International Clinical and Medical Case Reports Journal
Case Report (ISSN: 2832-5788)

Primary Undifferentiated Pleomorphic Sarcoma of the Penis: A Case Report and Comprehensive Literature Review

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Citation: Ashwini Kadam. Primary Undifferentiated Pleomorphic Sarcoma of the Penis: A Case Report and Comprehensive Literature Review. Int Clinc Med Case Rep Jour. 2026;5(8):1-7.

Received Date: 30 August 2026; **Accepted Date:** 04 September 2026; **Published Date:** 06 September 2026

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ABSTRACT

Background: Primary penile malignancies account for less than 1% of all male genitourinary cancers, with non-epithelial mesenchymal neoplasms comprising fewer than 5% of these cases. Among primary penile sarcomas, undifferentiated pleomorphic sarcoma (UPS)—previously categorized as malignant fibrous histiocytoma (MFH)-represents an exceedingly rare, aggressive histological subtype with limited published data to guide standardized management.

Case Presentation: A 59-year-old African male presented with a 6-month history of a painless, progressively enlarging nodular mass on the penile shaft. Physical examination revealed a 7 × 6 cm, non-ulcerated, firm mass fixed to the underlying corpora cavernosa without palpable inguinal lymphadenopathy. Core needle biopsy demonstrated a high-grade spindle cell neoplasm with 10–12 mitoses per high-power field (HPF). Positron emission tomography–computed tomography (PET-CT) demonstrated a hypermetabolic, locally infiltrative penile mass involving the bilateral corpora cavernosa and corpus spongiosum, regional bilateral inguinal lymphadenopathy, and a suspicious lesion in the right adrenal gland. The patient underwent total penectomy with perineal urethrostomy. Histopathological and immunohistochemical (IHC) profiling confirmed the diagnosis of primary undifferentiated pleomorphic sarcoma (vimentin-positive; Pan-CK, S100, CD34, CD21, HMB-45, and SOX10 negative). The patient subsequently completed six cycles of palliative systemic chemotherapy with doxorubicin and ifosfamide before being lost to follow-up.

Conclusions: Primary UPS of the penis is an aggressive diagnostic entity that requires prompt histological confirmation and immunohistochemical exclusion of sarcomatoid carcinoma, melanoma, and specific soft tissue sarcomas. Radical surgical resection with negative margins remains the cornerstone of local disease control, whereas multimodal systemic therapy is indicated for advanced or metastatic disease.

Keywords: Undifferentiated Pleomorphic Sarcoma; Malignant Fibrous Histiocytoma; Penile Sarcoma; Penectomy; Immunohistochemistry; Case Report.

INTRODUCTION

Carcinoma of the penis is an uncommon malignancy in developed countries, accounting for less than 1% of male neoplasms, with squamous cell carcinoma (SCC) representing more than 95% of cases [1,2]. Primary soft tissue sarcomas of the penis are exceptionally rare, constituting fewer than 5% of all primary penile malignancies [2,3]. Within this subgroup, the most commonly documented histologies include Kaposi sarcoma, leiomyosarcoma, epithelioid sarcoma, and vascular sarcomas (angiosarcoma) [1,4].

Undifferentiated pleomorphic sarcoma (UPS)-formerly termed malignant fibrous histiocytoma (MFH) before reclassification under the World Health Organization (WHO) classification of soft tissue tumours-is the rarest mesenchymal malignancy of the penis [3,5]. Because UPS lacks specific lines of lineage differentiation, it remains a diagnosis of exclusion that demands rigorous immunohistochemical and histopathological workups [5,6]. Due to the scarcity of reported cases worldwide, established therapeutic consensus and clinical guidelines remain limited. Herein, we present a rare case of advanced primary penile shaft UPS treated with radical total penectomy, perineal urethrostomy, and palliative systemic chemotherapy, alongside a comprehensive review of the current literature.

CASE PRESENTATION

Clinical History and Physical Examination

A 59-year-old diabetic African male presented to the outpatient urology clinic with a 6-month history of a painless, progressively enlarging mass on the shaft of the penis. He reported no associated dysuria, hematuria, urethral discharge, or penile bleeding. There was no antecedent history of local trauma, sexually transmitted infections, or radiation therapy. Systemic review was negative for B-symptoms, including fever, night sweats, anorexia, and unintentional weight loss. Physical examination revealed a discrete, firm-to-hard, non-tender mass measuring approximately 7 × 6 cm along the mid-shaft of the penis. The overlying cutaneous tissue was intact without ulceration, discoloration, or induration. The mass was fixed to the underlying corporal bodies. Bilateral inguinal regions revealed no clinically palpable lymphadenopathy, and digital rectal examination was unremarkable.

[Core Biopsy: Spindle Cell Neoplasm]
|
▼
[Pelvic MRI & Whole-Body PET-CT]
(Locally invasive corporal mass + Inguinal & Adrenal lesions)
|
▼
[Total Penectomy + Perineal Urethrostomy]
|
▼
[Histopathology & IHC: Final Diagnosis of UPS]
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▼
[Adjuvant/Palliative Chemotherapy: Doxorubicin + Ifosfamide]

Diagnostic Workup and Imaging

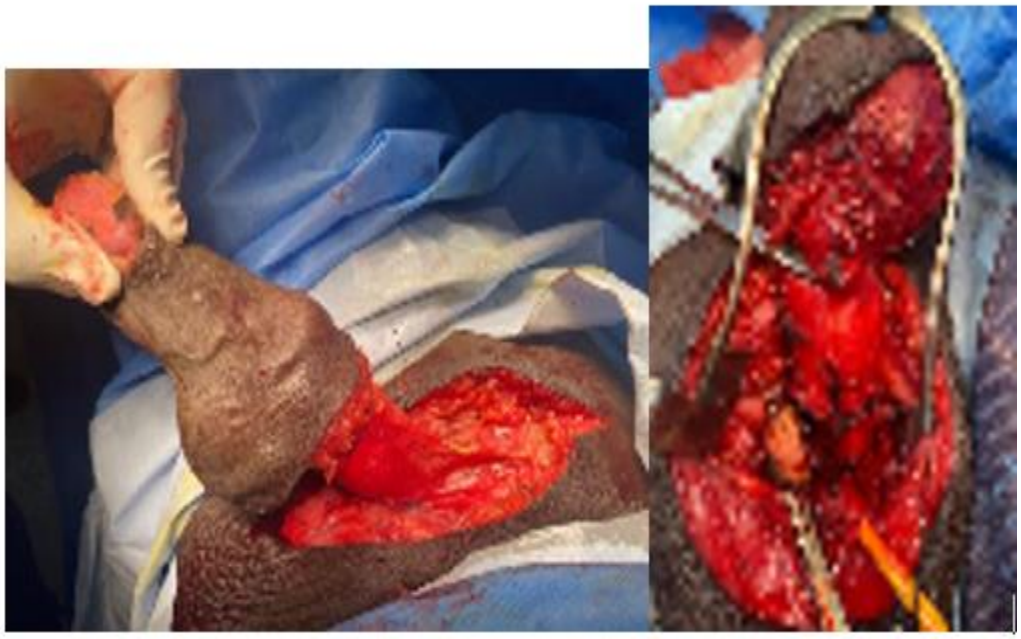
An initial ultrasound-guided core needle (Tru-Cut) biopsy demonstrated an atypical spindle cell neoplasm with 10–12 mitotic figures per high-power field (HPF) and frequent atypical mitoses, with no definitive epithelial elements. The differential diagnoses included sarcomatoid (spindle cell) carcinoma, malignant melanoma, and soft tissue spindle cell sarcoma.

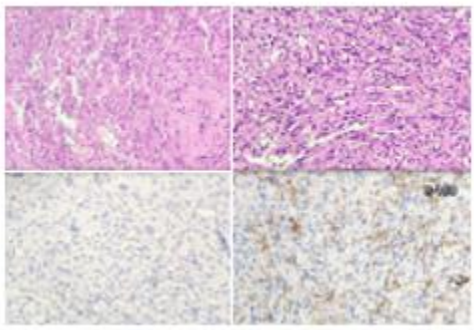
Contrast-enhanced magnetic resonance imaging (MRI) of the pelvis showed an infiltrative corporal lesion with bilateral small-volume inguinal lymphadenopathy. Subsequent whole-body 18F-fluorodeoxyglucose (FDG) Positron Emission Tomography–Computed Tomography (PET-CT) revealed a large, heterogeneously enhancing, hypermetabolic soft tissue mass infiltrating the shaft, bilateral corpora cavernosa, corpus spongiosum, and extending into the dermis. Furthermore, metabolically active bilateral inguinal lymph nodes and a hypermetabolic lesion in the right adrenal gland were identified, indicating advanced/metastatic disease.

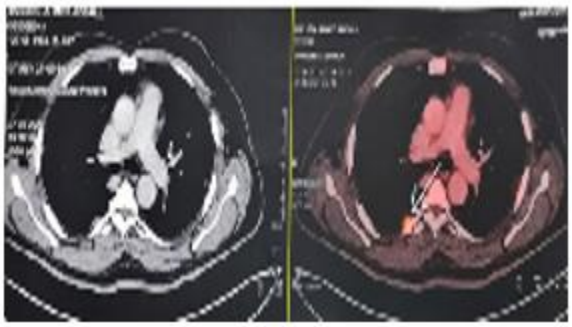
SURGICAL INTERVENTION AND PATHOLOGICAL FINDINGS

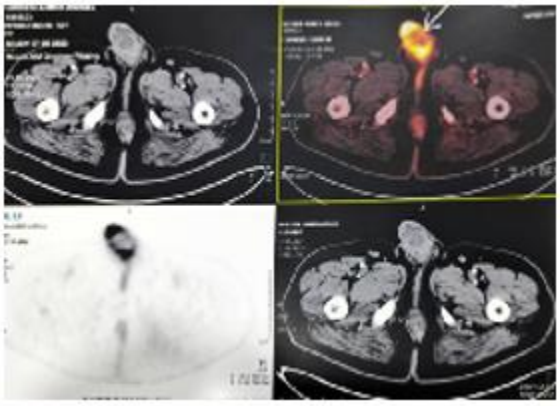
Operative Procedure

The patient underwent definitive surgical cytoreduction via total penectomy with perineal urethrostomy. Intraoperatively, the mass deeply invaded the bilateral corporal bodies and the corpus spongiosum. Adequate surgical margins were established, and a tension-free spatulated perineal urethrostomy was fashioned.









Gross and Histopathological Examination

- Gross Examination: The resected specimen measured 10 × 7.5 × 2.5 cm and harbored an ill-defined, lobulated, grayish-white mass located 1.2 cm from the proximal corporal resection margin. The proximal urethral and skin margins were histologically free of tumor.
- Microscopic Examination: Hematoxylin and eosin (H&E) staining demonstrated dense sheets and fascicles of pleomorphic spindle cells intermingled with multinucleated giant cells, hyperchromatic and vesicular nuclei with prominent nucleoli, high mitotic index (>10 mitoses/10 HPF), and focal necrotic foci.
- Immunohistochemical (IHC) Panel:
  - Vimentin: Diffusely positive (confirming mesenchymal origin).
  - CD68: Patchy reactivity (indicating tumor histiocytic component).
  - Epithelial Membrane Antigen (EMA): <5% tumor cell positivity (non-specific).
  - S100: <5% tumor cell positivity.
  - Pan-Cytokeratin (Pan-CK): Negative (ruling out sarcomatoid carcinoma).
  - HMB-45 & SOX10: Negative (ruling out malignant melanoma).
  - CD34 & CD31: Negative (ruling out vascular sarcomas/angiosarcoma).
  - Desmin & Smooth Muscle Actin (SMA): Negative (ruling out leiomyosarcoma/rhabdomyosarcoma).

Based on the cytomorphological pleomorphism, high mitotic activity, and comprehensive exclusion of differentiated lineages, a final diagnosis of Primary Undifferentiated Pleomorphic Sarcoma of the Penis (FNCLCC Grade 3) was established.

Postoperative Course and Follow-up

The postoperative course was uneventful, with primary wound healing and functional perineal urethrostomy voiding. Baseline post-resection chest radiography and comprehensive liver and renal function tests were within normal reference ranges.

Given the presence of regional nodal and right adrenal metabolic activity on baseline PET-CT, the multidisciplinary tumor board initiated palliative systemic chemotherapy consisting of:

Doxorubicin (60 mg/m² IV) + **Ifosfamide** (2.5–3.0 g/m²/day IV with MESNA uroprotection), administered in 3-week cycles.

The patient completed **six cycles of systemic chemotherapy** with manageable hematological toxicity. Following the completion of the sixth cycle, the patient was unfortunately lost to follow-up.

DISCUSSION AND REVIEW OF THE LITERATURE

Epidemiology and Classification

Primary mesenchymal neoplasms of the penis represent a clinical rarity. According to the Armed Forces Institute of Pathology (AFIP) and international oncologic databases, sarcomas account for less than 1–2% of all primary penile malignancies [1,3,7]. Primary penile sarcomas are broadly divided into:

1. Superficial sarcomas: Arising from the prepuce, dartos tunic, and subcutaneous connective tissue.
2. Deep-seated sarcomas: Developing directly from the tunica albuginea, corpora cavernosa, corpus spongiosum, or intercavernosal septum [2,7].

Historically designated as pleomorphic malignant fibrous histiocytoma (MFH), UPS was redefined by the WHO as an unclassified pleomorphic spindle cell neoplasm lacking evidence of identifiable cell lineage differentiation [5,8]. Penile UPS is among the least common penile sarcomas, with fewer than 15 well-documented cases reported in contemporary urologic literature [1,3,5,6].

Pathological Parameter	Sarcomatoid Carcinoma	Leiomyosarcoma	Undifferentiated Pleomorphic Sarcoma (UPS)
Origin	Dedifferentiated Epithelium	Smooth Muscle / Vascular Wall	Undifferentiated Mesenchyme
Pan-Cytokeratin / p63	Strongly Positive (+)	Negative (−)	**Negative (−)**
SMA / Desmin	Variable / Negative	Strongly Positive (+)	**Negative (−)**
Vimentin	Positive (+)	Positive (+)	**Positive (+)**
S100 / SOX10	Negative (−)	Negative (−)	**Negative (−)**

Clinical Presentation and Diagnostic Pitfalls

Penile UPS most commonly affects men in the 5th to 7th decades of life, though rare pediatric and adolescent presentations have been documented.6 The classic initial presentation is an asymptomatic, slow-growing,

subcutaneous or intracavernosal indurated nodule.1,3 Because the overlying penile integument frequently remains intact and ulceration is typically absent in the early stages, the lesion is routinely misdiagnosed as benign pathologies-such as Peyronie's disease, organized cavernosal hematoma, thrombosed superficial vein, or sebaceous cysts.3,7 This misattribution leads to diagnostic and therapeutic delays ranging from 3 to 18 months [1].

High-resolution pelvic MRI with gadolinium is the imaging modality of choice to assess the depth of tunical and corporal invasion and to evaluate corporal fascia disruption [5,7]. Whole-body 18F-FDG PET-CT serves a crucial staging role in identifying subclinical locoregional lymphatic spread and occult distant hematogenous metastases (predominantly lung, bone, and visceral organs) [1,3].

Differential Diagnosis and Immunohistochemistry

The definitive diagnosis of UPS is strictly a histopathological and immunohistochemical diagnosis of exclusion.5,8 The primary differential diagnosis on initial core biopsy is sarcomatoid (spindle cell) squamous cell carcinoma, which carries distinct lymphatic predilection and differing surgical-lymphadenectomy paradigms [2,7]. Immunohistochemical exclusion is mandatory:

- Epithelial markers (Pan-CK, AE1/AE3, CK5/6, p63, p40): Negative in UPS; positive in sarcomatoid carcinoma.
- Melanocytic markers (HMB-45, Melan-A, SOX10, S100): Negative in UPS; rules out mucosal amelanotic melanoma.
- Myogenic markers (SMA, Desmin, Myogenin): Negative in UPS; excludes leiomyosarcoma and rhabdomyosarcoma.
- Vascular markers (CD31, CD34, ERG): Negative in UPS; rules out epithelioid hemangioendothelioma and angiosarcoma.

Therapeutic Strategies and Prognosis

Due to the scarcity of randomized controlled trials, treatment protocols for penile UPS are extrapolated from extremity and trunk soft tissue sarcoma guidelines:

- Surgical Management: Complete surgical resection with microscopically negative margins (R0) is the cornerstone of curative-intent treatment [1,7]. Small (<2 cm), low-grade, superficial lesions confined to the prepuce or dartos may be managed with wide local excision. Conversely, large (>3–5 cm), high-grade, deep-seated corporeal lesions invading the cavernous bodies—as in our patient—mandate partial or total penectomy with perineal urethrostomy to prevent immediate local recurrence [2,7].
- Regional Lymphadenectomy: Unlike penile SCC, penile sarcomas primarily disseminate hematogenously rather than lymphatically. Routine prophylactic bilateral inguinal lymph node dissection is generally not indicated unless suspicious, FDG-avid lymphadenopathy is identified on staging imaging or biopsy [1,3,7].
- Adjuvant and Systemic Chemotherapy: Chemotherapy with anthracycline-based regimens (Doxorubicin + Ifosfamide / Mesna) is the primary systemic standard for advanced, high-grade, or metastatic UPS [1,3,9]. While objective response rates in soft tissue sarcomas remain modest (20-35%), systemic therapy may provide cytoreductive symptom palliation and disease stabilization in metastatic cases [1,9].

- Prognosis: High-grade penile UPS carries a guarded prognosis, marked by high rates of local recurrence (up to 40%) and rapid hematogenous dissemination, with median survival in metastatic disease ranging from 12 to 18 months [1,3,6].

CONCLUSION

Primary undifferentiated pleomorphic sarcoma of the penis is an extraordinarily uncommon, highly aggressive mesenchymal malignancy. Because early physical signs mimic benign urological conditions, clinicians must maintain a high index of suspicion for any solid, persistent, or progressive penile nodule. Early core biopsy paired with a comprehensive immunohistochemical panel is essential to rule out sarcomatoid carcinoma and other specific soft tissue sarcomas. Radical surgical resection with tumor-free margins provides the best chance for local disease control, while multidisciplinary anthracycline-based systemic chemotherapy remains the mainstay for locally advanced and metastatic presentations.

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