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Metastatic Urothelial Carcinoma of Occult Primary Origin Revealed by a Necrotic Inguinal Lymph Node: A Rare Case Report

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Abstract

Introduction: *Occult primary urothelial carcinoma is an extremely rare entity that may present as isolated lymph node involvement without visible bladder or ureteral lesions, making diagnosis particularly challenging.*

Case Presentation: *We report the case of a 91-year-old man presenting with a left inguinal swelling evolving over four years. Examination revealed a necrotic, fistulized mass with no urothelial lesions on cystoscopy. Biopsy showed a poorly differentiated carcinoma (CK7+/CK20+/p63+/p40+/GATA3−), initially suggesting squamous differentiation, but the lymphatic distribution and suspicious ureteral thickening supported an occult urothelial origin. A multidisciplinary management approach was undertaken. Systemic chemotherapy was not initiated due to age and comorbidities. Local wound care and antibiotic therapy led to partial improvement and clinical stabilization without visceral progression.*

Discussion: *This case illustrates the diagnostic complexity of dedifferentiated urothelial carcinomas with atypical immunohistochemical profiles. Loss of GATA3 expression, though uncommon, does not exclude urothelial origin, especially in high-grade tumors. Presentation as isolated inguinal lymphadenopathy is exceedingly rare.*

Conclusion: *Diagnosis of occult urothelial carcinoma requires multidisciplinary collaboration and careful integration of clinical, radiological, and pathological data. In elderly or frail patients, a conservative, symptom-oriented approach is often the most appropriate. Reporting such rare cases is essential to improve understanding of the atypical presentations and dissemination pathways of urothelial carcinoma.*

Keywords: Urothelial Carcinoma, Occult Primary, Inguinal Lymphadenopathy, GATA3, Immunohistochemistry, Case Report.

Introduction

In cancer diagnosis and management, accurately identifying the primary origin of tumor cells is crucial, as it directly guides therapeutic decisions. Occult cancer refers to a rare condition in which the primary lesion remains clinically undetectable, making diagnosis challenging. In such cases, the metastatic lesion is typically identified first through clinical evaluation and histopathological examination. Occasionally, the microscopic primary tumor is only discovered post-mortem during autopsy examinations [1].

Most reported cases of occult malignancy involve breast cancer, with fewer instances observed in thyroid and gynecologic origins [1, 2]. Rarely, certain occult somatic tumors may initially present as acute cerebral infarction [3, 4]. The incidence of occult cancer remains very low, representing only 0.3% to 1.0% of

newly diagnosed breast cancers [5, 6].

Urothelial carcinoma (transitional cell carcinoma) arises from the transitional epithelium of the urinary tract. Although it typically develops within the urinary bladder, ureter, or renal pelvis, distant metastases are uncommon and usually appear only in advanced disease stages following diagnosis. To date, presentation of urothelial carcinoma with metastasis as the initial clinical manifestation has been exceedingly rare.

Case Presentation

A 91-year-old male with no significant surgical history had a past medical history notable for tuberculous pericarditis successfully treated five years earlier. The patient's history dated back approximately four years, marked by the gradual onset of a painless left inguinal swelling, associated with edema of the left lower limb. The course was slowly progressive, with a gradual increase in tumor size over the past two years, without fever or pain, evolving in a context of apyrexia and relatively preserved general condition. On physical examination, the patient was alert, in good general condition, with a Performance Status (PS) of 1. The conjunctivae were normally colored, and edema of the left lower limb was noted.

Urological examination showed a preserved diuresis, without lumbar tenderness or suprapubic pain. Locally, there was a left inguinal swelling fistulized to the skin, firm and painless, without acute inflammatory signs. The external genitalia appeared normal. Digital rectal examination revealed a prostate estimated at 50 grams, firm and regular, with a supple bladder base.

Biological investigations showed hemoglobin at 12.7 g/dL, C-reactive protein (CRP) at 184 mg/L, and leukocytosis at 14,310/µL, indicating a biological inflammatory syndrome. Renal function was preserved (creatinine 12.7 mg/L, urea 0.35 g/L) and serum potassium was normal (4.58 mEq/L). Urine culture was sterile, and total PSA was 3.14 ng/mL, within normal limits for the patient's age.

Inguinal ultrasound performed in October 2021 revealed bilateral hypogastric and left inguinal lymphadenopathy, some with suspicious features. Thoraco-abdominopelvic CT (TAP) demonstrated a dilated and tortuous lumbar ureter, upstream of a parietal thickening at the L5–S1 level, measuring approximately 36 mm and enhancing after contrast injection—suggestive of a possible ureteral infiltrating lesion. The urinary bladder contained a right lateral wall diverticulum without suspicious thickening or mucosal irregularity, while the prostate was enlarged (66.8 mL). At the left inguinal region, there was a heterogeneous, ulcerative-necrotic mass, poorly demarcated, with heterogeneous post-contrast enhancement and central necrotic areas.

The mass encased the superficial femoral artery and vein (which remained patent), infiltrated the sartorius muscle laterally and the adductor longus medially, and was associated with diffuse infiltration of adjacent subcutaneous fat. Bilateral iliac lymphadenopathy was also noted, more pronounced on the left side (largest node measuring 24.9 × 20.5 mm).

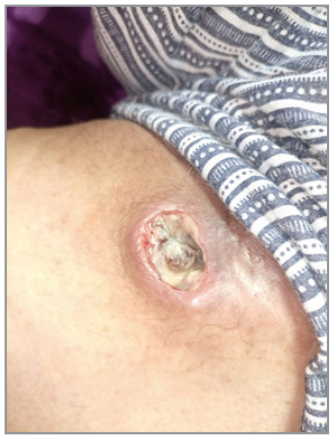

Figure 1: Left inguinal mass fistulized to the skin, showing a necrotic ulceration with seropurulent exudate.

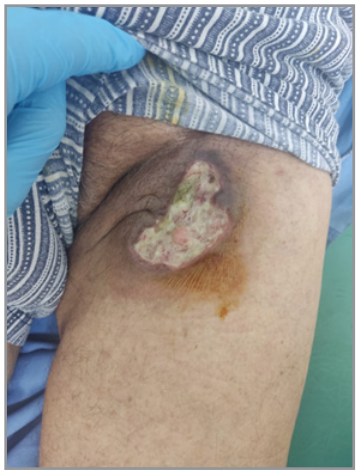

Figure 2: Evolution after three months: drier ulcerated necrotic wound with reduced exudation, indicating partial local improvement.

At the thoracic level, there was circumferential pleural thickening of the right hemithorax and three hepatic arterial phase enhancements. Cystoscopy showed a normal urethra, two visible ureteral orifices, and a bladder of good capacity, with a diverticulum of the right lateral wall and bladder base, but no mucosal lesions or suspicious thickening.

Biopsy of the left inguinal mass revealed a secondary subcutaneous localization of a poorly differentiated carcinoma.Immunohistochemical (IHC) staining demonstrated a CK7+/CK20+, p63+, p40+, and GATA3− profile, initially suggestive of a squamous cell carcinoma.

However, several morphological and clinical findings—notably the enhancing ureteral thickening, the presence of a thick-walled bladder diverticulum, and the pelvic and inguinal nodal distribution—strongly supported a possible occult urothelial origin. Although GATA3 negativity is more typical of squamous differentiation, it does not exclude urothelial carcinoma, particularly in high-grade dedifferentiated tumors, where GATA3 loss has been reported in up to 10–20% of cases.

The absence of any identifiable cutaneous, rectal, prostatic, or digestive primary lesion further strengthened the hypothesis of a high-grade metastatic urothelial carcinoma of unknown primary origin. PET-CT revealed hypermetabolic superficial and femoral left inguinal lymph nodes, consistent with secondary involvement, and a right bladder diverticulum with a thickened wall requiring further evaluation. It also showed diffuse interstitial pneumonia with mediastinal hypermetabolic lymph nodes, likely inflammatory or infectious, and no other suspicious foci of hypermetabolism, particularly in the soft tissues of the lower limbs.

Follow-up CT TAP confirmed the persistence of necrotic left inguinal lymph nodes, with increase in size and persistent cutaneous fistulization.The posterolateral bladder diverticulum remained unchanged and non-suspicious, and hepatic cystic lesions corresponded to simple biliary cysts. Finally, colonoscopy demonstrated a normal rectocolonic mucosa with no evidence of malignancy.

Taken together, the morphological, radiological, and immunohistochemical findings a CK7+/CK20+, p63/p40+ carcinoma, associated with pelvic and inguinal lymph node metastases, suspicious ureteral thickening, and a bladder diverticulum with wall irregularity favored the diagnosis of a metastatic urothelial carcinoma of occult primary origin.

This case illustrates the rarity and diagnostic complexity of dedifferentiated urothelial carcinomas, which may mimic squamous cell carcinoma and initially present with isolated inguinal lymphadenopathy. A multidisciplinary management approach was undertaken, involving the urology, medical oncology, and pathology teams. Locally, control of the inguinal mass initially relied on daily local wound care, including cleansing of the cutaneous fistula, application of absorbent and antiseptic dressings, and infection prevention.

A probabilistic antibiotic therapy was initiated because of the infectious risk related to tumor necrosis and cutaneous fistulization, resulting in favorable clinical evolution and progressive drying of the wound.

On a systemic level, after multidisciplinary discussion, systemic chemotherapy was not initiated due to the expected tolerance profile in a very elderly patient and the high risk of hematologic and renal toxicity. An oral chemotherapy regimen or carboplatin-based treatment was considered but not implemented, given the frailty of the patient and borderline renal function.

Immunotherapy, which is recommended in locally advanced or metastatic urothelial carcinomas not eligible for platinum-based chemotherapy, was also discussed.

However, due to the absence of a histologically confirmed primary urothelial lesion in the bladder or ureter, and uncertainty regarding the exact tumor origin, this option was not pursued. Radiological follow-up showed persistent necrotic left inguinal lymphadenopathies, with an increase in size and persistent cutaneous fistulization, but no evidence of new distant metastases.

Clinically, the patient remained stable over several months, with preserved diuresis, absence of pelvic pain, and an overall well-maintained general condition. This relatively slow progression, in the absence of rapid visceral dissemination, suggests a low-grade or indolent carcinoma, compatible with certain differentiated urothelial tumor variants exhibiting an atypical immunohistochemical profile (notably loss of GATA3 expression). A multidisciplinary management approach was undertaken, involving the urology, medical oncology, and pathology teams.

Locally, control of the inguinal mass relied on daily wound care, including cleansing of the cutaneous fistula, application of antiseptic dressings, and prevention of secondary infection.

Empirical antibiotic therapy was initiated, resulting in local improvement and progressive drying of the wound. Systemically, after multidisciplinary discussion, systemic chemotherapy was not initiated due to the high risk of toxicity and the expected limited tolerance in a 91-year-old patient. An oral or carboplatin-based chemotherapy regimen was considered but ultimately not administered due to the patient's frailty and borderline renal function.

Immunotherapy, which is recommended for locally advanced or metastatic urothelial carcinoma in patients unfit for platinum-based regimens, was discussed but not initiated in the absence of a histologically confirmed primary tumor.

Radiological follow-up showed persistent necrotic left inguinal lymphadenopathies, with increased size and ongoing cutaneous fistulization, but no evidence of new distant metastases.

Clinically, the patient remained stable for several months, with preserved diuresis, absence of pelvic pain, and overall good general condition. This slow progression, without rapid visceral dissemination, supports the hypothesis of a low-grade or indolent carcinoma, consistent with certain differentiated urothelial tumor variants exhibiting an atypical immunohistochemical profile (loss of GATA3 expression).

Discussion

This case illustrates the diagnostic and therapeutic complexity posed by metastatic urothelial carcinoma (UC) tumors without an identified primary focus (i.e., "urothelial carcinoma of unknown primary"). Although the urothelial origin is the most frequent for this type of tumor in the genitourinary system, presentation as a fistulized inguinal lymph node in an elderly patient, in the absence of a bladder or ureteral tumor visible on imaging and endoscopy, remains an exceptional entity [7, 8].

Carcinomas of unknown primary (CU) represent approximately 3–5% of malignant solid tumors and are often associated with a poor prognosis due to delayed diagnosis and a lack of targeted therapy [9]. In this context, UC of unknown primary is even rarer, and few series report it [10]. The fact that our patient presents with a pelvic and inguinal lymph node mass, suspicious ureteral thickening, and a bladder diverticulum with wall irregularity reinforces the hypothesis of a urothelial origin, although this is not confirmed.

In the literature, a few isolated cases describe metastases (pulmonary, lymph node, bone) revealing occult urothelial carcinoma (UC), such as the case reported by Bu et al. (2019) in a patient with multi-organ involvement and no identifiable primary lesion [10]. Our case falls within this category and illustrates one of the most extreme forms of the diagnostic challenge in urology-oncology.

The diagnosis of occult UC requires exhaustive investigation using morphological imaging: thoraco-abdomino-pelvic CT scan, MRI if necessary, and PET-CT to identify occult foci. In our case, the CT scan revealed enhanced ureteral thickening (36 mm) and a right lateral bladder diverticulum, two structural features that could suggest a small or infiltrative primary focus.

Cystoscopy/ureteroscopy is essential to visualize any macroscopic bladder or ureteral lesion. Here, the cystoscopy was normal, except for the diverticulum, which showed no visible lesion. Ureteroscopy focused on the area of ureteral thickening could have provided additional information. Molecular biology using NGS panels or molecular signatures (basal vs. luminal classifications, genomic alterations such as FGFR3, ERCC2, TP53) could help confirm the urothelial origin, guide treatment (e.g., targeted therapy), or inform the follow-up strategy, especially in the absence of a visible primary focus.

The use of an immunohistochemical panel is essential to guide tumor origin in cases of isolated metastasis. The GATA3 marker is widely used in pathology to identify urothelial differentiation [11]. However, several studies have shown that loss of GATA3 expression can occur in high-grade urothelial carcinomas and dedifferentiated forms, which limits its diagnostic value in isolation. For example, in a study of 2710 bladder carcinomas, GATA3 positivity was 59.9% for pT2-4 stages, compared to 98-99% for superficial tumors (pTa) [12]. This loss of expression has been correlated with increased tumor aggressiveness and a greater capacity for invasion/metastasis [13]. The study by Li et al. It has also been shown that GATA3 suppression induces increased migration and invasion of urothelial cancer cells via MMP-2 and MMP-9 activation, suggesting a suppressive role for GATA3 in the urothelium [14].

In this case, the CK7+/CK20+, p63+, p40+, GATA3− immunophenotype is consistent with a dedifferentiated entity and suggests that GATA3 loss should not rule out the possibility of urothelial urothelial carcinoma. Furthermore, some variants (plasmacytoid, sarcomatoid) frequently exhibit a lack of GATA3 [15]. Therefore, it is recommended to use a broad panel of antibodies (uroplakin, CK5/6, p40/p63, GATA3, etc.) and correlate the findings with clinical and imaging findings. Urothelial carcinomas of the bladder typically spread via the lymphatic system to the obturator, internal/external iliac, and then common iliac lymph nodes. Primary inguinal involvement is very rare [16]. The fact that our case presents with a large left inguinal lymph node and an ulcerated-necrotizing mass invading the femoral region suggests atypical lymph node involvement or secondary dissemination via unusual collateral drainage, possibly related to an undetected primary ureteral or lower bladder lesion.

Therapeutic choice is all the more complex in this type of case because the absence of an identified primary focus limits the application of standardized protocols for urothelial cancer. Treatments such as platinum-based chemotherapy or anti-PD-1/PD-L1 immunotherapy are generally recommended for metastatic urothelial cancers. However, in a 91-year-old patient with borderline renal function and a fragile constitution, aggressive treatment was not warranted. Furthermore, the slow progression, the absence of rapid visceral dissemination, and the maintenance of a good general condition suggest a low-progressive form, which may indicate better-differentiated variants or less aggressive tumor proliferation.

Conclusion

This case highlights the rarity and diagnostic challenge of occult primary urothelial carcinoma, which may initially present as isolated inguinal lymphadenopathy without detectable bladder or ureteral involvement. The integration of morphological, radiological, and immunohistochemical data remains essential to guide diagnosis in such atypical clinical presentations.

Although GATA3 negativity is uncommon, it does not exclude a urothelial origin, particularly in poorly differentiated or dedifferentiated forms. This case also underscores the importance of a multidisciplinary approach involving urology, pathology, and oncology teams to develop an appropriate diagnostic and therapeutic strategy tailored to the patient's condition.

In elderly and frail patients, management should focus on symptom control, infection prevention, and close follow-up. Finally, such rare presentations emphasize the need for further documentation to improve understanding of the atypical lymphatic dissemination mechanisms of urothelial carcinoma.

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