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Dedifferentiated liposarcoma composed predominantly of rhabdoid/epithelioid cells: a frequently misdiagnosed highly aggressive variant☆,☆☆

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Summary Dedifferentiated liposarcoma is one of the most common sarcoma types in adults with a predilection for the retroperitoneum. We have recently encountered 6 cases of DDL composed predominantly of rounded, rhabdoid or epithelioid cells mimicking rhabdoid melanoma, epithelioid rhabdomyosarcoma or undifferentiated carcinoma. Patients were 5 males and one female aged 64 to 81 years (median, 68). Tumors originated in the retroperitoneum (n = 5; 3 in the psoas muscle) and deep soft tissue of the thigh (n = 1). All 3 patients with follow-up died of metastatic disease within 4 to 8 months. Preoperative biopsy diagnoses never suggested dedifferentiated liposarcoma as a possibility; instead carcinoma, rhabdomyosarcoma and lymphoma were on top of suggestions. Five resected tumors were composed predominantly (70%-100%) of anaplastic rounded to oval rhabdoid cells with prominent central nucleoli and paranuclear rhabdoid inclusions. Bi- and multinucleation was a constant feature. The background stroma showed variable myxoid changes and minor mixed inflammatory cells. Two cases showed homologous dedifferentiation and another had sclerosing spindle cell nodule but a well-differentiated lipomatous component was not seen in any. One biopsied case showed solely monotonous small round blue cells with scattered rhabdoid cells. Immunohistochemistry showed expression of MDM2 (6/6), CDK4 (5/6), pancytokeratin AE/1AE3 (4/6) and diffusely desmin and myogenin (2/6). All cases showed high-level co-amplification of *MDM2*/*CDK4* by in situ hybridization. The SWI/SNF complex components (SMARCB1, SMARCA2, SMARCA4, ARID1A and PBRM1) were intact in all cases. This highly aggressive liposarcoma variant needs to be distinguished from a variety of neoplasms including undifferentiated carcinoma, melanoma, lymphoma, rhabdomyosarcoma and others.

1. Introduction

Dedifferentiated liposarcoma (DDL) is the most frequent undifferentiated sarcoma in the retroperitoneum but it also

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occurs in other sites including the paratesticular area, the extremities, the head and neck and the trunk [1,2]. It is defined as a non-lipogenic sarcoma that develops within a well-differentiated liposarcoma (WDL), as a recurrence of the former or de novo as an undifferentiated sarcoma showing amplification of *MDM2* and *CDK4* (both mapping to chromosome 12q14-15) and occurring at anatomic sites where DDL typically occurs [1,2]. Dedifferentiation occurs in approximately 10% of WDL, but 90% of DDL arise de novo without detectable WDL component [1,2]. Mainly middle-aged adults are affected with equal gender distribution [2].

The morphological spectrum of DDL has been ever growing to include in addition to the most frequent undifferentiated pleomorphic sarcoma (MFH/UPS-like) and spindle cell sarcoma not otherwise specified/NOS [3] unusual patterns such as low-grade dedifferentiation [4], heterologous dedifferentiation (corresponding to any of the other mesenchymal lineage such as bone, cartilage, smooth muscle, rhabdomyoblastic) [3-5], meningothelial-like whorls [6], inflammatory myofibroblastic tumor-like [7], myxofibrosarcoma-like [3], myxoid liposarcoma-like [1] and homologous dedifferentiation mimicking pleomorphic liposarcoma [8]. In this study, we describe our experience with DDL with a striking predominance of small to medium-sized cells showing rhabdoid, epithelioid or non-descript round cell morphology closely mimicking a variety of other neoplasms.

2. Materials and methods

Cases were retrieved from our surgical pathology files (n = 1) and from the consultation files of two of the authors (n = 5; A.A. & M.M.). None has been published before. Immunohistochemistry (IHC) was performed on 3-μm sections cut from paraffin blocks using a fully automated system ("Benchmark XT System", Ventana Medical Systems Inc, 1910 Innovation Park Drive, Tucson, Arizona, USA) and the following antibodies: pancytokeratin (clone AE1/AE3, 1:40, Zytomed Systems, Berlin, Germany), MDM2 (clone IF1, 1:50, CalBiochem), CDK4 (clone DCS-156, 1:100, Zytomed), desmin (clone D33, 1:250, Dako), myogenin (clone F5D, 1:50, Dako), SMARCA4 (anti-BRG1 antibody, clone EPNCIR111A, dilution, 1:100, Abcam, Cambridge, UK), SMARCA2 (polyclonal antibody, 1:100, Atlas Antibodies AB, Stockholm, Sweden), SMARCB1/INI1, clone MRQ-27, dilution, 1:50, Zytomed), ARID1A (rabbit polyclonal antibody, ab97995, 1:100; Abcam) and PBRM1 (clone CL0331, 1:50, Atlas Antibodies). Several other mesenchymal, epithelial and hematolymphoid markers were used in a routine setting to exclude other differential diagnoses according to our routine laboratory staining protocol (details available upon request; see Table 2). Assessment of the SWI/SNF markers was done the same way as reported previously, i.e. only unequivocal absent staining in the nuclei of viable tumor tissue (away from necrotic areas) was considered "deficient or lost" as opposed to "intact" expression (intense expression in the tumor cells that is equivalent to the staining of non-neoplastic cells in the background). As a control, the presence of homogeneous strong nuclear staining of stromal fibroblasts, inflammatory cells, vascular endothelial cells or other normal cells in the background was a prerequisite for assessable staining in the tumor. A "reduced expression" was assigned if viable tumor cells displayed homogenous very weak but still recognizable staining as opposed to stronger staining in normal cells in the background. Specimens lacking strong staining in the background non-neoplastic cells were considered not assessable.

2.1. MDM2 and CDK4 FISH testing

To detect copy number variations in the *MDM2* and/or *CDK4* gene loci, fluorescence in situ hybridization (FISH) was performed on sections cut from formalin-fixed paraffin-embedded tissue blocks using the Zyto*Light*® *SPEC MDM2/CEN12* and Zyto*Light*® *SPEC CDK4/CEN12* Dual Color Break Apart Probes (ZytoVision, Bremerhaven, Germany) with standard protocols according to the manufacturer`s instructions. Fifty tumor cells were visually inspected using a fluorescence microscope. The presence of two pairs of green and orange signals was considered normal findings. On the other hand, clusters of green *MDM2* or *CDK4* signals are considered indicative of amplification. The *MDM2* gene locus was assessed in Case 1 to 3 also using a chromogenic ISH probe (CISH method) from same manufacturer.

3. Results

3.1. Clinical features

The main clinical and demographic features of the patients are summarized in Table 1. The patients were 5 males and one female aged 64 to 81 years (median, 68). Tumors originated in the retroperitoneum (n = 5) and the deep soft tissue of the thigh (n = 1). Three of the 5 retroperitoneal tumors were located in the psoas muscle/iliac fossa. Imaging diagnoses were non-liposarcoma in all cases and included psoas abscess, lymphoma and sarcoma (Fig. 1).

Follow-up was available for 4 patients. Three died of metastatic disease at 4, 6 and 8 months (median: 6). One patient was alive with progressive disease under palliative chemotherapy after R2 resection 6 months after surgery. Metastases affected the GI tract (one stomach and one vermiform appendix), peritoneum (2) and wide-spread bone sites (1).

3.2. Pathological findings

Preoperative image-guided biopsy was obtained in three patients and was interpreted as poorly differentiated rhabdoid