



# Plasmacytoid Urothelial Carcinoma of the Bladder: Case Report and Review of the Literature

## *Carcinoma urotelial de vejiga, variante plasmocitoide: Reporte de un caso y revisión de la literatura*

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### Abstract

**Introduction** Plasmacytoid urothelial carcinoma (PUC) of the bladder is a rare histological variant, accounting for 1 to 3% of the invasive urothelial carcinomas, and it is typically aggressive. So far, it has not been well characterized, and the literature is based on reports and case series.

**Case Report** A 70-year-old male patient presenting with 4 months of constitutional and urinary symptoms, with an ultrasound finding of bilateral hydronephrosis and diffuse thickening of the bladder walls. In the cystoscopy, trigone of infiltrated appearance, a biopsy was performed, whose immunohistochemistry revealed a PUC. The abdominopelvic image showed an infiltrative lesion that compromised the muscle of the bladder and extended to the perivesical fat, without adequate plane of cleavage with the prostate and a single hypogastric adenopathy suspected of malignancy. It was classified as cT3b vs cT4aN1M0 (chest computed tomography [CT] negative for malignancy), and the patient was submitted to a radical cystoprostatectomy, extended pelvic lymphadenectomy and non-continent urinary diversion with ileal conduit. The pathology revealed a diffuse PUC with prostatic stromal involvement and 22 of 39 lymph nodes positive for malignancy. Finally, the patient presented a series of postoperative complications and died.

**Conclusion** Plasmacytoid urothelial carcinoma of the bladder is a rare entity, characterized by high aggressiveness, an advanced stage at the time of diagnosis, and a poor prognosis. Currently, an aggressive approach is recommended due to its high invasive potential.

### Keywords

- ▶ plasmacytoid urothelial carcinoma
- ▶ urothelial carcinoma
- ▶ bladder
- ▶ treatment
- ▶ prognosis

### Resumen

**Introducción** El carcinoma urotelial plasmocitoide (CUP) de la vejiga es una variante histológica poco frecuente; representa el 1 al 3% de los carcinomas uroteliales invasivos y es típicamente agresiva. Hasta el momento no ha sido bien caracterizada, y la literatura se basa en reportes y series de casos.

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**Palabras-clave**

- ▶ carcinoma urotelial plasmocitoide
- ▶ carcinoma urotelial
- ▶ vejiga
- ▶ tratamiento
- ▶ pronóstico

**Reporte de Caso** Paciente masculino de 70 años presentando por 4 meses síntomas constitucionales y urinarios, con hallazgo ecográfico de hidronefrosis bilateral y engrosamiento difuso de las paredes vesicales. En la cistoscopia, trígono de apariencia infiltrada, se realizó biopsia cuya inmunohistoquímica reveló un CUP. En imagen abdominopélvica, se evidenció lesión infiltrativa que comprometía la muscular de la vejiga y se extendía a la grasa perivesical, sin adecuado plano de clivaje con la próstata y un único ganglio hipogástrico sospechoso de malignidad. Se clasificó como cT3b vs cT4aN1M0 (TAC tórax negativo para malignidad) y fue llevado a cistoprostatectomía radical, linfadenectomía pélvica extendida y derivación urinaria no continente con conducto ileal. La patología reveló un carcinoma urotelial variante difusa plasmocitoide con compromiso de estroma prostático y 22 de 39 ganglios positivos para malignidad. Finalmente, el paciente presentó una serie de complicaciones posoperatorias y falleció.

**Conclusión** El carcinoma urotelial de vejiga variante plasmocitoide es una entidad poco frecuente, caracterizada por alta agresividad, un estadio avanzado al momento del diagnóstico, y un pobre pronóstico. En la actualidad, se recomienda un enfoque agresivo dado su alto potencial invasivo.

**Introduction****Epidemiology**

Bladder cancer is the most frequent neoplasia affecting the urinary tract, and the 9th neoplasia diagnosed worldwide.<sup>1</sup> Most bladder malignancies present as epithelial tumors, with 90% of the cases being urothelial.<sup>2</sup> In recent decades, multiple variants of this type of tumor have been investigated, and some properties regarding their treatment and prognosis have been described.<sup>2</sup>

Plasmacytoid urothelial carcinoma (PUC) of the bladder is a rare histological variant of the urothelial carcinoma (UC). It was recognized by the World Health organization (WHO) in 2004.<sup>3,4</sup> Its first description was made by Sahin et al in 1991.<sup>5,6</sup> The incidence of PUC is higher in males (3:1), with a mean diagnosis age of 69 years old, and represents between 2.7 and 3% of all urothelial bladder cancers.<sup>7,8</sup> There have been less than 100 cases described in the literature;<sup>6</sup> therefore, the biology, prognosis and treatment of this pathology are still hard to establish.<sup>9</sup> It is considered a very aggressive variant with a tendency to recur and to develop metastasis early in its course,<sup>5,10</sup> presenting with invasion at the time of the diagnosis in 81.9% of the cases.<sup>11</sup> Keck et al published one of the largest series of cases (32 cases), proving PUC to be high grade in 100% of the patients, and with distant metastasis at the time of the diagnosis in 60% of the cases.<sup>12</sup>

**Clinical Presentation**

The clinical presentation of PUC is frequently late onset.<sup>5</sup> Its main debut symptom is hematuria; however, it will only appear in late stages. Other symptoms include: urgency, urinary frequency increase, and low abdominal pain.<sup>8</sup> Metastasis often affects adjacent pelvic structures such as the bones, the peritoneum, the gastrointestinal tract, and the scrotum,<sup>3,6,13,14</sup> and even heart distant metastasis have been

described.<sup>15</sup> Ricardo-Gonzalez et al evaluated 15 patients with PUC and found this tumor presenting with recurring extension to the peritoneum, often compromising serous surfaces.<sup>16</sup>

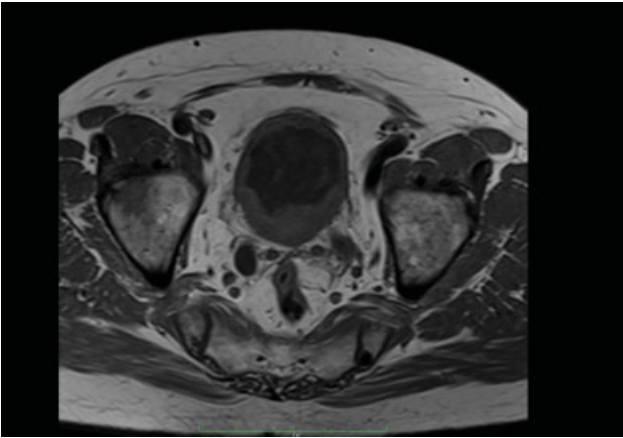
One of the hypotheses for the aggressiveness of this tumor and its extension pattern is the loss of E-cadherin (a necessary protein for cell to cell adhesion),<sup>6,17</sup> which is absent in most PUCs and can help distinguish it from other types of UCs.<sup>11</sup> It is postulated that the absence of E-cadherin leads to loss of cellular differentiation, allowing the PUC cells to invade the surrounding tissues along the fascial planes and toward the lymph nodes.<sup>14,18</sup>

**Case Report**

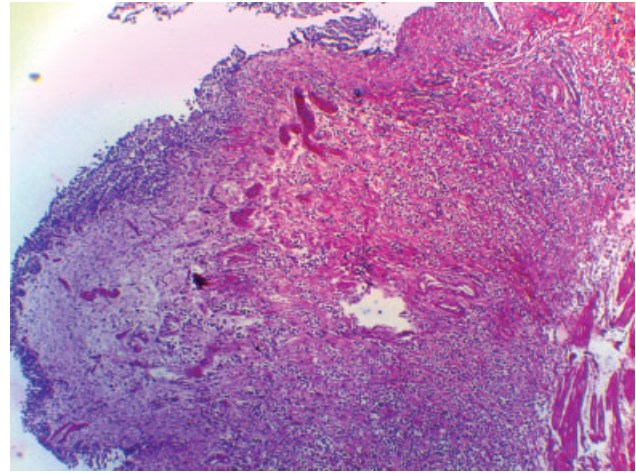
We present the case of a 70-year-old male patient, hypertensive, who arrived at the consultation reporting 4 months of constitutional symptoms (asthenia, adynamia, weight loss), decrease in urinary stream gage, post urination drip, nycturia, rectal exam negative for malignancy, and an ecographic finding of thickened bladder walls and bilateral hydronephrosis. Bilateral nephrostomies were placed, and a cystoscopy was performed, revealing an infiltrated-like trigone, without defined masses. The results of this tissue biopsy reported carcinomatosis.

Immunohistochemistry studies of this biopsy evaluated cytokeratin 7 (CK7), cytokeratin 20 (CK20), endothelial transcription factor 3 (GATA3), cytokeratin 5/6 (CK 5/6), P63, prostate-specific antigen (PSA) and prostate-specific acid phosphatase (PSAP), resulting positive for CK7 and GATA3, supporting the diagnosis of PUC.

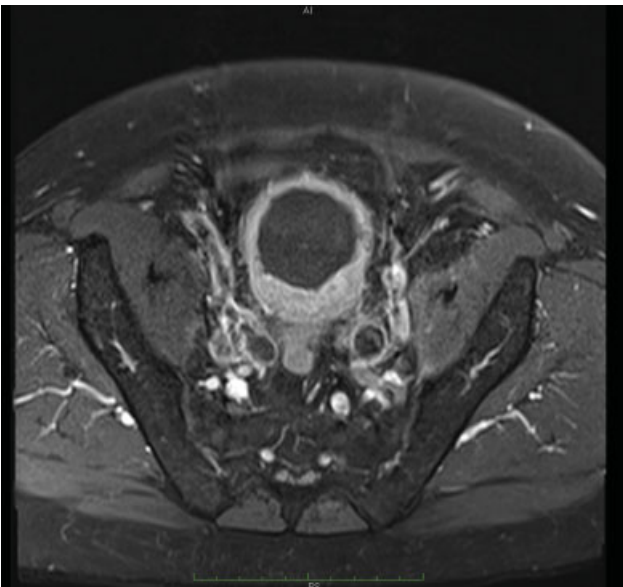
An infiltrative lesion is shown in the magnetic resonance imaging (MRI) (► **Figs. 1** and **2**) on the posterior and lateral walls of the bladder, extending to the perivesical fat, infiltrating ureterovesical junction and resulting in hydroureteronephrosis. It relates to the prostate gland



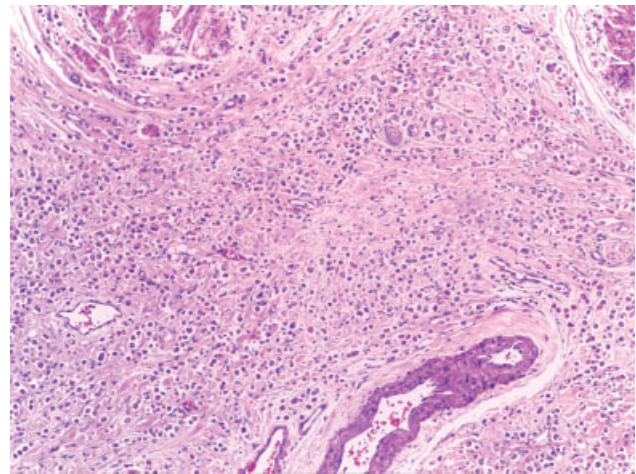
**Fig. 1** Lesion with infiltrating aspect on the posterior wall of the bladder.



**Fig. 3** Tumor with urothelial origin, invading the muscle of the bladder.



**Fig. 2** Lesion with infiltrating aspect on the lateral walls of the bladder.



**Fig. 4** Tumor cells; notice the big cell nucleus, the discohesive pattern, and the plasmacytoid morphology.

without an adequate cleavage plane, with a sole hypogastric node of 7 mm, suspicious of malignancy. The lesion was classified as CT3b vs cT4aN1M0. A computed tomography (CT) of the chest was negative for pulmonary metastasis.

The patient was submitted to radical cystoprostatectomy, extended pelvic lymphadenectomy, and non-continent urinary heterotopic derivation, with the intention of performing adjuvant chemotherapy later. During the surgery, we observed both ureters with macroscopic compromise in their distal third. However, the freeze biopsy turned out negative for malignancy.

Pathology samples (→ **Figs. 3** and **4**) note: PUC, invading the perivesical tissue and compromising the stroma of the prostate, the left ureter, and the left seminal vesicle. Lymphovascular invasion present. Out of a total of 39 nodes, 22 were compromised by the carcinoma.

During the evolution of the disease, the patient developed postoperative ileus and required reoperation for an unnoticed rectum lesion, presenting fecal peritonitis, abdominal sepsis, and eventual death 14 days after the first intervention.

## Discussion

### Diagnosis

Plasmacytoid urothelial carcinoma of the bladder is often diagnosed at a late stage due to the absence of hematuria and of a bladder tumor identifiable by conventional methods. Cystoscopic findings are usually mucosal induration and thickened vesical wall,<sup>19,20</sup> although other series describe focal masses.<sup>21,22</sup> In the case described in the present article, the patient presented with unspecific symptoms, never with hematuria, and the cystoscopic findings only revealed an infiltrated trigone.

Histologically, this tumor is characterized by a discohesive growth of cells with plasmacytoid morphology, with eccentric nucleus and eosinophilic cytoplasm, frequently extending to the vesical floor and to the perivesical fat tissue.<sup>21</sup> The architectural

patterns of PUC may vary. Cells may present in simpler lines, small nests or discohesive patterns diffusely disposed in layers.<sup>23</sup> These aggressive growth patterns explain the poor prognosis of PUC.<sup>23</sup> When the histological appearance is highly suspicious of PUC, immunohistochemistry plays a key role in the diagnosis,<sup>2</sup> since the PUC cells present cytoplasmic immunoreactivity to cytokeratins, especially those with high molecular weight, of which CK7 and CK20 play an important role. CD138 is a cytoplasmic cellular differentiation marker also positive in PUC.<sup>24,25</sup> Other patterns of immunohistochemistry found in PUC are: CK8, CK18, CK19, 34 $\beta$ E12, CD15, and GATA3.

Generally, this pathology is negative for the common antigens found in leucocytes: multiple myeloma-1/interferon regulatory factor-4 (MUM1/IRF4), light chains, human melanoma black-45 (HMB-45), S-100, desmin, chromogranin, synaptophysin, vimentin, and specific prostatic antigens.<sup>20,21,26,27</sup>

Recently, GATA3 has shown to be of value in UC, including PUC.<sup>3,22</sup> Zhao et al reported high specificity of GATA3 as a diagnostic marker in PUC, showing a higher expression in regional metastasis.<sup>28</sup> Therefore, GATA3 seems to be an appropriate marker for differential diagnosis, useful in recognizing the urothelial lineage of PUC in metastatic patients.<sup>29</sup> In our case, CK7 and GATA3 were positive.

The differential diagnosis of PUC includes other tumors with plasmacytoid morphology, such as plasmacytoma, lymphoma, diffuse gastric cancer, breast lobular cancer, neuroendocrine carcinoma, and rhabdomyosarcoma.<sup>21,23</sup>

### Treatment

The therapeutic approach for this pathology remains in discussion due to its rarity. So far, due to the few cases reported in the literature, there are no clear guides for the treatment of PUC.<sup>21</sup> Radical cystectomy is considered the first line of treatment for PUC when it is non-metastatic or non-muscle-invading.<sup>5</sup> A possible benefit with adjuvant chemotherapy is also suggested.<sup>20</sup>

The role of chemotherapy as a neoadjuvant for PUC remains uncertain; only a small number of cases have been published on this subject.<sup>11,26,30</sup> Kohno et al described an advanced case of PUC with complete response to neoadjuvant chemotherapy with two cycles of methotrexate, etoposide, vinblastine and cisplatin.<sup>31,34</sup> This data is consistent with the latest study by Gunaratne et al, which reports the case of another patient with muscle-invading PUC treated with four cycles of chemotherapy with gemcitabine and cisplatin, leading to a complete histologic response (pT0).<sup>30</sup>

The optimal scheme of chemotherapy in this pathology persists to be concerted, used as a neoadjuvant. Preliminary researches indicate satisfactory results, although larger and longer follow-up studies are needed.<sup>30</sup>

### Prognosis

The diagnosis of late onset PUC indicates a poor prognosis, especially because a third of the cases are metastatic at the time of presentation.<sup>11,32</sup>

In a series of 30 patients, the mean global and specific survival rate was of 19 and 22 months respectively.<sup>18</sup> Another series of 31 patients found a mean survival rate of 17.7 months.<sup>11</sup>

Cockerill et al<sup>33</sup> evaluated results after radical cystectomy in patients with PUC compared with a control group with pure UC. It was found that the PUC patients had more extravesical disease ( $\geq$  pT3) (83 versus 43%) and more positive margins at the surgery stage (31 versus 2.1%). Additionally, PUC was associated with a smaller global survival rate (27% versus 45% at 5 years, risk ratio [RR]: 1.4;  $p = 0.04$ ), a smaller specific survival rate than cancer (36% versus 57% at 5 years, RR: 1.7;  $p = 0.01$ ), and a smaller survival free of local recurrence (63% versus 81% at 5 years, RR: 2;  $p = 0.01$ ).<sup>33</sup> Kaimakliotis et al<sup>18</sup> found in their study a greater incidence of positive ureteral margins in patients with PUC (32%) when compared with patients with conventional UC (3.7%) or with the micropapillary variant (17.9%), resulting in statistically significant data.<sup>18</sup>

### Conclusion

Plasmacytoid urothelial carcinoma is a very infrequent variant of urothelial carcinoma, with very few reports in the literature; because of this, its biology, prognosis and treatment are not clearly established. It is considered a very aggressive variant, with a tendency to recur and to present metastasis at an early stage. Its diagnosis is generally late, due to clinical manifestations happening in advanced disease cases and cystoscopic findings resulting unspecific most of the times. Its histologic characteristic is discohesive growth of plasmacytoid morphology cells, with a generally invading behavior. In immunohistochemistry stains, these cells are positive for different markers, which enable their distinction from conventional UC. The therapeutic approach remains in discussion due to the rarity of this tumor. Radical cystectomy is the gold standard treatment in muscle-invasive tumors without metastasis. Chemotherapy has been used as a neoadjuvant and adjuvant treatment, so far with promising results. However, larger studies are required to draw conclusions and to reach a consensus.

### Note

The present study was conducted at IPS Universitaria Clínica León XIII, Medellín – Antioquia, Colombia.

### Ethical Considerations

The present work followed the rules for research with human being according to what is provided by resolution no 008430/1993 in the 2013 Declaration of Helsinki. It was a non-experimental research with minimal risk. Even though the main goal of medical researches is to produce new knowledge, this goal will never prevail over the rights and interests of the people participating in them.

### Conflicts of Interests

The authors have no conflict of interests to declare.

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