisfactory postoperative recovery. Thirteen months after surgery, the patient was admitted with pain, moderate intermittent fever, and right waist ache. A physical examination revealed that the right renal region had positive percussion pain. An enlarged right kidney was seen on CT (Fig. 1E). Enhanced CT also revealed hydronephrosis with internal segregation (Fig. 1F). Blood and urine cultures were negative, and regular blood tests revealed a slight increase in the total leukocyte count. The hydronephrosis was likely caused by significant mucosal inflammation, but her first diagnosis was pyelonephritis. After a week of empirical intravenous antimicrobial therapy, no improvement in symptoms was seen. The patient experienced only sporadic, mild pain in the right lumbar area one month following drainage. There were no indications of pyelonephritis, and CT revealed that the hydronephrosis had resolved (Fig. 1G). Two weeks after the ureteral stent was removed, the patient developed intermittent fever and worsened right waist pain. CT revealed hydronephrosis and pyelonephritis (Fig. 1H, I).

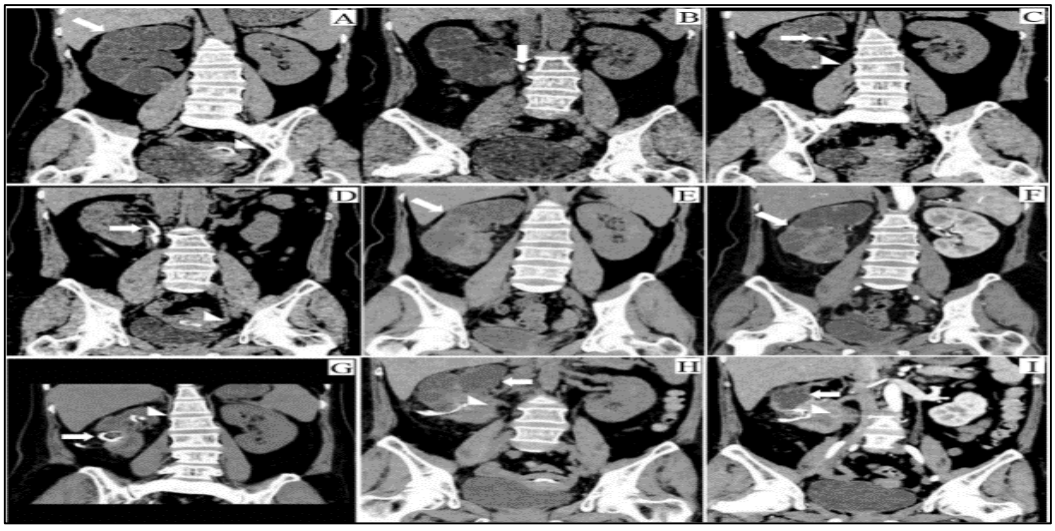

Figure 1: Axial CT of the right kidney

A right nephrectomy was carried out due to the uncontrollable infection and hydronephrosis of the right kidney, which had aberrant morphology and poor function. The macroscopic specimen showed erosion of the inferior renal calyx and surrounding tissues with purulent discharge and hazy borders, as well as atrophy of the polycystic renal parenchyma. The tumour was found in the kidney's lower calyces, where stones had previously been found. Necrosis and abscess formation were seen in the prepared kidney segment, and tumour invasion was also seen in the renal nerves. Cancerous tissue was found in the collagen fibrous tissue around the ureter, despite the tumour margins being negative.

Based on the histological and immunohistochemical findings, the final diagnosis was high-grade invasive renal pelvic urothelial carcinoma with uncommon histological variations, such as squamous and sarcomatoid differentiation. According to the American Joint Committee on Cancer (AJCC) staging recommendations, the pathological stage was pT3NxMx. After the procedure, the patient's fever and right waist pain disappeared, and now she is undergoing routine intravenous cisplatin-based chemotherapy and intravesical perfusion treatment.

Discussion

The UUTUC reported in this case not only had two histological variants squamous and sarcomatoid variation but also happened in the renal pelvis demonstrating an extremely rare variance. In addition to highlighting the case's rarity, the patient's simultaneous presentation of pyelonephritis and hydronephrosis obscured the clinical and imaging signs of renal pelvic carcinoma, adding to the diagnostic and therapeutic complexity and delaying the diagnosis.[2] Because the preoperative clinical data did not support the diagnosis of a malignant tumour of the renal pelvis and strongly suggested pyelonephritis and hydro nephrosis in a patient with reduced kidney function, only a nephrectomy was performed in this case, and the patient declined additional residual ureter and bladder cuff resection. She is still undergoing regular postoperative chemotherapy, which includes bladder perfusion and cisplatin. Cystoscopies and standard imaging examinations are performed as follow-up procedures. On rare occasion, pyelonephritis and hydro nephrosis also accompany with pelvic cancer. Patients with intractable hydro nephrosis and pyelonephritis should be investigated for renal pelvic carcinoma and have a comprehensive diagnostic workup. Chemotherapy and immunotherapy can increase survival, and radical surgery is advised.[3]

Conclusion

Pyelonephritis and hydronephrosis can conceal the usual imaging and clinical signs of renal pelvic urothelial carcinoma. Patients with hydronephrosis or intractable pyelonephritis should have their risk of renal pelvic carcinoma assessed. There is no one-size-fits-all treatment for renal pelvic cancer, which can take several pathological forms. Radical surgery is regarded as a good substitute that should be performed as soon as is practical. Chemotherapy and immunotherapy may increase patient survival.

Early diagnosis and radical nephrectomy are essential for treating renal pelvic carcinoma masked by chronic infection

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