REVIEW PAPER

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Paratesticular liposarcomas: A rare but crucial diagnosis. Case series and review of literature

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Introduction Soft tissue sarcomas arise from mesenchymal tissue, with liposarcomas being the largest subgroup. These malignancies are classified into five subtypes by the WHO: atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLPS), dedifferentiated liposarcoma (DDLPS), myxoid liposarcoma, pleomorphic liposarcoma, and myxoid pleomorphic liposarcoma. WDLPS and DDLPS are the most prevalent, the latter being associated with higher metastatic rates (15–30%) and a 5-year mortality of 28–30% if metastases are present. This report discusses three cases of rare paratesticular liposarcomas, a subgroup originating from the tunica vaginalis and spermatic cord.

Material and methods Case 1 involved a 62-year-old man with a scrotal mass diagnosed as WDLPS after extensive examinations. Case 2 was a 72-year-old man with testicular swelling. Pathology revealed ALT/WDLPS with dedifferentiated zones, necessitating further wide resection due to positive margins. Case 3 described a 63-year-old man with a ductus deferens nodule diagnosed as WDLPS. Negative margins were achieved, and follow-up showed no recurrence.

Results Diagnosis of liposarcoma remains challenging due to overlapping imaging characteristics with benign conditions. Advanced modalities like positron emission tomography – computed tomography and magnetic resonance imaging can aid in differentiating liposarcomas based on metabolic activity and tissue characteristics. Surgical resection with negative margins remains the gold standard for treatment. Recurrence risks increase with positive margins and dedifferentiated histology. Adjuvant radiotherapy and chemotherapy show limited efficacy, emphasizing the importance of precision in surgical and pathological evaluation. Emerging therapies targeting the MDM2 and CDK4 pathways show promise for advanced or recurrent cases.

Conclusions This report highlights the complexity of diagnosing and managing paratesticular liposarcomas, underlining the importance of multimodal approaches for improved outcomes.

Key Words: liposarcoma ‹› paratesticular ‹› case series ‹› well-differentiated ‹› de-differentiated

INTRODUCTION

Soft tissue sarcomas originate from different types of mesenchymal tissue. In Europe, they have an incidence of 4.7 per 100,000 per year [1]. Liposarcomas, derived from an adipocytic precursor, represent the largest subgroup of the soft tissue sarcomas [1–3]. The most common locations are the trunk, extremities, retroperitoneum, paratesticular, mediastinum, and neck [4]. The World Health Organization (WHO) recognizes 5 different subtypes: atypical lipomatous tumor (ALT) or well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), myxoid liposarcoma, pleomorphic liposarcoma, and myxoid pleomorphic liposarcoma [2]. The WDLPS and DDLPS are the most prevalent subtypes. WDLPS is a slow-growing tumor and has a low metastatic potential, unlike its dedifferentiated counterpart. DDLPS is defined as an 'atypical lipomatous tumor

or well-differentiated liposarcoma associated with a non-lipogenic dedifferentiated component in the primary tumor or in a recurrence' [3, 5]. This subtype has a high metastatic rate of 15–30%, with a 5-year mortality of 28–30% if distant metastases are present [4] where the 15-year survival rate for liposarcomas in general is 50% [6].

We report three cases of paratesticular liposarcoma. These are a rare subgroup of the liposarcomatoid tumor arising from the tunica vaginalis, epididymis, spermatic cord, or inguinal cord [7, 8]. The patients presented to our department with different stories, demonstrating the difficult diagnosis of paratesticular liposarcoma.

CASES DESCRIPTIONS

Case 1

A 62-year-old patient, with a history of a left-sided varicocele correction during childhood, consulted the urology department because of an evolving scrotal mass in his left hemiscrotum. Two years earlier, the patient had undergone a scrotal examination due to a small epididymal nodule. Diagnostic ultrasound showed a small cystic lesion measuring 2 cm, which was diagnosed as a spermatocele. At the time, tumor markers (α-foetoprotein [AFP], β-human chorionic gonadotropin [β-HCG], lactate dehydrogenase [LDH]) were within reference range. New sonographic evaluation showed a dense cystic lesion measuring 3 cm, without Doppler signals. Scrotal exploration was performed, and excision of a beige colored homogenous mass was found, located in the vascular funiculus rather than the epididymis. The lesion measured 4 × 4.5 cm. The pathology report showed a well-differentiated liposarcoma with an inflammatory variant. Immunohistochemistry (IHC) for mouse double minute-2 (MDM2) was positive; a FISH array confirmed MDM2 amplification. Staging with chest-abdomen computed tomography (CT) showed small, nonspecific enlarged lymph nodes in the para-aortic and inguinal region. Definite inguinal orchiectomy with high ligation of the funiculus revealed a well-differentiated liposarcoma confined to the funiculus, with negative surgical margins. CT follow-up was every 6 months. At 12 months post-surgery, there was no evidence for recurrence on CT or clinical examination.

Case 2

A 72-year-old male was examined in the urological department because of a subacute testicular swelling that had been, present for two weeks. Diagnostic ultrasound showed an active orchido-epididymitis and a hypo-echogenic, spindle-like structure in the ductus deferens with the differential diagnosis of granuloma or hematoma. Testicular tumor markers showed a non-significantly elevated AFP of 9 ng/ml. After two weeks of antibiotics, a resolution of the infection was seen, but the spindle-like structure persisted. A re-evaluation 6 weeks later showed a slight AFP decrease to 8.2 ng/ml, but a volume increase of the indeterminate hypo-echogenic structure (Figure 1).

Therefore, the patient underwent an inguinal orchiectomy with preoperative CT staging. Imaging

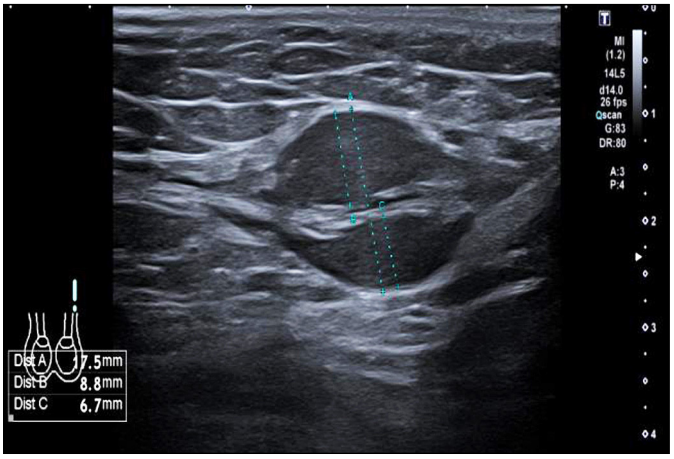

Figure 1. *Ultrasound, hypo-echogenic paratesticular structure.*

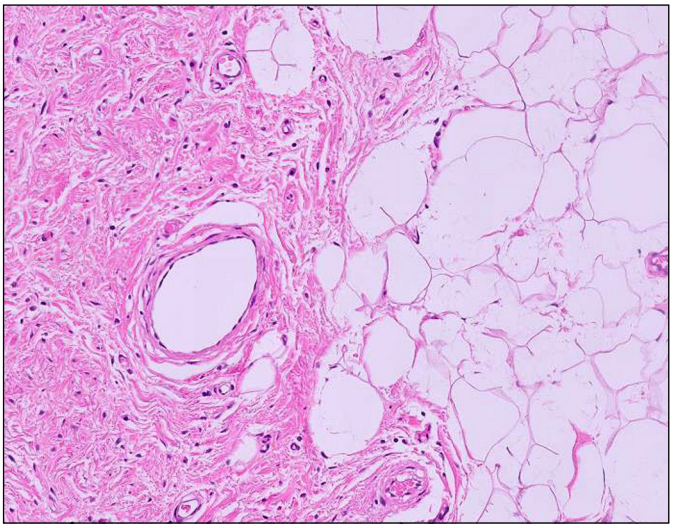

Figure 2. *Histological appearance in haematoxylin and eosin stain of well-differentiated liposarcoma showing as lipoblastic cells surrounded by spindle-like cells. In contrast with the abrupt change to dedifferentiated zones is shown as hyperchromatic nuclei in a non-adipocytic environment.*

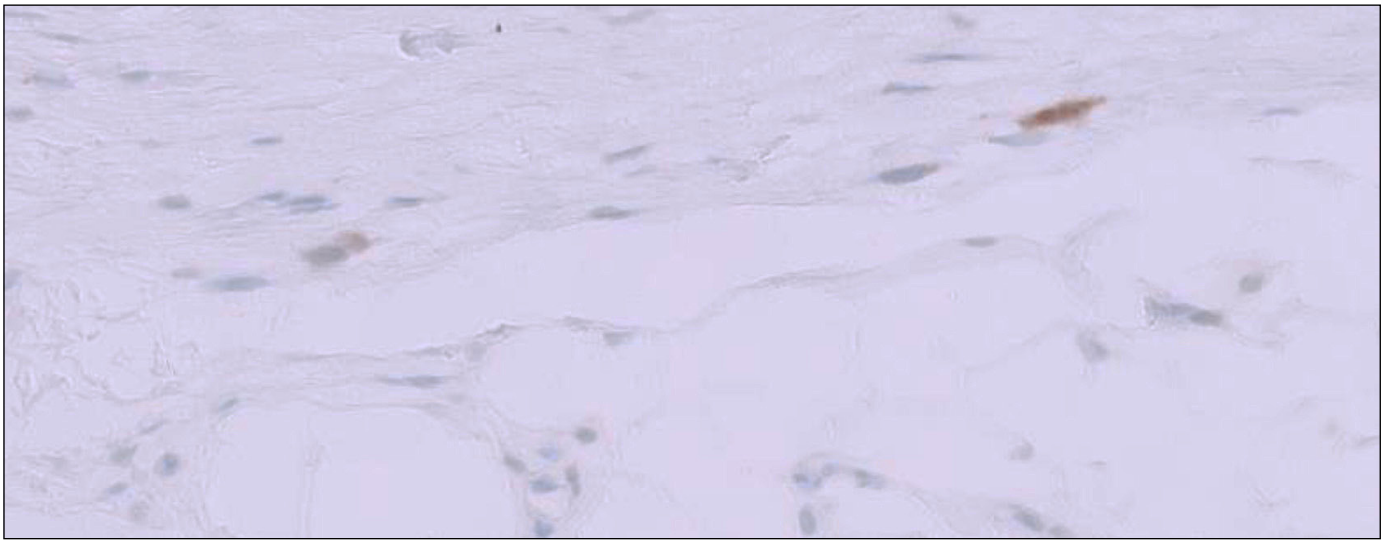

Figure 3. *Immunohistochemical stains showing limited MDM2 presence.*

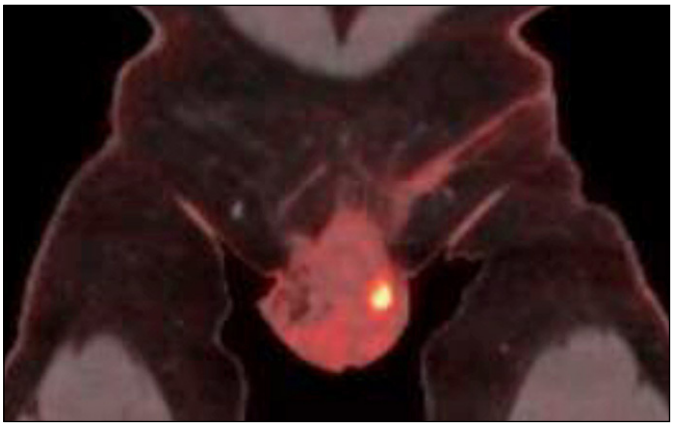

Figure 4. *Coronal section of scrotum on PET-CT, FDG-avid hotspot after surgery.*

was negative for distant malignant lesions or malignant lymph nodes. The pathology report showed a 4.2 × 1.9 cm nodular structure on the ductus deferens. Microscopical evaluation showed spindle-shaped cells with irregular hyperchromatic nuclei, lipoblast-like cells, and few polynuclear cells (Figure 2). MDM2 was positive on IHC (Figure 3). The diagnosis of ALT/WDLPS with zones of dedifferentiated liposarcoma was postulated. Atypical cells were present in the proximal surgical margin.
Therefore, an additional short-term follow-up with a PET-scan was planned. Imaging three months post-surgery showed an active FDG-hotspot on the scrotal skin (Figure 4). A wide resection was performed, with removal of the remaining hemiscrotum. The pathology report showed no residual malignancy. Follow-up at 6 months with magnetic resonance imaging (MRI) was negative for recurrence.

Case 3

A 63-year-old patient, without a significant medical history, presented with a hard nodule in the ductus deferens. Ultrasound-guided examination showed a non-cystic hyperechogenic structure without vascularization. Staging with CT chest-abdomen was negative. An inguinal orchiectomy was performed. The pathology report described a 6.5 × 5.0 cm myxoid, lipomatous structure. Based on the morphological characteristics (atypical spindle-shaped cells, multinuclear cells containing hyperchromatic nuclei, surrounded by sclerotic myxoid matrix), an inflammatory myofibroblastic tumor was initially suggested. IHC was positive for MDM2, with MDM2 amplification on FISH, making the diagnosis of a well-differentiated liposarcoma with sclerosing, myxoid and inflammatory subtypes more likely. Surgical margins were negative, testicular invasion was absent. A follow-up strategy was started using MRI 3 months after surgery, followed by CT every 6 months. Follow-up after two years remained negative.

DISCUSSION

In the first case, the diagnosis of the tumor posed significant challenges. Due to the lesions increased density, a scrotal exploration with biopsy was deemed necessary. Initially, the lesion was presumed to be a benign entity, such as a hematoma or spermatocele. Consequently, a primary inguinal orchiectomy was not performed during the initial scrotal exploration. This decision was made in consultation with the patient, opting instead to pro-

ceed with orchiectomy only after histopathological confirmation of malignancy.

Pre-operative identification of lipomatous and liposarcomatoid structures is known to be difficult. Sonographic characteristics of liposarcoma are non-specific and often confused with benign conditions such as inguinal hernia, hematoma, cyst, lipoma [7]. WDLPS is seen as a well-described, multilobulated heterogeneity, but it is difficult to discern from a lipoma [9]. Shimamori et al. found hypovascularity as a returning sonographic characteristic in WDLPS, where DDLPS has an additional focus of hypervascularization in the dedifferentiated area [10]. CT or MRI findings are more useful, as 75% of the WDLPS contains pure fat and the remaining 25% contain thick (>2 mm) or nodular septations and small (<2 cm) non-lipomatous areas making differentiation between lipoma and WDLPS possible [9, 11]. DDLPS identifies as a non-lipomatous focus measuring more than 1 cm in addition to the typical WDLPS characteristics [9]. MRI images consist of non-specific, low to intermediate signal intensity on T1-weighted images and intermediate to high signal intensity on T2-weighted images.

Performing imaging guided biopsy of both components is needed to confirm the diagnosis of DDLPS [9].

PET-CT has been useful in differentiating lipomatous lesions using standard uptake values (SUV), where benign lipomas have a SUV-mean of 0.81, and higher values correlated with malignancy as found by Suzuki et al. [11]. Several other studies examined the relationship between SUV-max and the type of liposarcoma: a SUV-max around 2.5 correlated with WDLPS, but for DDLPS the value ranged around 6.2, thus proving a significant correlation between SUV and tumor grade [12, 13]. Using PET-CT as a staging tool has been proven to be superior in detecting malignant lymph nodes and bone lesions compared to CT, but worse at detecting pulmonary metastasis [14].

Liposarcoma analysis discovered amplifications on the chromosomal region 12q14-15. Both subtypes show alterations in the MDM2 and cyclin-dependent kinase-4 (CDK4) genes. The MDM2 gene amplification results in inhibition of the tumor suppressor protein p53, causing unregulated cell cycling. The presence of MDM2 amplification is an excellent factor to distinguish WDLPS and DDLPS from different sarcomas with a sensitivity ranging from 90 to 100% [5]. The CDK4 amplification causes dysregulation of retinoblastoma 1, a tumor suppressor protein. Highly amplified CDK4, more common in high-grade DDLPS, is proven to have a worse prognosis with a shorter recurrence-free survival [3].

The gold standard for the treatment of liposarcoma is a wide resection of the tumor, if anatomically possible with surrounding tissue [4, 8]. Liposarcomas located in the retroperitoneum have a worse overall survival than in any other origin, due to their relation to surrounding organs and difficult margin-free resection [4]. Cases where surgical margins were positive showed a shorter recurrence-free survival [3]. Because of the positive proximal surgical margin and postoperative PET avidity, we performed a wider resection in the second case.

Kamitani et al. reviewed 285 cases of paratesticular liposarcomas over a period of 40 years [8]. They demonstrated a significant difference in recurrence when an inguinal orchiectomy with high ligation was performed, in contrast to a simple, organ-sparing tumorectomy. Tumor size, dedifferentiated histology and positive surgical margins were risk factors for recurrence. They found 3-year recurrence-free survival rates of 54.2% for those with positive and 88.6% for those with negative margins [8]. A select group of seven patients with positive margins received adjuvant radiotherapy, but no benefit in recurrence-free survival was found [8].

In the recurrent or neoadjuvant setting, the use of radiotherapy is still debated, but it is sometimes useful in pre-operative tumor size reduction [3, 4]. The sensitivity to chemotherapy in liposarcomas is poor, with WDLPS and DDLPS known for their very low response rate [4]. The use of anthracyclines such as doxorubicin has been the mainstay of therapy. The addition of ifosfamide in the unresectable or metastatic setting of WDLPS and DDLPS showed minor improvement with a progression-free survival benefit ranging from 2,5 to 5 months [4, 15]. An important conclusion of several studies was the low overall response rate which, depending on chemotherapeutical, ranged from 11 to 22% [4]. Second line treatments consist of dacarbazine, docetaxel and gemcitabine [4]. New research investigates several agents working on the amplification of MDM2, for example the class of Nutlins and agents targeting the CDK4 pathways, for example palbociclib [3, 4].

CONCLUSIONS

We report three cases of paratesticular liposarcomas. The diagnosis of this rare type of cancer is difficult and requires a thorough sonographic evaluation with additional biopsy if possible. PET-CT could help to differentiate in histological type before surgery. Wide resection of the tumor has been the mainstay of therapy and the most significant prognostic factor. Further research

is needed to improve systemic therapies for advanced disease.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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