Case Report
Clear cell sarcoma of the penis: a case report

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Abstract: Clear cell sarcoma of the penis is exceedingly rare with only one prior case involving the penis reported in the literature. We present the case of a 32 year old male who presented with an infiltrative neoplasm at the base of the penis as well as extensive metastatic disease to the lymph nodes and bone. Morphologic, immunohistochemical and cytogenetic findings established the diagnosis of clear cell sarcoma. Despite chemotherapy the patient's disease was rapidly progressive and the patient died of disease within 8 months of diagnosis.

Keywords: Penis, neoplasms, sarcoma, clear cell, melanoma, human

Case report

A 32 year-old African-American male presented to the emergency room with a mass at the base of his penis that he first noticed 2 years prior to presentation. The patient reported pain with erections. He denied any hematuria or dysuria. He had no history of sexually transmitted diseases, urinary tract infection, trauma or recent travel. He denied recent weight loss or anorexia, and had no personal or family history of cancer. He denied any history of intravenous drug use. He was sexually active with a single female partner. On exam he was uncircumcised and had an immobile, round, "woody" mass within the proximal dorsal portion of the penis deep to the skin. The skin overlying the mass was free of erythema, pigmentation, ulceration or palpable fluctuance. The remainder of the physical exam was unremarkable. The plan after this initial visit was to obtain an MRI of the penis to better evaluate the mass.

The patient did not return for follow-up but instead presented to the emergency room 6 months later for increasing penile pain. The patient reported that the penile mass had increased in size. He did not however have any urinary difficulty. A complete blood count and basic metabolic profile were within normal limits. Liver function test revealed elevated alkaline phosphatase at 177 IU/L. Upon examina-

tion, the mass was noted to be larger with coexisting right inguinal lymphadenopathy. An MRI demonstrated a 4 × 4 × 3 cm infiltrative enhancing dorsal penile mass with invasion into both corpora carvernosa and with extensive necrosis (**Figure 1**). Bilateral inguinal lymphadenopathy up to 1.5 cm in size with necrosis was detected. Diffuse osseous metastases in the pelvis, thoracic and lumbar spine were also seen on MRI.

The patient underwent cystoscopy and biopsy of the penile mass and inguinal lymph nodes. Cystoscopic examination was within normal limits. The biopsies of the mass showed nests and clusters of atypical small epithelioid and spindled cells set in a fibrous stroma. The epithelioid and spindled cells contained a small amount of clear to lightly eosinophilic cytoplasm, hyperchromatic nuclei and occasional conspicuous nucleoli (**Figure 2**). The neoplastic cells lacked cytoplasmic melanin or evidence of glandular or squamous differentiation. Immunohistochemical studies demonstrated reactivity of neoplastic cells for melanocytic markers (S100, HMB45 and Melan A). Additionally, neoplastic cells showed reactivity for synaptophysin, CD56 and vimentin. The tumor showed non-reactivity for epithelial (cytokeratin AE1/AE3, epithelial membrane antigen, CAM 5.2 and CK20), lymphoid (CD45 and CD30), neuroectodermal (CD99) or germ cell markers (OCT 3/4 and pla-
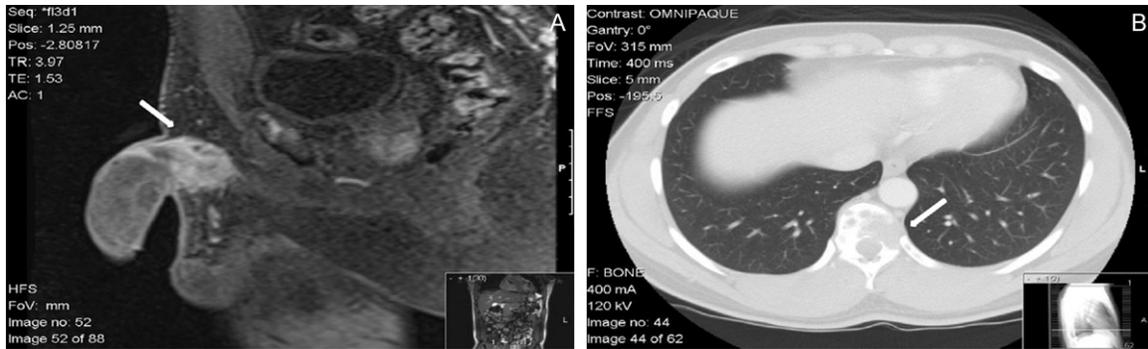
Figure 1. A. MRI of penile mass at the base of the penis (see arrow). B. Destructive bony metastasis within the thoracic spine on CT (see arrow).

cental alkaline phosphatase). The proliferation index (as assessed by Ki-67) was 30%. In combination with the histologic findings, the immunoreactivity pattern was consistent with clear cell sarcoma or metastatic melanoma.

Fluorescence in situ hybridization (FISH) was then performed using DNA probes for EWSR1 (Abbott Molecular/Vysis, Des Plaines, IL) per manufacturer's instructions, to assess for the presence of an EWSR1 rearrangement. The recurrent translocation, t(12;22)(q13;q12), resulting in the fusion of the EWSR1 and ATF1 genes is seen in >90% of cases of clear cell sarcoma, distinguishing it from malignant melanoma which possesses a similar histologic and immunohistochemical profile [1]. FISH analysis using the EWSR1 break-apart probe in this patient's tumor demonstrated that 80% of cells possessed an EWSR1 rearrangement confirming the diagnosis of clear cell sarcoma (**Figure 3**).

The patient was referred to medical oncology for further management. At this time the patient was unable to walk and complained of severe back pain. Bisphosphonates were started due to the patient's extensive bony disease burden. A bone scan confirmed widespread metastatic bone disease involving the ribs, sternum and left frontal region of the skull. A MRI of the brain was negative for cerebral metastasis.

Two weeks following the biopsy the patient was hospitalized for hypercalcemia (serum calcium 15.9 mg/dL) and acute renal failure (serum creatinine 1.9). Workup during this hospitalization included an MRI of the spine for persistent complaints of back pain which revealed a T10 pathological fracture and moderate cord com-

pression. The patient underwent palliative radiotherapy of the spine. He also was started on a chemotherapy regimen consisting of carboplatin and dacarbazine.

After three cycles of chemotherapy, a PET/CT demonstrated a decrease in the size of the penile mass to 2 cm. Given this response, three additional cycles of treatment were planned. After 2 additional cycles, the patient presented to the emergency room with altered mental status, severe hypercalcemia (serum calcium 17 mg/dL) and respiratory failure. The patient was intubated and admitted to the MICU. During hospitalization the hypercalcemia was reversed and the patient was able to be extubated. His mental status remained altered, and an MRI of the brain demonstrated posterior reversible encephalopathy syndrome (PRES), most likely secondary to hypercalcemia. The patient was clinically stabilized and transferred to hospice care where he expired 8 months after diagnosis.

Discussion

Non-epithelial tumors of the penis are unusual and may include mesenchymal and lymphoid tumors. Malignant neoplasms of mesenchymal type (sarcomas) represent less than 5% of malignant penile tumors [2]. Sarcomas of vascular origin (including Kaposi sarcoma) are the most common primary sarcoma followed by leiomyosarcoma [3]. Sarcomas of the penis that present superficially tend to be lower grade, with low tendency for distant metastasis. Deep lesions involving the spongy or cavernous bodies typically are more aggressive with poorer prognosis [4]. Other reported sarcomas of the penis include leiomyosarcomas and
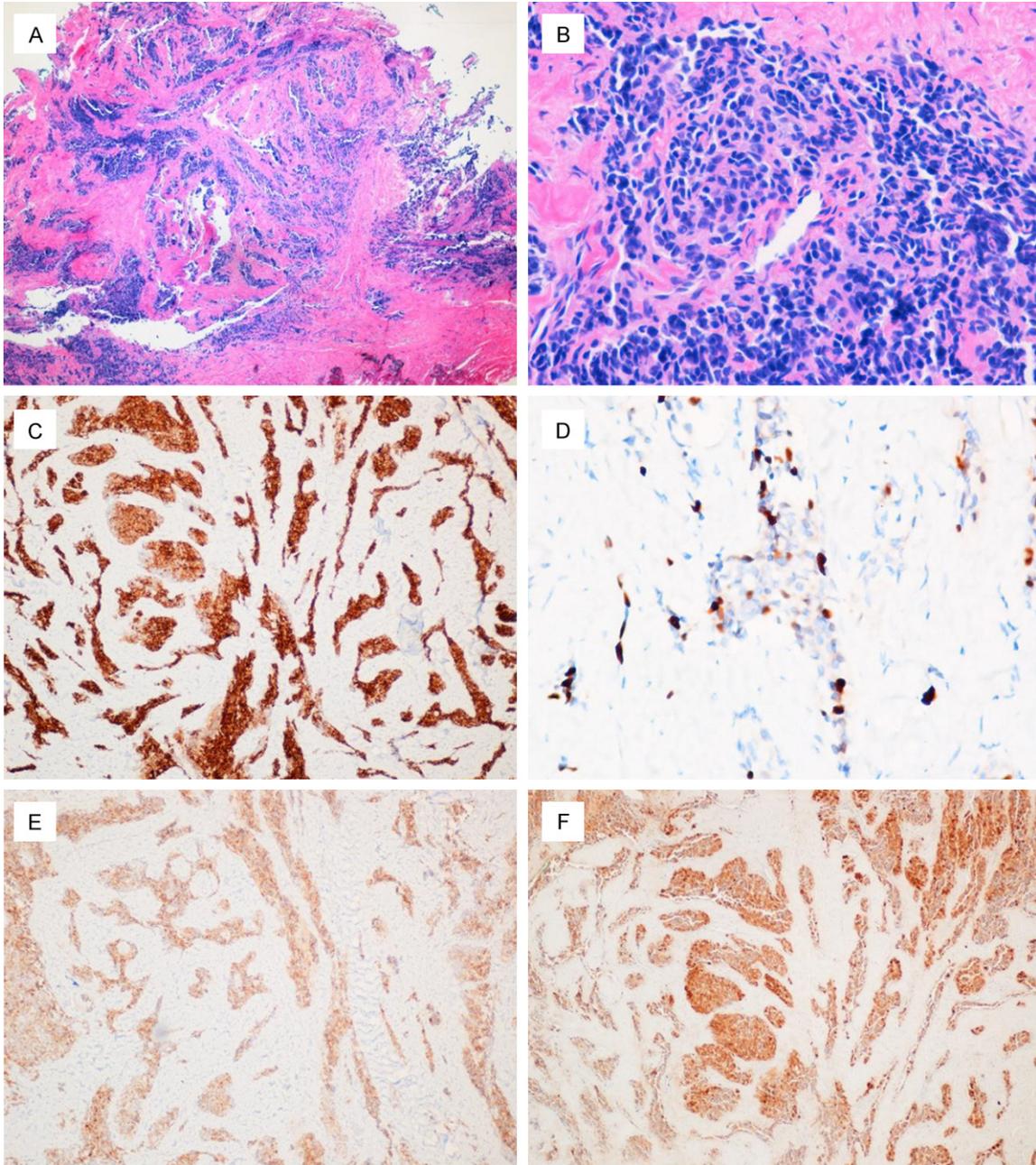
Figure 2. A. Tumor nests separated by fibroconnective tissue, 100x, H & E. B. Tumor cells with epithelioid and spindle appearance and small amount of clear cytoplasm, 400x, H & E. C. Tumor showing HMB45 immunoreactivity, 100x. D. Tumor showing reactivity of MIB1 antibody against ki67 protein in up to 30% of cells. 400x. E. Tumor showing immunoreactivity for Melan A, 100x. F. Tumor showing immunoreactivity for S100, 100x.

fibrosarcomas. Rare examples of additional sarcomas that have been reported include epithelioid sarcoma, chondrosarcoma, osteosarcoma, rhabdomyosaroma, Ewing sarcoma and clear cell sarcoma.

Clear cell sarcoma of tendons and aponeuroses/malignant melanoma of soft parts original-

ly described by Enzinger in 1965 is a rare tumor that represents only 1% of all soft tissue tumors [5]. Typically it presents as a slow-growing painless mass, though it may be painful in up to 50% or remain stable with sudden rapid growth in up to 25% [6]. It occurs most frequently in the extremities, lower more often than upper, though cases presenting in the gastrointestinal
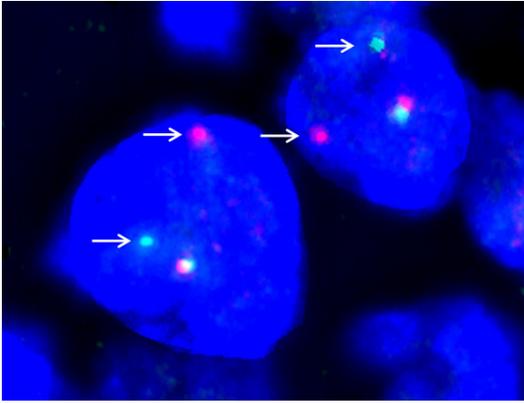
Figure 3. Dual color interphase fluorescence in situ hybridization utilizing the EWSR1 break-apart probe. Split red and green signals within a single cell demonstrates the presence of a EWSR1 rearrangement (indicated by white arrows).

tract have been reported [7]. A previous case of clear cell sarcoma of the penis is reported in a 10-year-old male who presented with a 7-month history of a slowly growing 8 cm mass at the base of the penis resulting in difficulty urinating [8]. After incisional biopsy confirmed the possibility of an undifferentiated sarcoma the patient underwent a course of radiation and chemotherapy (vincristine, cyclophosphamide and adriamycin) with 50% reduction of tumor size. The patient then underwent total penectomy given persistence of the tumor. Pathologic examination revealed strong S-100 reactivity, and presence of pre-melanosomes and melanosomes on electron microscopy consistent with clear cell sarcoma. No long term follow-up was reported for this patient.

Clear cell sarcoma is also referred to as malignant melanoma of soft parts due to its similar histological appearance to malignant melanoma. Immunohistochemical staining reveals antigenicity similar to that seen in melanocytic lesions including reactivity for HMB-45, Melan A and S-100. In patients presenting without prior history of a cutaneous or mucosal melanoma, differentiation between the two entities may be difficult. Clear cell sarcoma however is characterized by the presence of a t(12;22) (q13;q12) translocation which can be readily detected on cytogenetic analysis by FISH using an EWSR1 break-apart probe [1]. This translocation results in a fusion protein consisting of the Ewing sarcoma oncogene (EWSR1) on chromosome 22q and the activating transcription factor 1 (ATF1) oncogene on chromosome 12q.

This chimeric protein has been shown to be present in >90% of clear cell sarcoma, and is not found in malignant melanoma [1, 7]. The genetic pathway through which clear cell sarcoma develops differs from that of melanoma with BRAF and NRAS mutations occurring only rarely in clear cell sarcoma. Clear cell sarcoma is instead postulated to represent a sarcoma in which the ATF1 EWS fusion gene and its chimeric protein result in MITF activation resulting in melanin synthesis.

Tumor size greater than 5 cm, presence of necrosis, metastasis and local recurrence all are poor prognostic factors in clear cell sarcoma. The most common sites of metastasis are to lymph nodes, lung, skin, bone, liver, heart and brain. Though the patient's tumor was 4 cm in size, the presence of necrosis not only within the primary tumor, but also within the regional lymph nodes, as well as the presence of wide spread bony metastases at the time of diagnosis provided evidence of the aggressive nature of his tumor.

Surgical management involves wide local excision with small case series demonstrating an overall 5-year survival for patients with clear cell sarcoma presenting in the extremities of approximately 50% [7]. Given the relative rarity of clear cell sarcoma no standardized treatment algorithm exists. Radiotherapy may be employed to improve local control. The role for chemotherapy remains undefined. In general clear cell sarcoma is poorly sensitive to standard chemotherapy used for sarcoma although anecdotal reports of responses to regimens containing dacarbazine, ACNU and vincristine have been documented [9]. More recently, use of multikinase inhibitors such as sunitinib have been reported to effect tumor response [10]. This is likely due to inhibition of the PDGFR beta pathway which is activated in clear cell sarcoma. In a case in which sunitinib induced a long lasting response, cellular immunity to melanocytic antigen (Melan A/Mart 1) with consequent T lymphocyte infiltration of the tumor was found to play a role in tumor regression [11]. This case raises the hope for immunotherapies such as tumor vaccines or antibodies directed against immunological checkpoints as a potential therapeutic option that awaits further study.

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