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## **SQUAMOUS CELL CARCINOMA OF THE URETHRA SECONDARY TO URETHRAL DIVERTICULUM IN A WOMAN. A CASE REPORT**

**Keywords:** Urethral Neoplasms; Urologic Neoplasms; Carcinoma,  
Squamous Cell.

**Palabras clave:** Neoplasias uretrales; Neoplasias Urológicas;  
Carcinoma de Células Escamosas.

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## RESUMEN

**Introducción.** El cáncer de uretra es una entidad rara que representa menos del 1% de los tumores genitourinarios. Su incidencia aumenta con la edad y, aunque su etiología no se ha esclarecido del todo, se ha establecido que los principales factores de riesgo son inflamación crónica y presencia del virus del papiloma humano. En mujeres el tipo histológico más frecuente es el adenocarcinoma, seguido por el carcinoma de células escamosas.

**Presentación del caso.** Mujer de 69 años que ingresó al servicio de urgencia de una institución de segundo nivel de atención de Maldonado (Uruguay) por síntomas urinarios persistentes. Al examen físico se evidenció un tumor en la uretra, por lo que la paciente fue valorada por el servicio de urología, el cual ordenó una resonancia magnética (RM) abdominal y pélvica que mostró un divertículo uretral que en su interior contenía un nódulo sólido con características sospechosas de malignidad. Dados los hallazgos, se realizó la resección completa del divertículo urotelial. El estudio histopatológico evidenció un carcinoma escamoso de uretra moderadamente diferenciado, invasor, y con márgenes positivos. La paciente continuó con los síntomas y fue evaluada por el servicio de oncología, que ordenó una nueva RM abdominal y pélvica que mostró carcinoma escamoso de uretra localmente avanzado con invasión de estructuras adyacentes y compromiso compromiso ganglionar, el cual era irresecable. Se inició tratamiento concurrente con radioterapia y quimioterapia (cisplatino y 5-fluorouracilo) con buenos resultados, pero a los 6 meses presentó progresión de las lesiones, por lo que se inició tratamiento sistémico de primera línea con paclitaxel, el cual no fue bien tolerado y, finalmente, la paciente falleció.

**Conclusiones.** El diagnóstico del cáncer de uretra suele ser tardío debido a que sus manifestaciones clínicas son inespecíficas. Este reporte resalta la importancia de considerar esta enfermedad en el diagnóstico diferencial en pacientes con síntomas urinarios persistentes, la necesidad de un enfoque multidisciplinario en su manejo y la limitada eficacia de los tratamientos para sus estadios avanzados.

## ABSTRACT

**Introduction:** Urethral cancer is a rare disease that accounts for less than 1% of genitourinary tumors. Its incidence increases with age and, although its etiology has not been fully elucidated, it has been established that the main risk factors are chronic inflammation and the presence of human papillomavirus. In women, the most common histological type is adenocarcinoma, followed by squamous cell carcinoma.

**Case presentation:** A 69-year-old woman presented to the emergency room of a secondary care institution in Maldonado (Uruguay) due persistent urinary symptoms. Physical examination detected a tumor in the urethra, so the patient was evaluated by

the urology department, which requested abdominal and pelvic magnetic resonance imaging (MRI) that showed a urethral diverticulum containing a solid nodule with suspicious features suggestive of malignancy. Given the findings, she underwent complete resection of the urothelial diverticulum. The histopathological study indicated a moderately differentiated squamous cell carcinoma of the urethra, which was invasive and had positive edges. Symptoms did not improve and the patient was referred to the oncology department, which requested new abdominal and pelvic MRI, evidencing locally advanced squamous cell carcinoma of the urethra with invasion of adjacent structures and unresectable lymph node involvement. Combined radiotherapy and chemotherapy (cisplatin and 5-fluorouracil) was started with good outcomes, but the lesions progressed after 6 months. First-line systemic treatment with paclitaxel was then initiated, but it was not well tolerated and eventually the patient died.

**Conclusions:** Urethral cancer is often diagnosed late because its clinical manifestations are nonspecific. This case report emphasizes the importance of including this disease in the differential diagnosis of patients with persistent urinary symptoms, the need for a multidisciplinary approach for its treatment, and the limited efficacy of treatments for advanced stages.

## INTRODUCTION

Urethral cancer is a rare neoplasm that accounts for less than 1% of genitourinary tract tumors, is more common in men, and increases with age (1-3). Although its etiology has not been fully elucidated, it has been established that its risk factors are multifactorial and may differ between men and women. In men, chronic inflammation resulting from a history of sexually transmitted infections, urethral stricture, irritation from intermittent catheterization, and prior radiotherapy increase the risk of urethral cancer. Meanwhile, in women, sexually transmitted infections, chronic inflammation and irritation from urinary tract infections, and urethral diverticula are associated with a higher probability of developing this malignancy (3,4). Moreover, it has been reported that a significant risk factor for the onset of urethral cancer in both sexes is infection with human papillomavirus (3,5-7).

Urothelial carcinoma is the most common histological type of urethral cancer (54-65%), followed by squamous cell carcinoma (16-22%), and adenocarcinoma (10-16%) (8,9). However, it has been established that adenocarcinoma predominates in women (38-47%), followed by squamous cell carcinoma (25-28%) and urothelial carcinoma (25-28%), while secondary urethral carcinoma is the most common type in men (78%), followed by squamous cell carcinoma (12%) and adenocarcinoma (5%) (8,9).

Urethral cancer is frequently diagnosed late due to its nonspecific clinical manifestations, while urinary symptoms may be mistaken for recurrent urinary tract infections; additionally, confirmation requires cystoscopy with biopsy

and urinary cytology (8,9). Similarly, given its low frequency, there are no established therapeutic guidelines, and treatment relies on strategies used for other genitourinary neoplasms. In most cases, the responses obtained are partial, exhibiting low survival rates (8-10). This article describes the case of a patient with squamous cell carcinoma of the urethra secondary to a urethral diverticulum, emphasizing the diagnostic and therapeutic challenges in the treatment of this rare disease.

## CASE PRESENTATION

A 69-year-old woman presented to the emergency room of a secondary care institution in Maldonado (Uruguay) in February 2023, exhibiting urinary symptoms (nocturia, pollakiuria, and dysuria) that had persisted for the past six months. Prior to admission, the patient had attended multiple medical appointments for the same reason.

Upon admission, the patient did not present with hematuria, fever, vaginal discharge, or other symptoms, and reported no significant family history. Her medical history included gastritis, treated with omeprazole, and a benign spinal disease, treated with tramadol and tizanidine. The patient reported observing a small, painful lump in the vagina while washing three months before admission.

Physical examination revealed a hard, oval-shaped lump measuring approximately 3cm in the urethra, which extended proximally (3cm) and distally (1cm) above the vaginal introitus. No inguinal lymphadenopathy was observed upon palpation. On the same day, the patient was assessed by the urology department, which requested abdominal and pelvic magnetic resonance imaging (MRI) that revealed a urethral diverticulum measuring approximately 2.7cm and containing a solid nodule of 2.4cm with features suggestive of malignancy. The study did not show lymph node involvement or invasion of adjacent structures.

Based on these findings, the urology department recommended total resection of the urothelial diverticulum via hydrodissection, with urethral closure around a silicone catheter and reconstruction of the vaginal wall. Cystoscopy was not performed as the MRI provided sufficient information to ensure successful surgical planning, and the surgery took place three weeks after the patient's admission due to logistical difficulties at the hospital that delayed procedure coordination. The excised diverticulum, due to cancer suspicion, underwent histological analysis, which revealed a moderately differentiated squamous cell carcinoma of the urethra, characterized as aggressive with positive edges. No residual diverticular epithelium was identified.

The patient was discharged five days after later; however, at the postoperative follow-up with urology, it was found that urinary symptoms persisted, prompting a consultation with the oncology department. In this consultation, which took place 20 days following the intervention, a chest computed tomography (CT) scan was requested, showing no secondary lesions. Additionally, abdominal and

pelvic MRI revealed irregular, stenosing thickening of the urethral walls with total involvement, exhibiting an intermediate signal on T2 with diffusion restriction. This indicated an irregular thickening measuring approximately 28x36x40mm infiltrating the vesicovaginal septum, the anterior vaginal wall, the bladder floor, and the external sphincter, which was not observable. The MRI detected potential involvement of the left ureter at the ureterovesical junction, characterized by thicker walls, and a 19mm adenomegaly with irregular edges in the left internal iliac chain. Furthermore, nodes measuring up to 6mm with similar characteristics were noted in the right internal iliac chain.

The tumor board deliberated on the case and, due to the presence of locally advanced squamous cell carcinoma of the urethra with invasion of adjacent structures and unresectable lymph node involvement, recommended combined treatment with radiotherapy (RT) and chemotherapy (CHT).

In March 2023, 20 days after the oncology consultation, the patient initiated RT at a dose of 45Gy to the pelvis and 60Gy to the tumor and lymph node regions, administered in 25 fractions over 5 weeks, Monday through Friday. Moreover, she underwent concomitant CHT with cisplatin and 5-fluorouracil, which was administered during the first and last week of RT. She had adequate tolerance and a favorable clinical and imaging response and continued with clinical and imaging follow-up, with her last appointment in the oncology department taking place in August 2023.

However, in November 2023, the patient exhibited progression of the existing lesions, prompting the initiation of first-line systemic treatment: weekly paclitaxel at a dose of 80mg/m<sup>2</sup> for two months with palliative intent. However, she experienced poor tolerance, clinical deterioration, further lesion progression, and ultimately passed away in January 2024.

## DISCUSSION

Primary urethral carcinoma is a rare cancer, with a higher incidence in men compared to women, which is typically identified around the sixth decade of life (1,2), as in the reported case. Over 70% of women diagnosed with primary urethral carcinoma experience recurrent urinary tract infections, irritative voiding symptoms, and dyspareunia (4), as observed in our patient. This fact is of paramount importance, as the nonspecificity of the clinical manifestations of this disease poses a challenge and delays the diagnosis, as mentioned earlier (10).

In order to make a definitive diagnosis of primary urethral carcinoma, cystoscopy with biopsy must be performed (3,8,9,11). Nonetheless, in this case, this endoscopic examination was not necessary because the MRI was sufficient to facilitate the complete resection of the urothelial diverticulum, as it provided sufficient information for surgical planning. Regional, local, and distant disease extension are evaluated through cross-sectional imaging, which includes positron emission tomography, CT, and MRI (3).

In women, adenocarcinoma is the most common histological form of urethral cancer. However, the histopathological examination of the tumor revealed that our patient had squamous cell carcinoma, the second most frequent subtype in this population (9). In a cohort study that included 2 131 patients with primary urethral cancer (1 268 men and 869 women), Sui *et al.* (12) reported that women more frequently presented with high-grade tumors, locally advanced disease ( $\geq cT2$ ), and positive lymph nodes. This is consistent with the reported case, in which the patient presented with locally advanced squamous cell carcinoma of the urethra with invasion of adjacent structures and unresectable lymph node involvement.

Given the low frequency and complexity of primary urethral cancer, as well as the need for multidisciplinary treatment, it is recommended to arrange for a multidisciplinary care team including urologists, medical oncologists, and radiation oncologists (13); in the present case, the selection of treatment was discussed by a tumor committee. Primary urethral cancer treatment is based on reports of small case series and literature reviews (9,14) and on the extrapolation of the treatment of other urinary tumors (3,14), such as bladder cancer (10), as the literature on this subject is scarce and limited to case reports. Accordingly, the methods for treating these tumors vary widely and include cystectomy, transurethral resection, urethrectomy (partial or total), prostatectomy, penectomy, cystoprostatectomy plus urethrectomy, RT, CHT, among others (4,14-17). These methods may be used alone, i.e. as monotherapy (surgery or radiation), combined as multimodal therapy, which may be dual (surgery+radiation, surgery+chemotherapy, or chemotherapy+radiation), or as triple therapy (surgery+radiation+chemotherapy) (14,15).

In locally advanced tumors, such as the one in the reported case, it has been established that the primary treatment of patients with unsuspicious lymph nodes consists of chemoradiation and possibly surgery, neoadjuvant CHT with consolidative surgery, or RT monotherapy, while consolidative surgery is optional in combination with CHT and/or RT in patients with clinically positive lymph node metastases (14). In the present case, following an assessment by the tumor committee and in line with the literature, combined RT and CHT with a possible subsequent surgery was defined as treatment, which resulted in a short-lived partial positive response, since six months after the end of treatment (November 2023), the lesions showed local progression.

The literature on relapse and metastasis treatment in cases of primary urethral carcinoma is scarce, stating that patients usually have a poor prognosis and their management is based on multimodal treatment (4). Likewise, it has been described that treatment with fluorouracil and mitomycin C with co-adjuvant external irradiation therapy is an option to consider in patients with locally advanced primary squamous cell carcinoma of the urethra (8). In the present case, upon progression of the disease, a weekly regimen with paclitaxel was used, but

the patient did not tolerate it and the expected response was not achieved. This demonstrates the aggressiveness of squamous cell carcinoma of the urethra and the therapeutic difficulties associated with this type of advanced tumors.

It is worth noting that while independent prognostic factors for survival and local control of urethral cancer encompass involvement of the entire urethra; tumor size, histologic features and stage, and nodal status and disease site (18), information on the relationship between prognostic factors and treatment outcomes is scarce given that this type of cancer is extremely rare (17,18). Therefore, international health authorities aim to optimize the treatment of advanced urethral cancer to improve oncologic efficacy and quality of life in patients with this disease (17).

## CONCLUSIONS

The present case illustrates the diagnostic difficulty of squamous cell carcinoma of the urethra in women given its nonspecific presentation and the lack of standardized clinical guidelines. This patient was diagnosed late because her clinical manifestations consisted of urinary symptoms that are usually associated with benign diseases, thus highlighting the importance of considering this disease in the differential diagnosis of patients with persistent urinary symptoms.

This case also demonstrates the need for a multidisciplinary approach and the value of timely access to specialized evaluation to optimize the treatment of urethral cancer. Furthermore, despite treatment with CHT and RT, the patient's progress was unfavorable, reflecting the limited efficacy of current treatment strategies in advanced stages and the pressing need to develop prospective studies to define better treatment plans and provide better therapeutic alternatives for this disease.

## ETHICAL CONSIDERATIONS

Informed consent was obtained from the patient for the preparation of this case report. She agreed to the use and publication of her medical data. Confidentiality of the information was guaranteed throughout the document.

## CONFLICTS OF INTEREST

None stated by the authors.

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