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# Unusual manifestations of secondary urothelial carcinoma

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**Abstract** High-grade papillary urothelial carcinoma regularly invades the bladder wall, adjacent prostate, seminal vesicles, ureters, vagina, rectum, retroperitoneum, and regional lymph nodes. In advanced stages, it may disseminate to the liver, lungs, and bone marrow. On rare occasions, unusual metastatic foci like skin have been reported. The incidence of urothelial carcinoma has increased with associated rise in variants of urothelial carcinoma and unusual metastatic foci. It is imperative that urologists and pathologists are aware of the unusual variants and unusual metastatic locations to expedite the diagnostic process. Hereby we report an unusual case of secondary involvement of spinal nerve by conventional urothelial carcinoma. Also a second case of rhabdoid variant of urothelial carcinoma showing synchronous involvement of bladder and subcutaneous tissue of upper extremity is presented.


## 1. Introduction

Urothelial carcinoma (UC) is the fifth most common malignancy in the USA with rising incidence [1]. Aggressive urothelial carcinomas invade the bladder wall and usually extend into the adjacent organs like prostate, seminal vesicles, ureters, vagina, rectum, and retroperitoneum. Distant metastasis by hematogenous dissemination usually occurs in bone, lung, liver and peritoneum. The behavior of UC cannot be clinically predicted; however findings like extension beyond the bladder wall on bimanual examination, infiltration of the ureteral orifices, lymph node metastases, and systemic dissemination are associated with poor prognosis. Life expectancy for metastatic UC is usually three years or less and there is rarely any cure; therefore early diagnosis is of utmost importance.

Several variants of UC have been illustrated in the current WHO classification [2]. More common variations like UC with squamous or glandular differentiation appear not to affect the outcome, but less common variants like nested, micropapillary, lymphoepithelioma-like, plasmacytoid, small cell, and sarcomatoid UC show more aggressive behavior and poor outcome.

Unusual metastasis of UC rarely occurs where determination of urothelial origin may be challenging. It is very important that urologists and pathologists are aware of unusual metastatic foci of the UC to expedite the diagnosis and proper management. To our knowledge, secondary involvement of a spinal nerve trunk in the absence of

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disseminated UC has not been reported in the English literature. In addition, we report a unique case of rhabdoid variant of UC with synchronous presentation in bladder wall and subcutaneous soft tissue of upper arm.

## 2. Case report

### 2.1. Case # 1

A 71-year-old male, a known case of UC, underwent therapeutic radical cystoprostatectomy. The specimen revealed an ulcerated tumor on right posterolateral bladder wall measuring 3.5 × 2.5 × 0.8 cm. Histopathology revealed an invasive UC with squamous differentiation extending into perivesical fat (pT3b). Tumor was noted to invade nerve bundles with perineural spread approaching the surgical margin on the right side. No tumor cell was identified at the margin; therefore all margins were reported free from tumor. The accompanying right pelvic lymph node dissection revealed 4 benign lymph nodes (pN0). The prostate contained an incidental focus of low grade prostate adenocarcinoma (Gleason score 3 + 3 = 6, pT2b N0). The patient tolerated the operation well and left the hospital without any complication.

Nine months later, the patient returned with progressive unilateral right lower extremity pain radiating down the leg with associated weakness, numbness, right-sided foot drop and unsteady gait. The pain partially improved but was not eradicated by oxycodone. He also complained about fecal incontinence. No clinical evidence of recurrent UC was noted. MRI of the spinal cord showed asymmetric thickening with increased signal in the right lumbosacral trunk involving the S1 and S2 roots (Fig. 1A & B). The sciatic nerve revealed non-enhancing thickening just beyond sciatic notch extending distally in the right thigh to the level of the hamstring complex. Right gluteus muscles and thigh extensors showed significant edema and fatty atrophy. Biopsy of right sciatic nerve at the level of the sciatic notch revealed metastatic UC with focal squamous and glandular differentiations – similar to prior UC – involving the nerve trunk (Fig. 1C). Tumor cells stained positive for CK7, P63 and high molecular weight cytokeratin (HMWCK), supporting the diagnosis (Fig. 1D, Table 1). CK20 was negative in the tumor cells.

Palliative radiation therapy to the sacrum and sciatic nerve (total doze 59.4 Gy) with neuroleptic medications was administered. Initially, significant pain alleviation and improved strength in the right lower extremity were reported; however fecal incontinence did not improve. A few weeks

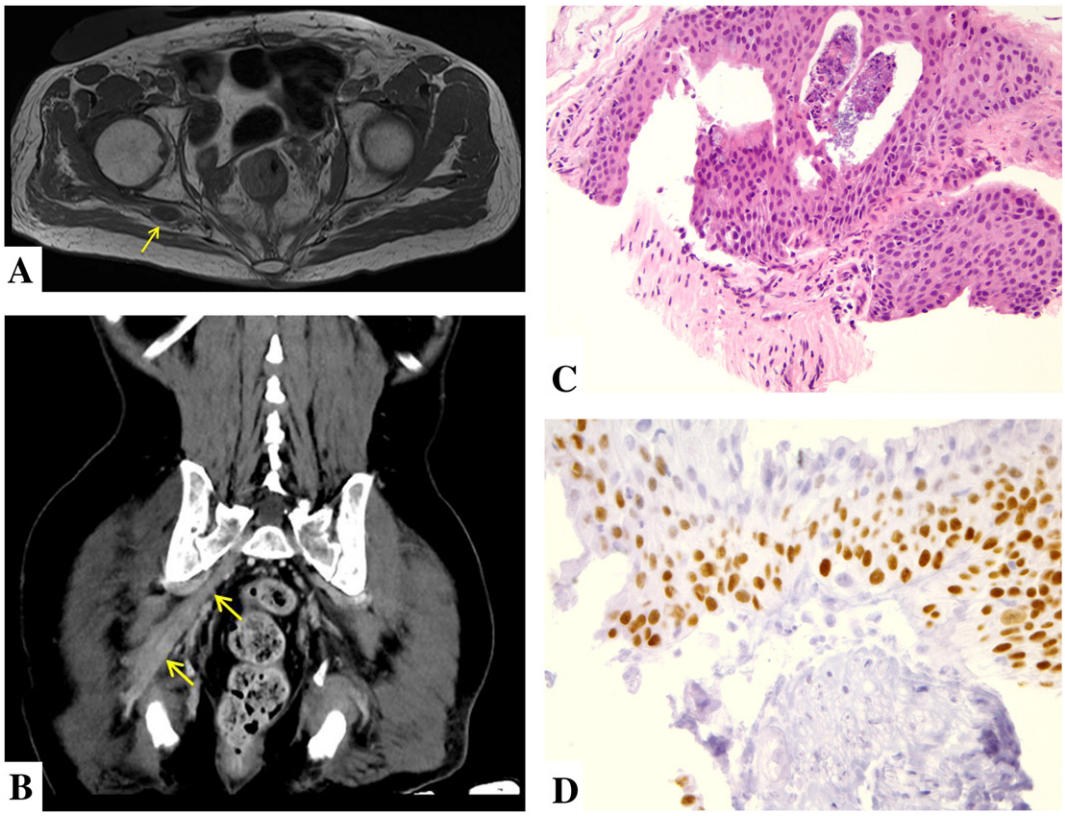


**Fig. 1** Case 1. (A) Axial T1-Weighted Non-Contrast MRI of the Pelvis. Fusiform enlargement of the right sciatic nerve just distal to the greater sciatic foramen (arrow). Note also made of lipoatrophy of the right gluteal musculature. (B) Coronal Contrast-Enhanced CT of the Abdomen and Pelvis. Enhancing fusiform enlargement of the right sciatic nerve as it exits the greater sciatic foramen (arrows). (C) Metastatic UC involving the sciatic nerve (H&E staining 100×). (D) Expression of P63 in the metastatic focus confirmed urothelial origin (200×).

**Table 1** Immunohistochemical antibodies used for diagnosis of cases.

| Case | Location | Antibody | Result |
|---|---|---|---|
| Case 1 | Sciatic nerve | Cytokeratin 20 (M; KS20.8; DAKO) | Negative |
| | | Cytokeratin 7 (M; OV-TL 12/30; DAKO) | Positive |
| | | P63 (M; 4A4; Biogenex) | Positive |
| | | Cytokeratin 903 (M; 34BE12; Enzo) | Positive |
| | | GATA3 (M; L50-823; Biocare Medical) | Positive (focal) |
| Case 2 | Bladder | P63 (M; 4A4; Biogenex) | Positive |
| | | Cytokeratin 903 (M; 34BE12; Enzo) | Positive (focal) |
| | Right arm | P63 (M; 4A4; Biogenex) | Positive (focal) |
| | | Cytokeratin cocktail (M; AE1, AE3, CAM5.2, KA4, and UC2/PR-10-11; DAKO, Becton-Dickenson and Zymed) | Positive |
| | | Cytokeratin 903 (M; 34BE12; Enzo) | Positive (focal) |
| | | Cytokeratin 19 (M; RCK 108: DAKO) | Negative |
| | | CD31 (M; JC/70A; Cell Marque) | Negative |
| | | CD34 (M; QBEnd/10; DAKO) | Negative |
| | | Bcl-1 (Cyclin D1) (R; EP12; DAKO) | Positive |
| | | Calponin (M; CALP; DAKO) | Negative |
| | | Desmin (M; 33; Accurate) | Negative |
| | | Synaptophysin (M; 27G12; Vector) | Negative |
| | | EMA (M;E29; Cell Marque) | Positive |
| | | Melan-A (M; A103; DAKO) | Positive (focal) |
| | | S-100 Protein (DAKO) | Negative |
| | | HMB-45 (M; HMB45; Enzo) | Negative |
| | | Calretinin (M; Z11-E3; Zymed) | Negative |
| | | CD57 (Leu 7) (M; HNK-1; Cell Marque) | Negative |
| | | Ewing's Sarcoma (MIC2, p30/32, HBA71) (M; O13; Signet) | Negative |
| | | Myogenin (M; F5D; Cell Marque) | Negative |
| | | MITF (M; C5/D5; Cell Marque) | Negative |
| | | TFE-3 (P; Sigma) | Negative |
| | | Inhibin (M; R1; DAKO) | Negative |
| | | GATA3 (M; L50-823; Biocare Medical) | Positive |

Antibody provider list (alphabetical order): Accurate (Westbury, NY); Becton Dickenson (Franklin Lakes, NJ); Biocare Medical (Concord, CA); Biogenex (Fremont, CA); Cell Marque (Rocklin, CA); DAKO (Carpinteria, CA); Enzo Life Sciences (Farmingdale, NY); Sigma Aldrich (St. Louis, MO); Signet (Waltham, MA); Vector Laboratories (Burlingame, CA); Zymed Life Technologies (Grand Island, NY). M: monoclonal primary antibody; P: polyclonal primary antibody

later the patient returned with recurrent pain and increased right lower extremity weakness. There was no weakness or pain in the contralateral extremity. A follow-up MRI after six months showed no radiological progression. Patient was continued on palliative therapy.

## 2.2. Case # 2

A 77-year-old female presented with new onset hematuria. Patient denied any prior urinary symptom. A large solid bladder tumor was identified and transurethrally resected in another facility. Histopathology revealed UC with tumor cells showing abundant eosinophilic cytoplasm, pleomorphic large vesicular nuclei and prominent nucleoli infiltrating the lamina propria of the bladder with extensive necrosis. Muscularis propria was not present in the specimen (at least pT1). Tumor cells expressed P63 and HMWCK, supporting the diagnosis.

Ten days after the first procedure, she was referred to our hospital with a palpable hard, non-mobile mass in the soft tissue of the right arm. Overlying skin was clinically unremarkable. No record of the subcutaneous lesion was available from the referring facility; however the patient reported a 50%–75% increase in size in two weeks. With a clinical diagnosis of concurrent soft tissue sarcoma, a radical excision was performed.

The specimen revealed a well-circumscribed mass measuring 5.1 × 4.0 × 3.0 cm involving subcutaneous connective tissue and skeletal muscle. Tumor was composed of loose sheets of anaplastic epithelioid cells showing deeply eosinophilic cytoplasm, peripherally located large vesicular nuclei and prominent eosinophilic nucleoli (Fig. 2A & B). There were brisk mitotic activity and geographic necrosis. Based on the presentation and morphology, a broad differential list was considered and a battery of immunohistochemical markers was performed (Table 1). Tumor cells expressed cytokeratin cocktail but did not express smooth muscle, melanoma, Ewing's sarcoma or vascular markers. At this point and after reviewing the bladder lesion, P63, HMWCK and GATA3 were added that were positive in the tumor cells (Fig. 2C & D). No loss of expression of INI1/SMARCB1 [clone25/BAF47] was noted. A diagnosis of

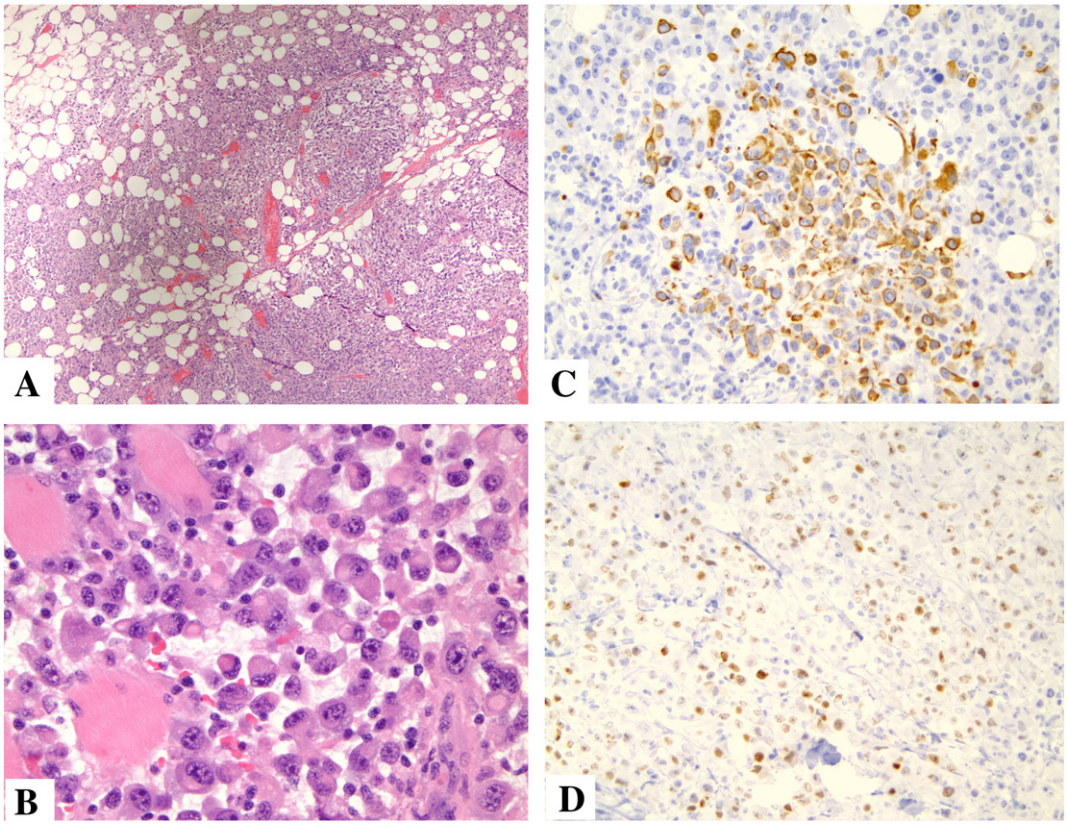


**Fig. 2** Case 2. (A, B) Metastatic high-grade urothelial carcinoma in the right arm (A, 40×; B, 400× H&E staining). (C) Patchy positive CK903 expression (200×). (D) Positive expression of P63 (200×).

synchronous cutaneous metastasis of high grade UC with rhabdoid differentiation was rendered.

Comprehensive metastasis work up did not show any evidence of distant metastasis or lymphadenopathy. Patient returned to the original facility for palliative care.

## 3. Materials and methods

### 3.1. Hematoxylin and Eosin (H&E) stain preparation

The specimens were fixed in 10% (wt/vol) phosphate-buffered formalin for 24–48 h and processed for routine histology. After standard histological processing and embedding in paraffin, 5-μm-thick sections were prepared for H&E staining.

### 3.2. Immunohistochemical staining

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded sections. Stains were performed using an Envision Flex Visualization, Encision+ Dual Link System, Peroxidase (Dako), or a standard streptavidin technique (Jackson) with a DAB or Nova Red (Vector) chromogen. A complete list of antibodies used and provider information is provided in Table 1.

## 4. Discussion

Hematogenous metastasis of conventional UC adversely affects the prognosis (median survival <12 months) [3]. Presence of variants of UC is also associated with worse overall survival and recurrence-free survival, and predicts upstaging and higher lymph node metastasis [4].

### 4.1. Spinal nerve involvement by UC

The phenomenon of symbiotic relationship between prostate adenocarcinoma (PCa) and neural tissue is reported. Ayala et al reported evidence of increased neurogenesis in PCa with direct association between perineural invasion (PNI) density and stage [5]. Yang et al reported a biologic interaction between cancer cells and neural microenvironment resulting in decreased apoptosis in PNI [6].

There are reports of disseminated UC involving spinal nerve trunks following vertebral bone metastasis without understanding the mechanism and prognostic significance [7]. Possible explanations for sciatic nerve metastasis in our case include direct extension through perineural spaces and hematogenous spread. We identified extensive PNI of the UC with extension adjacent to the lateral pelvic margin. Meticulous examination of the specimen did not reveal lymphovascular invasion or lymph node metastasis. Imaging

studies demonstrated diffuse enlargement of the right sciatic nerve throughout its course, extending from the right lumbosacral plexus and progressing distally. The associated contrast enhancement was suggestive of metastatic neuronal infiltration. Metastatic workup identified no additional distant metastasis.

In our first case, tumor cells expressed p63, HMWCK, GATA3 and CK7; but failed to stain with CK20. Absence of CK20 expression has been reported and does not exclude UC [8].

### 4.2. Subcutaneous tissue metastasis of UC

Skin metastasis of UC most commonly involves abdomen and perineum [9]. The overlying skin may reveal urticarial or other non-specific rashes, or appear unremarkable [10]. Skin metastasis may occur by direct invasion, surgical implantation or lymphatic/hematogenous spread [3,11]. Regardless of the mechanism, cutaneous metastasis of UC is a dismal sign [10].

UC and its cutaneous metastasis usually emerge metachronously with the metastasis developing months to years after the initial bladder tumor. The index patient often shows concomitant metastasis to other distant organs or lymph nodes. In a study in canine UC, the mean and median intervals between occurrence of UC and metastasis were 123 and 38 days, respectively [12].

In our second case, UC and skin metastasis occurred synchronously and were diagnosed 10 days apart. Involvement of upper extremity by UC is uncommon and occurs only by hematogenous spread; however, comprehensive work up found no other metastasis. Morphologically, the tumor showed rhabdoid differentiation, a rare variant of UC reported to show aggressive behavior with poor outcome [13].

Due to unusual presentation and histomorphology, several differential diagnoses were considered. Pleomorphic rhabdomyosarcoma, a rare variant of rhabdomyosarcoma most frequently occurring as well-demarcated mass in skeletal muscle of extremities in adults >45 years old, was excluded based on absence of muscle marker expression.

Tumor cells in our case infiltrated subcutaneous adipose tissue, mimicking dedifferentiated liposarcoma with round cells. Dedifferentiated liposarcoma is more common in retroperitoneum; less than 1% is reported in the subcutaneous sites [14]. Current tumor showed no evidence of low-grade/well differentiated liposarcoma or dedifferentiated spindle cell liposarcoma. Other pleomorphic sarcomas were excluded based on morphology (i.e. lack of smooth muscle features) and/or immunohistochemistry (i.e. absence of vascular markers and retained INI1 expression).

Atypical fibroxanthoma (AFX) commonly emerges as a rapidly enlarging exophytic and ulcerative mass <2 cm in size in elderly male [15]. Arising in sun damaged skin; AFX shows pushing borders without infiltration of the subcutis. Absence of superficial skin changes and presence of invasion into subcutaneous tissue, brisk mitotic activity and geographic necrosis in our case excluded AFX.

Melanoma, PEComa, pleomorphic dermal sarcoma and lymphoma were excluded based on strong expression of cytokeratins and lack of expression of corresponding markers. Specifically, expression of P63, GATA3 and HMWCK supported an urothelial origin.

Hereby we report two unusual metastases of UC, involving the sciatic nerve trunk and subcutaneous soft tissue of the right arm. In both cases, appropriate clinical information and immunohistochemistry were crucial in achieving the diagnosis. Such unusual clinical scenarios indicate that UC does not necessarily show a predictable course, and require multidisciplinary approach with effective communication of the relevant information between treating physicians to reach an accurate diagnosis in a timely fashion.

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