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Case Report

Invasive Urothelial Carcinoma of the Renal Pelvis, Staghorn Calculus, Right Renal Pyo nephrosis, and Hepatic Necrosis: Review and Case Report

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Abstract:

Upper urinary tract urothelial carcinoma is less common than bladder carcinoma, although it shares nearly identical risk factors and generally carries a worse prognosis. We report the clinical case of a 56-year-old female patient who presented to the hospital with right flank pain. Laboratory tests showed a leukocytosis, acidosis, and elevated infection-related blood parameters. A Computed Tomography scan shows the presence of a large staghorn calculus, pelvicalyceal dilatation, functional exclusion of the right kidney, hypoenhancing focal hepatic lesions. Is inserted a percutaneous nephrostomy drainage catheter. An urgent nephroureterectomy was performed. Histopathological examination of the surgical specimen revealed a staghorn calculus, and a conventional invasive urothelial carcinoma of the renal pelvis. Postoperatively, the patient was transferred to the ICU, where she experienced an unfavorable clinical course and subsequently died.

The etiopathogenic and risk factors are: smoking, exposure to carcinogens, lithiasis, obstruction, inflammation, chronic infections, alcohol use, unhealthy diet, sedentary, chromosomal alterations, radiotherapy and immunosuppressants treatment used as therapy in other diseases. The radical nephroureterectomy is the standard treatment.

Key words: urothelioma; invasive; lithiasis; staghorn; pyonephrosis; liver; necrosis

Introduction

Upper urinary tract urothelial carcinoma (UUTUC) is less common than bladder carcinoma. Although both share identical risk factors, UUTUC typically carries a worse prognosis. The standard diagnostic approach involves imaging of the upper urinary tract using computed tomography urography (CT-IVU). In cases of diagnostic uncertainty, ureterorenoscopy with biopsy, along with urine cytology, may be performed. Treatment primarily depends on tumor stage and grade. Based on the extent and location of the disease, either organ-sparing approaches or radical nephroureterectomy may be indicated. In high-risk UUTUC, perioperative systemic therapy can be administered in both neoadjuvant and adjuvant settings. However, current evidence on neoadjuvant chemotherapy and immunotherapy does not yet support a standardized approach. For metastatic disease, a multimodal treatment strategy may include cisplatin- or carboplatin-based chemotherapy, immunotherapy, and treatment with enfortumab vedotin. In selected cases, salvage surgery, radiotherapy, or metastasectomy may also be considered [1, 2, 3].

Between 22% and 47% of patients with upper urinary tract urothelial carcinoma (UUTUC) develop bladder cancer (BC) recurrence following radical nephroureterectomy. Moreover, the impact of surgical treatment for UUTUC-associated BC has not been well validated. The aim of this study was to assess the effect of a standard primary BC surgical strategy on the survival of patients diagnosed with UUTUC-associated BC [1, 2, 3].

Perioperative systemic treatment for high-risk UUTUC may be administered in both neoadjuvant and adjuvant settings. However, current evidence on neoadjuvant chemotherapy and immunotherapy does not yet support standardized application. For metastatic disease, a multimodal treatment approach may include cisplatin- or carboplatin-based chemotherapy, immunotherapy, and treatment with enfortumab vedotin and pembrolizumab. In selected cases, salvage surgery, radiotherapy, and metastasectomy may also be considered [1, 2, 3].

Case Presentation

A 56-year-old female with a medical history of hypertension**,** hypercholesterolemia**,** and overweight presented to the emergency department with right flank pain for approximately 2 months. Initially, the pain was mild, dull, and continuous, progressively increasing in intensity, without associated fever.

Laboratory results: Glucose: 125 mg/dL, Creatinine: 0.95 mg/dL, C-reactive protein: 29.90 mg/dL, Leukocytes: 10.7 × 10^3/µL, Hemoglobin: 11.5 g/dL, Platelets: 489 × 10^3/µL, Urine analysis: Leukocytes 100, Hematuria 250, Proteins 150, Urine culture: Negative (15 days prior).

Physical examination**:** Positive right renal punch percussion. A large mass palpated in the right flank, suggestive of an enlarged kidney**.** Positive renal ballottement**,** slightly painful

Plain abdominal X-ray (Figure. 1) showed right kidney (RK) enlargement with a large staghorn calculus**.**

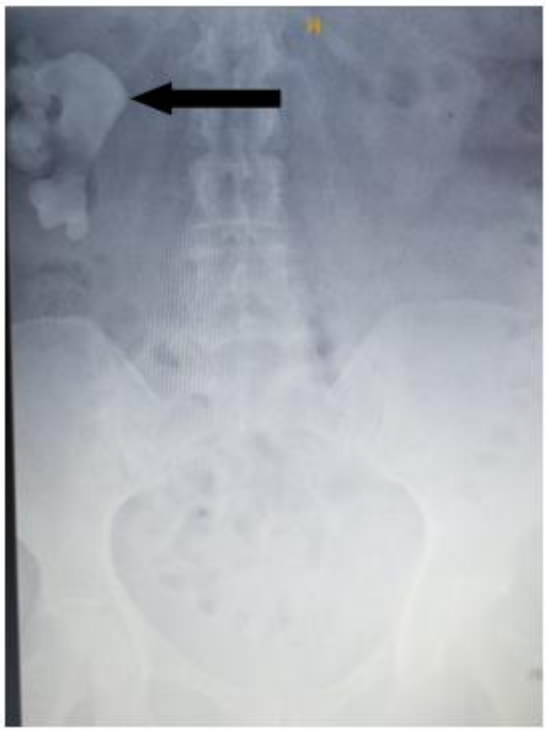

Figure 1: Plain abdominal X-ray**:** Right kidney enlargement with a large staghorn calculus (black arrows).

The patient was admitted to the Urology department for further investigation and treatment, where she developed worsening pain and fever of 38-39ºC. An abdominopelvic CT scan with intravenous contrast (Figure. 2) revealed a large staghorn calculus in the RK with significant pelvicalyceal dilation. No contrast elimination was observed. Inflammatory changes in the perirenal fat were noted. A portocaval adenopathy conglomerate was present. Several hypoenhancing hepatic lesions were identified.

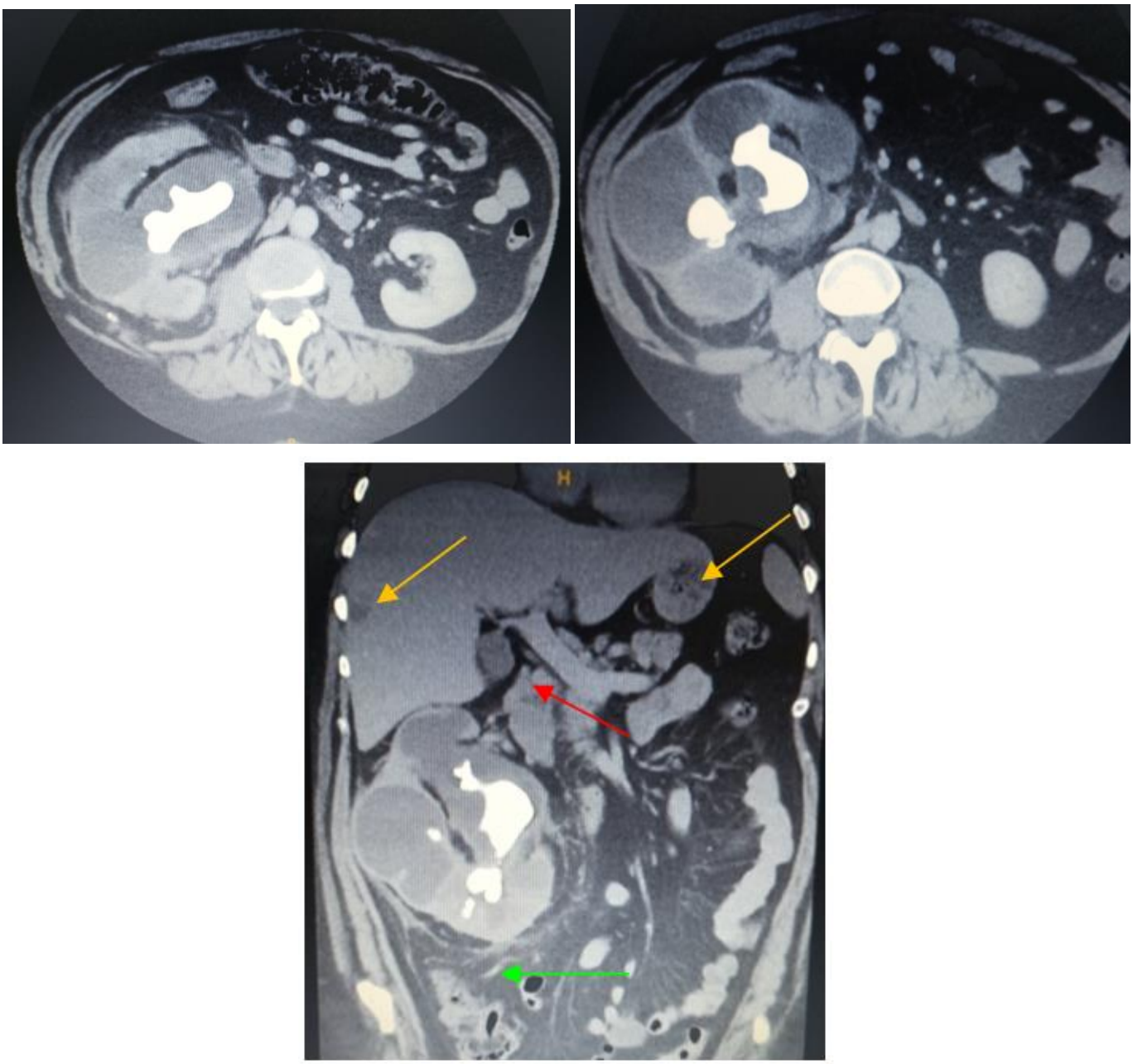

Figure 2: Abdominopelvic CT scan with intravenous contrast staghorn calculus in the RK, significant pelvicalyceal dilation. Inflammatory changes in the perirenal fat (green arrows). A portocaval adenopathy conglomerate (red arrow). Hypoenhancing hepatic lesions (yellow arrows).

Broad-spectrum antibiotic therapy was initiated (Meropenem 1 gram IV every 8 hours) pending results of blood and urine cultures, with pain control and hydration. Interventional Radiology performed an urgent nephrostomy (Figure. 3).

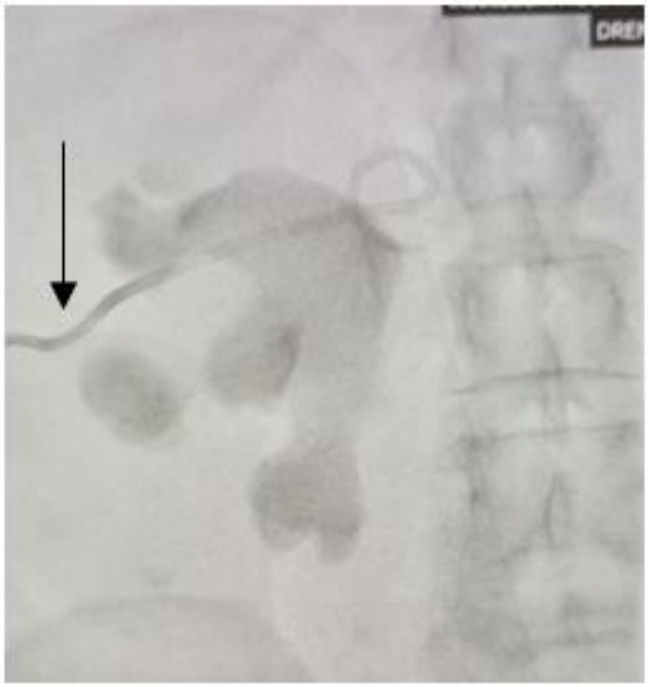

Figure 3: Nephrostomy drainage. (black arrows)

Due to the presence of pyonephrosis**,** worsening clinical condition, right hypochondrial pain**,** and deteriorating laboratory parameters with elevated acute phase reactants and acidosis, a repeat CT scan with contrast (arterial and portal phases) was performed to rule out complications, comparing it with the previous study (Figure. 4).

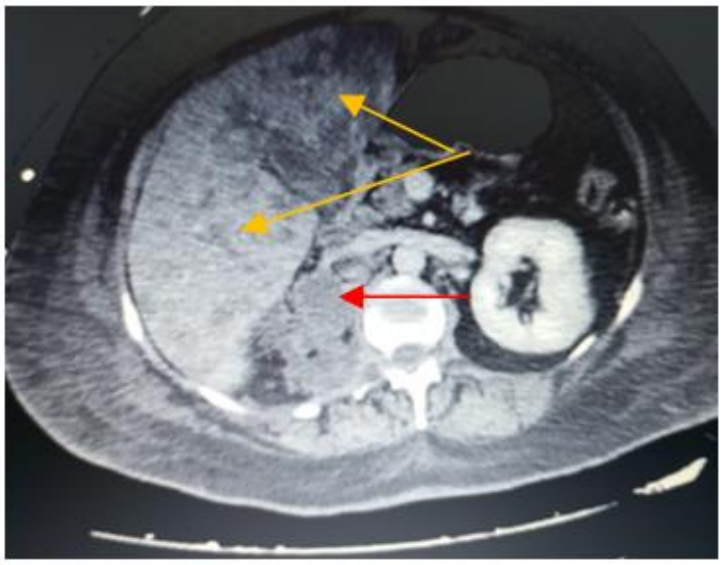

Figure 4: Uro CT scan: Enlarged necrotic portocaval lymph node cluster (red arrow). Multiple hypodense liver lesions (yellow arrow) consistent with abscessed lesions.

The findings were as follows: RK: 14 cm, globular with large staghorn calculus, nephrostomy catheter in the middle calyceal group. Persistent calyceal dilation in other calyceal groups. Multiple cortical abscesses and significant reduced enhancement and cortical differentiation compared to the previous study. Increased necrotic portocaval adenopathy, marked right adrenal thickening of recent onset. Hepatic lesions: Normal liver size and morphology, with multiple new hypodense lesions, the largest being heterogeneous and irregular in segment IV (yellow arrows). These lesions suggest hepatic abscesses given the clinical context, though other causes cannot be excluded. Perihepatic free fluid, in both paracolic gutters and pelvis. Normal left kidney (LK) and bladder, no significant findings in gynecological structures. Multiple micronodules in the pulmonary bases, new and diffuse, not seen in prior studies. Probable xanthogranulomatous pyelonephritis on the right, with hepatic lesions suggestive of abscesses, and newly appearing micronodules in the lung bases.

Right nephroureterectomy was performed. The macroscopic description of the surgical specimen is as follows:

Macroscopic Description: RK: Nephrectomy specimen measuring 20 x 13.5 x 10.2 cm, including a 10 cm ureteral segment. The specimen is difficult to decapsulate and weighs 1134 g. On sectioning, there is marked dilation of the pelvicalyceal system, with a yellowish staghorn calculus of

approximately 4 cm, impacted. The specimen contains abundant purulent and hematic coagulated material within the lumen of the pelvicalyceal system. The kidney shows whitish areas and yellowish regions. In the renal pelvis, there is a somewhat raised, papillary lesion, dark brown in appearance, measuring 5.3 x 3 cm. This lesion has a moderate consistency and whitish section planes, appearing to respect the renal parenchyma. Two possible lymphadenopathies are identified in the perirenal fat. A whitish nodule of 0.8 x 0.8 cm is observed in the periarterial zone.

Microscopic description: Nephroureterectomy Right. Tumor localization: Renal pelvis. Tumor size: 5.3 x 3 cm. Histological type: Invasive urothelial carcinoma, conventional. Histological grade: High grade. Tumor extension: Invades renal parenchyma. Lymphovascular invasion: Present (abundant), involving both large and small vessels. Tumor configuration: Papillary (non-invasive component). Margins: Renal surface: Free of tumor. Ureteral margin: No signs of tumor. Hilar margin: Affected by carcinoma (perivascular invasion). Lymph nodes: Not sent or isolated in the sample. Pathological staging: pT3. Other findings: Chronic pyelonephritis, renal parenchyma with atrophic and hyalinized areas**.**

Extensive necrotic zones**.** Nephrolithiasis**.** Comments**:** Extensive perineural and perivascular invasion observed.

In the postoperative period, the patient was transferred to the ICU where her condition worsened, and she died.

Discussion

The etiopathogenic factors for UUTUC are the same as those for ureteral and bladder tumors. The risk increases with age. Tobacco use**,** particularly cigarette smoking, is a major risk factor for these tumors. Tobacco contains carcinogenic substances, which, after being excreted by the kidney, accumulate in the urine. This exposes the urothelium to high concentrations of these carcinogenic substances, which damage the DNA of the urothelial lining cells, favoring tumor development. Thus, the prevention and attempt to modify these unhealthy lifestyle habits plays a key role in this process, where primary care physicians (PCP) have a fundamental role. Other risks factors are alcohol use, unhealthy diet, sedentary lifestyle and lack of physical activity, environmental factors, Evidence and recommendations for cancer prevention strategies through screening in asymptomatic patients, as well as early detection of signs and symptoms in the average and high-risk population, are important [4]. The global incidence of cancer has continued to increase due to the aging of the population and the growing trend toward unhealthy lifestyles [5, 6, 7]. Also associated risks factors are: Family history of urothelial tumors, chromosomal alterations of various genes, among which we have HRAS (Harvey rat sarcoma), RB1 (retinoblastoma gene), PTEN / MMAC1 (phosphatase and tensin homolog / Mouse Monoclonal Antibody), NAT2 (Network Address Translation) and GSTM1 (Glutathione-S-transferase) [8], exposure to various industrial aromatic amines in workers in the paint, dye, metal or petroleum products industry, radiotherapy treatment in the pelvis, immunosuppressants used in the therapy against other cancers: cyclophosphamide and ifosfamide, consumption of Aristolochia fangchi, (herb native to China), consumption of water with high concentrations of arsenic [9], Schistosomiasis caused by the parasite *Schistosoma haematobium*, common in Africa and the Middle East, but uncommon in the United States and Europe, urinary catheterization and lithiasis long-standing, due to the irritating factor it causes in the urothelium [10]. UUTUC is a rare malignancy, accounting for approximately 5% to 10% of all urothelial carcinomas (UC), with a higher prevalence in males and older adults. It includes various histological subtypes and, unlike bladder UC, more frequently presents as invasive disease at diagnosis. Molecular studies have identified frequent mutations in FGFR3 (fibroblast growth factor receptor 3) and TP53 (tumor protein p53, a 53 kDa tumor suppressor), which are increasingly guiding therapeutic decisions. Lynch syndrome (LS), a hereditary cancer predisposition syndrome, is a significant risk factor for UUTUC, particularly in younger patients. Current treatment strategies emphasize platinum-based chemotherapy following surgical resection, although immunotherapy has shown promise, especially in patients with LS-associated UUTUC. Continued molecular research is essential to improve diagnostic accuracy and optimize individualized treatment approaches [11,12,13]. Although data are accumulating, in many areas there is still insufficient high-level evidence to provide solid recommendations regarding the therapeutic management of UUTUC. Patient stratification based on histology and clinical examination (including imaging) and assessment of patients at risk for *LS* will aid management. Renal sparing management should be offered as a primary treatment option for patients with low-risk UUTUC and two functioning kidneys. Particularly for patients with high-risk or metastatic UUTUC, new treatment options have become available. In high-risk UUTUC, platinum-based chemotherapy after radical nephroureterectomy and adjuvant nivolumab for patients unfit or who refuse chemotherapy are options. For metastatic disease, gemcitabine/carboplatin chemotherapy is recommended as first-line treatment for patient's ineligible for cisplatin. Patients with PD-1/PD-L1 (programmed death ligand 1)-positive tumors should be offered a checkpoint inhibitor: pembrolizumab or atezolizumab, agents that inhibit PD-L1, found on the surface of tumor cells, and PD-1, found on activated T and B cells and macrophages. This immunotherapy treatment can help halt or slow the growth of many types of cancer that have PD-L protein. These drugs are capable of blocking the PD-1 receptor present on the surface of lymphocytes, or the PD-L1 and PD-L2 ligands expressed by cancer cells. This would prevent the two from binding, blocking the immunomodulatory signal and allowing T cells to remain active against the tumor. The therapeutic target of pembrolizumab and nivolumab is PD-1, the PD-L1 receptor protein on immune cells [14, 15, 16, 17], An evaluation of the pathological factors for prognosis, intravesical recurrence and distant metastasis of UUTUC was carried out, concluding that it is necessary to take into account the specific clinical characteristics of each patient are key to determining the optimal treatment regimen based on the risk stratification of these tumors. UUTUC is rare, but since 60% of these tumors are invasive at the time of diagnosis, a timely and accurate diagnosis is crucial. There are several known risk factors: High-grade tumors have a poor prognosis and often develop distant metastases, suggesting the need for careful postoperative follow-up. Those with lymphatic invasion or tumors 3 cm or larger in diameter frequently develop intravesical recurrence and distant metastases, respectively, indicating the need for close follow-up [14, 15, 16, 17]. The European Association of Urology (EAU) guidelines panel on UUTUC has updated the guidelines to aid clinicians in evidence-based management of UUTUC. Even though data are accruing, for many areas there is still insufficient high-level evidence to provide strong recommendations. Patient stratification on the basis of histology and clinical examination (including imaging) and assessment of patients at risk of *L*S will aid management. Kidney-sparing management should be offered as a primary treatment option to patients with low-risk UUTUC and two functional kidneys. In particular, for patients with high-risk or metastatic UUTUC, new treatment options have become available. In high-risk UUTUC platinum-based chemotherapy after radical nephroureterectomy, and adjuvant nivolumab for unfit or patients who decline chemotherapy, are options. For metastatic disease, gemcitabine/carboplatin chemotherapy is recommended as first-line treatment for cisplatin-ineligible patients. Patients with PD-1/PD-L1-positive tumours should be offered a checkpoint inhibitor (pembrolizumab or atezolizumab) [18].

UUTUC and his relation with the litiasis:

Cases of association of renal pelvis tumors with urolithiasis have been published.

One clinical case of a patient with squamous cell carcinoma (ECC) in a duplicated renal pelvis, after percutaneous nephrolithotomy. The ECC of the renal pelvis is a rare tumor with poor prognosis, associated with stone disease and chronic infection. Taking biopsies from suspicious lesions

during percutaneous nephrolithotomy may help early diagnosis and improve survival [19].

Other case of a well-differentiated mucoproducing adenocarcinoma of the right renal pelvis in a patient treated for a right renal pelvis lithiatis who was subsequently diagnosed with ultrasound and CT scan showed a hypodense tumor in the lower pole with hyperdense areas in the interior of the right renal pelvis. A right nephrectomy was performed. Biopsy showed a well-differentiated mucoproducing adenocarcinoma of the right renal pelvis [20].

There is some controversy in the terminology used for transitional cell tumors with mucinous differentiation. A 50-year-old male with history of recurrent lithiasis whose radological tests discovered a heterogeneous renal pelvis lesion. The histologic study of the lesions determined the diagnosis of transitional cell carcinoma of the renal pelvis with ample mucinous differentiation. They are rare tumors in such location and the mucinous differentiation does not seem to influence prognosis [21].

Cancer is one of the leading causes of morbidity and mortality. Environmental factors, along with lifestyle factors, tobacco and alcohol use, unhealthy diet, sedentary lifestyle, and lack of physical activity are some of the risk factors that have led to an increase in cancer. Evidence and recommendations for cancer prevention strategies through screening in asymptomatic patients, as well as early detection of signs and symptoms in the average- and high-risk population, are important. The global incidence of cancer has continued to increase due to the aging of the population and the growing trend toward unhealthy lifestyles [22]. Tobacco is the leading cause of cancer and cancer-related death. The decline in smoking rates and the increase in obesity rates suggest that obesity will displace tobacco as the main preventable cancer risk factor in the coming decades. Notable risk factors include exposure to occupational carcinogens, air pollution, infectious agents, and certain aspects of sexual and reproductive life. Given this complex landscape of threats to population health, disease prevention and the promotion of healthy lifestyles are presented as fundamental and essential measures, which must be promoted at the political and economic levels, and not only by scientific societies or the healthcare system. Furthermore, it is essential that they involve the entire community. Therefore, the role of community-based strategies (based on evidence and measurable with objective indicators) is essential [23, 24].

UUTUC and bladder urothelial carcinomas share many common biological pathways. However, UUTUC is more frequently associated with specific conditions such as Balkan endemic nephropathy and hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome)**,** the molecular mechanisms of which are increasingly being elucidated (25)**.** A wide range of potential biomarkers have been investigated in an effort to identify reliable prognostic indicators for UUTUC. Ongoing advances in our understanding of UUTUC biology may, in the future, facilitate the discovery of novel druggable targets, the development of clinically applicable biomarkers, and the optimization of treatment strategies for this rare but aggressive malignancy [26, 27, 28].

Conclusions

UUTUC have a high potential for aggressiveness and an unfavorable prognosis. The standard diagnostic test is imaging of the upper urinary tract using CT scan-IVC. in cases with diagnostic uncertainty, the ureterorenoscopy with biopsy and urine cytology can be performed. The gold standar treatment is e radical nephroureterectomy. Is important to consider to be aware of the risk factors for this disease, they are the same for bladder tumor: smoking, alcohol, healthy lifestyle and work with, exposure to carcinogens, environmental pollution, hereditary syndromes (LS), family history of urothelial tumors, chromosomal alterations of various genes, lithiasis, obstruction, inflammation, infection (bacterial, parasitic) chronics, radiotherapy treatment in the pelvis, immunosuppressants used in the therapy against other cancers, Health prevention activities are also of great importance. The radical nephroureterectomy It is the standard treatment, as well as perioperative systemic treatment for high-risk UUTUC (the neoadjuvant and adjuvant chemotherapy and immunotherapy, but do not yet allow for standard application. For metastatic disease, a multimodal treatment consisting in cisplatin or carboplatin chemotherapy, immunotherapy, and treatment with enfortumab vedotin and Pembrolizumab can be considered. In rare cases, salvage surgery, radiotherapy and metastasectomy are available.

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