

Pathohistological and Immunohistochemical Diagnostics in Well-Differentiated Paratesticular Liposarcoma with Dedifferentiated (DD) Component – Two Rare Clinical Cases with a Literature Overview

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Abstract

Paratesticular liposarcomas are rarely diagnosed neoplasms. This article presents two clinical cases with paratesticular liposarcomas. 42-year-old patient with a large right-sided paratesticular formation. After radical surgery, microscopic and immunohistochemical examination is a proven rare histological variant of floret-type giant cells inflammatory well-differentiated liposarcoma originating from the seminal cord. 46-year-old patient with a giant-sized right-sided paratesticular tumor. After a right-sided orchiectomy, microscopic and immunohistochemical examination the dedifferentiated liposarcoma (DDLs) with testicular infiltration and epididymis is reported. Against the backdrop of a literary review is focused on the pathohistological dedifferentiation of well-differentiated liposarcoma (WDLS) and the necessary immunohistochemical panel for differential diagnosis (DD) with pathohistological-like benign and malignant paratesticular tumors. The presence of a dedifferentiated non-lipogenic component in WDLS, determines their malignant potential, which must be complied with the optimum therapeutic approach.

Keywords: Dedifferentiated Paratesticular Liposarcoma; Giant-Cell Inflammatory Well- Differentiated Liposarcoma; Floret-Type Multinucleated Giant Cells; Immunohistochemistry; Differential Diagnosis

Introduction

The paratesticular area includes the seminal cord, epididymis, and fascia, which accompanies the testicle during its embryonic displacement from the pelvis into the scrotum [1,2]. Paratesticular liposarcoma is an extremely rare malignant neoplasm diagnosed in 12% of all liposarcomas, 3-7% of all scrotal sarcomas [3-7], and in 90% originating in the seminal cord [8]. The first patient with seminal cord sarcoma was described by Lesauvage in 1845 [5,9]. Liposarcoma is a soft tissue sarcoma of adipocyte origin, with various clinicopathological subtypes, some of which are characterized by distinct molecular cytogenetics abnormalities, including a well-differentiated liposarcoma (WDLS)/atypical lipomatous tumor, dedifferentiated liposarcoma (DDLs), and round cell myxoid type liposarcoma [10]. Among its various histological subtypes, the myxoid type is the most common, followed by a WDLS with or without dedifferentiated (DD) component (25%): round cell myxoid type liposarcoma (15%) and pleomorphic liposarcoma (10%) [11]. The identification of various histological types within the DD component and marginal status of excised DDLs has been observed to have prognostic relevance [12].

We present two extremely rare histological subtypes of paratesticular liposarcoma, in order to discuss the hampered pathological diagnosis, as well as a differential diagnostic plan with other paratesticular malignant and benign tumors.

Clinical Case No 1

We present a 42-year-old patient with a large right-sided paratesticular formation. The patient has pains and bumps in the right scrotal area with prolonged prescription of about 5 months. A large, slowly growing formation is established (Figure 1A). Complete blood count with biochemistry and serum levels of tumor markers alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG) are within a normal range. Radiography of the lung does not prove lung metastases. CT of abdomen and pelvis with

intravenous contrast: There are no pathological abnormalities of abdominal organs, kidneys and adrenals in the norm, without pathologically enlarged paraaortic, pelvic and inguinal lymph nodes. There is no free encapsulated fluid in the abdomen. Bladder normally presented. Right-sided inguinal orchiectomy with high ligation of the seminal cord has been performed. A tumor formation of the scrotum, tightly growing to the cordon, has been removed at the same time as the right testicle.

Histological Result

Macroscopic – Testicle with dimensions 5 cm/3 cm/4 cm, with a cordon to it 13cm, in the proximal end of which a tumor formation 17 cm /14cm is found (Figure 1/B). In the cut surface, the tumor has a yellowish, non-homogeneous color, lobulated in appearance, with a soft-elastic consistency and an external view similar to adipose tissue with the presence of myxoid and necrotic areas (Figure 1/C).

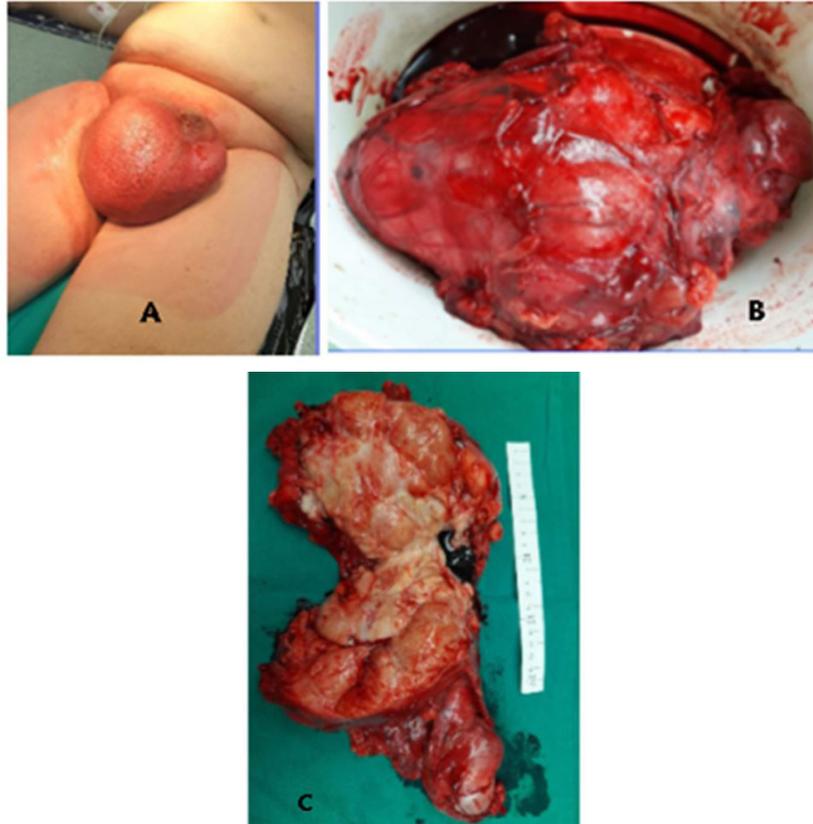


Figure 1: A: Preoperative photograph of paratubular liposarcoma; B: Macroscopic appearance of tumour formation with dimension 17/14cm at the proximal end of the the seminal cord; C: In the cut surface, the tumor has a yellowish, non-homogeneous color, lobulated in appearance, with a soft-elastic consistency and an external view similar to adipose tissue with the presence of myxoid and necrotic areas

Microscopic Description

The tumour with a lobulated structure, composed of atypical lipocytes with a light and moderate nuclear polymorphism, among which are scattered single nucleated giant cells of the lipoblastic type with a centrally located hyperchromic nucleus and multi vacuolated cytoplasm. Other multi-nucleated cells are found with moderate nuclear polymorphism and scarce cytoplasm. The stroma has a pronounced interstitial fibrosis, focal and interstitial lymphocyte infiltrates, focal fat necrosis, including the formation of small lipogranulomas, thin and thick-walled blood vessels (Figure 2 & 3).

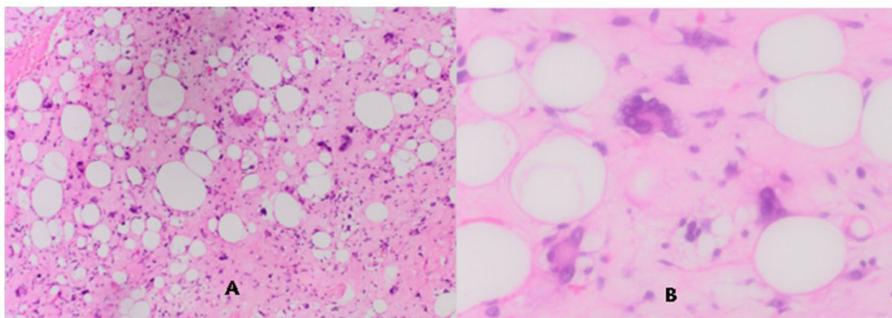


Figure 2: Photomicrography of A: Giant cell inflammatory variant of well-differentiated paratesticular liposarcoma H/E x 200; B: Floret-type multinucleated giant cells H/E x 400

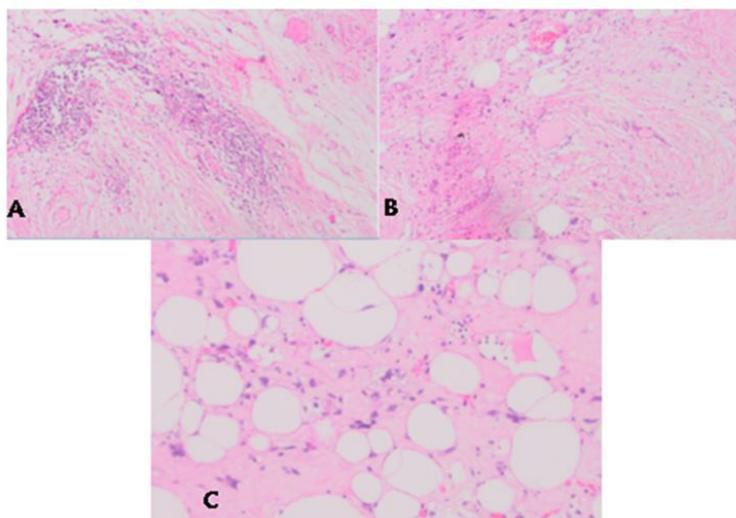


Figure 3: Photomicrography of **A:** Nodular lymphoplasmacytic infiltrates H/E x 100; **B:** Fibroblastic stroma H/E x 100; **C:** Atypical lipoblastic cells H/E x 200

Immunohistochemical (IHC) Analysis

S100 protein with almost diffuse expression (Figure 4/A); CD 34 with positive expression in single tumor cells and with positive expression in blood vessels (Figure 4/B); Desmin with positive expression in the giant cells (Figure 5); Ki 67 Index 26% (350 to 1350) (Figure 6).

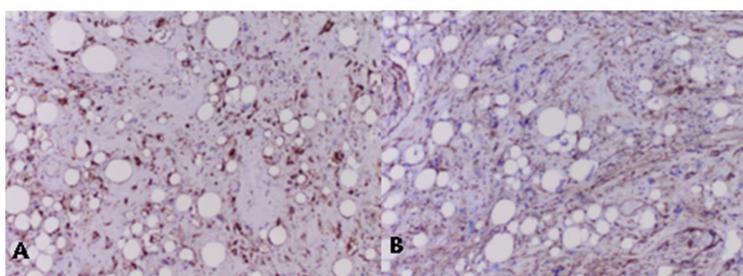


Figure 4: Photomicrography of IHC- **A:** S100 protein with positive expression in tumour cells x 100; **B:** Positive CD 34 in single tumour cells and with positive expression in blood vessels x 100

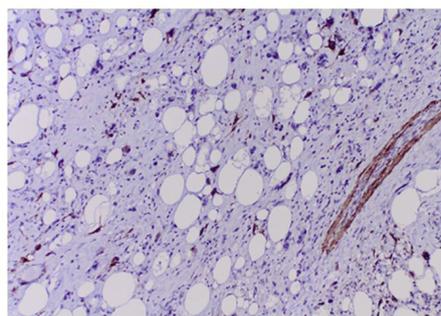


Figure 5: Photomicrography of IHC - Desmin with positive expression in the giant cells and in the endothelial cells of blood vessels x 100

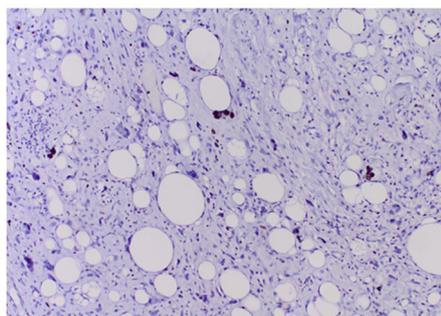


Figure 6: Photomicrography of IHC - Ki 67 Index 26% x 100

Conclusion

The histological morphology of paratesticular well-differentiated liposarcoma, lipoma-like and inflammatory variant with giant atypical cells/ floret-type giant cells.

Clinical Case No 2

46-year-old patient with a giant-sized right-sided paratesticular tumor (Figure 7A & 7C). After a right-sided orchiectomy, microscopic and immunohistochemical examination the dedifferentiated liposarcoma (DDLs) with an infiltration of the testicle and epididymis is reported. The preoperative CT of the abdomen and pelvis showed fibrous structure at the level of the perineum. The enlarged right scrotal area with an inhomogeneous structure, shaping of septi, hydrocele and initial low-stage varicocele is displayed. In the area of the right testicle heterogenous strengthening tumor mass with a maximum coronary rate of about 13cm/9cm/12cm, with the presence of a collateral blood supply and necrotic areas. Smaller lesions in the right scrotal area with maximum dimensions in the coronary plan about 5.27 cm. Lymph Nodes in the area of common and right external iliac chain, with a maximum size of 2.34 cm. Intraoperative finding- A tumor formation is involved, engaging the right testicle and growing to the skin of the scrotum. The cystic formation next to the left testicle of which leaked necrotic liquid 200 ml was found. Additionally, the necrotic skin from the scrotum is excised.

Microscopic Description

The tumor formation of irregular shape with dimensions 20cm/14cm/11cm (Figure 7B & 8).



Figure 7: A/C: Preoperative photography of paratcular liposarcoma; **B:** Macroscopic appearance of tumour formation of irregular shape with dimension 20cm/14cm/11cm. In the cut surface, the tumor has a yellowish, non-homogeneous color, lobulated in appearance

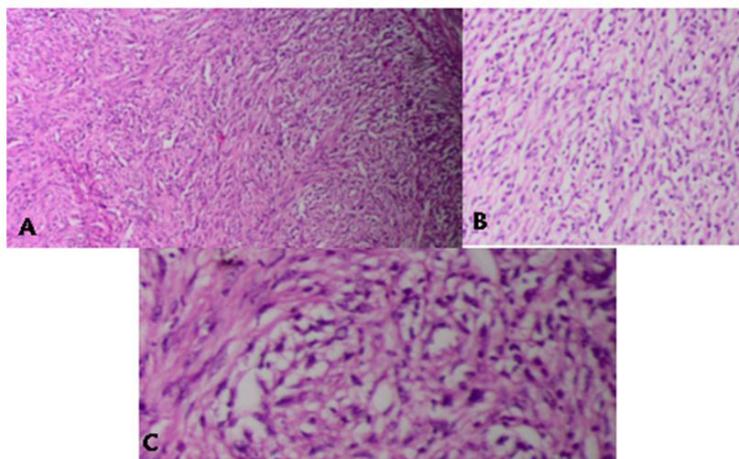


Figure 8: Photomicrography of DDLs- **A:** Storiform pattern histology with numerous spindled tumor cells containing hyperchromatic nuclei, irregularly admixed with lipogenic tumor cells H/E x 100; **B:** spindle-shaped cells with round and oval nuclei and moderate nuclear polymorphism H/E x 100; **C:** atypical lipoblastic cells H/E x 400

Microscopic Description

A tumor with a gentle structure consisting of spindle-shaped cells with round and oval nuclei with identified nucleolus and moderate nuclear polymorphism, whose cytoplasm is vacuolised, scattered correct and incorrect mitoses, areas with total and focal necrosis. The stroma has a well-pronounced interstitial fibrosis. The lymphocytic-neutrophilic infiltrates, thin and thick-walled blood vessels (thin-walled are branched and thick-walled with hyalinosis) are present. In the epididymis, a satellite tumor node with tumor embolus in the venula is detected. The histological foot thus described is relatively homogeneous in all preparations, but with ranging from low to highly pronounced cellularity.

Immunohistochemical (IHC) analysis- S100 protein with scantily positive expression (Figure 9A); Alpha SMA with scantily positive expression (Figure 9B); CD 34 with negative expression (Figure 10A); Desmin with negative expression (Figure 10B); Vimentin with positive expression; CD68 with a focal positive expression; Ki 67 Index 34% (Figure 11).

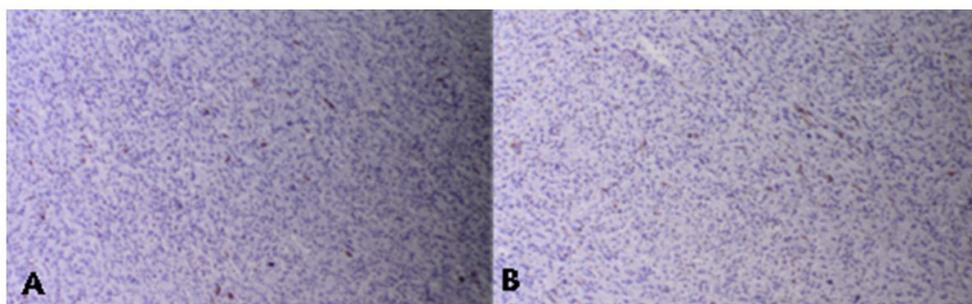


Figure 9: Photomicrography of IHC – A: S100 protein with scantily positive expression x 100; B: SMA with scantily positive expression x 100

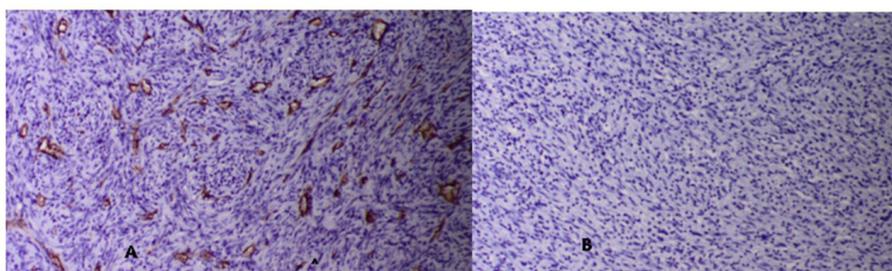


Figure 10: Photomicrography of IHC A: CD 34 with negative expression in tumour cells and with positive expression in blood vessels x 100; B: Desmin with negative expression x 100

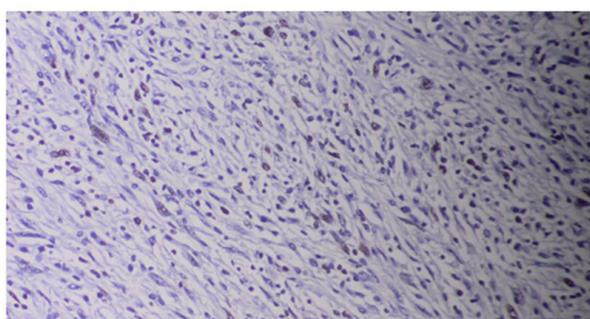


Figure 11: Photomicrography of IHC -Ki 67 Index 34% x 100

Histological Diagnosis

The histological morphology of dedifferentiated liposarcoma/ spindle cell variant with a high degree of malignancy, with infiltration of right testicle and epididymis, without the involvement of the seminal cord and skin of the scrotum.

Discussion

WHO classification of soft tissue tumors defines liposarcoma in 5 pathohistological categories: myxoid, well-differentiated, dedifferentiated, round cell and pleomorphic [13]. Histological subtypes of well-differentiated liposarcoma or atypical lipomatous tumors are divided into adipocytoma (Lipoma-like), sclerosing, inflammatory and spindle cell [14]. The inflammatory well-differentiated liposarcoma/ IWDLS is a rare histological subtype characterized by the following key characteristics:(1) nodular lymphoplasmacytic aggregates; (2) intervening paucicellular stroma containing fibroblastic elements, frequently with plasma cell-rich zones and scattered atypical, often multinucleate cells; (3) merging of atypical adipocytic and inflammatory elements; and (4) adjacent clearly defined zones of lipoma-like or, more rarely, sclerosing-type liposarcoma [15,16].

Molecular genetic studies revealed no evidence of clonal rearrangement of the T cell receptor gene, supporting the interpretation of these lymphocytes as reactive. Awareness of the existence of this variant of inflammatory liposarcoma should prevent its misinterpretation as a primary lymphoproliferative process [17]. A very rare pathohistological finding in the giant-sized liposarcoma is the presence of giant lipoblasts with a large round or blocky hyperchromatic nuclei [4]. In 2006, an inflammatory well-differentiated retroperitoneal liposarcoma was published for the first time with the presence of giant cells, followed by two more cases in 2013 [18,19]. In these giant tumors, mature lipocytes with nests of fibrosis, inflammatory infiltrates of lymphocytes and plasmatic cells, scattered lipoblasts with large hyperchromatic pleomorphic nuclei and pale, granular and vacuolated cytoplasm, together with multinucleated giant cells are observed [20]. Atypical mitoses are also observed which are uncommon [20,21]. In the three publications, there was no IHC analysis of multinucleated giant cells.

All key pathohistological characteristics of IWDLs are reported in clinical case No 1 (Figure 2A & 3). From IHC analysis we consider S100 protein with almost diffuse expression (Figure 4A); CD 34 positive expression in single tumour cells and in blood vessels (Figure 4B); Desmin positive expression in the multinucleated giant cells (Figure 5); Ki 67 Index 26% (Figure 6). The pathomorphological characteristic combines two subtypes of liposarcoma (Lipoma-like and inflammatory) or a mixed subtype of paratesticular liposarcoma [21] with the presence of floret-type multinucleated giant cells with scarce cytoplasm, Desmin positive expression and moderately high proliferative index Ki 26% (Figure 2B & 6).

The presence of floret-type giant cells requires differential diagnoses (DD) with spindle cell/pleomorphic lipomas [22-24] and giant cell fibroblastoma [25]. The pleomorphic lipoma is a relatively uncommon benign adipocytic tumor with a variable lipomatous component, spindle-shaped cell component and floret-like giant cells with nuclear pleomorphism [23]. Giant cell fibroblastoma is a juvenile form of dermatofibrosarcoma protuberans, which is also CD34-positive and can have a similar giant cell-rich picture on cytology [25]. However, floret-type giant cells are rarely seen in WDLs, and then only in small numbers [26]. The floret-like multinucleated cells were observed in sclerotic regions [27]. Similar to myxoid liposarcomas, WDLs occasionally may have a predominantly myxoid appearance. In the inflammatory, well-differentiated liposarcoma dedifferentiated areas are non-lipogenic and can stand out as firm nodules or be more diffusely admixed with low-grade areas. Chronic inflammatory cells (B > T cells) with occasional lymphoid follicles scattered in a cellular fibro collagenous stroma with sparse multinucleate atypical cells are observed [28].

A similar pathohistological finding was observed in a clinical case No 1 (Figure 3). Multinucleated giant cells (MNGCs) are a special class of giant cells formed by the fusion of monocytes/macrophages abundantly found in human tissues [29] and can actively protect the tissue from inflammatory damage [30]. They can be activated by some therapies to promote antitumor immunity [31]. It is important that floret-type giant tumor cells be differentiated from giant multinucleated macrophages, resulting from the fusion of single macrophages. They are characteristically detected in infectious and non-infectious chronic inflammatory conditions including schistosomiasis, atherosclerosis, sarcoidosis, and Langerhans cell histiocytosis [29,32,33]. Macrophages originate in monocytes and divide into M1 macrophages that encourage inflammation, and M2 macrophages that decrease inflammation and encourage tissue repair [29,34]. Depending on the localization, they are defined as adipose tissue macrophages and as soft tissue macrophages/ histiocytes leading to giant cells.

In straightforward cases of mammary fat necrosis, the histopathology is characterized by destruction of adipocytes leading to cytoplasmic vacuoles containing necrotic lipid material and gross cystic degeneration, followed by an influx of chronic inflammatory cells including numerous histiocytes, lymphocytes, plasma cells, and multinucleated giant cells [35-37]. Due to their histiocyte nature, macrophages express CD 68, which is a typical IHC marker for histiocytes and histiocytic tumors [38]. Cellular spindled histiocytic pseudotumor is a benign tumor, comprising a moderately cellular proliferation of spindled histiocytes arranged into short fascicles and often surrounded by areas of mammary fat necrosis. A variably dense chronic inflammatory cell infiltrate may be prominent, comprising lymphocytes and plasma cells, and there are often scattered multinucleated giant cells [39]. We consider a positive expression to Desmin in the MNGCs and moderately high proliferative index Ki 26% (Figure 5 & 6). The positive expression of Desmin is specific for myoblasts, myofibroblasts and smooth muscle cells [40].

Myofibroblastic cell origin is evidenced by positive expression to SMA, Desmin and often to CD 34 [41]. Pathological positive expression to Desmin was observed in: 1/differentiated leiomyoma, as well as in the case of dedifferentiated liposarcoma with leiomyoma, in which a positive expression is reported to SMA; 2/ inflammatory myofibroblastic tumor and malignant fibrous histiocytoma, but in both diseases, the IHC expression to Desmin may be negative; 3/ pleomorphic liposarcoma, in which Desmin is expressed in 13%, often accompanied by positive expression to S100-P and SMA. In general, WDLs are possible for heterologous cell components with positive expression to Desmin and Actin [4]. After the above examined detailed pathomorphological and IHC data consider inflammatory well-differentiated liposarcoma with large lipoblasts, part of which express SD 34 (Figure 4B) and non-lipogenic myofibroblastic components, manifested by Desmin positive floret-type MNGCs (Figure 5).

In clinical case No 2, we present a giant-sized paratesticular dedifferentiated liposarcoma/ spindle cell subtype. Spindle cell liposarcoma is a rare variant of WDL. It is diagnosed predominantly in adults with infiltration most commonly of subcutaneous soft tissues. Well-differentiated spindle cell liposarcoma represents a rare atypical/low-grade malignant lipogenic neoplasm that has been regarded as a variant of the atypical lipomatous tumor with atypical spindled tumor cells often staining positively for CD34 [42]. Morphologically, it is composed of neuronal-resembling spindle cell proliferation on the fibrous and/or myxoid basis associated with atypical lipogenic components [43]. Histologically, the variably cellular neoplasms were composed of atypical

lipogenic cells showing variations in size and shape, and spindled tumor cells with slightly enlarged, often hyperchromatic nuclei. The concept of tumor dedifferentiation is defined by the presence of an undifferentiated tumor component in the proximity of a differentiated tumor, invariably of low-grade or of borderline malignant type [10] or is a combination of an atypical lipomatous tumor (WD component) in juxtaposition to a “non-lipogenic” sarcomatous component (DD component) [44].

Critical histopathological analysis of 25 dedifferentiated liposarcomas (DDLs) reported that the most common WD component was the adipocytic type; the most common DD component was pleomorphic sarcomatous [13] (52%), followed by myxofibrosarcoma (MFS)-type [6] (24%) [10]. DDLs may show rarely a diffuse transition from the atypical lipomatous tumor component to a non-lipogenic sarcomatous tissue that may show a low-grade, spindle cell, fibroblastic morphology [45], and has to be distinguished from well-differentiated spindle cell liposarcoma [42]. From IHC analysis of the presented DDLs, we consider predominant pleomorphic sarcomatous components, mixed with lipoblasts, without clearly demarcated boundaries between WD component and DD component (Figure 8). In pleomorphic liposarcoma, there is a proliferation of G3 pleomorphic tumor cells with several lipoblasts, but without a well-differentiated liposarcoma, i.e. WD component [46]. The IHC analysis included a positive expression for Vimentin, SMA in 45%, S100-P in 33% in the lipogenic areas, as possible to CD 34. Recent studies have shown that some DDLs can show lipoblastic differentiation in the DD, high-grade component, resulting in areas indistinguishable from pleomorphic liposarcomas, leading to consideration of the revision of initial criteria for its diagnosis [47,48].

Pleomorphic sarcoma (formerly called malignant fibrous histiocytoma/MFH) is characterized by the presence of fibroblasts, myofibroblasts and histiocyte-resembling cells without lipomatous tumor differentiation [49]. In the pleomorphic sarcoma, a positive IHC expression is reported to CD 68 and Vimentin and negative to CD34, Desmin, and S100-P. Among various IHC markers, S100-P was useful in substantiating adipocytic differentiation and was negative in areas of dedifferentiation [50]. We observe that the IHC analysis of the presented DDLs is overcovered with the pleomorphic sarcoma, and S100-P with scantily positive expression proves lipoblastic differentiation in the DD component (Figure 8C & 9A). The presented clinical case No 2 of giant size DDLs with a pleomorphic sarcomatous component is an example of the cellular transformation of spindle cell WDLS with non-lipogenic cellular components to pleomorphic liposarcoma and subsequently to pleomorphic sarcoma.

Differential Diagnosis (DD)

Preoperative DD of paratesticular liposarcoma is significantly hampered by a number of benign diseases such as inguinal hernia, lipoma, hydrocele, epididymal cyst or seminal cord cyst, as well as from other primary malignant testicular tumors [7,51-54]. DD with testicular germ cell neoplasms requires a study of serum levels of tumor markers AFP and HCG, which in our case are within the normal range. The pathohistological DD of WDLS encompasses spindle cell lipoma, pleomorphic lipoma, neurofibroma, dermatofibrosarcoma protuberans. Spindle cell lipomas with positive IHC expression to CD34 and negative to MDM2, CDK4, and S100, are mainly diagnosed on the neck and upper back [26]. WDLS should also be differentiated from malignant neoplasms such as lymphoma, malignant fibrous histiocytoma, mesothelioma [55]. Sometimes the abundance of lymphoplasmacytic infiltrates in the IWDLS resembles an inflammatory fibrotic pseudotumor (15.17) and an inflammatory myofibroblastic tumor that does not express CD34, S-100, and Desmin [4]. Differential diagnosis includes Hodgkin's lymphoma and the disease of Castleman [17], as well as G3 liposarcoma with the presence of inflammatory cells [15].

Adverse Prognostic Factors

The following high-risk factors worsening local tumor control in soft tissue sarcomas (STS) are identified: large tumors > 10 cm, G3, deeply located, radically operated in the limb area [57]. The presented two clinical cases are giant paratesticular liposarcomas with deep localization. The clinical TNM classification of STS is based on the degree of differentiation (G) of sarcomatous cells, which is a significant prognostic factor [58]. Pathohistological classification is based on three pathomorphological characteristics: G, degree of necrosis and the value of the mitotic activity Ki 67. At high-risk liposarcoma, the proliferative index Ki 67 > 30% was significantly the predicted factor [57], directly related to the survival of patients. In the two giant liposarcomas consider high proliferative index Ki 67-26% and 34% (Figure 6 & 11). This IHC marker is required for DD between lipoblasts and adipocytes, i.e. between liposarcoma of the lipoma [56]. In clinical case No 1 the increased index Ki 67 is a consequence of non-lipogenic histiocyte resembling cells with a myofibroblastic characteristic, and in clinical case No 2 of the vast areas with a pleomorphic sarcomatous component, anaplastic tumor cells with high malignant potential.

Conclusion

We present two extremely rare clinical cases of giant-sized well-differentiated paratesticular liposarcomas with dedifferentiated myofibroblastic and pleomorphic sarcomatous components. The increased values of Ki 67 are a consequence of these two components, consisting of anaplastic tumor cells with a high proliferative and mitotic index. The large volume with the abundance of the necrotic adipose tissue in the giant-sized well-differentiated paratesticular liposarcomas is a favorable factor for the development of non-lipogenic sarcomatous components. The pathogenesis of floret-type giant tumor cells in inflammatory well-differentiated liposarcoma is associated with the transformation of preexisting histiocytes, causing myofibroblastic proliferation. The non-lipogenic pleomorphic sarcomatous component in the giant-sized DDLs is an example of lipoblastic transformation to pleomorphic liposarcoma with high malignant potential, which must be adapted to the optimal therapeutic approach.

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