

## **Urothelial Cancer: A Case Report of Macroscopic Hematuria**

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### **ABSTRACT**

A 67 year - old male patient with painless macroscopic haematuria of 3 weeks of evolution being his only symptom. Auxiliary laboratory exams were non-conclusive. In the histopathological study of the lesion, renal pelvis with scant epithelium with atypia consistent with low-grade non-invasive urothelial carcinoma. The patient underwent a right nephroureterectomy as treatment for his condition.

**KEYWORDS:** urothelial cancer, renal pelvic cancer, tuberculosis, tobacco

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### **INTRODUCTION**

The urothelium corresponds to the epithelium that covers the surface of the structures that forms the urinary tract, encompassing calyces, renal pelvis, ureters, bladder, and urethra. (1) 90% of these urothelial tumors are located in the bladder, only 5-10% are located at the pyelocalyceal level. According to the Peruvian Cancer Registry of the National Institute of Neoplastic Diseases (INEN) between 2013-2015, renal pelvic cancer ranked 46th in frequency, registering only 92 cases of renal pelvic cancer in all of Metropolitan Lima. (7) Most cases occur between the sixth and seventh decade of life, being more frequent in men (represents 7-8% of renal tumors in men). (2)

Various exogenous factors predispose to the formation of tumors in the renal pelvis. The Cancer Society of Canada associates chronic tobacco consumption as the main factor causing urothelial cancer (3). Among other triggers we find recurrent urinary tract infections, chronic kidney stones (4), substances or chemicals (arsenic, industrial paint amines, etc.), radiation, genetic diseases (Lynch Syndrome) and the chronic use of analgesics (acetaminophen, aspirin, etc.) (5). The initial diagnosis is purely clinical, based on physical examination and complementary laboratory and imaging tests. Among the differential diagnoses, the main one to consider is renal tuberculosis, due to the similarity of the clinical presentation.

### **CASE PRESENTATION**

A 67-year-old male, hypertensive and heavy smoker for 31 years with a rate of approximately 5 cigarettes per day until 20 years ago, electrical engineer by profession in rural-

marginal areas. Patient was admitted to the emergency room for 3 weeks presenting painless macroscopic hematuria that was progressing and increasing in volume, associated with the presence of clots in the urine. Two weeks prior to admission, the patient went to the emergency room due to persistent hematuria, where he was evaluated and received outpatient management by a urologist. Twelve days before admission, the patient returns to the urology office, where he is re-evaluated and requested a contrast-enhanced tomography urography (uro-tem). One week later, the patient returns to the office where he is informed that the studies were not contributory.

The auxiliary laboratory tests showed results such as azotemia (creatinine: 1.22 mg/dl) together with a pathological urine test showing hematuria (+3) and proteinuria (+1). Due to his history and clinical picture, different tests were requested during hospitalization, such as direct Bk in urine, sedimentation rate, antinuclear antibodies (ANA), anticytoplasmic antibodies (ANCA), ELISA test, and GenXpert MTB/RIF in urine; however, none was contributory. Likewise, the Mantoux and Papanicolaou tests (PAP test) in urine were performed, the results of which were negative.

The images, such as magnetic resonance urography (uro-resonance), reported that there was an inflammatory process with an infectious appearance in the right kidney with involvement of the lower and middle calyceal groups, as well as the renal pelvis and proximal ureter in association with inflammatory changes in the ipsilateral pararenal fat.

Subsequently, an ureterorenoscopy was performed. In this procedure, the urinary system of the right kidney was

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explored and an exophytic proliferative compromise was found at the level of the renal pelvis. Five samples were taken from said lesion for biopsies and a urine sample, which were sent to Pathology and Microbiology. The results of the PAP, Bk and culture of *M. tuberculosis* in urine were negative.

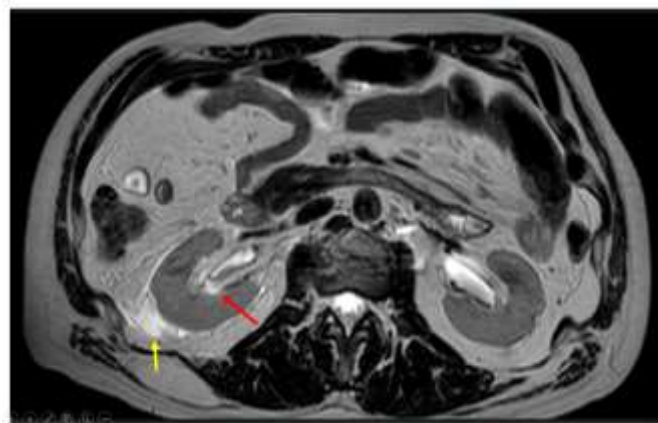
### Pathology Report

Renal pelvis biopsy: scant urothelium with atypia consistent with low-grade non-invasive urothelial carcinoma.

With the results of the renal pelvis biopsy, a right nephroureterectomy was performed, the sample of which was sent to Pathology.

### Pathology Report

Right kidney and ureter biopsy: infiltrating and exophytic tumor measuring 2.6 x 1.5 x 1.2 cm, whitish, friable involving the mucosa of the renal pelvis and the lower pole major calyces and adjacent renal tissue, 16 cm distant from the margin ureteral. Renal parenchyma and calyces of the upper pole without alterations.



**Uro MRI: moderate inflammatory changes are observed in the perirenal fatty tissue, predominantly posterior (yellow arrow), also evidence of thickening and compromise of the lower and middle calyceal groups, as well as the right renal pelvis, compatible with an inflammatory process with an infectious appearance. (Red Arrow)**



**Uro MRI: truncation and less representation of the lower calyces is observed, and to a lesser extent the middle calyceal group of the right kidney, evidencing thickening and abnormal enhancement of its walls, the walls of the right renal pelvis and of the proximal segment of the ipsilateral ureter with content that restricts dissemination**



**Surgical piece: Kidney and right ureter after radical nephroureterectomy**

### DISCUSSION

Renal pelvic cancer represents between 10-13% of all urinary tract neoplasms nationwide. It includes urothelial carcinomas, squamous cell carcinomas, and adenocarcinomas (15). Approximately 90% of these tumors are of urothelial origin (15). Within the upper urinary tract, tumors are twice more frequently located at the pyelocalyceal level, compared to the ureteral region. According to data from the Peruvian Cancer Registry of the National Institute of Neoplastic Diseases (INEN), between the years 2013-2015, 54 cases of renal pelvis cancer were registered in men and 38 in women between the sixth and seventh decade of life. These epidemiological data are related to the age and sex of the patient.

Urothelial cancer presents multiple risk factors that predispose to its appearance. In the literature, tobacco consumption is described as the most prominent in Western countries (11), increasing its risk by 3.1 times in heavy smokers and the risk is even 7.2 times greater in patients with

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a history of smoking over 45 years (3). There is a decreased risk if cigarette smoking ceases; however, this is not eliminated and remains high compared to non-smokers (11). Likewise, there are other important risk factors such as the age (greater than 65 years), industrial exposure to carcinogenic chemicals, occupational including electrical workers, miners, laborers, transport operators and jobs that involve the manufacture of carpets, paints, plastics and industrial chemicals, environmental pollution, among others (11). In this case, the patient mentioned tobacco use for 31 years and, although he reports that this harmful habit ended 20 years ago, the risk of developing said disease continues and remains high. In addition, he has other risk factors such as his profession, such as electrical engineering, and the age of 67.

Most patients can have an asymptomatic clinical presentation for years. However, for those who present symptoms, painless macroscopic and microscopic hematuria (80-90%) is usually the most relevant debut symptom (13). Other symptoms include abdominal pain in the flanks (24-37%) and symptoms of bladder irritation (15-20%) such as pollakiuria, nocturia, tenesmus (13). It can also be associated with other systemic symptoms such as fatigue, hyporexia, night sweats, and weight loss that are more compatible with metastatic conditions (13). In the clinical case, painless macroscopic hematuria is described as the main symptom in the absence of systemic symptoms.

The diagnosis of urothelial cancer is based on imaging tests and ureterorenoscopy (15). Laboratory tests are not a fundamental part of the diagnosis of urothelial cancer. However, one in particular stands out: urine cytology or urine PAP (13, 15). The sensitivity of this test varies from 43-78% depending on the population studied (13). In general, a positive result is associated with high-grade or invasive urothelial cancer (13). However, the cytological examination in urine is the least reliable in terms of cancer of the urothelium of the upper tract (renal pelvis and ureter) (15). In the case of the patient, two urine PAP tests were performed, the first urine sample was given by the patient himself and the second sample was obtained in the operating room while performing ureterorenoscopy using a double J catheter. Both results were negative, which expresses correlation with the literature.

Within the imaging studies used, ultrasound serves as an initial image to identify any alteration at the level of the urinary tract. Both computed tomography and magnetic resonance urography have shown greater efficacy for the detection of tumors at the pyelocalyceal level, and both are reliable and effective methods for the analysis and characterization of renal masses. Tomography urography has a high sensitivity and specificity close to 92 and 95% respectively, while resonance urography with sensitivity and specificity rates ranging between 97-100% (12).

Magnetic resonance urography has a sensitivity of 75% in tumors >2 cm after contrast injection, and is indicated in

patients with contraindications for tomography or with inconclusive previous images (16). There are other procedures that confirm the diagnosis and allow not only internal visualization of the urinary tract and adjacent structures, but also allow the collection of samples from the lesion, as in the case of ureterorenoscopy with biopsy (6). In the case of the patient, a computed tomography urography was requested, without any conclusive results, that's why a resonance urography was performed, which revealed an inflammatory process with an infectious appearance that compromised the lower and middle calyceal groups, as well as the renal pelvis and proximal ureter in association with inflammatory changes in the ipsilateral pararenal fat plane. The results of the ureteral resonance report in relation to the unspecified inflammatory process were sufficient to request a uretero-renal cystoscopy with biopsy, which allowed a pathological diagnosis consistent with low-grade non-invasive urothelial carcinoma.

Primary tumors of urothelial origin are histologically differentiated into three types: transitional cell carcinoma, squamous cell carcinoma, and adenocarcinoma (1). Transitional cell carcinoma being the most frequent. The classification and morphology of urothelial cell carcinoma of the upper urinary tract is often complicated due to the complexity of obtaining adequate samples, making it difficult to distinguish between non-invasive papillary tumors, flat lesions in situ, or invasive carcinoma. According to statistics in Peru, 95.6% of urothelial cancers in the renal pelvis are of invasive origin, while 4.6% are in situ (1). In the case of uroepithelial carcinomas, the histological grade is sufficient for clinical decision-making and is closely related to the pathological stage. The classification is based on tumor, lymph node metastasis established by the WHO and the International Society of Urological Pathology. In relation to the tumor, T0 is considered when there is no evidence of a primary tumor, T1 if it invades subepithelial connective tissue, T2 if it invades the muscle layer, T3 if it invades beyond the muscle layer towards peripelvic fat or renal parenchyma; and T4 when it invades adjacent organs or extends through the kidneys into perirenal fat. In relation to regional lymph nodes, Nx when it cannot be evaluated, N0 without metastasis, N1 metastasis in a single node of 2 cm or less; and N2 when there are single-node metastases larger than 2 cm or multiple lymph nodes. Finally, in relation to distant metastases, M0 is considered when there is no distant metastasis and M1 if there is distant metastasis. (16)

The final treatment is radical nephroureterectomy, which has been shown to be associated with a reduction in associated morbidity (16). Post-surgery prognosis is favorable with low recurrence rates at 5 years. (9) Resection of the distal portion of the ureter is indicated in cases of low-risk tumors, while complete ureterectomy is the best option to cover larger margins and avoid invasion of adjacent tissues. The use of chemotherapy is reserved only for stages where metastasis is evident. In the case described in this article, radical

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nephroureterectomy was performed without complications. The results of the histopathology of the surgical piece indicated the presence of an infiltrating and exophytic tumor measuring 2.6 x 1.5 x 1.2 cm, whitish, friable that compromises the mucosa of the renal pelvis and the lower pole major calyces and the adjacent renal tissue, 16 cm distant from the ureteral margin. Renal parenchyma and calyces of the upper pole without alterations.

In patients with similar symptoms, the possibility of renal tuberculosis should be considered. This can be a great mimic of urothelial cancer. This disease occurs in vulnerable patients such as those who are immunocompromised (patients with HIV, diabetes, silicosis, being treated with corticosteroids, etc.), belonging to the male sex, smokers, alcoholics, among others (17). In 2015, the Ministry of Health of Peru (MINSA) made a statistical report on tuberculosis in the country with a total of 20,203 new cases. Of these, 80.08% were pulmonary and 19.02% were extrapulmonary (18). Approximately 8-10% of extrapulmonary TB affects the kidney (19).

Likewise, renal tuberculosis affects more men than women with a ratio of 2:1 (8). It does not have a specific clinical picture, some symptoms might be painless hematuria, crampy low back pain (usually unilateral) and dysuria, with hematuria being the most typical presentation (8,10). Other symptoms such as weight loss, anorexia or fever are less frequent (10). If suspected, the Mantoux test, a urinalysis showing hematuria and leukocyturia with a negative urine culture, is recommended (20). To confirm the diagnosis, a renal biopsy is needed to show caseous granulomas and inflammation. It is recommended to expand the studies with an abdominal tomography to rule out complications and other diseases (20). Other studies suggest the use of uro-tomography where the findings are the initial erosions in the renal calyces, as well as their progression to papillary necrosis, hydronephrosis, calyceal dilation and cavitation of the renal parenchyma (21). Renal TB was considered as a differential diagnosis due to the endemic environment in which the patient is located and the exposure received thanks to constant travel because of his profession. In addition, other risk factors such as cigarette smoking and the possibility of having been exposed to tuberculosis were recognized. That explains the laboratory tests requested to rule out this diagnosis. Due to the fact that the tomography of the kidney and urinary tract did not obtain the expected results, an uro-magnetic resonance was ordered, which found truncation and less representation of the lower renal calyces and, to a lesser extent, the middle calyceal group of the right kidney, thus evidencing thickening. and abnormal enhancement of the walls of the right renal pelvis; This is consistent with what has been reviewed in the literature. However, tests such as PPD and BK in serial urine were negative, which led away from this diagnosis.

## **CONCLUSION**

In conclusion, urothelial cancer is a diagnosis that must be taken into account when the only symptom is painless macroscopic hematuria. Associating cigarette consumption and the majority frequency in men are important risk factors. Likewise, keep in mind the differential diagnosis of renal tuberculosis, which is essential due to the epidemiological environment and the respective exposure by the patient's profession. In addition, consideration of prompt diagnosis of both conditions should be highlighted, since its delay could lead to extensive damage to the renal parenchyma, and could progress to end-stage chronic kidney disease.

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## **COMPETING INTERESTS**

All authors declare that there are no conflicts of interest

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