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Case Report

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Upper Tract Urothelial Carcinoma Complicated by Skeletal Muscle Metastases

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Abstract

Urothelial carcinoma typically metastasizes via a lymphatic route to sites such as lymph nodes, bone, and liver. As in other malignancies, metastasis to skeletal muscle is rare. We present a case of a 66-year-old male with severe muscular pain after diagnosis of upper tract urothelial carcinoma, who was found to have extensive metastasis to skeletal muscles including gluteal, sternocleidomastoid, deltoid, vastus lateralis, and gastrocnemius muscles. Literature review demonstrated 18 previously reported cases of urothelial cell carcinoma with skeletal muscle metastasis, all male and all with bladder involvement. This case emphasizes the importance of thoroughly evaluating all muscular pain in patients with a history of malignancy as it may represent skeletal muscle metastasis with an associated increase in morbidity and mortality.

Keywords: Upper tract urothelial carcinoma; Urothelial carcinoma; Skeletal muscle metastasis; JAK2

Introduction

Urothelial carcinoma arises from the urothelium and predominantly presents as urinary bladder cancer, with upper tract urothelial carcinoma (UTUC) comprising only 5-10% of cases [1]. UTUC, defined as neoplastic growth of the urinary tract anywhere from the renal calyx to the distal ureter, has a 5-year survival rate of less than 60% [2]. UTUC commonly metastasizes to lymph nodes, lung, liver, bone, and peritoneum [3]. Regardless of cancer type, metastasis to skeletal muscle is a rare oncologic event due to muscle-protective factors such as contractility, pH, and lactic acid removal [3]. We report the first known case of isolated UTUC with skeletal muscle metastasis.

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Case Report

Investigations

We present a case of a 66-year-old male with medical comorbidities including primary thrombocythemia with *JAK2* mutation, chronic obstructive pulmonary disease, type 2 diabetes mellitus, hypertension, hyperlipidemia, and more than 50-pack-years of tobacco use, who was initially evaluated in the outpatient setting for a 3-month history of macroscopic hematuria and intermittent right flank pain. Magnetic resonance (MR) imaging of the abdomen revealed a 3.1-cm cystic mass of the right renal superior pole with septations, initially concerning for abscess. A fine needle aspiration of the renal mass was diagnostic of high-grade urothelial carcinoma of the right renal pelvis, stage T3; further pathologic analysis demonstrated positivity for KRT7, GATA3, P40, KRT 34betaE12, and uroplakin-2, and negativity for CA-IX, KIT, PAX8, CD68-KP1, CDX2, TTF1-SPT24, and napsin. Cystoscopy was performed and was negative for bladder involvement of urothelial carcinoma.

Prior to initiation of cancer-directed therapies and 31 days after renal biopsy that diagnosed UTUC, the patient was hospitalized for severe left lower extremity pain and edema. He had no associated numbness, decreased range of motion, or history of recent trauma. The initial physical exam was notable for exquisite tenderness to palpation and 1+ pitting edema of the entire left lower extremity without significant abnormalities of the contralateral lower extremity. Computed tomography (CT) scan on hospital day 0 and ultrasound of the left lower extremity on hospital day 6 did not reveal fracture or deep vein thrombosis; lower extremity venous ultrasound did show a 5.1 × 1.9 × 14.6 cm area of abnormality thought to be a hematoma. Further imaging including CT of the chest, abdomen, and pelvis on hospital day 8 revealed new pulmonary nodules, right middle lobe consolidation with central necrosis, hepatic subcapsular fluid collection, and abdominal lymphadenopathy; all these findings were suspicious for widespread metastasis of known urothelial carcinoma. An ultrasound-guided aspiration of the hepatic fluid collection was consistent with metastatic urothelial carcinoma without signs of concomitant infection.

The patient began to experience intermittent fevers, hypotension, and altered mental status. He was started on broad-spectrum antibiotics without improvement in clinical status. Extensive infectious and rheumatologic evaluations were un-

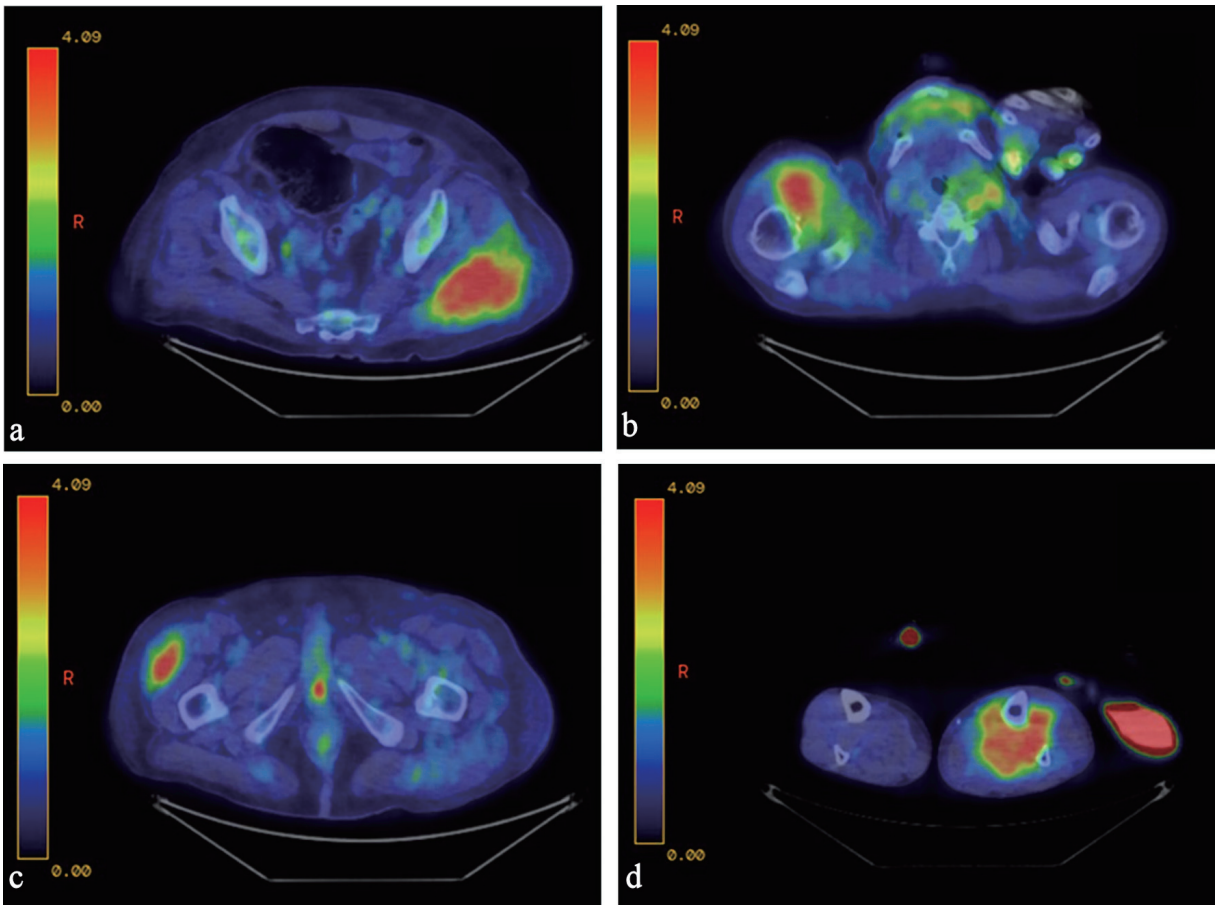

Figure 1. Widespread intramuscular metastases, axial views, seen in areas of increased uptake depicted with warmer colors. (a) Left gluteal muscle. (b) Right deltoid muscle. (c) Right vastus lateralis muscle. (d) Left calf musculature.

remarkable. After thorough workup, these decompensation episodes were attributed to cancer progression.

Diagnosis

The pain and edema in the left lower extremity continued to worsen. He subsequently developed new areas of excruciating pain in the bilateral shoulders and gluteal region, requiring management from the pain medicine team and a patient-controlled analgesia system. Fluorodeoxyglucose-positron emission tomography (FDG-PET) on hospital day 9 demonstrated widespread intramuscular metastases that correlated with regions of pain and edema; it also confirmed known areas of neoplastic involvement (Figs. 1, 2). Muscles impacted included proximal right deltoid, left sternocleidomastoid, paracervical musculature, distal left biceps, left gluteus maximus, proximal right vastus lateralis, left anterior thigh musculature, and left gastrocnemius muscle; all these skeletal muscle lesions also had surrounding soft tissue edema. The left gluteus maximus lesion was the largest at 7.2 × 5.4 cm and was easily accessible, facilitating biopsy. Left gluteal lesion biopsy on hospital day 14 confirmed metastatic urothelial carcinoma with positive GATA3, CK7, p63, and 34BE12 markers and negative CK20.

Treatment

Due to extremely rapid progression of metastatic spread of UTUC, he was urgently started on gemcitabine and cisplatin. He received two cycles while hospitalized, on hospital days 10 and 26, approximately 2 weeks apart.

He received symptomatic management for pain from skeletal muscle metastases, including opioids, topicals, and dronabinol. The pain medicine team assisted with management. They deemed the risks of steroid injections outweighed the potential benefits. Additionally, he was determined to not be a candidate for localized radiation of skeletal muscle metastases due to widespread nature of lesions and severity of clinical picture.

Despite initiation of chemotherapy and ongoing symptomatic management, the patient continued to decompensate and required transfer to the intensive care unit on hospital day 10. He developed an extensive clot burden including arterial thrombus in the thoracic and abdominal aorta, likely due to a combination of underlying *JAK2* mutation and malignancy. He died from these complications on hospital day 27 and within

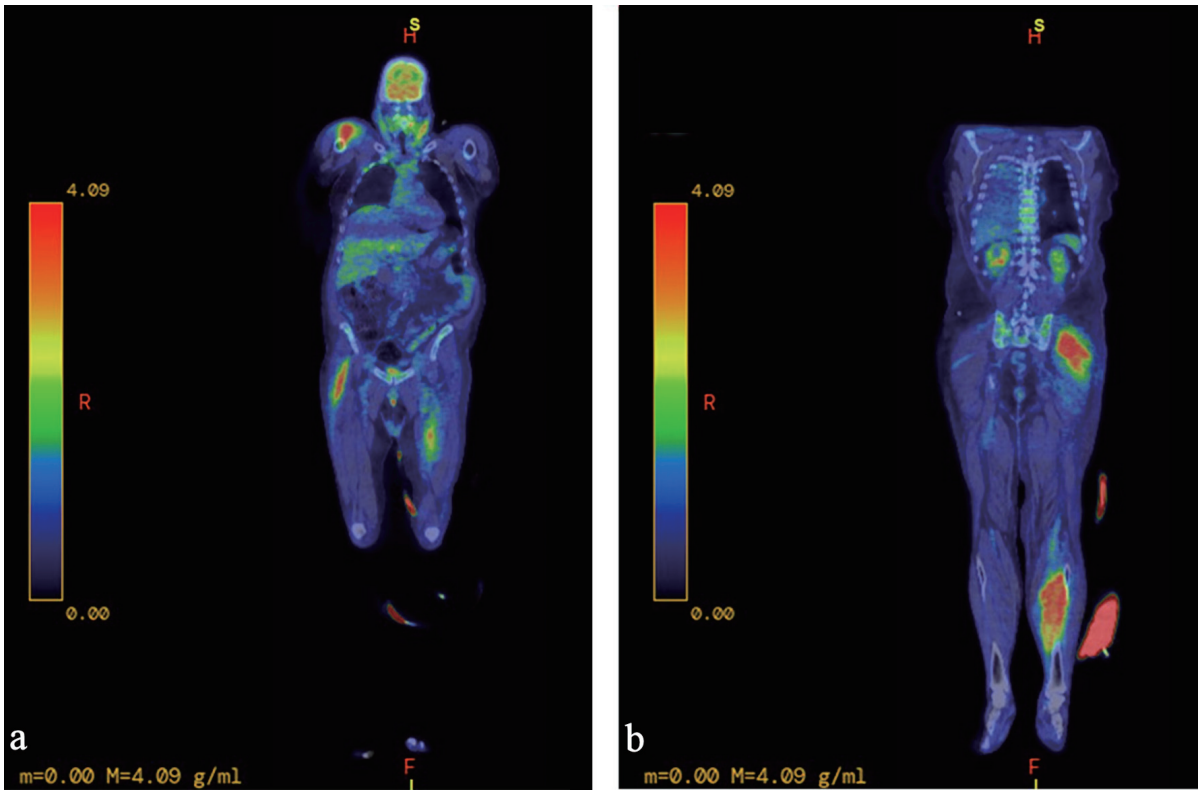

Figure 2. Widespread intramuscular metastases, coronal views, seen in areas of increased uptake depicted with warmer colors. (a) Left sternocleidomastoid, right deltoid, right vastus lateralis, and left thigh intramuscular metastases visible. (b) Left gluteal and left calf intramuscular metastases visible.

8 weeks of initial urothelial carcinoma diagnosis and within 4 weeks of skeletal muscle metastasis discovery.

Discussion

Urothelial carcinoma accounts for more than 90% of bladder cancers [4]. UTUC develops from the lining of the region from the distal ureter to the renal calyx and is uncommon, representing approximately 7% of all renal tumors and up to 10% of urothelial tumors [1]. Approximately 20% of UTUC cases also have bladder involvement at diagnosis [1]. However, newer studies suggest that UTUC should be considered a distinct disease process from bladder cancer due to its unique genotypic and phenotypic profiles [5]. For example, UTUC tends to more commonly have microsatellite instability and hypermethylation while bladder cancer is more prone to have abnormalities in DNA damage repair [5]. Smoking is a known risk factor, as is a history of exposure to aromatic amines [1]. UTUC is more commonly seen in men than women with a ratio of approximately 2:1 [1]. The most common presenting symptom is hematuria, and flank pain is the second most common [2]. It is uncommon for patients to experience symptoms such as fatigue, fevers and chills, night sweats, or weight loss; if these are present, the disease is likely much more advanced [1]. Early disease is often clinically silent, making diagnosis difficult and approximately 25% of cases are metastatic at presentation [1, 6]. Typically, urothelial carcinoma progresses by local invasion or lymphatic spread with hematogenous spread occurring less often [4]. Some of the most common areas of metastasis include lymph node, lung, and bone [7].

Skeletal muscle metastasis of urothelial carcinoma is extremely rare with less than 20 cases previously reported. Less than 0.3% of urothelial cancers have been reported to metastasize to skeletal muscle [8]. Some autopsy studies suggest a higher incidence, with clinically insignificant micrometastases seen in 0.8-16% of malignancy-associated deaths; these muscle micrometastases were most commonly found in the diaphragm or the anterior chest and/or abdominal wall musculature [3, 9]. Metastasis to skeletal muscle has been reported from other cancers, including breast, lung, colon, pancreatic, pulmonary, and gastric although it is similarly uncommon [9, 10]. Patients with skeletal muscle metastasis typically have advanced disease, with over 80% having widespread metastatic disease [3].

Localized pain and swelling is the typical presentation of skeletal muscle metastases, commonly in larger muscles and accompanied by mass effect on surrounding soft tissue with associated edema [10]. These symptoms are typically persistent despite concentrated attempts at pain management.

Initially, skeletal muscle metastasis may be mistaken for an abscess [3]. Imaging findings are typically nonspecific, further complicating diagnosis. CT scans can show edema and a ring-enhancing lesion with hypoattenuation of the inner region [9]. MR may show T1 low to intermediate intensity and T2

high-signal intensity [11]. FDG-PET can also be considered, as UTUC metastases can be visualized with the radiotracer; the primary tumor is typically more difficult to see on FDG-PET due to excretion of the radiotracer through the urinary tract [12]. Biopsy is recommended for definitive diagnosis [9].

Treatment of skeletal muscle lesions is typically palliative; excision, chemotherapy, and radiation may all be considered although data are limited for all of these approaches [8]. Chemotherapy is the most frequently favored option, given the frequency of widely metastatic disease in patients with skeletal muscle metastases [8]. Prognosis of urothelial carcinoma with skeletal muscle metastasis is extremely poor with mean survival of less than 9 months [13].

Skeletal muscle metastasis is paradoxically rare since skeletal muscle typically accounts for approximately 50% of body mass and receives a considerable proportion of cardiac output [9]. A range of muscle-specific factors have been postulated to protect against hematogenous spread to these regions. Cancer cells rely on their production of lactic acid to induce tumor vascularity and proliferation; however, skeletal muscles are adept at removing lactic acid [10]. Additionally, muscle contractility with associated pressure changes can result in mechanical destruction of tumor cells [4]. Muscle pH may also be less hospitable to tumor cells [4]. Localized trauma may predispose skeletal muscle to successful invasion by cancer cells since trauma alters striated muscle physiology, impairing the protective factors previously discussed [10]. Focal edema may also increase blood flow and the likelihood of hematogenous spread [10].

All prior reported cases of urothelial carcinoma metastatic to muscle have had bladder involvement, making this case the first reported occurrence of skeletal muscle metastasis in urothelial cell carcinoma without bladder involvement. Additionally, all the prior case reports except two have shown metastasis to two muscles at most, with the majority of these metastases presenting in large muscles and none in the head/neck region. There are also no reported cases of *JAK2* mutation in patients with skeletal muscle metastasis, further differentiating this case. On review of the literature, 18 cases of urothelial cell carcinoma metastatic to skeletal muscle were identified. All patients were male, with age ranging from 27 to 83 at time of skeletal muscle metastasis diagnosis. The majority of the metastases were found in large muscles, typically of the pelvis region and/or lower extremities, such as the psoas, gluteal musculature, and sartorius. None of the cases identified head/neck involvement; our patient had metastasis to the left sternocleidomastoid and paracervical musculature. Chemotherapy was the most common treatment modality among the reported cases, although local radiation was utilized in at least eight of the cases and resection of the muscle lesion(s) occurred in at least two of the cases. Of the 18 reported cases, eight died within a year, four were alive at the time of the writing of the respective case report, and the outcome was not reported in six of the cases. Further data can be seen in Table 1 [3, 4, 7-9, 11, 13-20].

In conclusion, we report the first known case of skeletal muscle metastasis complicating UTUC without bladder involvement. Strengths of this report include increasing awareness of a rare and serious oncologic complication; limitations include paucity of prior data on this topic. Skeletal muscle metastasis is an extremely rare complication of urothelial carcinoma and is associated with advanced disease and worse prognosis. Therefore, it is crucial to evaluate muscular pain in any patient with a history of urothelial malignancy.

Learning points

We would like to highlight the importance of fully evaluating all persistent muscular pain in patients with active or prior malignancy, particularly if there is associated soft tissue edema. Imaging and biopsy should be used as indicated to evaluate painful muscular lesions in this population. Skeletal muscle has a variety of factors that are protective against neoplastic invasion such as pH, contractility, and lactic acid removal systems. Although rare, skeletal muscle metastases may be underdiagnosed and are typically associated with widely metastatic disease and a more serious prognosis, requiring prompt treatment initiation.

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Conflict of Interest

The authors have no competing interests that are relevant to this article's content.

Informed Consent

Consent was waived as information was anonymized per Safe Harbor deidentification criteria, and no identifying images were included. Mayo Clinic Research Compliance Office confirmed appropriate deidentification.

Author Contributions

J.F. wrote the main manuscript text and prepared figures and tables. All authors reviewed the manuscript.

Data Availability

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Table 1. Review of the Literature of Urothelial Cell Carcinoma With Skeletal Muscle Metastasis

Citation	Sex	Age (years)	UCC stage	Skeletal muscle metastasis location	Treatment(s)	Outcome
Dang et al, 2022 [14]	Male	72	Unknown	Posterior muscles of left thigh	Unknown	Unknown
Dell'Atti, 2015 [8]	Male	65	pT2a	Left obturator	Chemotherapy, local radiation	Alive at 6 months
Doo et al, 2012 [9]	Male	45	T2	Left sartorius	Chemotherapy, local radiation	Unknown
Ekici et al, 1999 [15]	Male	41	Unknown	Right deltoid	Unknown	Unknown
Guidi et al, 2016 [11]	Male	76	T3	Right flexor digitorum superficialis and profundus	Resection, local radiation, chemotherapy	Died within 5 months
Kashyap et al, 2010 [16]	Male	64	Unknown	Right adductor brevis, quadriceps femoris, gastrocnemius; left quadriceps and semitendinosus	Unknown	Unknown
Katafigiotis et al, 2014 [17]	Male	51	pT2	Left sartorius	Resection, local radiation, chemotherapy	Alive at 5 months
Koca et al, 2014 [4]	Male	62	T1G3	Right iliopsoas and right adductor longus	Chemotherapy	Died within 3 months
Mainwaring et al, 2019 [3]	Male	71	pT3aN0	Right vastus lateralis	Immunotherapy, local radiation, chemotherapy	Alive as of case report writing
Nabi et al, 2003 [13]	Male	65	T3	Medial thigh muscles	Chemotherapy	Died within 8 months
Nabi et al, 2003 [13]	Male	27	T3bN2	Left psoas	Chemotherapy, local radiation	Died within 6 months
Nabi et al, 2003 [13]	Male	62	T3a	Left rectus abdominis	Chemotherapy	Died within 12 months
Nabi et al, 2003 [13]	Male	70	T3bN2	Left psoas	Chemotherapy, local radiation	Died within 8 months
Nabi et al, 2003 [13]	Male	36	T3aN1	Left psoas	Chemotherapy	Died within 6 months
Nagao et al, 2004 [18]	Male	63	Unknown	Right gluteus maximus	Unknown	Unknown
Rossly et al, 2021 [7]	Male	55	pT2	Left gastrocnemius	Local radiation	Alive as of case report writing
Spinelli et al, 2018 [19]	Male	66	Unknown	Left gluteus	None	Died within 1 month
Ying-Yue et al, 2010 [20]	Male	83	Unknown	Bilateral psoas major, quadratus lumborum, iliacus, gluteus medius/minimus, obturator externus, quadratus femoris, adductor brevis/magnus	Chemotherapy	Unknown

UCC: urothelial cell carcinoma.

Abbreviations

UTUC: upper tract urothelial carcinoma; MR: magnetic resonance; CT: computed tomography; FDG-PET: fluorodeoxyglucose-positron emission tomography

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