

Case Report

Pathohistological and Immunohistochemical Diagnosis in a Rare Giant Cell Inflammatory Subtype of Well-Differentiated Paratesticular Liposarcoma - Clinical Case with Literature Review

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In the English language medical literature, this histological subtype liposarcoma with giant cells was published in three clinical cases with giant-sized retroperitoneal liposarcomas.

We present 42 year old man with a large right-sided paratesticular liposarcoma originating from the seminal cord. Right-sided inguinal orchiectomy with high ligation of the seminal cord are performed. After microscopic and immunohistochemical examination, a rare histological variant of giant cell inflammatory subtype of well-differentiated paratesticular liposarcoma is proven. Given the radical operation with clean resection edges is judged for prolonged dispensary observation.

This article discusses the Pathohistologic and immunohistochemical diagnostics of this extremely rare well differentiated liposarcoma. The literary overview focuses on the pathohistological liposarcoma characteristic, the necessary immunohistochemical panel for differential diagnosis and the optimal treatment approach.

Keywords: Giant-Cell Inflammatory Well-Differentiated Liposarcoma; Giant Paratesticular Liposarcoma; Pathohistology; Immunohistochemistry; Radical Inguinal Orchiectomy

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 [8,9]. 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, De-Differentiated 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 De-Differentiated (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 extremely rare histological subtype 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

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 1/A). 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 13 cm, 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).

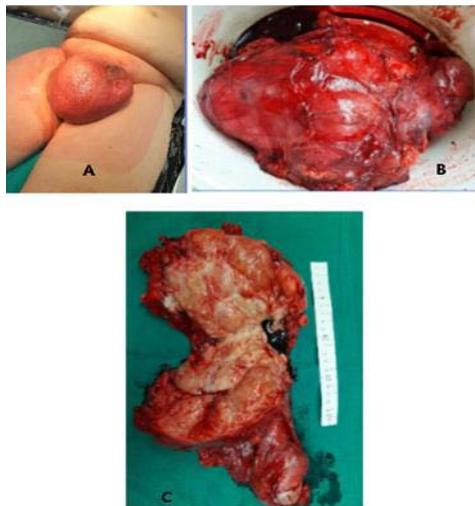


Figure 1: A: Preoperative photograph of paratesticular liposarcoma; B: Macroscopic appearance of tumour formation with dimension 17/14 cm at the proximal end of the the seminal cord; C: In the cut surface, the tumor has a yellowish, non-homogeneous color, lobulated in appearance, with a soft-elastic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

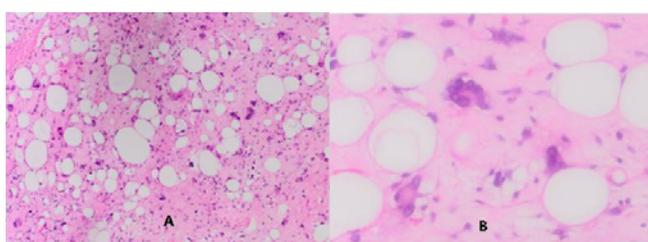


Figure 2: Photomicrography of A: Giant cell inflammatory variant of well-differentiated paratesticular liposarcoma H/E x 200; B: Floret-type multinucleated giant cells H/E x 400.

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 vacuolised 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/A,B; Figure 3 /A,B,C).

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).

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

Discussion: WHO classification of soft tissue tumors defines liposarcoma in 5 pathohistological categories: myxoid, well-

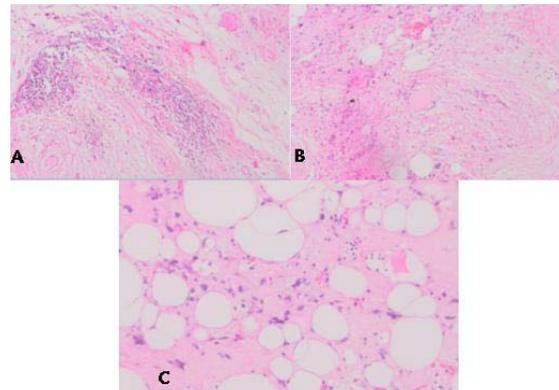


Figure 3: Photomicrography of A: Nodular lymphoplasmacytic infiltrates H/E x 100; B: Fibroblastic stroma H/E x 100; C: Atypical lipoblastic cells H/E x 200.

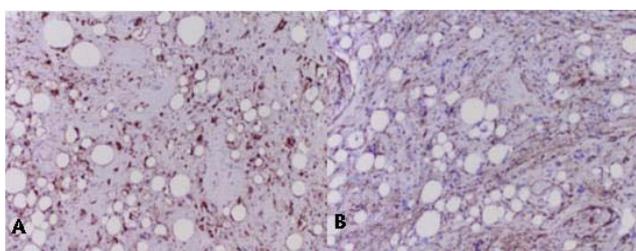


Figure 4: Photomicrography of IHC- A: S100 protein with positive expression in tumour cells x 100; B: Positive CD 34 in single tumour cells and with positive expression in blood vessels x 100.

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 [18], followed by two more cases in 2013 [19,20]. 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 vacuolised cytoplasm, together with multinucleated giant cells are observed [18-20]. Rare atypical mitoses are also observed [20-21]. In the three publications, there was no IHC analysis of multinucleated giant cells [18-20]. All key pathohistological

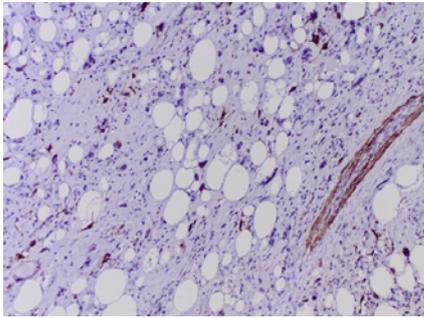


Figure 5: Photomicrography of IHC - Desmin with positive expression in the giant cells and in the endothelial cells of blood vessels x 100.

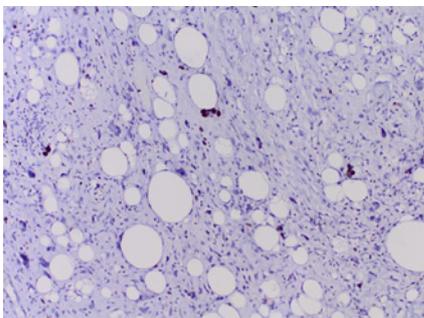


Figure 6: Photomicrography of IHC - Ki 67 Index 26% x 100.

characteristics of IWDLs are reported in clinical case №1 (Фиг.2/A; Figure3/A, B, C). From IHC analysis we consider S100 protein with almost diffuse expression (Figure4/A); CD 34 positive expression in single tumour cells and in blood vessels (Figure 4/B); 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% (Figure2/B, Figure6).

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 [27]. 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 №1 (Figure 3/ A,B,C). Multinucleated giant cells (MNGCs) are a special class of giant cell 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 monocyte 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 и Figure 6). The positive expression of Desmin is specific for myoblasts, myofibroblasts and smooth muscle cells [40]. Myofibrotic 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 [40], in which a positive expression is reported to SMA; 2/ inflammatory myofibroblastic tumor and malignant fibrous histiocytoma [40], but in both diseases, the IHC expression to Desmin may be negative; 3/ pleomorphic liposarcoma, in which Desmin is expressed in 13% [40], 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 4/B) and non-lipogenic myofibroblastic components, manifested by Desmin positive floret-type MNGCs (Figure 5).

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 [7,42-45]. 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 [46]. 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 [47]. The clinical TNM classification of STS is based on the degree of differentiation (G) of sarcomatous cells, which is a significant prognostic factor [48].

Pathohistological classification is based on three pathomorphological characteristics: G, degree of necrosis and the value of the mitotic activity Ki 67 [49]. At high-risk liposarcoma, the proliferative index Ki 67 > 30% was significantly the predicted factor [47], directly related to the survival of patients [50]. In the giant liposarcoma consider high proliferative indices Ki 67-26% (Figure 6). This IHC marker is required for DD between lipoblasts and adipocytes, i.e. between liposarcoma of the lipoma [51].

In clinical case the increased index Ki 67 is a consequence of non-lipogenic histiocyte resembling cells with a myofibroblastic characteristic.

Complex treatment

The optimal local treatment of paratesticular sarcomas in adults is radical surgery [1]. To achieve clean resection edges, extensive tumor excision is recommended, including orchiectomy with a high ligature of the spermatic cord [13]. The risk of local recurrence in a 10 mm resection line reaches 10% [4], and the pathohistologically positive of tumor cells is an unfavorable prognostic factor for early recurrences and distant metastases [52]. Some authors suggest adjuvant radiotherapy for local recurrences, inadequate (close) and positive resection margins, adverse pathohistological factors including G3 sarcomas and lymphatic invasion [13,52-54]. Due to the radical operation with clean resection lines, the presented patient was assessed for long-term observation and medical examination.

Conclusion

We present a extremely rare clinical cases of giant-sized well-differentiated paratesticular liposarcomas with dedifferentiated myofibroblastic sarcomatous component. The increased values of Ki 67 are a consequence of these 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. In well-differentiated liposarcomas, the tendency to distant metastasis is minimal, but local invasion is pronounced, which requires radical surgery with clean resection lines. The risk of local recurrence increases significantly after non-radical surgery. Adjuvant radiotherapy is available for local recurrences, inadequate (close) and positive resection margins, adverse pathohistological factors including G3 sarcomas and lymphatic invasion.

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