Histomorphological and molecular characteristics of liposarcoma (Review)

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Abstract. Liposarcomas represent the most prevalent subtype of soft-tissue sarcomas, comprising 15-20% of all documented cases. However, sarcomas demonstrate notable clinical and pathological variability, which complicates the processes of diagnosis and treatment. Histomorphological analysis can produce inconsistent results due to inter-examiner variability, which highlights the need for more reliable biomarkers. Genetic and epigenetic alterations may delineate the biological behavior of liposarcomas and assist in the prediction of liposarcoma prognosis. The present review highlights the related genomic alterations in sarcoma and their associations with relevant histomorphology, predilection, targeted therapy and prognosis. Well-differentiated and dedifferentiated liposarcomas exhibit amplified genes, MDM2 proto-oncogene and cyclin-dependent kinase 4, which are potential targets for therapy. Myxoid liposarcoma, characterized by the chromosomal translocations t(12;16) with fused in liposarcoma-DNA damage-inducible transcript 3 protein (DDIT3) fusion and t(12;22) with Ewing sarcoma RNA-binding protein 1-DDIT3 fusion, demonstrate a favorable response to treatment; however, myxoid liposarcoma displays elevated recurrence rates. Moreover, the complex karyotype and lack of specificity in pleomorphic liposarcoma are associated with poor treatment outcomes and increased recurrence rates. Integration of morphological features with molecular biomarkers may potentially enhance diagnosis, facilitate targeted therapies and improve sarcoma prognosis in the future.

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Contents

1. Introduction

Sarcoma is frequently misdiagnosed in ~30% of cases due to its challenging morphological features, which can cause delays in receiving appropriate treatment (1). Liposarcoma (LPS) is one of the most common types of soft-tissue sarcoma (STS), accounting for 15-20% of all instances (2,3). LPS tumors are characterized by notable clinical and pathological diversity, which complicate diagnosis and treatment strategies.

The classification of LPS is based on histopathological analysis, immunohistochemistry (IHC) and molecular profiling, which categorizes them into four distinct subtypes, namely, well-differentiated LPS (WDL), dedifferentiated LPS (DDL), myxoid LPS (ML) and pleomorphic LPS (PL) (3). Each subtype has unique morphological and molecular characteristics that affect disease progression and treatment responsiveness.

Challenges in aligning morphological findings with underlying molecular mechanisms persist despite advancements in understanding LPS tumors. Key genetic changes, such as MDM2 proto-oncogene (MDM2) and cyclin-dependent kinase 4 (CDK4) amplifications, have been noted in the well-differentiated and dedifferentiated subtypes (4). However, the role of genetic changes in disease variability and treatment

resistance is unclear. Additionally, the interactions of molecular pathways in more aggressive subtypes, namely, myxoid and pleomorphic, raise key questions that could improve prognostic accuracy and treatment efficacy (3-5).

Systemic therapies that target specific molecular pathways (MDM2, CDK4) demonstrate potential in overcoming the limitations of traditional treatments (surgical), especially for advanced and high-grade LPS (3-5). The histopathological images included in the present review were obtained from Dr Sardjito General Hospital (Yogyakarta, Indonesia). The selected representative slides, collected between 2021 and 2024, were chosen due to the rarity of the cases and their relevance to the discussion. The histopathological images were used solely for educational and illustrative purposes, without the inclusion of any identifiable patient data. The present review aims to provide a detailed overview of the morphological and molecular features of LPS, emphasizing how these factors may contribute to improved diagnostic precision, prognostic assessments, innovative therapeutic strategies and novel approaches for molecular targeting in the future.

2. WDL

WDL is the most common LPS subtype, accounting for 31-33% of all liposarcomas (1,5). WDL is typically found in the deep soft tissues of the limbs, especially the thigh and retroperitoneum, but can also appear in the chest wall, head and neck (5). WDL grows gradually but is often asymptomatic. However, retroperitoneal tumors may cause symptoms such as abdominal pain and bloating due to organ compression. Larger tumors may appear as bulges or swelling. WDL develops slowly and has a low risk of metastasis, but local recurrence is common, complicating complete surgical resection (1,5). WDL primarily affects adults aged 50-60 years (5). Imaging studies (MRI or CT) demonstrate WDL as a fatty mass with thickened septa or nodular elements that could indicate malignancy. The diagnosis involves imaging, biopsy and molecular testing for MDM2 or CDK4 amplification (3).

Histologically, WDL consists of mature adipocytes, atypical stromal cells and a few lipoblasts (Fig. 1). Moreover, MDM2 and CDK4 oncogenes, which facilitate the differentiation of WDL from benign lipomas through IHC or molecular testing, are often upregulated (4,6). WDL mainly arises from genetic alterations, especially amplification of the 12q13-15 region. This abnormality causes supernumerary rings or giant rod chromosomes, which are characteristic of WDL (4,6). Amplified genes, such as MDM2 and CDK4, are key in WDL and DDL. CDK4 activates D-type cyclins for hyperphosphorylation of retinoblastoma protein (RB) (3,5,7). Phosphorylated RB does not suppress E2F transcription factor 1, which is a key transcription factor for the G_1 to S phase transition, resulting in unregulated cell proliferation. CDK4 is amplified in ≤90% of LPS cases, causing persistent RB inactivation and tumor cells to bypass the G_1/S checkpoint, facilitating tumor growth (7).

In most WDL and DDL cases, the MDM2-p53 pathway is altered due to MDM2 gene amplification (3,5,8). MDM2, an E3 ubiquitin-protein ligase, inhibits p53, which is a key tumor suppressor. MDM2 typically promotes p53 degradation, keeping its levels low. However, stress phosphorylates p53, stabilizing it to regulate genomic stability and apoptosis (3,5,8). In WDL, increased MDM2 expression levels cause rapid p53 degradation, neutralizing its tumor-suppressive effects and promoting uncontrolled growth. This dysregulation emphasizes the malignant potential of WDL and identifies CDK4 and MDM2 as vital therapeutic targets (8).

The main treatment for WDL is surgery aimed at complete excision with clear margins (9). Recurrence rates depend on the tumor size and location, with retroperitoneal tumors having a higher recurrence compares with the limbs, retroperitoneum, paratesticular region, mediastinum and head and neck region (8,9). Radiation and chemotherapy are usually ineffective for WDL (9). The prognosis for extremity WDL is generally favorable with 74% overall survival rates; however, retroperitoneal WDL has a greater risk of progressing to more aggressive DDL (9).

WDL often exhibits an increase in the MDM2 oncogene, which inhibits p53, positioning MDM2 as a notable therapeutic target. For instance, idasanutlin, a small-molecule MDM2 antagonist, has demonstrated potential in preclinical and early clinical studies (3,8,9). Furthermore, CDK4 expression, often elevated in WDL, is key in cell-cycle regulation. Currently, palbociclib, a CDK4/6 inhibitor, is under study for its efficacy in tumor management (3,8,9). Therapeutic strategies that target and disrupt the PI3K/AKT/mTOR pathway have proven to be effective in LPS. Everolimus, an mTOR inhibitor, has been explored for tumor growth inhibition (10). Anti-angiogenic agents have been investigated in LPS due to a dependence on blood supply. Pazopanib, a multitarget tyrosine kinase inhibitor, blocks VEGFR and related pathways. Immune checkpoint inhibitors (ICIs) such as pembrolizumab [anti-programmed cell death protein 1 (PD-1)] were evaluated; however, their efficacy in WDL remains to be elucidated (5). Previous studies have explored epigenetic modulation with therapeutic agents such as histone deacetylase (HDAC) inhibitors (8). Vorinostat has demonstrated potential in the treatment of other sarcoma subtypes, such as synovial sarcoma and chondrosarcoma, it is undergoing clinical investigations for its efficacy in LPS (3,5,9).

LPS presents treatment challenges due to the varying immune microenvironments in each subtype, which affects prognosis and therapy response. DDL exhibits higher tumor-infiltrating lymphocyte (TIL) levels compared with WDL and ML, which is associated with improved overall survival (OS) and progression-free survival (PFS), emphasizing the potential of immunotherapy (11,12). DDL is key to sarcoma immune classes C, D and E, with sarcoma immune class E demonstrating the highest immune reactivity characterized by tertiary lymphoid structures (TLSs), which contain B and $CD8^+$ T cells that enhance antitumor immunity. Nonetheless, the tumor microenvironment of DDL remains immunosuppressive due to M2-like macrophages that impede antitumor responses. Conversely, ML contains fewer TILs compared with DDL, which makes ML less suitable for immunotherapy (11). Immunotherapy notably improves LPS, particularly in immune-active subtypes such as DDL. PD-1 and programmed death-ligand 1 (PD-L1) expression levels, which regulate immune evasion, vary across LPS subtypes and influence responses to ICIs. Previous studies have indicated that 100% of DDL cases have PD-1-positive lymphocyte infiltration,

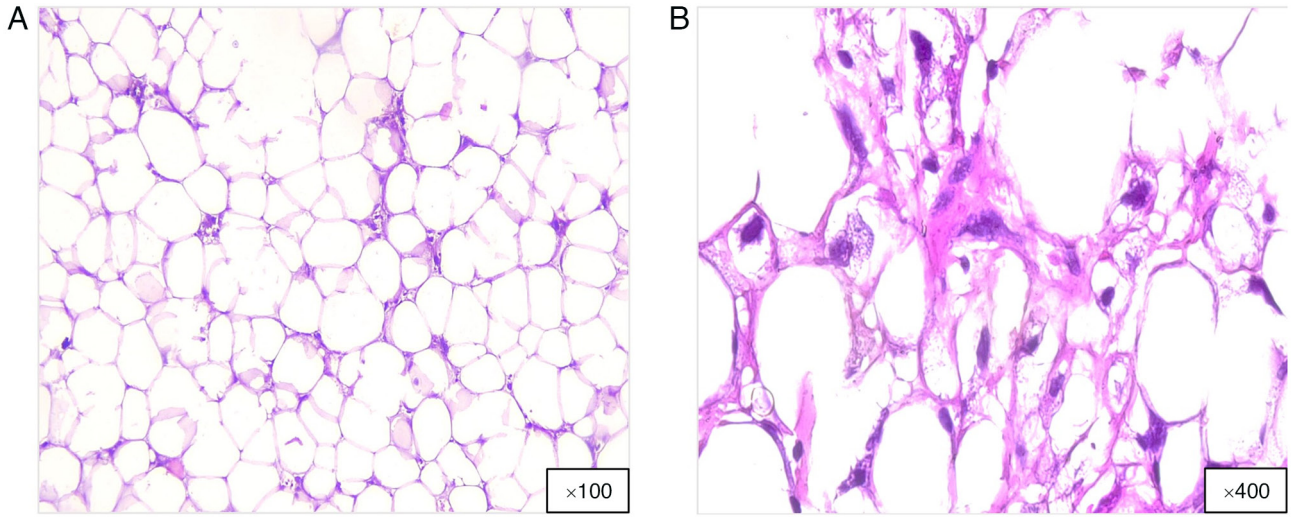

Figure 1. Histopathological images of WDL. (A) WDL tumor exhibiting mature adipocytes along with atypical stromal cells and (B) a small number of lipoblasts. Hematoxylin and eosin staining; magnification, x100 and x400, respectively. WDL, well-differentiated liposarcoma.

whereas only 10% of ML cases have PD-1-positive lymphocyte infiltration, demonstrating the differing immune checkpoint activity in LPS (11,13). Additionally, the presence of TLSs in retroperitoneal LPS is associated with greater immune infiltration, indicating that tumors rich in TLSs may demonstrate an improved response to ICIs. Current clinical trials on ICIs, such as anti-PD1 antibody pembrolizumab (NCT02301039) and anti-PD-L1 antibody atezolizumab (NCT03474094), have yielded mixed outcomes across STS subtypes, especially in WDL (11). Further research is warranted to enhance immunotherapies, identify biomarkers and optimize patient selection for improved treatment outcomes in patients with WDL (11).

WDL has a 5-year OS rate of 75-98%, depending on the tumor location, with extremity tumors exhibiting the highest OS (14). Treatment of WDL with more aggressive methods, such as surgery and radiotherapy (RT), resulted in lower local recurrence rates compared with surgery alone, although it did not markedly alter disease-specific survival (DSS) (15). The DSS for patients with WDL post-surgery is ~98.3% (16). In a previous study, treatment of WDL with radiation alone demonstrated a higher mortality rate compared with WDL treated with surgery alone, surgery combined with radiation or no treatment at all (17).

3. DDL

DDL often presents as a growing, initially painless mass (4). As it enlarges, it can cause discomfort by pressing on nearby structures. DDL typically originates from a well-differentiated subtype (4). Depending on the location of the tumor, symptoms include abdominal pain, bloating, bowel obstruction and urinary retention. DDL is typically diagnosed at a larger size owing to deep anatomical positioning (4,18). In the limbs, DDL may appear as a solid mass causing functional issues or localized pain. In trunk soft tissues, DDL can present as a palpable, non-tender mass (18). DDL exhibits rapid growth and higher recurrence rate compared with WDL, and can spread to the lungs or liver. Advanced stages may cause pain, weight loss and functional impairments. Furthermore, DDL commonly affects adults aged 50-70 years and is slightly more prevalent in men (18). Several cases of DDL have arisen from dedifferentiating previously diagnosed or undiagnosed WDL (4,18). CT or MRI indicate a heterogeneous mass with non-lipomatous areas, and calcifications or necrotic zones may indicate dedifferentiation (4,18).

DDL has unique histopathological characteristics that mark its evolution from a WDL; it includes differentiated adipose tissue combined with fibrous elements, and dedifferentiated areas may appear grayish-white and denser compared with fatty regions. Larger tumors may exhibit necrosis or hemorrhage, whereas tumors in the retroperitoneum often appear as large, multinodular masses (3,4). Microscopic analysis demonstrates a biphasic structure: A well-differentiated component with mature adipocytes and atypical stromal cells with hyperchromatic nuclei, and a dedifferentiated portion containing high-grade sarcomatous segments with spindle cells, hyperchromasia, mitotic figures and pleomorphism, resembling undifferentiated pleomorphic sarcomas or other high-grade sarcomas, namely, fibrosarcoma or myxofibrosarcoma (Fig. 2). In the dedifferentiated area, atypical spindle cells are arranged in a fascicular pattern with few lipoblasts. DDLs exhibit fibrous and myxoid traits and may contain fibrous, myxoid or cartilaginous materials, with rare cases demonstrating heterologous differentiation, including osseous or rhabdomyoblastic changes (4,18).

IHC is key for the identification of diagnostic markers. MDM2 amplification and upregulation can be detected by IHC or fluorescence *in situ* hybridization (FISH). Moreover, CDK4 exhibits amplification and upregulation, which is beneficial in distinguishing DDL from other sarcomas. Other markers, such as protein S100, indicate adipocytic differentiation under certain conditions (4). Previous genetic studies have reported amplification in the 12q13-15 region, particularly MDM2 and CDK4 oncogenes (3,5,8). Prognostic features demonstrate that increased mitotic activity in dedifferentiated areas is associated with aggressive behavior and worse outcomes. Necrosis often manifests a higher tumor grade and metastasis risk (4). Previous molecular studies have indicated that ~90% of

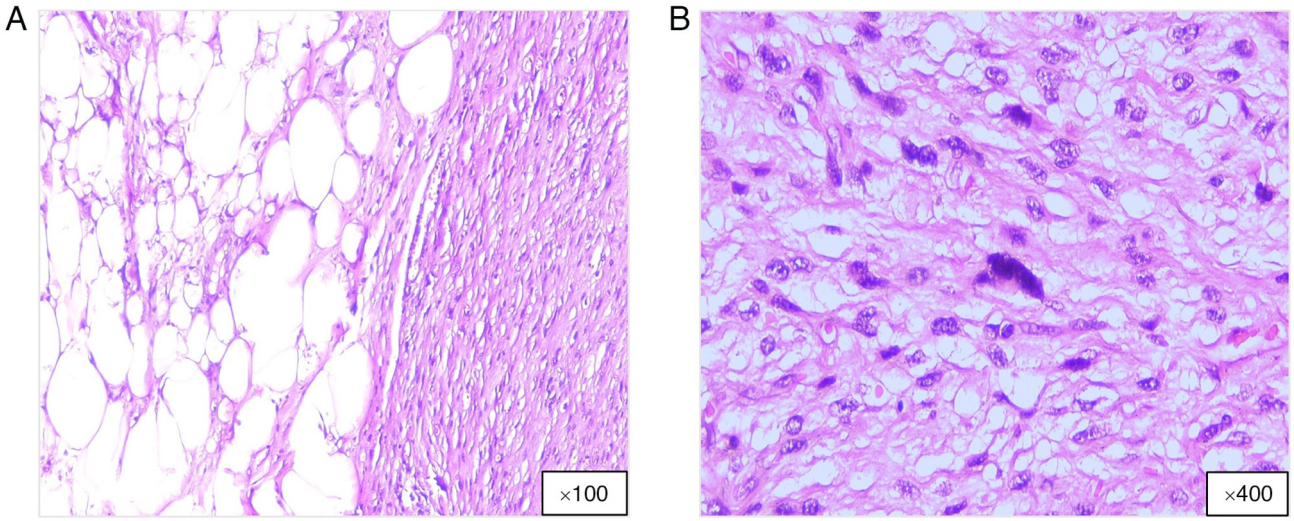

Figure 2. Histopathological images of DDL. (A) DDL including a well-differentiated adipose tissue component mixed with non-lipogenic elements, such as (B) a fibrosarcomatous component. Hematoxylin and eosin staining; magnification, x100 and x400, respectively. DDL, dedifferentiated liposarcoma.

WDL/DDL cases have MDM2 and CDK4 amplifications as primary oncogenic drivers (3,4). However, DDL has a more aggressive molecular profile compared with WDL, which is attributed to greater genomic complexity and instability (19). Furthermore, WDL is primarily defined by 12q13-15 region amplification, whereas DDL displays additional chromosomal aberrations, gene fusions and rearrangements, which contribute to the increased malignancy of DDL (19). A key feature that distinguishes DDL from WDL is its extensive genomic instability, which includes 11q23 loss, 6q23 or 1q32 amplification and gene fusions such as C15orf7::CBX3, CTDSP1::DNM3OS and CTDSP2::DNM3OS. By contrast, MDM2-CDK4 amplification remains as the primary oncogenic alteration of WDL (20).

DDL is defined by upregulated pathways for cell proliferation and survival, particularly PI3K/AKT/mTOR and DNA damage response, which are more pronounced in DDL compared with those in WDL (21). The PI3K/AKT/mTOR pathway in DDL promotes tumor growth and apoptosis resistance. Conversely, WDL relies on MDM2 and CDK4 for cell cycle dysregulation, which causes RB hyperphosphorylation and p53 suppression (Fig. 3). Additionally, DDL demonstrates more disruptions in cell-cycle regulation, especially at the G_2/M checkpoint and E2F target genes, which lead to faster tumor cell proliferation (21). Aurora A kinase is upregulated in retroperitoneal DDL and markedly contributes to metastasis and recurrence, which is less common in WDL (22). A notable difference is the higher somatic copy number alterations (SCNAs) in DDL. A previous study has linked specific SCNA clusters, such as 12q15 amplification, to a poor prognosis and reduced PFS (23). SCNAs can appear in WDL; however, they lack the same prognostic significance as in DDL (23). Therefore, although both WDL and DDL exhibit MDM2 and CDK4 amplification, DDL has greater genomic complexity, additional activated oncogenic pathways and enhanced proliferation, which marks DDL as a more aggressive LPS subtype. Understanding these molecular distinctions is key in the development of targeted therapies to potentially improve treatment outcomes and the survival of patients in the future.

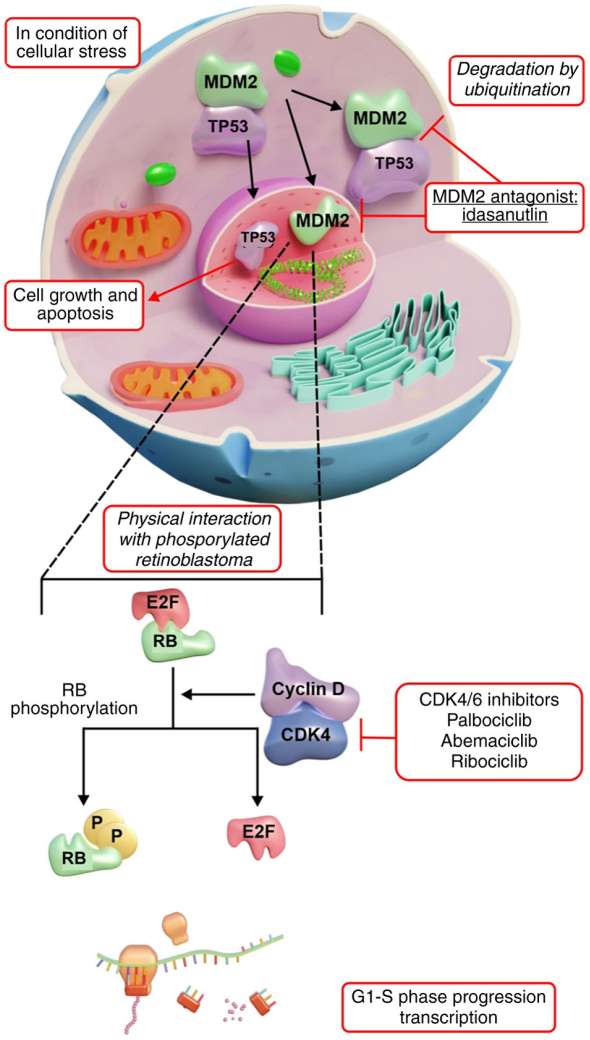

Figure 3. MDM2 and CDK4 involvement in the pathogenesis of liposarcoma. CDK4 gene amplification results in increased expression of the CDK4 protein, which promotes RB phosphorylation, thereby driving cell-cycle progression. MDM2 negatively regulates p53 through various mechanisms, inhibiting p53 transcription and facilitating p53 degradation by ubiquitination. MDM2, murine double minute 2; RB, retinoblastoma; CDK4, cyclin-dependent kinase 4; P, phosphorus.

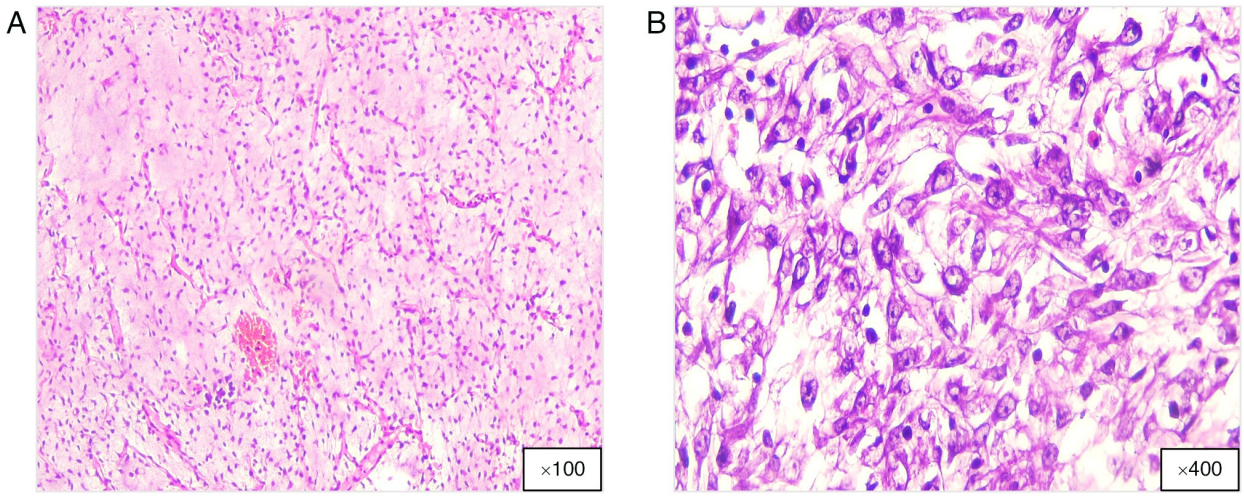

Figure 4. Histopathological images of ML. (A) ML comprising non-lipogenic mesenchymal cells with distinct myxoid background and a chicken wire vasculature, and (B) a high-grade ML, exhibiting a >5% round cell component alongside necrotic areas. Hematoxylin and eosin staining; magnification, x100 and x400, respectively. ML, myxoid liposarcoma.

The treatment of DDL focuses on local tumor control, the prevention of recurrence and the management of systemic disease. The aggressive nature and high recurrence rate of DDL presents notable treatment challenges. Surgical treatments involve wide local excision for complete resection and negative margins (5). However, the achievement of clear margins in retroperitoneal DDL is difficult due to the proximity of vital organs, which increases the recurrence risk. Complex cases may require a multidisciplinary approach. Recurrence often needs repeat surgeries, especially for retroperitoneal tumors. Radiation therapy can serve as an adjuvant or neoadjuvant treatment, which potentially reduces tumor size and improves resectability (5,24). Although effective for local control, radiation has a limited impact on distant metastases (5). Systemic therapies, including chemotherapy, have limited effectiveness against DDL, with standard drugs, such as doxorubicin and ifosfamide, typically used for unresectable or metastatic cases. Novel agents, including trabectedin and eribulin, demonstrate potential in the treatment of advanced stages (5,24). Targeted therapies, for example, MDM2 inhibitors (idasanutlin), are being clinically evaluated (8). CDK4 inhibitors (for example, palbociclib) may reduce tumor growth in MDM2/CDK4-amplified tumors. Studies of alternative pathways continue for effective targeted treatments (5,24). Palliative care aims to enhance quality of life through pain management and support, whereas radiation therapy alleviates symptoms from mass effect metastases (5,9,24).

DDL exhibits a 48-51.5% 5-year OS rate, which has been linked to tumor location and the quality of the treatment facility. Local recurrence occurs in 62.4% of cases. Surgical resection is the standard therapy, with complete resection preferred over marginal resection. Radiation is advisable for high-grade DDL in the extremity for improved local control, and chemotherapy is an option for DDL with a high recurrence risk (16,25-27).

4. ML

ML is a distinct subtype of LPS that represents 20-30% of all LPS cases and is characterized by its unique clinical behavior, histopathological features and molecular profile. ML is a slow-growing, painless mass that predominantly affects adults aged 30-60 years, with the most common site being the deep soft tissue of the extremities (28,29). ML is classified into two types based on the 5% cut-off of the round cell component, namely, low-grade ML (also called pure ML) and high-grade ML (30,31). Despite being radiosensitive and occasionally recurrent locally, ML tends to metastasize to unusual sites, including the soft tissues and bones (32,33). ML diagnosis and staging are challenging owing to the broad spectrum of clinical presentations. Staging of ML is usually performed by whole-body MRI and chest CT (3).

Histologically, ML exhibits a distinctive feature from WDL and DDL, and is marked by a unique gelatinous myxoid stroma interspersed with lipoblasts and a prominent capillary network (Fig. 4). High-grade ML frequently exhibits necrosis, hemorrhage and elevated mitotic activity, which are associated with a worse prognosis (3,34). Additionally, IHC serves a key role in the diagnosis of ML. DNA damage-inducible transcript 3 protein (DDIT3) is a sensitive marker for ML and is highly specific when diffusely present among tumor cells (35). In a previous study, the histological grade of ML was assessed using IHC with phospho-histone H3 and was determined to be associated with ML prognosis (36).

In most ML cases (>90%), a specific chromosomal translocation, t(12;16) (q13;p11), characterizes them and results in the formation of the FUS::DDIT3 fusion protein (37). In some cases, translocation t(12;22)(q13;q12) may occur, leading to the EWSR1::DDIT3 fusion protein. These protein fusions can be identified by FISH (38,39). Moreover, their presence may lead to the upregulation of oncogenic genes such as MET proto-oncogene, receptor tyrosine kinase (MET), ret proto-oncogene (RET) and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α (PIK3CA) (40). Upregulation and/or activation through RTKs, including MET, RET and VEGFRs, contribute to the high activity level of the PI3K pathway in ML (Fig. 5). Furthermore, the FUS-DDIT fusion is associated with the IGF-IR/PI3K/AKT and mTOR signaling pathways (41-43). In addition, a telomerase reverse transcriptase promoter

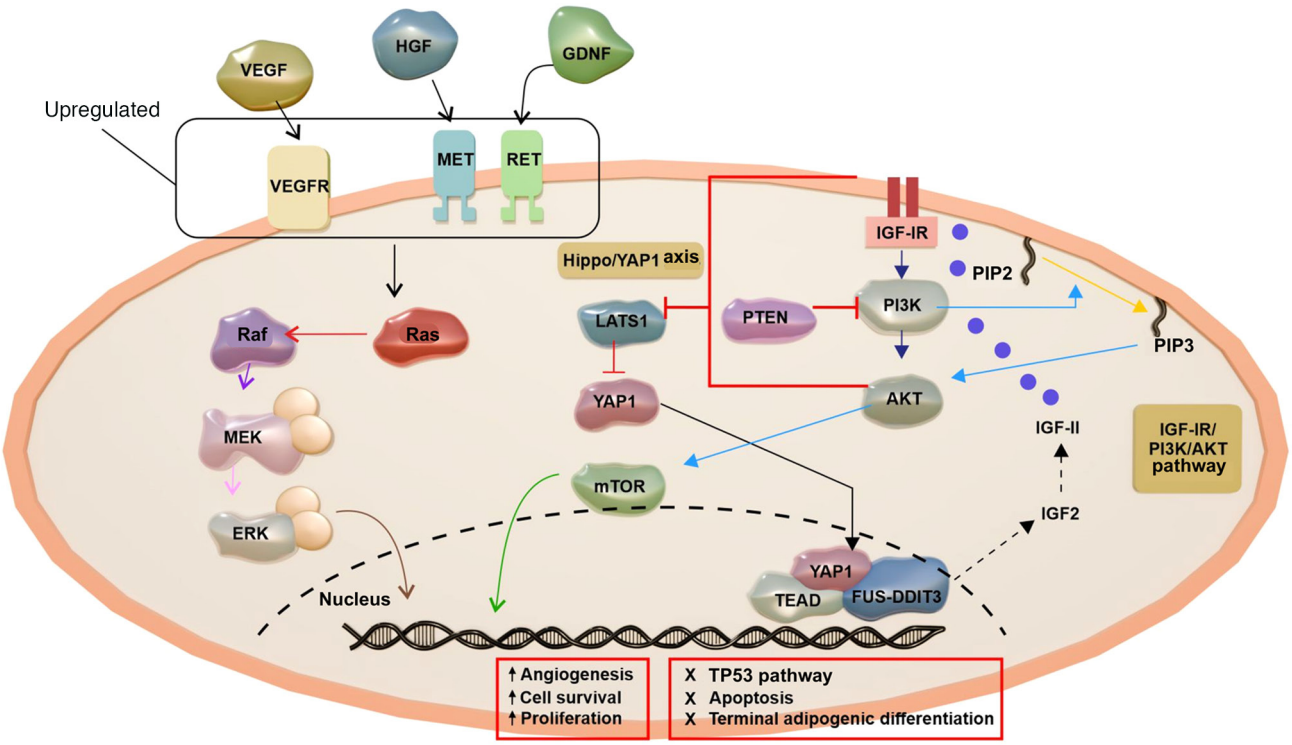

Figure 5. The pathogenesis of ML. ML pathogenesis involves the upregulation and activation of RTKs, including MET, RET and VEGFRs, leading to enhanced PI3K pathway activity. Growth factors that bind to RTKs, such as IGF-IR, activate PI3K, transforming PIP2 into PIP3 and triggering AKT signaling and phosphorylating downstream targets. PTEN inhibits PI3K signaling by conversion of PIP3 back to PIP2. Moreover, RTKs activate genes linked to angiogenesis, proliferation and survival by Ras and the PI3K/AKT pathway. ML is associated with AKT activation and PIK3CA and PTEN alterations. The oncogenic circuit includes FUS-DDIT3, the IGF-IR/PI3K/AKT pathway and the Hippo/YAP1 axis. FUS-DDIT3 induces IGF-2 expression, forming an autocrine IGF-II/IGF-IR signaling loop that activates the IGF-IR/PI3K/AKT pathway. Signals from IGF-IR and PI3K inhibit Hippo kinase LATS1, enabling nuclear accumulation of YAP1. FUS-DDIT3 interacts with YAP1/TEAD in the nucleus, regulating oncogenic gene programs involved in apoptosis, adipogenesis, the cell cycle and proliferation. ML, myxoid liposarcoma; RTK, receptor tyrosine kinase; MET, MET proto-oncogene receptor tyrosine kinase; RET, ret proto-oncogene; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol (3-5)-trisphosphate; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α; IGF, insulin-like growth factor; IGF-IR, IGF-1 receptor; FUS-DDIT3, fused in liposarcoma-DNA damage-inducible transcript 3; YAP1, Yes-associated protein 1; LATS1, large tumor suppressor kinase 1; TEAD, transcriptional enhanced associate domain; HGF, hepatocyte growth factor; GDNF, glial cell line-derived neurotrophic factor.

mutation is commonly observed in most ML cases, serving a key role in tumorigenesis (44,45).

Current management approaches involve a combination of surgical resection, adjuvant RT and chemotherapy. If the tumor location is deep, preoperative RT should be considered before surgical resection. Patients with metastatic ML should receive neoadjuvant chemotherapy (46). ML has a higher 5-year OS rate compared with DDL, ranging from 81 to 84% (15,47). ML is radiation-sensitive; thus, surgical resection with radiation is the primary treatment (48). Preoperative radiation is recommended for deep or large tumors before surgical resection, and chemotherapy is used for patients with a positive-margin resection and metastatic ML (46). Treatment with radiation alone is not recommended, as it has been associated with a higher risk of mortality (17).

5. PL

PL is the rarest and most aggressive subtype of LPS, accounting for <10% of cases and mainly affecting older adults aged 50-70 years. Owing to its rarity in young adults, PL diagnosis in this group should be differentiated from that of other LPSs (49). PL is histologically characterized by a pleomorphic cellular structure (Fig. 6), including bizarre, multinucleated tumor cells and pleomorphic lipoblasts (50). Most patients with PL present with a rapidly growing, painless mass, predominantly in the extremities (28,51). Although PL frequently develops in the deep soft tissues, it can also occur in the retroperitoneum and in superficial tissues such as the subcutis or dermis (52,53). PL pathogenesis involves complex genetic and molecular changes notable for the lack of unifying molecular alterations, which is frequently observed in STS with intricate karyotypes. Unlike other LPS subtypes, such as WDL and DDL, PL does not exhibit MDM2 or CDK4 amplification. This genetic complexity indicates that distinct dominant molecular abnormalities are unlikely to be the basis of PL tumorigenesis and progression (54).

PL exhibits molecular profiles that align more closely with other pleomorphic sarcomas than with atypical lipomatous tumors, WDL, DDL or ML. Molecular investigations of PL are hindered due to the rarity of PL. Genetic abnormalities in PL include complex karyotypic alterations, with TP53 mutations observed in 60% of cases and NF1 mutations in 5% of all PL cases (55). Tumors typically exhibit intricate patterns, demonstrating gains in regions 1p, 1q21-q32, 2q, 3p, 3q, 5p12-p15, 5q, 6p21, 7p and 7q22 (55). A previous study has reported losses in the areas of 1q, 2q, 3p, 4q, 10q, 11q, 12p13, 13q14, 13q21-qter and 13q23-24 (55). Other studies have demonstrated that

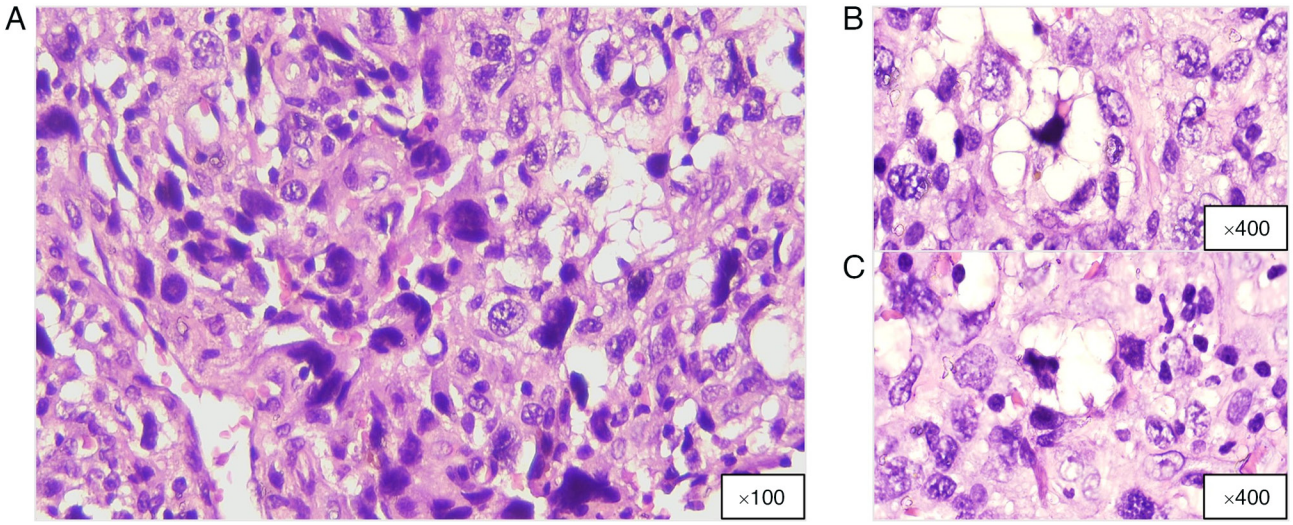

Figure 6. Histopathological images of PL. PL demonstrating (A) spindle to epitheloid pleomorphic cells, (B) pleomorphic lipoblasts with vacuolated cytoplasm and (C) other features of pleomorphic lipoblasts. Hematoxylin and eosin staining; magnification, x100, x400 and x400, respectively.

60% of PL cases feature a deletion at 13q14.2-q14.3, which encompasses the tumor suppressor RB1 (55-57). Amplified in PL, the mitotic arrest-deficient gene (MAD2) may serve a notable role (57). A previous study with a small sample size of PL cases reported a 13-fold upregulation of MAD2 compared with normal fat samples (57). Additionally, deletions in PL, specifically at 17p13 and 17q11.2, where the TP53 gene and sarcoma-associated tumor suppressor neurofibromatosis type 1 reside, have been observed (56,57).

The diagnosis of PL requires a multidisciplinary approach. MRI and CT are key for tumor staging. In PL, 60% of the cases appear as well-defined masses with heterogeneous features, which indicate necrosis and hemorrhage (51). Histopathological evaluation is the gold standard, often enhanced by IHC to differentiate PL from other high-grade sarcomas. The presence of spindle epitheloid pleomorphic cells and pleomorphic lipoblasts are characteristic of PL. IHC has limited value in diagnosing PL due to its non-specific immunoprofile and variable positivity for SMA, desmin and CD34, usually showing focal positivity. Other IHC markers, such as MDM2 and CDK4, are generally negative in PL, allowing differentiation from other LPS subtypes (50,58-60).

Managing PL is challenging due to its aggressive nature and high metastatic potential. Even with optimal surgical management, local and distant recurrence risks remain elevated. Preoperative RT may help reduce tumor size for improved surgical margins. PL prognosis is poorer compared with that of other LPS types, with stagnant survival rates of >20 years. Previously, doxorubicin combined with ifosfamide demonstrated some efficacy and neoadjuvant/adjuvant therapies were associated with improved survival. Trabectedin and eribulin are therapeutic options for advanced cases of PL. Ongoing efforts are key to developing new treatments; however, the identification of targetable aberrations, particularly the loss of p53 and RB pathway proteins, are difficult to utilize therapeutically (61-65).

PL exhibits local recurrence and metastasis rates that range from 30 to 50%. The overall 5-year survival rate is ~60%. Metastatic spread predominantly impacts the lungs and pleura. Various factors, including central tumor location, increased depth, larger size and a higher mitotic count, are associated with a less favorable prognosis (51,66).

Table I summarizes the genomic alterations in the LPS subtypes, detailing the demographics, morphology, immunophenotype, growth rates, recurrence, metastasis and therapy responses. WDL and DDL exhibit MDM2 and CDK4 amplifications on chromosome 12q13-15 (3,5,8-10). MDM2 inhibits p53, promoting unchecked cellular growth; thus, inhibitors such as idasanutlin are undergoing investigations to restore p53 function and induce apoptosis. CDK4 amplification disrupts cell-cycle regulation, which makes CDK4/6 inhibitors, such as palbociclib, a potential therapeutic agent for tumor control. Resistance to chemotherapy and RT is one of the key challenges in the treatment of WDL and DDL. Multitargeted tyrosine kinase inhibitors, including pazopanib, demonstrate antitumor effects. Current research on HDAC inhibitors, such as vorinostat, along with ICIs, including pembrolizumab, has demonstrated potential in the treatment of WDL (3,5,8-10). ML features chromosomal translocations such as t(12;16) and t(12;22), which result in FUS-DDIT 3 and EWSR1-DDIT 3 fusions (3,5,8). ML responds well to chemotherapy, especially anthracycline regimens. Novel immunotherapeutic strategies targeting cancer-testis antigens (for example, New York esophageal squamous cell carcinoma 1) demonstrate potential with vaccine-based approaches. Checkpoint inhibitors, such as atezolizumab, are evaluated with other treatments against ML tumors (3,5,8). PL is the most aggressive LPS subtype, lacking MDM2 and CDK 4 amplifications, and characterized by high pleomorphic histology (3,5,58,61). Treatment options are limited. However, doxorubicin and ifosfamide are effective, and eribulin and trabectedin are alternatives for advanced disease. Molecular studies point to VEGFR-2 as a target, prompting investigations into tyrosine kinase inhibitors such as apatinib (3,5,58,61).

6. Conclusion

Numerous studies have established the use of molecular biomarkers in elucidating the characteristics of sarcoma and

Table I. Summary of the genomic biomarkers of LPS.

LPS subtype	Age range, years	Predilection	Morphological features	Immuno-phenotype	Molecular markers/ genomics alterations	Growth rate	Likelihood of metastasis	Treatment	Recurrence	Therapy response (radiotherapy and chemotherapy)	Targeted therapy	(Refs.)
WDL	50-60	Extremities, retroperitoneum	Mature adipocytes, atypical stromal cells and a limited number of lipoblasts	MDM2(+), CDK(+), DDIT3(-), S100(+), CD34(-). p16(+), p53 wild-type	MDM2 and CDK4, 12q13-15 amplification	Slow	Low	Surgical resection with negative margins	Low	Poor	Idasanutlin, MDM2 antagonist; palbociclib, CDK4/6 inhibitor; everolimus, mTOR inhibitor; pazopanib, multitarget tyrosine kinase inhibitor; pembrolizumab (anti-PD-1, immune checkpoint inhibitors; vorinostat, histone deacetylase inhibitors)	(3,5, 8-10)
DDL	50-70	Extremities, retroperitoneum	Biphasic structure with i) WD component: Mature adipocytes intermingled with atypical stromal cells and hyperchromatic nuclei; and ii) DD component: Spindle cells, hyperchromasia, mitotic figures and pleomorphism	MDM2(+), CDK4(+), DDIT3(-), S100(+), CD34(-), p16(+), p53 wild-type or mutant	MDM2 and CDK4, 12q13-15 amplification and other chromosomal abnormalities	Rapid	High	Surgical resection, radiotherapy and chemotherapy/ targeted therapy	High	Poor	Idasanutlin, MDM2 antagonist; palbociclib, CDK4/6 inhibitor	(3,5,8,9)

Table I. Continued.

LPS subtype	Age range, years	Predilection	Morphological features	Immuno-phenotype	Molecular markers/ genomics alterations	Growth rate	Likelihood of metastasis	Treatment	Recurrence	Therapy response (radiotherapy and chemotherapy)	Targeted therapy	(Refs.)
ML	30-60	Thigh or other proximal extremities	Unique gelatinous myxoid stroma interspersed with lipoblasts and a prominent capillary network; occasionally exhibits necrosis, hemorrhage and elevated mitotic activity	MDM2(-), CDK4(-), DDIT3(+), PHH3(+), S100(+), CD34(-), p16(-), p53 wild type	t(12;16) with FUS-DDIT3 fusion t(12;22) with EWSR1-DDIT3 fusion	Slow	Low to medium, depends on the degree of differen-tiation	Surgical resection, radiotherapy and chemotherapy/ targeted therapies	High	Commonly sensitive	CMB305, immuno-therapeutic for NY-ESO-1; atezolizumab, anti PD-L1	(3,5,8)
PL	50-70	Lower and/or upper limbs	Pleomorphic cellular architecture, bizarre, multinucleated tumor cells and pleomorphic lipoblasts	MDM2(-), CDK4(-), DDIT3(-), S100(+), SMA(+), desmin(+), CD34(+), p16(+), p53 mutant hyper-expression	No MDM2 or CDK4 amplification; complex karyotype and lack of specificity	Rapid	High	Surgical resection, radiotherapy and chemotherapy	High	Poor	Apatinib, VEGFR-2 tyrosine kinase inhibitor	(3,5, 58,61)

+, positive; -, negative; LPS, liposarcoma; WDL, well-differentiated liposarcoma; DDL, dedifferentiated liposarcoma; ML, myxoid liposarcoma; PL, pleomorphic liposarcoma; MDM2, murine double minute 2; DDIT3, DNA damage-inducible transcript 3; SMA, smooth muscle actin; t, translocation; FUS, fused in liposarcoma; DDIT3, DNA damage-inducible transcript 3; EWSR1, EWS RNA-binding protein 1; anti-PD-1, anti-programmed cell death protein 1; HDAC, histone deacetylase; NY ESO 1, New York esophageal squamous cell carcinoma 1; anti-PD-L1, anti-programmed death ligand 1; SMA, smooth muscle actin; PHH3, phospho-histone H3; CMB305 (therapeutic vaccine regimen targeting NY-ESO-1 based on the lentiviral vaccine vector, LV305).

predicting its prognosis. Specific genetic alterations, such as MDM2 and CDK4, along with 12q13-15 amplification in WDL and DDL, are associated with a poor therapeutic response. By contrast, chromosomal translocations including t(12;16) with FUS-DDIT3 fusion and t(12;22) with EWSR1-DDIT3 fusion in ML are linked to sensitivity to therapy, although they confer higher recurrence rates. Furthermore, the complex karyotype and lack of molecular specificity in PL is associated with an unfavorable response to treatment and increased recurrence. MDM2 and CDK4 amplification serve a key role in diagnosis, prediction of tumor recurrence and prognosis. A comprehensive diagnosis of sarcoma requires further study into each molecular alteration and the current World Health Organization classification (28). Surgical intervention facilitates tumor removal and provides samples for subsequent molecular analysis. Further research is warranted to explore the integration of molecular biomarkers with the WHO grading system to enhance treatment decision-making, which may potentially lead to a more accurate diagnosis, prognosis and therapeutic strategies for the treatment of sarcoma in the future.

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Availability of data and materials

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Authors' contributions

ED conceptualized the article and wrote the first draft of the manuscript. RM, YP, SA, RB and AS collected materials (literature). RB and AS prepared the table and figures. IW contributed with pathological expertise. ED, RM, YP, SA, RB, AS and IW made significant contributions to the critical review, editing, revision and final decision to submit the manuscript for publication. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

The present review received ethical approval from the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Gadjah Mada University (Yogyakarta, Indonesia; approval no. KE/FK/1510/EC/2024).

Patient consent for publication

The requirement to obtain informed consent for the publication of histopathological images was waived by the Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Gadjah Mada University (Yogyakarta, Indonesia) in accordance with institutional guidelines for the use of anonymized, retrospective data.

Competing interests

The authors declare that they have no competing interests.

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