

# Analysis of Dedifferentiated Liposarcomas Emphasizing the Diagnostic Dilemmas

## Abstract

**Introduction:** Dedifferentiated liposarcoma (DDLPS) is defined as a progression of well-differentiated liposarcoma (WDLPS) to another nonlipogenic sarcoma. Since a variety of heterologous sarcomas can be encountered in dedifferentiation, clinical dilemmas arise. The present study analyzed the role of clinicopathologic and immunohistochemical (IHC) features in the diagnosis of DDLPS and its differentiation from mimics. **Materials and Methods:** A retrospective and prospective study was conducted wherein all cases of liposarcoma from 2012 to 2017 were reviewed. DDLPS cases were identified among pleomorphic lesions. Clinical and histopathological details for these cases were retrieved from medical records section and department archives. Histomorphology and immunohistochemistry (MDM2, S100, and Ki-67) were analyzed for these cases. **Results:** Among 37 cases of liposarcomas reviewed, DDLPS was diagnosed in 12 cases (32.4%). Mean age of the patients was 54.3 years with equal gender distribution (M:F =1:1.2). Two patients had recurrent tumors. Most were retroperitoneal (58.3%) with mean duration of symptoms being 8.7 months. Mean tumor dimension was 17.5 cm. High-grade dedifferentiated component was most common (83.3%) with only one case each (8.3%) of low-grade and homologous dedifferentiation. Undifferentiated pleomorphic sarcoma was the frequent nonlipogenic sarcoma. MDM2 overexpression was detected in 100%, focal S100 positivity seen in 66.6%, and mean Ki-67 labeling index was 24. **Conclusion:** DDLPS exhibits aggressive clinical behavior. Adequate sampling, correlation to clinical details, demonstration of transition from WDLPS to DDLPS aid in narrowing the differentials. Immunostaining with MDM2 helps in definite categorization and S100 highlights lipoblasts, when they are not easily identifiable. MDM2, CDK4, and p16 IHC panel is recommended in all cases and fluorescence *in situ* hybridization analysis where IHC is noncontributory.

**Keywords:** Dedifferentiated, liposarcoma, MDM2, sarcoma

## Introduction

Liposarcoma is the most common subtype of soft-tissue malignancies, accounting for around 20% of all adult soft-tissue sarcomas.<sup>[1]</sup> In the 2013 World Health Organization (WHO) classification, liposarcomas, classified under “adipocytic tumours,” are of four major histological subtypes, namely, atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLPS), dedifferentiated liposarcoma (DDLPS), myxoid liposarcoma (MLS), and pleomorphic liposarcoma (PLS).<sup>[2]</sup> These subtypes represent clinical and pathologically distinct entities with discrete cytological and molecular characteristics.<sup>[3]</sup>

The first description and proposal of the term “dedifferentiated” in liposarcoma was

given by Evans in 1979.<sup>[4]</sup> The progression of an ALT/WDLPS to a sarcoma of variable histological grade (usually nonlipogenic) is regarded as a DDLPS. Around 10% of ALT/WDLPS show dedifferentiation, the risk being higher in deep-seated and long-standing lesions.<sup>[5]</sup> Since there can be a wide range of histological morphologies in the dedifferentiated component, they can pose a diagnostic dilemma. This study focuses on the role of clinicopathologic and immunohistochemical (IHC) features in the diagnosis of DDLPS and differentiating it from its mimics. We also discuss in detail the differential diagnosis and approach to the difficult clinical scenarios.

## Materials and Methods

A 5 years’ retrospective and prospective study was undertaken in the department of pathology, wherein all cases of liposarcomas

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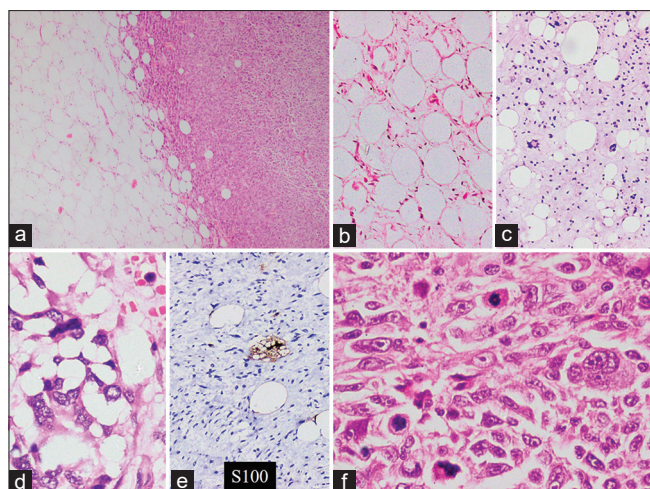
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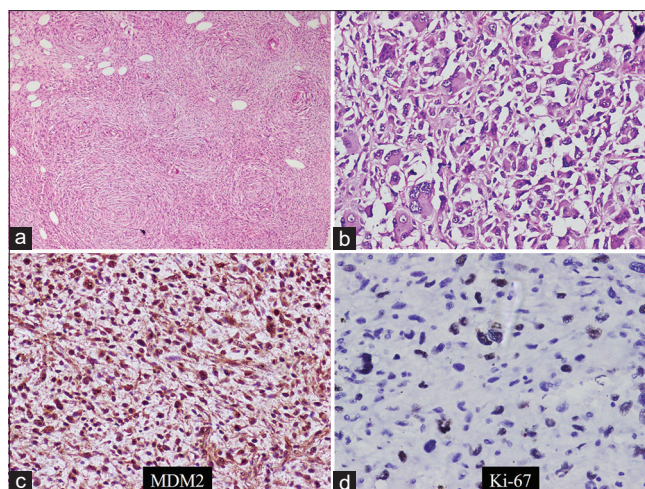


**Figure 1:** (a) Abrupt transition from well-differentiated liposarcoma to dedifferentiated liposarcoma (H and E, ×4) (b) Lipoma-like well-differentiated component (H and E, ×10) (c) Sclerosing well-differentiated component (H and E, ×10) (d and e) Lipoblasts seen within the tumour (H and E, ×20), highlighted by S100 immunostain (×20) (f) Atypical mitotic figures and tumour giant cells in dedifferentiated component (H and E, ×40)

from January 2012 to December 2017 were reviewed, after attaining the institutional ethics committee approval. The cases with clinical suspicion of liposarcoma, in whom either incisional or excisional biopsy was performed, were included in the study. Cases where tissue or paraffin blocks were not available were excluded.

Details pertaining to the clinical presentation such as duration of symptoms, size and site of the tumor, significant history were collected from the medical records section and departmental archives. Radiology findings, including the computed tomography scans, were also obtained and documented for these cases. The gross examination findings were collected, and microscopy slides were reviewed. Average number of slides reviewed was 17 per case (ranging from 2 to 43). Histologic grade was assigned using the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system.<sup>[5]</sup> The staging was performed according to the American Joint Committee on Cancer 8<sup>th</sup> edition.<sup>[6]</sup>

Microscopic details for the WDLPS and DDLPS were individually noted. The dedifferentiation was defined as the presence of homologous or heterologous sarcomatous component of variable histological grade occurring in close proximity to ALT/WDLPS. Areas with increased cellularity, higher mitotic activity, and pleomorphism, as compared to sclerosing WDLPS, were considered as a dedifferentiated component. This must be present in at least one low power field (×10 objective). The dedifferentiated component is usually required to have a mitotic count of at least 5 mitotic figures per 10 high power fields.<sup>[7]</sup> Immunostaining with Ki-67 was done for further correlation. The highest grade of the dedifferentiated component was considered for the final impression.



**Figure 2:** (a) Low-grade component as meningothelial-like whorls (H and E, ×4) (b) High-grade component as undifferentiated pleomorphic sarcoma (H and E, ×20) (c) MDM2 immunoreactivity (×20) (d) Ki-67 immunostaining (×40)

IHC staining was performed in all the cases on representative block of formalin-fixed, paraffin-embedded tissue with Murine Double Minute 2 (MDM2) (Abcam; Mouse monoclonal, clone 2A10, Product ID: ab16895), S100 (Dako Flex; Rabbit polyclonal, Ref: IS504), and Ki-67 (Dako Flex; Mouse monoclonal, clone MIB-1, Ref: IS626), according to the instructions provided by the manufacturer. The secondary antibody used was Dako REAL EnVision/HRP (Labeled polymer, Code K5007) against rabbit and mouse primary antibodies. MDM2 immunostain was read as “positive” when more than 20% of tumor cells showed moderate-to-strong nuclear positivity. S100 was considered “positive” when nuclear and cytoplasmic staining was seen. Ki-67 labeling index was calculated as the percentage of cells showing nuclear positivity among thousand cells examined at the most mitotically active focus. Additional IHC stains were studied as and when needed in individual cases-desmin, S100, SMA, EMA, bcl-2, CD99, Alk1 to name a few.

The collected data were analyzed with IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. (IBM Corp., Armonk, NY). The percentage analysis was done for categorical data. Mean and standard deviation were studied for continuous variables.

## Results

A total of 45 cases with clinical suspicion of liposarcomas were retrieved. Among them, 37 showed histomorphological features of liposarcomas. Initial diagnosis rendered included DDLPS in eight cases (21.6%) and PLS in six cases (16.2%). After careful microscopic evaluation and immunostaining with MDM2, four PLS cases (10.8%) were reclassified as DDLPS. Hence, DDLPS was the second-most common subtype, constituting 32.4% of all LPS. These DDLPS were included in the present study.

The mean age of the patients was 52.9 years (39–72 years) with majority aged between 60 and 69 years. Almost equal gender distribution (M:F = 1:1.2) was observed. A long-standing mass with a recent increase in size was the most frequent (83.3%) presenting complaint. Other clinical symptoms included pain, loss of appetite, and weight loss. The mean duration of symptoms was 8.7 months. The most common location was retroperitoneum (58.3%), followed by trunk and extremities (41.6%). One case involved the paratesticular region. Two cases had recurrent tumors in the retroperitoneum, previously diagnosed as DDLPS and ALT/WDLPS. They occurred 3 and 6 years prior to the current presentation, respectively [Table 1].

On radiography, three cases, including the two recurrent tumors, showed extension to the adjacent structures. For instance, one of the recurrent tumors showed the involvement of inferior surface of liver, inferior vena cava, and invasion into anterior abdominal wall. The mean tumor size (greatest dimension) was 17.5 cm (4–35 cm). On gross examination, most of the tumors were bosselated, encapsulated masses with yellow to gray-white, necrotic, and hemorrhagic cut surfaces. Myxoid and cystic change was seen focally in a few cases (41.6%).

Microscopically, in nine cases (81.8%), the well-differentiated component was lipoma-like, while two had sclerosing morphology. The transition was abrupt from WDLPS to DDLPS in seven cases (58.3%) and gradual in four (33.3%) [Figure 1a-c]. One case with only an incisional biopsy revealed DDLPS exclusively. The surgical margins were involved in 83.3% of the tumors, especially those located in the retroperitoneum. The dedifferentiated component was high-grade in eleven cases (91.6%) and low-grade in one case (8.4%). The high-grade component, in 10 cases, was undifferentiated pleomorphic sarcoma (UPS) showing vague storiform pattern and highly pleomorphic cells with bizarre forms [Figure 2b]. Homologous dedifferentiation from WDLPS to PLS was observed in one case, wherein the latter showed the presence of lipoblasts within the tumor. Low-grade component comprised of meningotheial-like whorls [Figure 2a]. FNCLCC histologic grade was three in most (83.3%) of the tumors. On immunohistochemistry, MDM2 was positive in all DDLPS [Figure 2c]. Based on MDM2 positivity, cases which were misclassified as PLS previously were also categorized as DDLPS following review of slides and identification of focal WDLPS areas at the periphery. S100 was focally positive in eight cases (66.6%) highlighting the lipoblasts [Figure 1d and e]. Mitotic count in all tumors was more than 5/10 high power fields [Figure 1f]. Ki-67 labeling index was variable and ranged from 2% to 70% [Figure 2d] with a mean of 24 [Table 1]. Most of the tumors were classified as pT<sub>4</sub> (33.3%) followed by an equal distribution among pT<sub>3</sub> and pT<sub>2</sub> (25% each). Stage group established in 70% tumors at presentation was III B. Postoperative radiotherapy was given to 41.6% of the patients and chemoradiation

administered in two cases (16.7%). On follow-up, one case showed lung and vertebral metastasis after 2 years of the primary diagnosis.

## Discussion

Among all LPS, the initial diagnosis rendered included DDLPS in eight cases (21.6%) and PLS in six cases (16.2%). Four PLS cases (10.8%) were reclassified as DDLPS on the identification of minimal well-differentiated component and/or MDM2 nuclear positivity. Hence, DDLPS constituted 32.4% of all LPS. Other authors have reported an incidence of 13.9%–16.2%.<sup>[8,9]</sup> However, few authors believe that the true incidence of DDLPS is underestimated due to inadequate sampling or misclassification of the lesions.<sup>[10]</sup> In the recent data at few referral centers, DDLPS is suggested to be the most common histological subtype.<sup>[11]</sup>

The mean age of the patients was 52.9 years with maximum cases presenting in the sixth decade. Almost equal gender distribution (M:F=1:1.2) was observed. These findings are similar to other studies.<sup>[12,13]</sup>

The most common location of DDLPS in our study was retroperitoneum, and two cases were recurrent tumors. According to the WHO, retroperitoneum is the most common site for DDLPS, outnumbering somatic soft tissue by at least 5:1.<sup>[5]</sup> It arises in a recurrent WDLPS or *de novo* and can itself recur in the retroperitoneal location.<sup>[13]</sup> The recent increase in the size of a long-standing painless swelling often indicates dedifferentiation, as seen in the present study.

These tumors are usually large in size, especially in the retroperitoneal location. In the present study also, the mean tumor size (greatest dimension) noted was 17.5 cm, with the largest tumor being 35 cm. Microscopically, we found abrupt transition from WDLPS to DDLPS in seven cases (58.3%) as was observed by Rekhi *et al.* in 72% cases.<sup>[13]</sup> Margins were involved in 83.3% of our cases. Margin clearance in retroperitoneal location is challenging due to the extension of the tumor into adjacent structures. Margin positivity adversely affects the prognosis leading to recurrences in these patients.<sup>[14]</sup>

In the present study, the dedifferentiated component encountered frequently was high-grade, in the form of UPS. The low-grade component observed in one case included meningotheial-like whorls. This is in accordance with other authors who also found high-grade dedifferentiation to be more common than low grade. Among high-grade dedifferentiation, they also demonstrated UPS most frequently.<sup>[13,15]</sup> Homologous dedifferentiation is the terminology proposed by the WHO, in 2013 classification, for tumors showing features of both WDLPS and PLS.<sup>[5]</sup> Earlier, these were classified as mixed liposarcomas.<sup>[16]</sup> In our study also, homologous dedifferentiation was found in one case. This can be a potentially misleading point

**Table 1: Details of dedifferentiated liposarcomas**

Case number	Age (years)/sex	Site	Chief complaint	Duration (months)	Procedure	Size (cm)	Margins	Transition component	FNCLCC grade	pT stage	Stage group	MDM2	S100	Ki-67 (%)
1	60/female	Right upper back	Swelling	30	Excision	4×3	Uninvolved	Abrupt	2	1	II	2+	Focal positive	5
2*	53/female	Retroperitoneum	Swelling and pain abdomen	6	Debulking surgery	23×20	Involved	Abrupt	3	4	IIIB	2+	Focal positive	4
3	65/female	Retroperitoneum	Swelling	12	Incisional	15×10	Involved	Only DDLPS	3	3	IIIB	2+	Negative	70
4*	43/male	Retroperitoneum	Pain abdomen	3	Excision	12×8.7	Uninvolved	Gradual	3	3	IIIB	3+	Negative	12
5	42/male	Retroperitoneum	Weight loss and pain abdomen	2	Excision	18×15	Involved	Gradual	3	4	IIIB	3+	Lipoblasts focal positive	2
6	66/male	Paratesticular	Swelling with pain	8	Excision	35×23	Involved	Abrupt	3	4	NA	3+	Focal positive	10
7	72/female	Retroperitoneum	Swelling per abdomen	1	Debulking surgery	26×26	Involved	Abrupt	3	4	IIIB	3+	Negative	20
8	40/female	Retroperitoneum	Abdominal distension with pain	10	Excision	31×22	Involved	Abrupt	3	4	IIIB	2+	Focal positive	40
9	40/female	Axilla	Swelling	18	Excision	9×5	Involved	Gradual	2	2	IIIA	2+	Focal positive	25
10	60/male	Retroperitoneum	Swelling	2	Excision	8×4	Uninvolved	Abrupt	2	2	IIIA	3+	Negative	50
11	39/male	Thigh	Swelling	4	Excision	12×8	Uninvolved	Abrupt	3	3	IIIB	3+	Focal	30
12	72/male	Thigh	Swelling	8	Excision	9×7	Involved	Gradual	3	2	IIIA	3+	Focal	22

\*Recurrence. DDLPS – Dedifferentiated liposarcoma; UPS – Undifferentiated pleomorphic sarcoma; PLS – Pleomorphic liposarcoma; NA – Not applicable

in accurate diagnosis. However, MDM2 positivity in the pleomorphic component facilitates a diagnosis ofDDLPS with homologous dedifferentiation.<sup>[17]</sup>

Considering thatDDLPS are frequent tumors in the deep-seated soft tissue, especially the retroperitoneum, other high-grade sarcomas are close differentials. The tendency of misdiagnosis is more in the core tissue samples. Ikoma *et al.*, in their study, found the diagnostic sensitivity of percutaneous biopsy to be 37% in these tumors. The incorrect diagnosis in their study included rhabdomyosarcoma, gastrointestinal stromal tumor (GIST), unclassified sarcoma, malignant fibrous histiocytoma, desmoid tumor, and low-grade B-cell lymphoma.<sup>[7]</sup>

AllDDLPS in our study were immunoreactive with MDM2 staining. Kashima *et al.* found amplification of MDM2 in 90%DDLPS cases while Touqan *et al.* reported it in all nine cases (100%).<sup>[18,19]</sup> S100 was focally positive in eight cases (66.6%), highlighting the lipoblasts in well-differentiated component, in our study. Lipoblasts in the dedifferentiated component were rarely (25%) positive. Rekhi *et al.*, in their study, found the expression of S-100P in well-differentiated components of six (75%)DDLPS. It was negative in the dedifferentiated component of seven tumors, except for focal positivity in two tumors containing lipoblasts.<sup>[13]</sup> Ki-67 labeling index in the present study was ranging from 2% to 70% with a mean of 24, indicative of a wide spectrum of histological grades that can be encountered in these lesions due to tumor heterogeneity.

For MDM2 testing, fluorescence *in situ* hybridization (FISH) analysis is more sensitive than immunohistochemistry alone. WDLPS andDDLPS harbor ring chromosomes and supernumerary chromosomes and most common mutations from the 12q 13–15 amplicon are MDM2 and CDK4.<sup>[5]</sup> Thway *et al.* have reported a high concordance rate of 95.7% between histology and FISH testing forDDLPS and an overall high concordance rate of 96.5% between histology and FISH analysis for WDLPS andDDLPS. Moreover, they have discussed that positive results on MDM2 FISH help to exclude the differentials of pleomorphic orMLS, both being close mimickers ofDDLPS, in some exceptional circumstances.<sup>[20]</sup>

The consensus for dedifferentiated lipomatous tumors is to use MDM2 and CDK4 immunostaining as a screening procedure, followed by FISH analysis in negative cases. Although the sensitivity of immunohistochemistry is low (around 55%–60%), the specificity is very high (90%–92%). Clay *et al.* concluded that 60% of patients would require IHC and FISH for a reliable diagnosis. They also opined that cases where slide review and IHC alone are inconclusive constitute only a minority of cases. In resource limited settings like ours, MDM2 and CDK4 can be used for screening followed by ancillary testing recommendation at higher referral centers for cases with high suspicion ofDDLPS. On IHC, the addition of p16 to

MDM2 and CDK4 further increases the test sensitivity to 71%.<sup>[21]</sup>

Differentiating betweenDDLPS and the invasion of a pleomorphic high-grade tumor into mature fat is a diagnostic dilemma. In such instances, careful observation for the presence of well-differentiated component aids in establishing the diagnosis. Moreover, MDM2 immunostaining is also useful in such cases.<sup>[10]</sup> Hence, extensive sampling and careful evaluation of the sections for WDLPS is essential. Another diagnostic dilemma arises when an incisional biopsy or core biopsy is performed. If only dedifferentiated part of the tumor is sampled, there is a tendency to misclassify the lesion. Similarly, we had one case wherein incisional biopsy showed features ofUPS. The identification of lipoblasts and immunostaining with MDM2 helped in definite categorization. S100 immunostain highlights the lipoblasts, if not readily recognizable.

The differential diagnosis ofDDLPS is extensive, and distinction can be challenging at various instances. These tumors can mimic diverse histomorphological patterns seen in tumors ranging from low-grade sarcomas to very pleomorphic high-grade sarcomas. The low-grade pattern can be mistaken for fibromatosis or low-grade fibromyxoid sarcoma. Very inflammatory tumors can mimic sclerosing lesions associated with IgG4 and inflammatory myofibroblastic tumors. Few patterns ofDDLPS can even mimic myxoid or PLS subtypes.<sup>[2,5,16]</sup> A list of differentials with immunohistochemistry and molecular testing approach is shown in Table 2.

A comprehensive approach is essential for ruling out these differentials. Correlating the site of involvement with peculiar histomorphological features, immunohistochemistry, and molecular genetics helps to rule them out with precision. We discuss here few very close and often misdiagnosed entities.

PLS predominantly occurs in the trunk or extremities of even older population group. Comparatively, they show a greater degree of pleomorphism and more abundant lipoblasts. The presence of lipoblasts is an essential diagnostic criterion in PLS. Homologous dedifferentiation inDDLPS can also pose a challenge in situations where well-differentiated component is minimal or totally absent. PLS is not associated with amplification of MDM2 and/or CDK4 since they are not associated with 12q 13–15 amplicon.<sup>[5]</sup>

MLS also very rarely occur in the retroperitoneum, so much so that it is recommended to aggressively search for a primary elsewhere ifMLS is encountered in the retroperitoneum. Moreover, the cellular details are typical forMLS which show small, uniform, ovoid nuclei with bland morphology. On the contrary, myxoid areas inDDLPS still show at least focal nuclear atypia and pleomorphism. MLS harbor DDIT3-FUS fusion mutations and rarely, DDIT3-EWSR1 fusion.<sup>[2,5]</sup>

**Table 2: List of differential diagnosis for dedifferentiated liposarcoma with low-grade and high-grade dedifferentiation - immunohistochemical and molecular findings**

Differential diagnosis	DDLPS <sup>[2,3]</sup>	Immunohistochemistry <sup>[5,13,22]</sup>	Molecular findings <sup>[5,13,22]</sup>
<b>DDLPS with low-grade dedifferentiation</b>			
Fibromatosis	MDM2 (IHC and/or FISH), CDK4, p16	Beta catenin, Cyclin D1, Calretinin	CTNNB1
Low grade fibromyxoid sarcoma		MUC4, CD99, Bcl2	t (7;16) with FUS-CREB3L2 fusion
Inflammatory myofibroblastic tumor		Vimentin, alpha smooth muscle actin, muscle specific actin, Alk1	t (2;5) - ALK and NPM, t (2;17) - ALK and CLTC
<b>DDLPS with high-grade dedifferentiation</b>			
High-grade fibrosarcoma	MDM2 (IHC and/or FISH), CDK4, p16	Vimentin, p53, type 1 collagen	Aneuploid
SFT with dedifferentiation		CD34, CD99, STAT6	Non-specific
Malignant peripheral nerve sheath tumor		CD99, S100, Leu7/CD57 (in neurofibroma-like areas)	Non-specific
Synovial sarcoma		TLE1, Cytokeratins, Bcl2, CD99	t (X; 18) - SYT-SSX1 or SYT-SSX2
High-grade myxofibrosarcoma		No specific stains, CD34	Highly complex karyotypes, often 6p-, 9q+, 12q+
Spindle cell rhabdomyosarcoma		MyoD1 (diffuse), Desmin, Myogenin, Actin (focal)	Recurrent MyoD1 mutations
Pleomorphic liposarcoma		Vimentin, S100, SMA	Complex karyotypes
Undifferentiated pleomorphic sarcoma		Diagnosis of exclusion, focal SMA positivity (few cases)	Complex karyotypes

IHC – Immunohistochemical; DDLPS – Dedifferentiated liposarcoma; SFT – Solitary fibrous tumor

Morphologically, IgG4 disease exhibits dense inflammatory infiltrate with storiform fibrosis. However, IgG4 related sclerosing lesions can easily be ruled out by correlation with systemic features since IgG4 related disease is now recognized as systemic disorder, characterized by high serum IgG4 levels (exceeding 135 mg/dl) and more than 10 IgG4 positive cells per high-power field.<sup>[22]</sup> Inflammatory myofibroblastic tumor involves the retroperitoneum quite often, especially in children and young adults. On morphology, it typically displays a mixture of three patterns– nodular fasciitis like cellular areas, spindled myofibroblasts and densely hyalinized stroma. However, unlike the inflammatory DDLPS, all these patterns do not display pleomorphism or atypical mitotic figures. IHC with alpha-smooth muscle actin, calponin, and Alk1 can help in the distinction in conjunction with MDM2 and CDK4.<sup>[23]</sup>

Solitary fibrous tumor (SFT) can also arise in the retroperitoneum and can rarely dedifferentiate. SFT harbors NAB2-STAT6 fusion transcripts with nuclear expression of STAT6 protein. A subset of DDLPS has also been found to express STAT6 and CD34. In such situations, diffuse expression of CD34, CD99, and bcl-2 can help to give a final call of SFT. All three are very unlikely to be expressed diffusely in DDLPS.<sup>[5,23]</sup>

Synovial sarcomas can involve the intra-abdominal sites, and though they are composed of monotonous population of cells, the spindle cells may show some degree of pleomorphism. However, the focal expression of cytokeratins, epithelial membrane antigen, and TLE1

positivity along with specific translocation *t* (X; 18) (p11.2; q11.2) saves the day often.

Malignant peripheral nerve sheath tumors (MPNST) can occur in the abdomen, show varied morphology with dedifferentiation to any lineage. Hence, the distinction can be challenging. Morphologically, MPNST will show, at least focally, cells with elongated, tapered hyperchromatic nuclei suggesting the neural origin. Moreover, they tend to lack the expression of MDM2, p16 or CDK4 and express CD99, S100 or p53.<sup>[24]</sup>

DDLPS can rarely show immunopositivity for CD117 and misdiagnosed as retroperitoneal GIST. GIST displays more uniform spindle cells lacking atypia. GIST expresses CD117 more diffusely and is typically positive for DOG-1. Moreover, they harbor KIT or PDGFRA mutations.<sup>[23]</sup>

One (8.3%) of our patients presented with pulmonary and vertebral metastasis after 2 years of primary diagnosis. Distant metastasis is usually observed in 15%–20% of DDLPS, tumors metastasizing frequently to lungs.<sup>[5]</sup> One case (8.3%) had recurrent DDLPS after 3 years in our study. The local recurrence rate is very high in DDLPS varying from 41% to 50% in various studies.<sup>[8,12]</sup> The recurrence duration in these studies is documented to be within a time span of 8.5 months–60 months.<sup>[8,12,25]</sup> Oh *et al.* found the 5-year disease-free survival of 22.1% and overall 5-year survival of 49% in DDLPS patients.<sup>[9]</sup>

Treatment options available for DDLPS include surgical resection, often associated with radiotherapy and/or

chemotherapy. MDM2 not only aids in the diagnosis of liposarcomas but also has been targeted by drugs, in both WDLPS and DDLPS. Nutlin is the first specific and potent MDM2 inhibitor discovered. Research is ongoing for other MDM2 inhibitors, including AT-219, RG7388, and Ascenta.<sup>[26]</sup> Considering the aggressive biological behavior of DDLPS, potential of targeted therapy and low disease-free survival rates, correct identification of these lesions constitutes an important milestone in patient management.

The limitation of the present study is the standalone use of MDM2 immunohistochemistry without FISH analysis, due to nonavailability at the center. A larger study with a greater number of cases and FISH analyses can help create an approach to the diagnosis of this category of tumors.

## Conclusion

Dedifferentiated LPS is a subtype of liposarcomas with more aggressive clinical behavior. They pose diagnostic dilemmas in unusual case scenarios. Adequate sampling of the lesion, correlation with clinical details, and demonstration of the transition of WDLPS to DDLPS aid in narrowing down the differentials. Immunostaining with MDM2 can help in definite categorization with high specificity. S100 staining can highlight the lipoblasts in tumors where they are not easily identifiable. A panel of IHC recommended for DDLPS must include MDM2, CDK4, and p16. Analysis with MDM2 FISH amplification is essential for cases where IHC is noncontributory.

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## Conflicts of interest

There are no conflicts of interest.

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