INTRODUCTION

Liposarcoma (LS), a malignant soft tissue sarcoma (STS) tumor of adipose origin, occurs rarely in the paratesticular region, and accounts for 3%–7% of spermatic cord tumors. Dedifferentiated LS (DDLS) and well-differentiated LS (WDLS) account for 2 of 5 subtypes of LS, with dedifferentiation occurring in 20% of cases. While WDLS shows proliferation of mature adipocytes with variation in cell size and nuclear atypia, DDLS contains abrupt, discontiguous transitions to nonlipogenic sarcoma. Amplification of 12q13-15, which contains the MDM2 gene, a key negative regulator of p53, is a common abnormality of the 2 subtypes. WDLS and DDLS can be easily confused with their benign counterparts, lipomas, as well as other STSs such as Ewing sarcoma (EWS) based on clinical presentation and morphology. EWS is a tumor of osseous origin composed of small round cells expressing high levels of CD99, which contributes to its aggressive nature. Eighty-five
percent of EWS stems from balanced translocations leading to fusion of EWSR1 on chromosome 22 with the transcription factor FLI1 on chromosome 11, which results in a chimeric protein leading to EWS development. There have been 66 cases of DDLS of the spermatic cord reported to date, but none present with a 22/22q trisomy without the fusion or rearrangement that commonly produces these aggressive tumors. Here we report a morphologically and immunohistochemically unique case of spermatic cord DDLS presenting with severe complications including herniation and compression of the testicular artery.

**CASE REPORT**

A 57-year-old male presented to the Emergency Department (ED) with a painful, swollen scrotal mass after he coughed and felt a pop in his left inguinal region. Family history consisted of a father with prostate, kidney, and colon cancer and a second-degree relative with Ewing’s sarcoma. On examination, there was an incarcerated herniated mass with local scrotal swelling causing phimosis and urinary retention. Ultrasound confirmed severe left hydrocele, minor right hydrocele secondary to mass effect, and asymmetric arterial waveforms suggesting possible compression of the left testicular artery. Computed tomography (CT) abdomen and pelvis with contrast detected a 15.7×8.3×9.3-cm calcified, solid inguinal mass with a portion herniating into the scrotum with significant inflammation (Fig. 1).

Three years prior to this event, the patient underwent an elective hernia repair during which a solid mass was discovered attached to the left spermatic cord distal to the deep inguinal ring. The mass was extensively dissected, leaving the cord structures intact, and was histologically diagnosed as a lipoma. The patient remained asymptomatic for the next 3 years until he noticed this recurrent, indurated mass in the same location. While initially painless, it gradually caused stabbing pain at the site, decreased energy and libido, and nighttime diaphoresis. Malignancy was suspected, and CT chest showed multifocal bilateral pulmonary metastases up to 2.3 cm. Radiolabeled fluorodeoxyglucose positron emission tomography (18F-FDG-PET) confirmed hypermetabolic activity in the pelvic tumor and pulmonary nodules.

Re-examination of the originally resected mass thought to be a lipoma (outside specimen) revealed atypical morphologic features indicative of WDLS (Fig. 2A), confirmed by MDM2 amplification in 71% of cells by fluorescence in situ hybridization (FISH). Core needle biopsy of the new, recurrent mass (Fig. 2B) showed a high grade round cell malignancy, with diffuse staining of FLI1 and CD99 (weak), and negative AE1/AE3, Cam 5.2, S100, desmin, TdT, LCA, Cd3, Cd20, TLE1, and Cd34. FISH revealed 94% of cells with MDM2 amplification (Fig. 3A), and a third copy of EWSR1 without evidence of rearrangement, suggestive of 22/22q trisomy (Fig. 3B). Additionally, next generation sequencing gene fusion panel (99 gene panel, RNA-based) showed no pathologic fusions including EWSR1, FUS, CIC, BCOR, and SS18. These findings were consistent with high-grade DDLS, in the context of
a previously misdiagnosed WDLS. Surgical intervention was deemed infeasible due to the mass size, risk of seeding of malignant cells, and extended healing time delaying systemic therapy; therefore, doxorubicin monotherapy was initiated.

The ED presentation occurred 2 weeks after his second chemotherapy cycle. Surgical intervention was considered to decompress the testicular artery, however shared decision making resulted in employing conservative measures with lower urinary tract drainage and hematology/oncology consultation. The mass was not removed at that time in order to continue chemotherapy.

Repeat scans one month after the event showed tumor growth despite doxorubicin therapy, and the chemotherapy regimen was switched to gemcitabine/docetaxel.

**DISCUSSION**

Although an accurate diagnosis of LS is often difficult, it is crucial for establishing the most effective and timely treatment for patients. In this case, misdiagnosis of the original WDLS led to improper surgical resection allowing for recurrence and dedifferentiation of the tumor. The treatment guidelines for the management of DDLS are currently based on case reports and retrospective studies, which due to its aggressive nature advocate for en bloc tumor resection with high spermatic cord ligation and radical orchiectomy to achieve negative margins. This patient’s recurrent mass, however, was deemed unresectable, and the patient and care team opted for chemotherapy to eliminate metastatic disease and shrink the tumor.

Adjuvant chemotherapy and radiation have not shown a survival benefit in treating DDLS, but can have a palliative role. Metabolic sarcomas are traditionally responsive to anthracycline...
chemotherapeutics such as doxorubicin, which does not have an overall survival difference in combination with evofosfamide in metastatic or unresectable STS.\textsuperscript{2-5} Doxorubicin failed to elicit a response in this case, which is not uncommon in patients with aggressive DDLS. Gemcitabine/docetaxel is a common second line treatment for advanced DDLS.\textsuperscript{4} Newer systemic therapies are being studied such as PD1 inhibitors, XPO1 inhibitors, MDM2 inhibitors, and CDK4 inhibitors which target unique aspects of DDLS biology and may lead to a change in the current treatment paradigm.\textsuperscript{4}

The morphologic appearance of small round blue cell sarcoma, in the context of the family history of EWS, make EWS or Ewing-like sarcoma reasonable considerations. However, a comprehensive sarcoma and solid tumor sequencing analysis detected no characteristic EWS gene fusions, thus further immunohistochemical exploration is helpful in this case.

EWSR1 frequently translocates with other genes leading to overexpression of transcription factors that produce tumorigenic chimeric proteins. This process is classic for EWS but is also reported in myxoid LS, desmoplastic small round cell tumors, and angiomatoid fibrous histiocytoma.\textsuperscript{6} EWSR1–FLI1 fusion is the most common of these translocations. While FLI1 normally regulates hemopoiesis and neural crest development, fusion with EWSR1 causes continuous erythropoietin signal transduction and uncontrolled proliferation.\textsuperscript{6} The expression of FLI1 in this patient’s tumor sample may explain the rapid growth of the tumor and significant mass effect. While there was no evidence of rearrangement, an extra copy of the EWSR1 gene was present, suggestive of a trisomy of 22/22q. EWSR1–WT1 trisomy has previously been reported in 2 cases of desmoplastic round cell tumor,\textsuperscript{7} but trisomy of EWSR1 alone has not been reported. This extra copy could be a point of genetic instability of unknown magnitude, which may have increased the odds of malignancy while also contributing to the “ewingoid” phenotype.

Furthermore, the diffuse positivity of CD99 in the biopsy introduces another layer of novelty. CD99 normally assists in lymphocyte differentiation and maturation; however, proinflammatory CD99 is reported in 90% of EWS cases and plays an important role in cell migration, adhesion, and metastasis as well as growth and differentiation.\textsuperscript{8} This may explain the severe degree of macroscopic inflammation and local hematoma that occurred, permeating several fascial planes, allowing for fluid extravasation into the penis and bilateral scrotum, and constituting a urologic emergency. The existence of only one previous report of a CD99+ small round blue cell tumor of the spermatic cord with CIC fusion indicates the rarity of an Ewing-like sarcoma of the spermatic cord.\textsuperscript{9}

Lastly, the biopsy showed MDM2 amplification in 94% of cells. MDM2 inhibits the activation domain of the p53 tumor suppressor gene, and its upregulation leads to a loss of p53-dependent activities such as apoptosis and cell-cycle arrest.\textsuperscript{10} Overamplification of MDM2 is present in one third of sarcomas, but exceptionally high MDM2 amplification (>90%) is more specific for WDLS/DDLS.\textsuperscript{10} This marker, in the context of the previously misdiagnosed WDLS and aggressive tumor recurrence, provides strong evidence that the best classification for this tumor is DDLS with ewingoid properties.

This is the first reported case of DDLS showing 22/22q trisomy without fusion or rearrangement. The complications arising from this spermatic cord LS were severe with significant implications for nearby anatomical structures, demonstrating a potential need for emergent treatment. Understanding malignant changes in tumors such as this can guide developing therapies which take advantage of specific biology implicated in DDLS.
NOTES

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REFERENCES


