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Sarcoma Pathology and Molecular Characterization

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Introduction

A diverse group of mesenchymal malignancies originating from retroperitoneal tissues and vessels are referred to as retroperitoneal sarcomas (RPS). Well-differentiated/dedifferentiated liposarcomas and leiomyosarcomas are the most common RPS, but there are also rare histological subtypes. Sarcoma pathology and molecular characterization have made significant progress in the past ten years. New therapeutic approaches based on tumor biology and the microenvironment has been developed as a result of these advancements, which have also resulted in significant modifications to their diagnostic management. The most prevalent RPS subtypes are discussed in this overview, along with the most recent pathological and molecular biology findings.

The rare cancers of mesenchymal origin known as soft tissue sarcomas (STS) are distinguished by their clinical, histological, and biological heterogeneity. New histopathological methods and advances in molecular biology have significantly reduced these tumors over the past few decades, with over 100 distinct subtypes included in the most recent WHO classification. Similar histological and molecular heterogeneity can be found in retroperitoneal sarcomas (RPS), which account for 10 to 15% of all STS. The most common RPS subtypes are well-differentiated/dedifferentiated liposarcoma (WDLPS/DDLPS) and leiomyosarcoma (LMS), but other histologies like solitary fibrous tumors (SFT), malignant peripheral nerve sheat tumors (MPNST) and undifferentiated pleomorphic sarcomas (UPS) can also be seen. Because it has an impact on clinical management and is a significant prognostic factor for patients' survival, the precise identification of the RPS subtype is essential. With a focus on liposarcoma and leiomyosarcoma, the purpose of this review is to present the state of the art as well as future prospects in RPS pathology and molecular biology [1].

Description

The majority of RPS found in radiological workups of unrelated symptoms is incidental findings, and tumors can grow to a significant size before causing symptoms. Malignant tumors are four times more common in the retroperitoneum than benign lesions, necessitating a quick diagnosis if benign soft tissue tumors are the majority in other parts of the body.

Multiple image-guided, percutaneous coaxial core needle biopsies using 14–16G needles, preferably through the retroperitoneum, are required for the standard diagnostic approach for RPS. A radiologist should conduct the biopsy after consulting with skilled surgeons or a multidisciplinary tumor board in a reference center. In the case of necrotic or cystic lesions, image guidance may assist in locating solid tumor regions. Growth biopsies ought to be quickly fixed in 4% supported formalin and consequently implanted in paraffin blocks. With FFPE material, middle-throughput RNA and DNA analyses are consistently possible. For the majority of retroperitoneal sarcomas, fresh frozen tissue collection is not required as a first approach. However, it may facilitate additional molecular analyses. To rule out benign tumors and other malignancies distinct from RPS that could be considered a differential diagnosis, a histological diagnosis is necessary. In addition, the pathological subtype of RPS must be precisely identified because it can influence prognosis and direct additional therapeutic strategies, such as surgical approaches and systemic treatments [2].

Recurrent amplification is what distinguishes WDLPS and DDLPS. This amplification is usually caused by super numerary ring or giant chromosomes that form as a result of break-fusion-bridge cycles but it can also be caused by chromotrypsis or chromoplexy. The first driving change in WDLPS and DDLPS are amplicons, which are present in the precursor cells and are shared by all cells in the resulting tumor mass. The Mouse Double minute homolog 2 (MDM2) gene is included in a number of studies that have shown that the amplicon is centered on an 856 kb sequence. As a result, MDM2, which is located in is largely overexpressed and amplified in both WDLPS and DDLPS. Amplification of MDM2, a TP53 functional antagonist, results in the inhibition of TP53-mediated gene transactivation. In addition, recent research has demonstrated that MDM2 binds to chromatin and promotes nucleotide synthesis, which in turn fuels LPS tumorigenesis. Amplification is missing in less than putting their diagnosis in doubt. While elective enhancements of MDM4 (otherwise called MDM2-like P53-restricting protein or MDMX), which quality has synergistic capabilities with in guideline, have been accounted for in a couple of cases, the system supporting the improvement of these uncommon cancers stay tricky.

The mRNA articulation and methylation profiles of WDLPS/DDLPS are heterogeneous, depicting a few groups upon non-directed progressive investigation. Despite the potential prognostic value of these molecular classifications, no single biomarker has yet been validated, preventing their widespread application in clinical practice. For instance, the frequency of PTPRQ and YAP1 amplifications in better-prognostic clusters is correlated with a better outcome, whereas the frequency of amplifications is not. Undifferentiated pleomorphic sarcomas (UPS) and myxofibrosarcomas (MFS), two subtypes of sarcomas that share similar epidemiological and morphological characteristics with DDLPS, cluster heterogeneously in comparison to other sarcoma subtypes [3].

WDLPS and DDLPS are regularly connected with safe invades and show macrophage and CD8 resistant penetration scores among the most noteworthy among all sarcoma subtypes. However, recent advancements in the study of the STS microenvironment have revealed that, like other STS subtypes, WDLPS and DDLPS exhibit a highly heterogeneous microenvironment. These tumors range from cold tumors lacking any significant infiltration of myeloid or lymphoid cells to hot tumors with massive immune infiltrates, high expression of immune-related signatures, high levels of immune checkpoints such as PD-L1, CTLA4, TIM3, or L This feature's underlying mechanisms are still a mystery.

WDLPS tumors still have a mature adipocytic differentiation, but they also have a small number of interspersed undifferentiated cells, often in fibrous tissues that cut through the tumor. These tumors are diverse and can contain large areas that look like lipomas, which are referred to as "lipoma-like" components. Core-needle biopsy may only sample a area whose malignancy can only be determined by molecular testing to screen for the presence of MDM2 amplification, most commonly by Fluorescent in situ hybridization (FISH) or chromogenic in situ hybridization despite the fact that all WDLPS contain typical areas of malignancy. Due to the low level of expression that tumor cells exhibit in this setting, immunohistochemistry-based screening of MDM2 expression cannot be used to diagnose WDLPS.

On the gross specimen, this WDLPS of the retroperitoneum encases the kidney and has a diffuse fatty appearance (A). WDLPS are composed of an adipocytic proliferation that is interrupted by marge fibrous septa, also known as "sclerosing liposarcoma". The nuclei of the tumor cells are large and hyperchromatic. In contrast, the component of DD-LPS is a tumor that has lost its adipocytic differentiation. The dedifferentiated part might have fluctuated morphological appearances, the most regular being that of a pleomorphic cancer. The image was provided by Dr. F. Pedeutour, Department of Genetics and University of Nice. On the genetic level, WD/DD LPS frequently have large chromosomes on their

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karyotype that contain genetic sequences for chromosome 12 Multiple copies of the MDM2 locus that are typically lumped together in clusters are shown in the interphasic FISH using probes spanning the MDM2 locus (marked in green) and the chromosome 12 centromere (marked in red), which is consistent with genetic amplification. Immunohistochemistry of these tumors can reveal amplification as an overexpression of MDM2, although it is only sensitive in the case of DD-LPS. Other copy number alterations, such as the 1p amplicon involving JUN (Image provided by Dr. D. Pissaloux, Centre Leon Berard, Lyon) that are uncommon in WD-LPS and are linked to the dedifferentiation process are found in the genomic profile of DDLPS on top of the amplification of chromosome [4].

Dedifferentiated liposarcomas are extremely diverse within the tumor bulk and between cases. The cytomorphology of the tumor cells is typically pleomorphic, and they can form fascicles or epithelioid sheets, which are similar to carcinomas. Rarely, the cells have a rather monotonous appearance that raises the possibility of synovial sarcomas or desmoid-type fibromatosis.

When working with small samples, it is possible to make a diagnosis if the "dedifferentiated" proliferation is close to WDLPS areas. Notwithstanding, these regions are many times lacking while managing little biopsy examples and might be by and large missing in the uncommon instances of all over again DDLPS, for which case the conclusion mostly depends on immunohistochemistry and sub-atomic testing. Contrary to WDLPS, immunostaining with the MDM2 antibody may reveal overexpression of the protein in the nuclei of tumor cells in 85 percent of cases. This is due to the greater and more diffuse amplification that DDLPS exhibits. MDM2 overexpression, on the other hand, is not limited to DDLPS but can also be found in UPS, myxofibrosarcomas, and MPNST. As a result, the hybridization assay-based genetic testing of MDM2 is typically used in conjunction with the immunohistochemistry examination in most cases.

It is still recommended to grade DDLPS using the French grading system, based on mitotic activity, tumor cell differentiation, and tumor necrosis, as well as the presence of myogenic differentiation, which is associated with poorer outcomes. DDLPS are associated with a heterogeneous clinical course. Leiomyosarcoma (LMS) addresses one of the most regular mesenchymal neoplasms and of all STS. They grow more often than not in the midsection or the retroperitoneum, the appendages, and the uterus. LMS accounts for approximately 30% of all RPS and is the second most common STS subtype in the retro peritoneum after WD/DDLPS. The walls of large retroperitoneal veins, such as the inferior vena cava and renal veins, or the retroperitoneal smooth muscle tissue are typically the sources of retroperitoneal LMS [5].

Conclusion

Physiopathology and molecular characteristics The LMS is a mesenchymal neoplasm that is associated with the proliferation of smooth muscle-differentiating cells. LMS is one of the sarcomas with complex genetics, which are characterized by frequent inactivation of tumor suppressor genes, multiple copy number alterations, and tetraploidization. In LMS, the majority of copy number variations are chromosomal deletions, with losses of occurring most frequently and gains and amplifications occurring less frequently. The tumor suppressor genes TP53 and RB1, whose biallelic inactivation is observed in more than are, targeted losses, respectively. With over 130 unbalanced segments in their genome, soft tissue LMS exhibit multiple chromosomal rearrangements consistent with these complex genomic profiles. These rearrangements, in contrast to translocation-associated sarcoma, are mostly unique to a single tumor and do not result in the expression of a chimeric oncogenic protein or fusion gene. On the other hand, oncogenic ALK fusions have been found in rare cases of LMS.

Acknowledgement

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Conflict of Interest

None.

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