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Myxoid pleomorphic liposarcoma

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Summary. Myxoid pleomorphic liposarcoma (MPL) is an extremely rare adipocytic tumor, recently recognized as a distinct entity in the 5th edition of the World Health Organization (WHO) Classification of Soft Tissue and Bone Tumors. Predominantly found in the mediastinum of young women, MPLs exhibit a combination of histological features characteristic of myxoid liposarcoma and pleomorphic (lipo)sarcoma. Their unique molecular features distinguish MPLs from other liposarcomas. Unlike myxoid liposarcomas and well-differentiated/dedifferentiated liposarcomas, MPLs lack specific *FUS/EWSR1::DDIT3* gene fusions and *MDM2/CDK4* gene amplifications, respectively. MPLs are associated with complex karyotypes, further highlighting their distinct genetic profile. They demonstrate aggressive growth patterns, high recurrence rates, and a high tendency to metastasize. These factors contribute to a poor prognosis, with a median survival of approximately 22.6 months. The aim of this review article is to provide a comprehensive summary of previously documented case reports and studies related to MPLs. By shedding light on the intricate details of MPLs, researchers and clinicians can gain valuable insights that may pave the way for improvements in diagnosis, treatment, and patient outcomes in the future.

Key words: Myxoid pleomorphic liposarcoma (MPL), Pleomorphic liposarcoma (PL), Myxoid liposarcoma (ML), Dedifferentiated liposarcoma (DDLP), Atypical spindle cell/pleomorphic lipomatous tumor (ASPLT), *Retinoblastoma 1 (RB1), MDM2, CDK4*

Introduction

Myxoid pleomorphic liposarcoma (MPL) has emerged as a distinct adipocytic tumor entity, recently classified in the 5th edition of the World Health Organization (WHO) Classification of Soft Tissue and Bone Tumors (Alaggio et al., 2020). Initially described in 2009 as a high-grade variant of myxoid liposarcoma (ML) (Alaggio et al., 2009), MPL exhibits unique clinicopathological and molecular characteristics that set it apart. Unlike myxoid liposarcomas, MPLs do not display *FUS/EWSR1::DDIT3* gene rearrangements (Boland et al., 2012).

Over the years, various studies have shed light on MPL's genetic traits. Research has revealed complex chromosomal alterations, a hyperdiploid/hypotriploid karyotype, and loss of the *Retinoblastoma 1* gene (*RB1*) (Creytens et al., 2014; Francom et al., 2019). Recent (epi)genetic studies have further demonstrated the complex karyotype of MPL, with a methylation profile similar to conventional pleomorphic liposarcomas (PLs) and distinct from MLs (Creytens et al., 2021).

This review aims to consolidate these findings, presenting MPL as a distinct category with specific genetic traits. By synthesizing existing research, this exploration seeks to deepen our understanding of MPLs, guiding future research directions, and improving diagnostic precision in clinical practice.

Epidemiology

MPLs primarily affect children and young adults (<30 years) and are more common in women with a female-to-male ratio of 2:1 (Alaggio et al., 2009; 2020; Creytens et al., 2014). In the study series by Alaggio et al. involving 82 cases of pediatric liposarcomas, MPLs account for about 15% of liposarcoma cases (Alaggio et al., 2009).

Clinical features

MPLs are predominantly observed in the mediastinum. Additionally, these tumors have been reported in various other locations including the neck, back, abdomen, pleura, perineum, cheek (including mandibula), and leg (including the thigh) (see Table 1 for a comprehensive overview of cases reported in literature) (Alaggio et al., 2009; Francom et al., 2019; Creytens et al., 2021). Notably, two cases of MPLs in the orbit and orbital floor have been documented (Dermawan et al., 2022, Tan et al., 2023).

Moreover, MPLs can be observed in patients with Li-Fraumeni syndrome, characterized by a germline mutation in the *TP53* tumor suppressor gene, resulting in

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the development of multiple tumors, particularly at a young age (Ognjanovic et al., 2012). To date, there have been four documented cases of MPLs in patients with Li-Fraumeni syndrome (specific details are provided in Table 1) (Francom et al., 2019; Sinclair et al., 2017; Zare et al., 2020; Tan et al., 2023).

MPLs typically manifest as deep-seated soft tissue masses, sometimes presenting as palpable swellings under the skin. These tumors usually present as large masses, with documented sizes ranging from 2.5 cm to 16 cm (Creytens et al., 2014; Hofvander et al., 2016). Because of their large size, these tumors can exert pressure on surrounding tissues, which can lead to symptoms such as pain and limited mobility.

Macroscopic characteristics

MPLs are multilobulated masses with a heterogeneous appearance, often displaying yellowish fat-like to myxoid/gelatinous features upon sectioning (Dermawan et al., 2022). These tumors lack encapsulation and have ill-defined infiltrating margins, contributing to the complexity of their treatment (Creytens, 2019, 2020).

Histopathological features

MPLs exhibit a diverse range of histological features. Typically, they show an ML pattern characterized by a low-grade component featuring abundant myxoid matrix containing bland round to oval cells (Fig. 1A). Creytens et al. described this abundant matrix as lymphangioma-like myxoid pools (Creytens et al., 2014). The proportion of this low-grade component varies, with Alaggio et al. reporting a range of 10-75%, while Creytens et al. observed it in 30-50%. The existing blood vessels are described as an arborizing or plexiform capillary network (Fig. 1B,C) (Alaggio et al., 2009; Creytens et al., 2021). The low-grade component transitions into more cellular areas with pleomorphic cells displaying high-grade features such as nuclear hyperchromasia, anisonucleosis, and an increased number of mitotic figures (Figs. 1D, 2A,B). Hofvander et al. documented occasional pseudo-inclusions within the nuclei, along with indistinct-to-small nucleoli and mitotic activity of up to two per high-power field (HPF) (Hofvander et al., 2016). High mitotic activity and the presence of atypical mitotic figures are documented across various studies (Alaggio et al., 2009; Hofvander et al., 2016). Occasionally, necrosis is observed in the background. The presence of pleomorphic lipoblasts and multinucleated tumor cells is also described (Fig. 2C) (Hofvander et al., 2016). The pleomorphic tumor component can manifest as diffuse sheets or solid nests (Alaggio et al., 2009; Creytens et al., 2021). Dermawan et al. additionally described xanthoma-like foamy cytoplasm in the pleomorphic cells. Interestingly, in 25% of their cases, they observed an area resembling well-differentiated liposarcoma, featuring paucicellular lipoma-like areas separated by fibrous strands, a characteristic also noted by Creytens et al. (Creytens et al., 2021; Dermawan et al., 2022).

Immunohistochemical features

The immunohistochemical profile of MPLs lacks complete specificity. Multiple studies, including those conducted by Hofvander et al. and Chitikela et al., have reported that tumor cells in MPLs are positive for S100 and negative for MDM2 and CDK4 on immuno-staining

Table 1. Overview and details of all previously described myxoid pleomorphic liposarcoma case reports and case series.

Author	Sample size	Sex	Age	Location	Tumor size	Intervention
Boland et al., 2012	3	F, M(2)	23-62y (median 48y)	Anterior and middle mediastinum (N=2), pleura (N=1)	NM	NM
Creytens et al., 2014	1	M	21y	Neck	16 cm	Excision
Hofvander et al., 2016	1	M	10y	Medial side of the left thigh	16 cm	Excision and adjuvant chemotherapy
Sinclair et al., 2017*	1	F	15y	Right perineal mass	3.7 cm	Primary excision and re-excision because of narrow margins
Francom et al., 2019*	1	M	11y	Mandibula	6.5 cm	Radical excision with postoperative radiation
Zare et al., 2020*	1	M	34y	Anterior chest wall	2.9 cm	Excision
Creytens et al., 2021	12	F(6), M(6)	17-58y (median 35y)	Mediastinum (N=5), back (N=1), neck (N=2), cheek (N=1), leg including thigh (N=3)	NM	NM
Dermawan et al., 2022	8	F(5), M(3)	10-68y (median 32y)	Mediastinum (N=7), orbital floor (N=1)	NM	NM
Chitikela et al., 2022*	1	F	9y	Neck involving thyroid	7.2 cm	Wide local excision and adjuvant chemotherapy
Choi et al., 2022*	1	F	24y	Right shoulder	9 cm	Local excision with postoperative radiation
Tan et al., 2023	1	F	12y	Orbita	4.9 cm	Orbitotomy and neoadjuvant chemoradiotherapy

*, patients with Li-Fraumeni syndrome; F, female; M, male; NM, not mentioned; N, number; Y, year.

(Chitikela et al., 2022; Hofvander et al., 2016). In Creytens' series of 12 tumors, in addition to the negativity for MDM2, diffuse CD34 and p16 expression were observed, accompanied by loss of nuclear Rb expression (Fig. 2D) in all examined cases (Creytens et al., 2021).

Molecular features

In 2012, Boland et al. demonstrated, using fluorescence in situ hybridization (FISH) analysis, that MPLs lack the typical *FUS/EWSR1::DDIT3* gene fusions commonly seen in MLs (Amary et al., 2007; Alaggio et al., 2009) . This finding was confirmed in subsequent studies by and Creytens et al. and Hofvander et al. (Hofvander et al., 2016; Creytens et al., 2021). Several researchers have also demonstrated the absence of *MDM2* gene amplification through FISH analysis (Hofvander et al., 2016; Creytens et al., 2021; Dermawan et al., 2022; Tan et al., 2023). In 2016, Hofvander et al. demonstrated near-haploidization and loss of the *RB1* gene (located on 13q14.2) in MLPs. Based on these findings, they suggested that the early loss of *RB1* triggers genomic instability, allowing tumor cells to tolerate significant ploidy changes during haploidization and subsequent polyploidization (Hofvander et al., 2016). This observation was confirmed by Creytens et al. in 2021 by FISH analysis, revealing a monoallelic deletion of *RB1* in 8 out of 12 cases (Demicco et al., 2019; Creytens et al., 2021; Tan et al., 2023). However, it is important to note that loss of *RB1* is not specific and is observed in various soft tissue (adipocytic) tumors (Barretina et al., 2010; Creytens et al., 2021). This category of tumor is sometimes referred to as *RB1*-deleted soft tissue tumors. This group includes benign tumors like myofibroblastoma and cellular

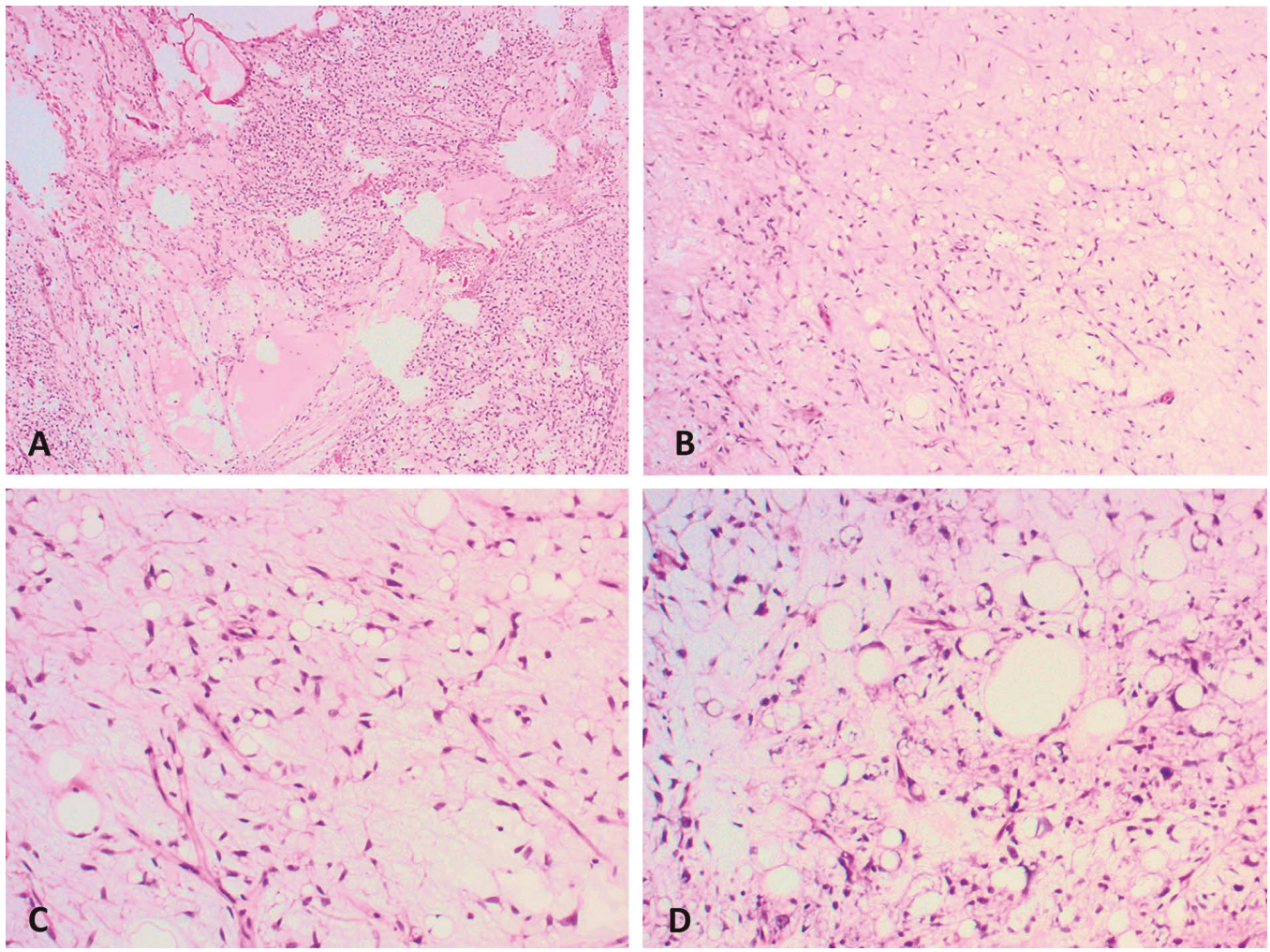

Fig. 1. Overview image of the low-grade component of MPL featuring typical lymphangioma-like myxoid pools **(A)**. Low-grade myxoid liposarcoma-like morphology with a chicken-wire capillary pattern and lipoblasts **(B, C)**. Areas exhibiting 'low-grade' myxoid liposarcoma-like morphology with increased atypia, pleomorphism, and lipoblasts **(D)**. (HE). A, x 40; B, x 100; C, D, x 200.

angiofibroma, as well as various adipocytic lesions such as spindle cell/pleomorphic lipoma and atypical spindle cell/pleomorphic lipomatous tumor (ASPLT), and malignant tumors like PLs. Unlike MPLs, these RB1-deleted soft tissue tumors are more commonly found in patients aged 50 and above (Libbrecht et al., 2021).

Initially, in 2015, Hofvander et al. and subsequently in 2014 and 2021, Creytens et al., utilized G-banding analyses and genome-wide copy number profiling, respectively, to reveal the complex genomic profile of MPLs (Creytens et al. 2014; 2021; Hofvander et al. 2016). Creytens et al. revealed numerous extensive gains and losses in all examined cases, with recurrent gains involving chromosomes 1, 6-8, 18-21, and recurrent losses involving chromosomes 13, 16, and 17. Monoallelic deletion of RB1 occurred in all cases, accompanied by the loss of neighboring tumor suppressor genes, including *RCTB2, DLEU1*, and *ITM2B*, in half of the cases, suggesting a role in tumorigenesis and tumor growth (Creytens et al. 2021).

Furthermore, in 2022, Dermawan et al. conducted mutational analysis, revealing widespread loss of heterozygosity (LOH), affecting approximately 80% of the genome on average (range: 64-100%). Their analyses of mutational and whole gene copy number alterations identified *TP53* mutations in all of their cases, which could potentially explain why these tumors are also observed in patients with Li-Fraumeni syndrome (Dermawan et al., 2022).

In 2021, Creytens et al. compared the methylation profiles of 12 MPLs with those of nine conventional PLs and 31 conventional MLs. The results revealed that

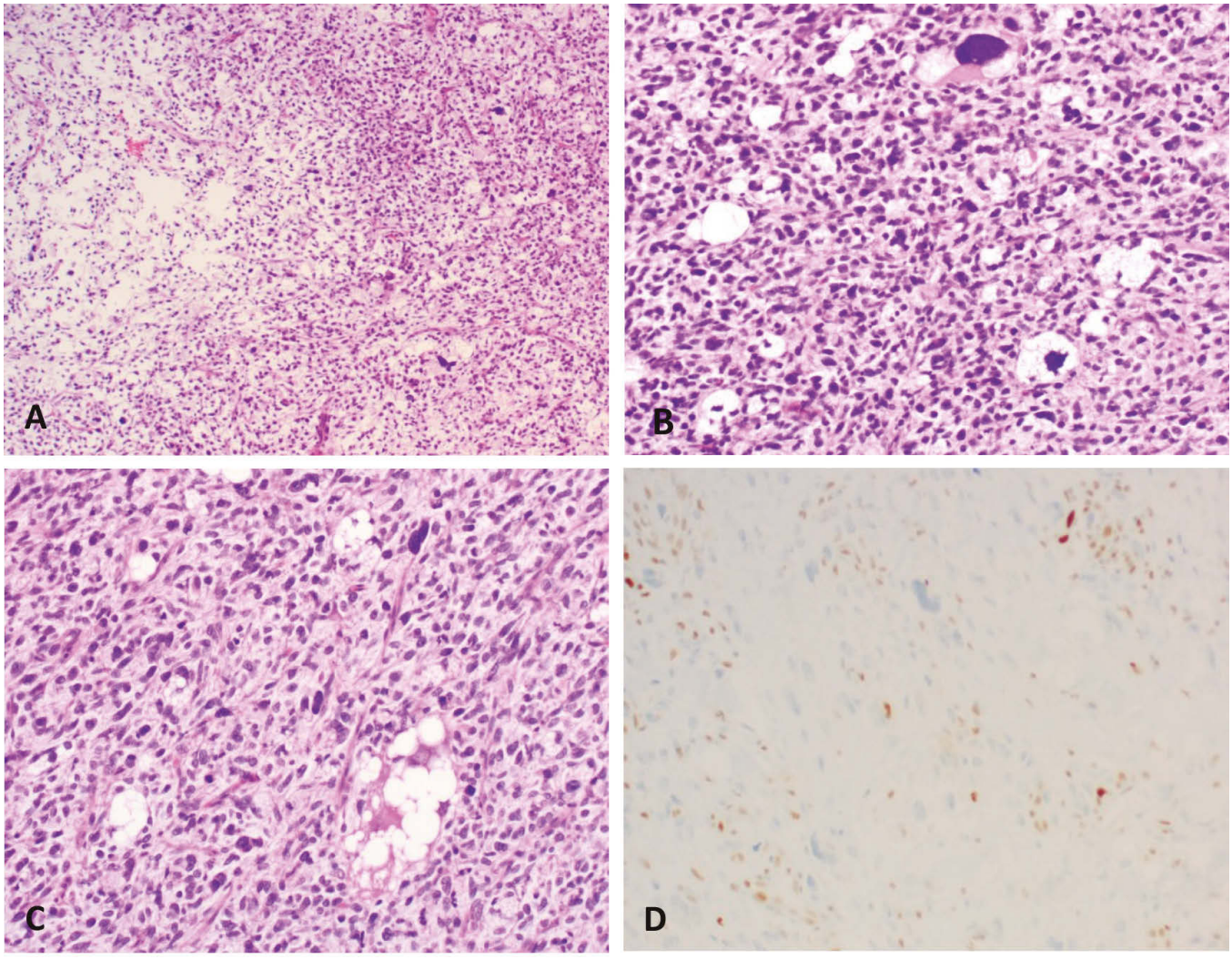

Fig. 2. Transition from 'low-grade' myxoid liposarcoma-like morphology to an area displaying pleomorphic (lipo)sarcoma-like morphology (HE) **(A)**. Pleomorphic (lipo)sarcoma-like morphology is characterized by high cellularity and pleomorphic lipoblasts (HE) **(B, C)**. Anti-Rb immunostaining shows loss of nuclear expression in the pleomorphic cells; note the positive internal control of endothelial cells from intervening vessels **(D)**. A, x 100; B-D, x 200.

MPLs and PLs share a common methylation cluster distinct from that of conventional MLs (Creytens et al., 2021).

Differential diagnosis

As previously mentioned, MPLs exhibit a combination of features from both MLs and PLs, making it challenging to distinguish these tumors. In particular, the myxofibrosarcoma-like variant of PL is a notable mimic. Other potential differential diagnoses include atypical spindle cell/pleomorphic lipomatous tumor (ASPLT) and dedifferentiated liposarcoma (DDLP) (Creytens, 2019).

Table 2 comprehensively outlines the clinical, histological, immunohistochemical, and molecular characteristics of these tumors.

Myxoid liposarcoma (ML)

ML is the most common subtype of liposarcoma in children and adolescents, primarily occurring in the extremities, especially in the thigh (Huh et al., 2011). Histologically, they are characterized by a monotonous population of small ovoid cells and varying numbers of lipoblasts. A typical feature of these tumors is the presence of chicken wire-like blood vessels (Chitikela et al., 2022). The stroma, as the name suggests, is myxoid. High cellularity and the presence of a round cell tumor component are important adverse prognostic factors.

Unlike MPL, ML is characterized by *FUS::DDIT3* or *EWSR1::DDIT3* gene fusions. The study by Baranov et al. showed that nuclear positivity on DDIT3 immunostaining serves as a very good surrogate marker for (high-grade) MLs, with a sensitivity of 96% and specificity of 98% (Baranov et al., 2021). Uchihashi et al. described a specific variant of ML with nuclear pleomorphism. These tumors, in addition to the classic features of MLs, exhibit giant and multinucleated cells. Unlike the conventional type of ML, this variant often harbors *TP53* gene mutations (Huh et al., 2011; Uchihashi et al., 2016; Choi et al., 2022).

MPLs can be distinguished from MLs by molecular testing, aimed at detecting various gene rearrangements, and DNA methylation profiling. This distinction between the two tumors was demonstrated by Creytens et al. who showed that these tumors exhibit different DNA methylation clusters (Creytens et al., 2021).

Table 2. Differential diagnosis of myxoid pleomorphic liposarcoma.

Differential diagnosis		MPL	ML	ASPLT	PL	DDLP
Clinical features	Age (peak)	<3rd decade	4th to 5th decade	6th decade	7th decade	6th decade
	Gender Predilection	F	no sex predilection	M	M	M
	Deep/superficial location	Deep	Deep	Subcutis	Deep	Deep
	Predilection site	Mediastinum	Extremities (thigh)	Limbs and limb girdles	Extremities (lower>upper)	Retroperitoneum
	Size (mean/median)	2.5 - 16 cm	>10 cm	5 - 8,5 cm	8 - 10 cm	>10 cm
Histology	Myxoid stroma	Yes	Yes	Variable	Variable (mostly in myxofibrosarcoma-like component)	Variable
	Pleomorphic MN cells	Yes	No	Yes	Yes	Variable
	Mitosis	Yes	Yes (in high-grade	Yes (scarce)	Yes	Yes
	Necrosis	Yes (occasional)	No	No	Yes (often)	Variable
	Lipoblasts	Yes (scattered)	Yes	Yes	Yes	Yes
	Other characteristics	Chicken wire capillary vasculature	Chicken wire capillary vasculature	/	Extra- and intracellular hyaline droplets	/
Immunohisto-chemistry	CDK4	Negative	Negative	Positive (rarely)	Negative	Positive
	MDM2	Negative	Negative	Positive (rarely)	Negative	Positive
	Other positive stains	p16, S100, CD34	S100, DDIT3	S100, CD34, Desmin	Keratin (epithelioid-type)	p16
Molecular features	MDM2 or CDK4 amplification	No	No	No	No	Yes
	RB1 loss	Yes	No	Yes (50-70%)	Yes	Variable
	FUS, EWRS1, DDIT3 rearrangement	No	Yes	No	No	No
	TP53 mutation	Yes	No	Variable	Yes	Yes
	TERT promoter mutation	No	Yes (50%)	No	No	Yes
	Complex karyotype	Yes	No	No	Yes	Yes

MPL: myxoid pleomorphic sarcoma, ML: myxoid liposarcoma, ASPLT: Atypical spindle cell/pleomorphic lipomatous tumors, PL: pleomorphic liposarcoma, DDLP: dedifferentiated liposarcoma, M: male, F: female, MN: multinucleated.

Pleomorphic liposarcoma (PL)

PLs are rapidly growing, high-grade liposarcomas that predominantly affect the older population, with a slight predilection for men, and that only rarely occur in children. They often manifest in the extremities (Alaggio et al., 2020; Hornick et al., 2004). Microscopically, PL consists of diffuse sheets of highly atypical spindle and pleomorphic cells with variable amounts of multivacuolated lipoblasts. The tumor cells are large and can be mononuclear or multinuclear. Mitotic activity and necrosis can be observed. Two different morphological subtypes have been described, namely the myxofibrosarcoma-like and epithelioid subtypes (Hornick et al., 2004). The immunohistochemical profile characterized by negativity for MDM2 and CDK4, is similar to MPLs (Dreux et al., 2010; Gjeorgjievski et al., 2022). They also do not show *FUS/EWSR1::DDIT3* gene fusions. The most common mutations in PLs involve *TP53* and *NF1*, while *RB1* loss is found in 50% of cases (Libbrecht et al., 2021; Wang et al., 2013). Additionally, PLs exhibit a complex karyotype with complex structural rearrangements, closely resembling the genetic profile of MPLs. These tumors share a common methylation profile, making the distinction between them challenging (Creytens et al., 2021). A summary of the clinical and morphological differences between MPL and PL is presented in Table 2.

Atypical spindle cell/pleomorphic lipomatous tumor (ASPLT)

ASPLTs, in contrast to MPLs, predominantly affect middle-aged individuals, especially men. These tumors are commonly located in the subcutaneous tissue, particularly in the limbs and limb girdles (Mariño-Enriquez et al., 2017). Microscopically, ASPLTs exhibit varying proportions of atypical spindle cells, adipocytes, lipoblasts, and pleomorphic cells, along with a variable collagenous and/or myxoid extracellular matrix. The adipocytic component typically displays a mature morphology with varying sizes and shapes of the adipocytes. Mitotic figures are scarce and tumor necrosis is absent (Mariño-Enriquez et al., 2017). Occasionally, heterologous differentiation, such as smooth muscle, cartilaginous, or osseous elements, may be observed (Mariño-Enriquez et al., 2017; Alaggio et al., 2020; Lecoutere and Creytens, 2020). In a study by Enriquez et al., it was demonstrated that immunohistochemical staining may reveal weak or focal positivity for *MDM2* or *CDK4* in 6% and 5% of the tumors, respectively. However, molecular analyses consistently showed absence of MDM2 or CDK4 gene amplification (Mariño-Enriquez et al., 2017). In over half of the cases, there is a deletion in 13q14, including *RB1* loss and loss of adjacent genes (Creytens et al., 2017; Mariño-Enriquez et al., 2017). The clinical features, including the tumor's localization in more superficial structures, along with distinctive histopathological characteristics, can differentiate this tumor from MPL (Creytens et al., 2021).

Dedifferentiated liposarcoma (DDLP)

DDLPs evolve from the progression of an atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLPS) to a higher-grade malignancy (Weisset and Rao, 1992). They are typically located in the retroperitoneum and are more prevalent in the elderly population with a male predilection (Ghadimi et al., 2011). Histologically, DDLPs often exhibit an abrupt transition from the well-differentiated component to the high-grade component, although the well-differentiated component can be absent or challenging to identify. DDLPs are characterized by moderate-to-marked atypical spindle cells arranged in loose fascicles, displaying a storiform or patternless architecture. The mitotic index varies and necrosis can be seen (Lecoutere and Creytens, 2020). In a minority of cases (5-10%), heterologous differentiation can occur, including osteo/chondrosarcomatous, rhabdomyosarcomatous or angiosarcomatous differentiation (Mariño-Enriquez et al., 2017).

A challenging differential diagnosis is DDLP with ''homologous'' lipoblastic (pleomorphic liposarcoma-like) morphology, as described by Enriquez et al. and Boland et al. (Boland et al., 2012; Mariño-Enriquez et al., 2017). This variant exhibits morphological features similar to both DDLP and PL with lipoblastic differentiation, with the difference being that a DDLP typically shows a well-differentiated liposarcoma component, at least if extensive sampling is performed (Mariño-Enríquez et al. 2010; Boland et al. 2010). Moreover, DDLPs are characterized by consistent amplification of *MDM2* and *CDK4* (12q14-q15). Amplifications of the *JUN* (1p32.1), *TERT* (5p15.33), *CPM*, and *MAP3K5* genes have also been described in DDLPS. In 30% of cases, there is a loss of ATRX (Demicco, 2019). Takahira et al. demonstrated that loss of heterozygosity and abnormalities in the RB1 gene are characteristic features of the dedifferentiated component in DDLP, which can play a role in progression to a higher grade (Takahira et al., 2005). Although the distinction between MPLs and DDLPs, especially the variant with a homologous lipoblastic tumor morphology, can be challenging, differentiation between these entities can be made through immunohistochemical analyses, specifically for MDM2 and CDK4, along with FISH analysis for *MDM2* and/or *CDK4*.

Treatment and prognosis

In 2009, Alaggio et al. demonstrated that these high-grade and aggressive tumors have a poor prognosis, with a high likelihood of recurrence (40%), metastasis (40%), and mortality (70%) within a 36-month follow-up period. The most common sites for metastasis were the lungs, bones, and soft tissues (Alaggio et al., 2009).

Dermawan et al. showed that the progression-free survival and overall survival of patients with MPL are significantly worse compared with PLs and high-grade myxoid (round cell) liposarcomas (HGMLPs). In their study, the median time to death for MPLs was 22.6 months, significantly shorter than the 75.9 months for PLs and 218.3 months for HGMLPs (Dermawan et al., 2022).

However, data regarding the treatment of MPL and its effectiveness are very limited. Examination of the reported cases, outlined in Table 1, reveals that surgery was the primary treatment approach in all cases, except that reported by Tan et al. where neoadjuvant chemoradiotherapy was administered prior to surgery (Tan et al., 2023). In two of the four case reports described in the context of Li-Fraumeni syndrome, specifically those by Chitikela et al. and Hofvander et al., patients received additional adjuvant chemotherapy. The patient described by Chitikela et al. showed recurrence after 4 months, while the patient described by Hofvander et al. showed no recurrence 1 year post-surgery (Hofvander et al., 2016; Chitikela et al., 2022). In one case reported by Choi et al., no additional therapy was given after achieving negative resection margins, while all other reported cases received adjuvant therapy. Surprisingly, this patient showed no signs of recurrence, 6 months post-surgery (Choi et al., 2022).

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