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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.*

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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).

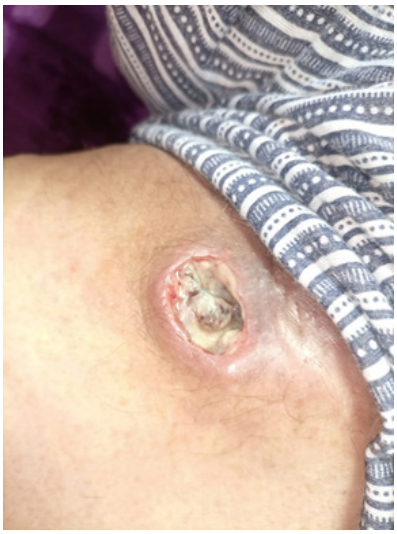

Figure 1: Left inguinal mass fistulized to the skin, showing a necrotic ulceration with seropurulent exudate.

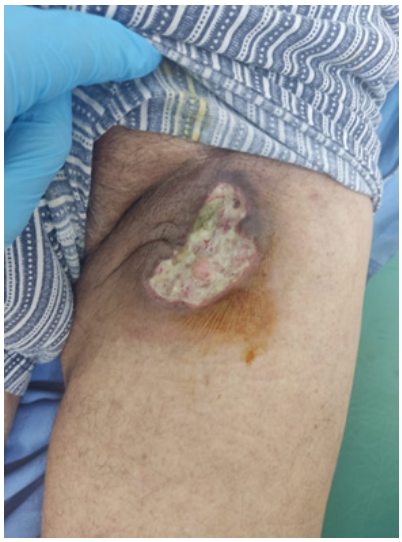

Figure 2: Evolution after three months: drier ulcerated necrotic wound with reduced exudation, indicating partial local improvement.

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 unde-

rtaken, 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) with no identifiable primary tumor — also referred to as urothelial carcinoma of occult origin. Although the urothelial tract remains the most common site of origin for such tumors within the genitourinary system, presentation as a fistulized inguinal lymphadenopathy in an elderly patient, without any visible vesical or ureteral lesion on imaging or endoscopy, represents an exceptional entity.

Cancers of unknown primary (CUP) account for approximately 3–5% of all solid malignant tumors and are often associated with a poor prognosis due to diagnostic delay and the absence of a targeted treatment approach [9]. Within this context, an occult-origin UC is even rarer, with only a few cases reported in the literature [10]. The presence in our patient of pelvic

and inguinal lymph node masses, a suspicious ureteral thickening, and a bladder diverticulum with wall irregularity supports a urothelial origin, although this could not be histologically confirmed.

In the literature, a few isolated cases have described metastatic presentations (pulmonary, nodal, osseous) revealing an occult UC, such as the case reported by Bu et al, involving multiorgan metastases without any identifiable primary lesion [10]. Our case aligns with this observation and illustrates one of the most challenging diagnostic scenarios in uro-oncology.

The diagnosis of an occult UC requires comprehensive evaluation through multimodal imaging, including thoraco-abdomino-pelvic CT (TAP), MRI when indicated, and PET-CT to identify hidden lesions. In our case, the TAP revealed an enhancing ureteral wall thickening (36 mm) and a right lateral bladder diverticulum—two structural abnormalities potentially corresponding to a small or infiltrative urothelial focus.

Cystoscopy and ureteroscopy remain essential for direct visualization of any vesical or ureteral lesion. In this patient, cystoscopy was unremarkable apart from the diverticulum without visible mucosal abnormality. A targeted ureteroscopy of the thickened ureteral segment could have provided additional diagnostic information. Molecular profiling using next-generation sequencing (NGS) panels or transcriptomic classifiers (basal vs. luminal subtypes, genomic alterations such as FGFR3, ERCC2, TP53) may help confirm urothelial origin, guide targeted therapy, and refine follow-up strategies, especially when no visible primary lesion is present.

The use of a comprehensive immunohistochemical (IHC) panel is critical for determining tumor origin in the setting of an isolated metastasis. The marker GATA3 is widely employed in pathology to identify urothelial differentiation [11]. However, several studies have shown that loss of GATA3 expression may occur in high-grade or dedifferentiated UCs, thereby limiting its diagnostic specificity when used alone.

For instance, in a cohort of 2,710 bladder carcinomas, GATA3 positivity was 59.9% in muscle-invasive invasive tumors (pT2–4) compared with 98–99% in superficial stages (pTa) [12]. This loss of expression correlated with increased tumor aggressiveness and metastatic potential [13]. Moreover, Li et al. demonstrated that GATA3 suppression enhances migration and invasion of urothelial carcinoma cells via MMP-2 and MMP-9 activation, suggesting a tumor suppressor role for GATA3 in the urothelium [14].

In our case, the immunophenotype CK7+/CK20+, p63+, p40+, GATA3− supports a dedifferentiated tumor entity and indicates that loss of GATA3 expression should not exclude a urothelial carcinoma diagnosis. Additionally, certain histologic variants (e.g., plasmacytoid or sarcomatoid) frequently exhibit GATA3 negativity [15]. It is therefore recommended to use an extended panel (uroplakin, CK5/6, p40/p63, GATA3, etc.) and to correlate IHC findings with clinical and imaging data.

Typically, bladder urothelial carcinomas spread through the lymphatic system to the obturator, internal/external iliac, and subsequently common iliac nodes. Primary inguinal involvement is exceedingly rare [16]. The presence in our case of a large necrotic inguinal lymph node mass invading the femoral region suggests atypical lymphatic dissemination or secondary spread through aberrant drainage pathways, possibly related to an undetected primary lesion in the distal ureter or lower bladder.

Therapeutic management is particularly challenging in such cases, as the absence of an identifiable primary site limits the applicability of standard treatment protocols for urothelial carcinoma. Platinum-based chemotherapy or PD-1/PD-L1 immunotherapy are generally recommended for metastatic UC. However, in a 91-year-old patient with frail condition and borderline renal function, aggressive therapy was not justified. Notably, the slow progression, absence of rapid visceral dissemination, and maintenance of overall good health point toward a low-grade, indolent tumor biology—possibly reflecting a well-differentiated variant or a tumor with limited proliferative potential.

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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