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Original Article

Application of adipocyte-related antibodies in undifferentiated sarcomas to identify dedifferentiated liposarcomas based on histological and clinical analysis

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Abstract: Background: Due to morphologic similarities between undifferentiated sarcoma (US) and dedifferentiated liposarcoma (DDLPS), some portions of US could be identified as DDLPS. In this study, we applied adipocyte-related antibodies in order to discriminate possible cases of DDLPS from US. Materials and methods: A total of 46 cases, previously diagnosed as US, were examined. Immunohistochemistry for MDM2, CDK4, calreticulin, FABP4, and stathmin were performed. Histological findings were reviewed and clinical data was analyzed retrospectively. Results: MDM2, CDK4, calreticulin, FABP4, and stathmin were positive in 17 (37.0%), 14 (30.4%), 3 (6.5%), 1 (2.2%), and 12 (26.1%) of the total 46 cases, respectively. MDM2/CDK4 positive cases showed more frequent positivity for calreticulin/FABP4/stathmin. Survival analysis, based on staining pattern, revealed a significantly better survival in the group where either MDM2 and CDK4 were positive and at least one of calreticulin, FABP4, or stathmin staining were positive. Conclusions: We conclude that when either MDM2-positive or CDK4-positive cases show any other positive results for calreticulin, FABP4, or stathmin, they have a significantly better survival and the possibility of DDLPS should be considered. Additional use of calreticulin, FABP4, or stathmin immunohistochemistry helps us to narrow the pool for further studies such as molecular analysis for a definite diagnosis.

Keywords: Dedifferentiated liposarcoma, undifferentiated sarcoma, MDM2, CDK4, calreticulin, FABP4, stathmin

Introduction

Undifferentiated sarcomas (US) are soft tissue sarcomas showing no identifiable line of differentiation when analyzed by immunohistochemistry or molecular biologic techniques [1]. Dedifferentiated liposarcoma (DDLPS) is a high grade non-lipogenic soft tissue sarcoma usually from an atypical lipomatous tumor [1]. DDLPS exhibits a less aggressive clinical course than other types of high-grade pleomorphic sarcoma [1, 2]. Therefore, identification of DDLPS from US is clinically important. Due to morphologic similarities between US and DDLPS, some portions of US could be identified as DDLPS. MDM2 and CDK4 are well-known adipogenic markers. They are expressed in atypical lipomatous tumors and DDLPS [3, 4]. In addition to these markers, other adipocyte-related markers have been reported in previous studies [5-7]. In this study, we applied MDM2, CDK4, calreticulin, FABP4, and stathmin, which are known to be reactive with adipocyte-related antigens. The objective of this study was to determine whether potential cases of DDLPS could be differentiated from US based on histological and clinical data.

Materials and methods

A total of 46 cases, previously diagnosed as US, were used for this study. For comparison, five cases of DDLPS, two cases of leiomyosarcoma, and two cases of myxofibrosarcoma were also included in this study. Clinical and histological reviews were performed for these cases. All histological slides were reviewed by authorized pathologists. Tissue microarray (TMA) blocks were made. These blocks were then sectioned in 4 μm thickness and mounted on glass slides. Immunohistochemistry (IHC) was then performed with the following steps:

Table 1. Clinical summary of 46 cases previously diagnosed as undifferentiated sarcoma

Sites	No		Age	No	Sex	N.
Upper extremities	5 (10.9%)		21-30	3 (6.5%)	Male	27 (58.7%)
Lower extremities	25 (54.3%)		31-40	6 (13.0%)	Female	19 (41.3%)
Thigh		21 (45.7%)	41-50	11 (23.9%)		
Buttock		3 (6.5%)	51-60	10 (21.7%)		
Ankle		1 (2.2%)	61-70	9 (19.6%)		
Trunk	6 (13.0)		71-80	5 (10.9%)		
Chest wall		3 (6.5%)	81-90	2 (4.3%)		
Back		2 (4.3%)				
Abdominal wall		1 (2.2%)				
Intra-abdomen	7 (15.2%)					
Omentum		1 (2.2%)				
Retroperitoneum		4 (8.7%)				
Pelvis		1 (2.2%)				
Kidney		1 (2.2%)				
Neck	2 (4.3%)					
Pleura	1 (2.2%)					
Total	46			46		46

de-paraffinization, antigen retrieval using a heated water bath, endogenous peroxidase blockade with H_2O_2-methanol solution, phosphate-buffered saline (0.01 M, pH 7.4) washing at each step, primary antibody reaction, secondary antibody reaction, diaminobenzidine (DAB) solution preparation, counter staining with hematoxylin, and sealing. We used the following primary antibodies for IHC: MDM2 (polyclonal; 1:50; GeneTex, CA, USA), CDK4 (polyclonal; 1:100; GeneTex, CA, USA), Calreticulin (polyclonal; 1:100; GeneTex, CA, USA), FABP4 (monoclonal; 1:50; Abnova, Taiper, Taiwan), and Stathmin (monoclonal; 1:50; Cell Marque, Darmstadt, Germany). Tissues of breast cancer, gastric cancer, hepatocellular carcinoma, normal salivary glands, and carcinoma *in situ* of uterine cervix were used as control tissues for MDM2, CDK4, calreticulin, FABP4, and stathmin staining, respectively. For convenience, we divided these antibodies into two sets: 'Set 1' included MDM2 and CDK4; 'Set 2' included calreticulin, FABP4, and stathmin. IHC was interpreted in the following three semiquantitative categories: 1) no staining at all (negative), 2) weak staining of cells (weak positive), and 3) distinct staining for most cells (positive). Staining was considered positive when nuclear and/or cytoplasmic staining was found for MDM2, CDK4, and FABP4, when nuclear staining was found for stathmin, or when cytoplasmic staining was found for calreticulin. We also compared IHC results with morphologic findings of hematoxylin and eosin (H&E) slides and clinical data. For clinical correlation, we grouped these cases as follows: 1) group A, both antibodies of 'Set 1' were positive regardless of 'Set 2' versus the remainder; 2) group B, at least one antibody of 'Set 1' was positive regardless of 'Set 2' versus the remainder; 3) group C, all antibodies of 'Set 1' and 'Set 2' were positive versus the remainder; 4) group D, both antibodies of 'Set 1' and at least one antibody in 'Set 2' was positive versus the remainder; and 5) group E, at least one antibody in 'Set 1' and at least one antibody 'Set 2' were positive versus the remainder. We used Chi-square test and Kaplan-Meier survival analysis to analyze statistical significance using SAS software version 8 (SAS Inc., Cary, NC, USA). A *P*-value of less than 0.05 was considered statistically significant. This study was approved by the Institutional Review Board of St. Vincent hospital, the Catholic University of Korea (approval number: VC14SISI0264).

Results

Anatomic sites of occurrences of the 46 US cases varied. They included 5 (10.9%) upper extremities, 25 (54.3%) lower extremities, 6 (13.0%) trunks, 7 (15.2%) intra-abdomen, 2 (4.3%) necks, and 1 (2.2%) pleura. Age distributions also varied. Most cases were found in the age-range of 40 to 80 years. Twenty-seven (58.7%) cases were men and 19 (41.3%) cases were women (**Table 1**). Immunohistochemically, MDM2 showed tendency of nonspecific background staining. Five cases of previously diagnosed DDLPS showed positive reactions to all five antibodies used while two cases of leio-

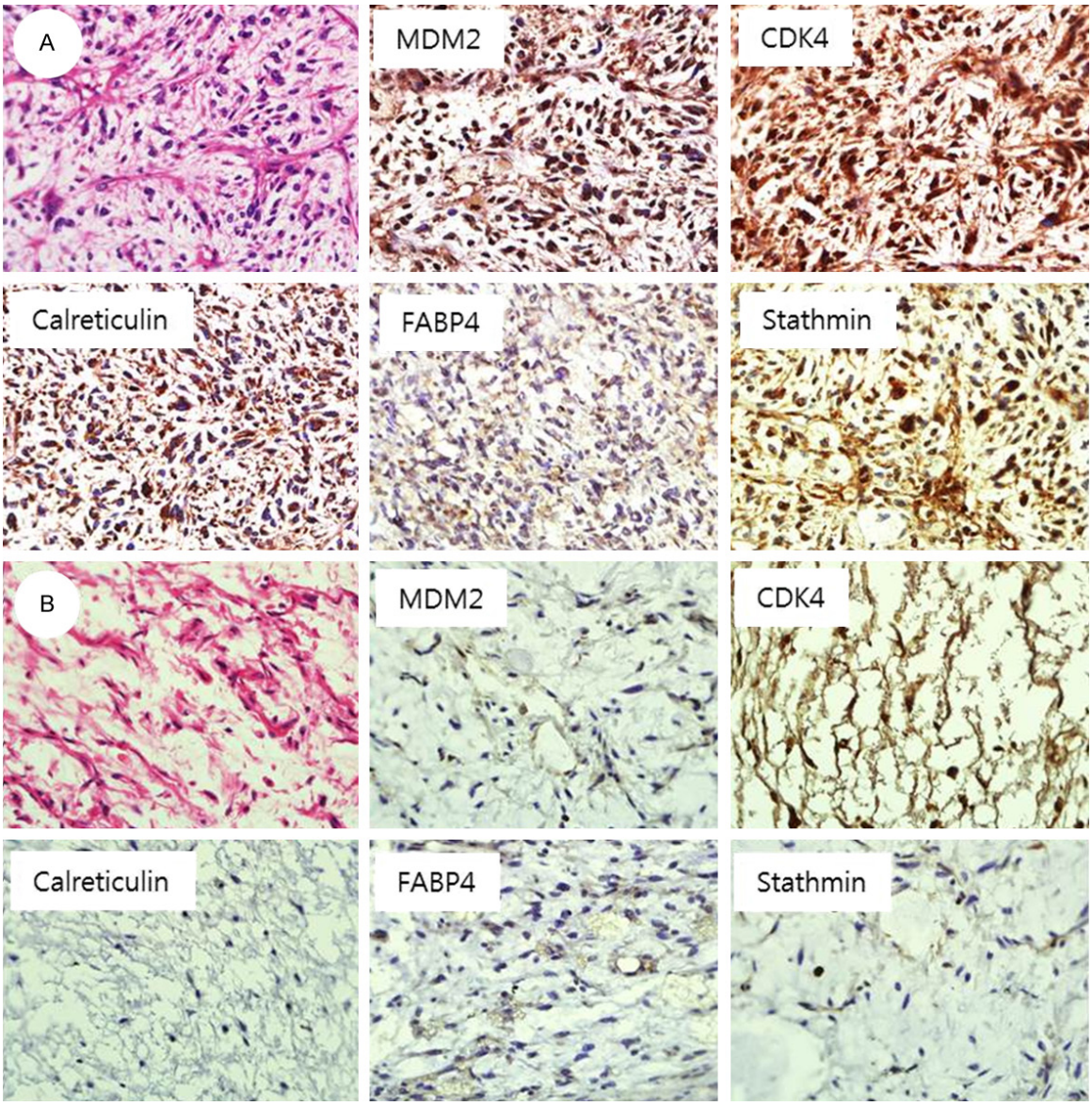

Figure 1. Immunohistochemical findings. DDLPS shows positive immunohistochemical reaction to MDM2, CDK4, calreticulin, FABP4, and stathmin (A). Myxofibrosarcoma shows negative reaction to MDM2, calreticulin, FABP4, and stathmin. Staining of CDK4 is relatively nonspecific (B).

myosarcomas and two cases of myxofibrosarcomas showed negative reactions to all five antibodies (**Figure 1**). IHC results of the 46 study cases were as follows: (1) For MDM2, 17 (21.7%), 10 (41.3%), and 19 (41.3%) cases were positive, weakly positive, and negative, respectively; (2) For CDK4, 14 (30.4%), 6 (13.0%), and 26 (56.5%) cases were positive, weakly positive, and negative, respectively; (3) For calreticulin, 3 (6.5%), 17 (37.0%), and 26 (56.5%) cases were positive, weakly positive, and negative, respectively; (4) For FABP4, 1 (2.2%), 14 (30.4%), and 31 (67.4%) cases were positive, weakly positive, and negative, respectively; (5) For stathmin, 12 (26.1%), 7 (15.2%), and 27 (58.7%) cases were positive, weakly positive, and negative, respectively (**Table 2**). Details of site of involvement and IHC staining pattern is fully described in **Table 2** and representative staining patterns are depicted in **Figure 2**.

Immunohistochemical staining results were compared in groups. 'Set 1' consisted of MDM2 and CDK4 and 'Set 2' consisted of calreticulin, FABP4, and stathmin. The number of positive

Table 2. Immunohistochemical results of the 46 cases previously diagnosed as undifferentiated sarcoma

Cases	Sex	Age	Sites	Immunohistochemical results				
				MDM2	CDK4	Calreticulin	FABP4	Stathmin
1	M	32	Forearm	n	n	n	n	n
2	F	44	Distal femur	p	n	n	n	wp
3	M	59	Thigh	n	n	n	n	n
4	M	43	Chest wall	n	n	n	wp	n
5	M	50	Back	n	n	n	n	n
6	M	76	Chest wall	p	p	wp	n	wp
7	M	70	Buttock	p	p	wp	n	p
8	M	22	Omentum	p	p	wp	wp	p
9	F	55	Arm	n	p	n	wp	n
10	F	67	Thigh	p	n	n	n	wp
11	F	88	Ankle	n	n	n	n	n
12	M	63	Distal thigh	n	wp	p	wp	wp
13	F	44	Retroperitoneum	p	p	n	n	n
14	M	78	Back	p	p	wp	wp	p
15	F	62	Retroperitoneum	wp	n	n	n	n
16	M	66	Neck	wp	n	n	n	n
17	F	48	Thigh	p	p	wp	n	p
18	M	56	Pelvis	wp	wp	n	n	n
19	F	51	Abdominal wall	n	n	n	n	n
20	M	32	Thigh	wp	n	n	n	n
21	M	53	Arm	n	n	wp	n	n
22	F	56	Retroperitoneum	n	n	n	n	n
23	M	72	Buttock	n	n	n	n	n
24	F	55	Arm	n	n	n	n	n
25	M	64	Thigh	n	n	n	n	n
26	M	68	Thigh	wp	p	wp	wp	p
27	F	41	Chest wall	p	p	wp	wp	wp
28	M	34	Kidney	n	n	n	n	n
29	M	36	Thigh	n	n	n	wp	n
30	F	51	Thigh	wp	n	wp	n	n
31	F	43	Leg	p	n	wp	n	n
32	M	67	Neck	p	p	p	wp	p
33	M	22	Thigh	n	n	n	n	n
34	F	75	Thigh	wp	wp	wp	n	n
35	M	55	Thigh	wp	n	wp	wp	p
36	M	39	Thigh	wp	n	n	n	n
37	F	37	Retroperitoneum	p	wp	wp	wp	p
38	M	28	Thigh	n	wp	n	n	n
39	M	42	Pleura	p	p	wp	wp	p
40	M	56	Thigh	wp	n	n	n	wp
41	F	49	Thigh	p	p	wp	n	p
42	M	44	Thigh	n	n	n	n	n
43	F	62	Thigh	p	wp	p	wp	wp
44	M	74	Elbow	p	p	wp	wp	p
45	F	47	Hip	p	p	wp	p	p
46	F	86	Thigh	wp	n	n	n	n

n: negative, wp: weakly positive, p: positive.

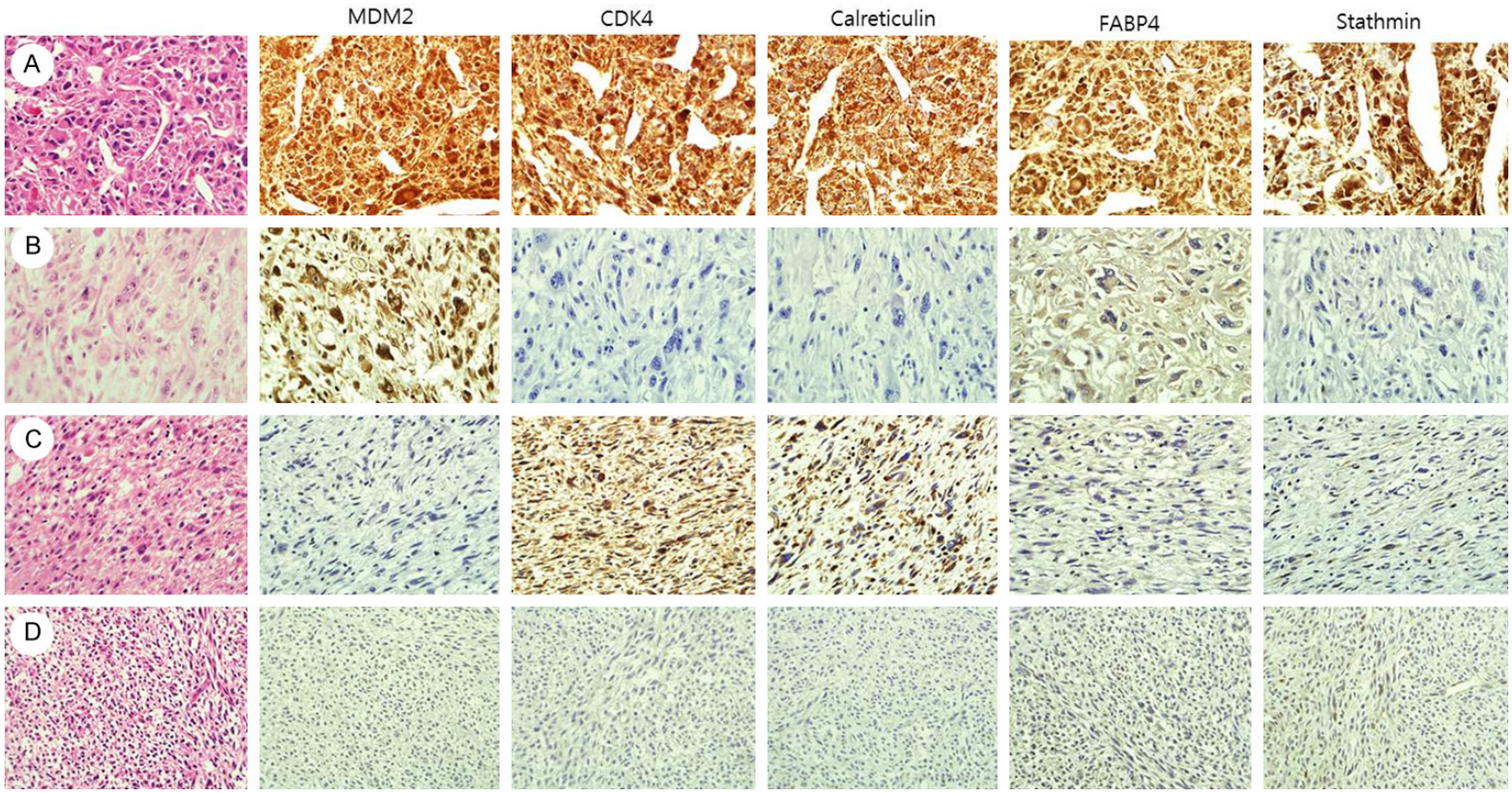

Figure 2. Immunohistochemical correlation between a set of the MDM2/CDK4 and a set of the calreticulin/FABP4/stathmin. (A) Shows MDM2+/CDK4+ and calreticulin+/FABP4+/stathmin+. (B) shows MDM2+/CDK4-, but among the set of calreticulin/FABP4/stathmin, only FABP4 shows weak positive reaction. (C) is MDM2-/CDK4+ and accompanied by positive reaction to calreticulin and focal positive reaction to stathmin. (D) is MDM2-/CDK4- and shows entire negative reaction to the set of calreticulin/FABP4/stathmin.

Table 3. Correlation between immunohistochemical results of 'Set 1' (MDM2/CDK4) and'Set 2'

No		Set 2				Total
		0	1	2	3	
Set 1	0	12 (80.0%)	3 (20.0%)	0 (0.0%)	0 (0.0%)	15 (100.0%)
	1	6 (42.9%)	6 (42.9%)	0 (0.0%)	2 (14.3%)	14 (100.0%)
	2	2 (11.8%)	1 (5.9%)	4 (23.5%)	10 (58.8%)	17 (100.0%)
Total		20 (43.5%)	10 (21.7%)	4 (8.7%)	12 (26.1%)	46 (100.0%)
P-value						<0.001

Calreticulin/FABP4/stathmin.

Table 4. Overall survival in groups, according to immunohistochemical staining patterns

		Mean survival time			Log Rank comparison *P*-value
		Estimate	Standard error	95% confidence interval	
[A]	1	130.816	19.026	93.524~168.107	0.445
	0	108.705	14.818	79.643~137.768	
[B]	1	141.331	12.236	117.349~165.313	0.314
	0	93.408	18.532	57.085~129.732	
[C]	1	149.556	17.390	115.472~183.639	0.435
	0	103.452	14.427	75.174~131.730	
[D]	1	155.231	12.268	131.185~179.277	0.282
	0	101.551	14.621	72.895~130.297	
[E]	1	159.263	8.504	142.596~175.931	0.046
	0	90.417	16.126	58.089~122.024	

Group [A], both markers of 'Set 1'† were positive regardless of 'Set 2'‡ (1) versus the remainder (0); group [B], at least one of the 'Set 1' markers was positive regardless of 'Set 2' (1) versus the remainder (0); group [C], all 'Set 1' and 'Set 2' markers were positive (1) versus the remainder (0); group [D], both markers of 'Set 1' and at least one of the 'Set 2' marker was positive (1) versus the remainder (0); and group [E], at least one of 'Set 1' marker and at least one of 'Set 2' marker were positive (1) versus the remainder (0). †'Set 1': MDM2/CDK4. ‡'Set 2': calreticulin/FABP4/stathmin.

markers between 'Set 1' and 'Set 2' had a strong correlation ($P<0.001$). Among the 17 cases that were both positive for MDM2 and CDK4, 10 (58%) cases showed positivity in all three 'Set 2' markers. Among the 15 cases that were both negative for MDM2 and CDK4, 12 (80.0%) cases were negative for all three 'Set 2' markers (**Table 3**).

Histologically, US showed a spindle cell or pleomorphic pattern in general. However, cases in the MDM2+/CDK4+/calreticulin+/FABP4+/stathmin+ group showed more epithelioid features and could be discriminated as possible candidates of DDLPS. Survival analysis was compared in five groupings as follows: Group [A], both markers of 'Set 1' were positive regardless of 'Set 2' versus the remainder; group [B], at least one of the 'Set 1' markers was positive regardless of 'Set 2' versus the remainder; group [C], all 'Set 1' and 'Set 2' markers were positive versus the remainder; group [D], both markers of 'Set 1' and at least one of the 'Set 2' marker was positive versus the remainder; and group [E], at least one of 'Set 1' marker and at least one of 'Set 2' marker were positive versus the remainder. All five groupings displayed a better overall survival in the positive groups, however, only group [D], where both markers of 'Set 1' and at least one of the 'Set 2' marker was positive, had a statistically significant difference (**Table 4**; **Figure 3**). Histologic grade and presence of metastasis were also analyzed according to IHC pattern groups but there was no statistical significance (**Table 5**).

Discussion

Lipogenic tumors are the most common soft tissue tumor while liposarcomas are the most frequent soft tissue sarcoma [8]. DDLPS can arise from atypical lipomatous tumors in the form of high grade non-lipogenic sarcoma [1]. Its incidence has been estimated to be about 4% [9]. At present, a few markers have been proven to be related to lipogenic tumors. Murine double-minute 2 (MDM2) is a well-known marker that is expressed in atypical lipomatous tumors and DDLPS [1, 10]. Fluorescent *in situ* hybridization (FISH) method using MDM2 has shown high sensitivity and specificity [11, 12]. Molecular pathologic techniques might be useful for a definite diagnosis. However, their application is not always possible [13]. In atypical lipomatous tumors and DDLPS, expression levels of HMGI-C, CDK4, and MDM2 are increased [14]. Adipocyte P2/fatty acid-binding protein 4 (aP2/FABP4) is expressed in benign lipomas, hibernomas, spindle cell/pleomorphic lipoma, atypical lipo-

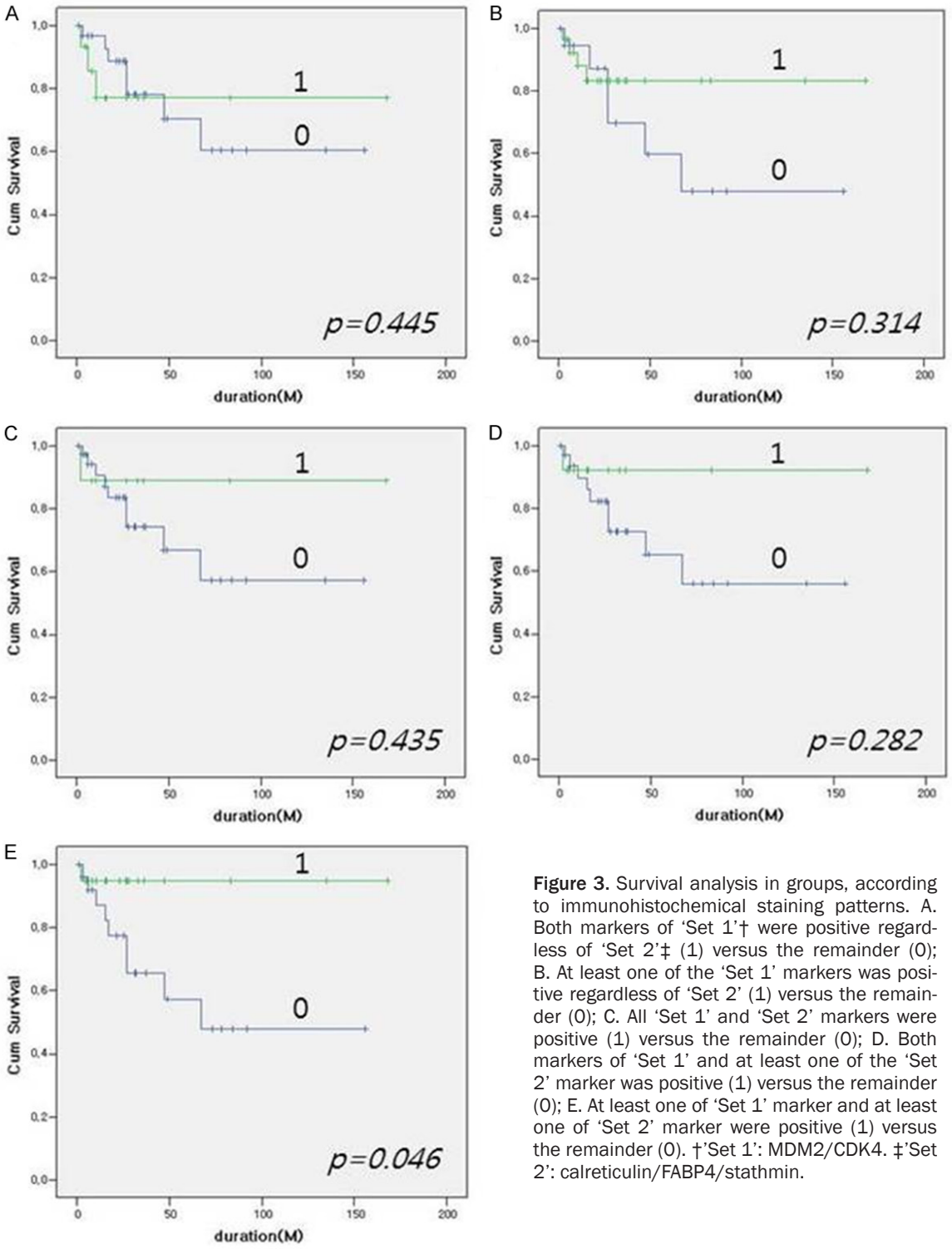

Figure 3. Survival analysis in groups, according to immunohistochemical staining patterns. A. Both markers of 'Set 1'† were positive regardless of 'Set 2'‡ (1) versus the remainder (0); B. At least one of the 'Set 1' markers was positive regardless of 'Set 2' (1) versus the remainder (0); C. All 'Set 1' and 'Set 2' markers were positive (1) versus the remainder (0); D. Both markers of 'Set 1' and at least one of the 'Set 2' marker was positive (1) versus the remainder (0); E. At least one of 'Set 1' marker and at least one of 'Set 2' marker were positive (1) versus the remainder (0). †'Set 1': MDM2/CDK4. ‡'Set 2': calreticulin/FABP4/stathmin.

matour tumors/well-differentiated liposarcomas, myxoid/round cell liposarcomas, and immature fat cells or lipoblasts are found in pleomorphic liposarcomas. Therefore, this marker may help differential diagnosis between lipogenic tumors and other soft tissue tumors [7]. Calreticulin is a Ca^{2+}-buffering protein. It is known as an inhibitor of adipocytic differentiation. This marker is not expressed in normal adipose tissue or lipomas. However, it is

Table 5. Correlation of histological grade and presence of metastasis in groups, according to IHC staining patterns

		Groupings according to immunohistochemical results									
		[A]		[B]		[C]		[D]		[E]	
		0	1	0	1	0	1	0	1	0	1
Histologic grade	2	14 (45.2)*	5 (33.3)	9 (47.4)	10 (37.0)	17 (45.9)	2 (22.2)	15 (45.5)	4 (30.8)	12 (44.4)	7 (36.8)
	3	17 (54.8)	10 (66.7)	10 (52.6)	17 (63.0)	20 (54.1)	7 (77.8)	18 (54.5)	9 (69.2)	15 (55.6)	12 (63.2)
P-value			0.533		0.552		0.270		0.510		0.763
Metastasis**	Absent (%)	26 (83.9)	13 (86.7)	15 (78.9)	24 (88.9)	31 (83.8)	8 (88.9)	28 (84.8)	11 (84.6)	23 (85.2)	16 (84.2)
	Present (%)	5 (16.1)	2 (13.3)	4 (21.1)	3 (11.1)	6 (16.2)	1 (19.6)	5 (15.2)	2 (15.4)	4 (14.8)	3 (15.8)
P-value		1.000			0.424		1.000		1.000		1.000

Group [A], both markers of 'Set 1'† were positive regardless of 'Set 2'‡ (1) versus the remainder (0); group [B], at least one of the 'Set 1' markers was positive regardless of 'Set 2' (1) versus the remainder (0); group [C], all 'Set 1' and 'Set 2' markers were positive (1) versus the remainder (0); group [D], both markers of 'Set 1' and at least one of the 'Set 2' marker was positive (1) versus the remainder (0); and group [E], at least one of 'Set 1' marker and at least one of 'Set 2' marker were positive (1) versus the remainder (0). †'Set 1': MDM2/CDK4. ‡'Set 2': calreticulin/FABP4/stathmin. *% within groupings. **Fisher's exact test.

expressed in atypical stromal cells of atypical lipomatous tumors and cells of DDLPS [5]. Stathmin (p16) is expressed in atypical lipomatous tumors and DDLPS like CDK4 and MDM2 [4]. Syndecan-1 (SDC-1/CD138) is known to be intensely expressed in DDLPS [15]. Peripheral UPS with MDM2 amplification is in fact DDLPS [16]. STAT6 is amplified in a subset of dedifferentiated liposarcomas [17]. It has been reported that all MDM2+/CDK4+/p16+ tumors are DDLPS while MDM2-/CDK4-/p16- tumors are undifferentiated sarcomas [3]. MDM2 amplification and expression is potentially very useful for distinguishing between DDLPS and other undifferentiated high-grade spindle and pleomorphic sarcomas, even though a few other sarcomas also show MDM2 amplification and expression [18]. p16 is highly sensitive for retroperitoneal DDL. However, lack of specificity limits its diagnostic utility compared to more established markers, MDM2 and CDK4 [6]. Lipogenic tumor markers CDK4 and MDM2 can be used as surrogate immunohistochemical markers for diagnosis of malignant lipomatous tumors with high sensitivity. Approximately 26% of retroperitoneal/thigh UHGPS cases have been found to be positive for PPAR-gamma, CDK4, or MDM2 by immunohistochemistry, showing characteristic CDK4 and MDM2 gene amplification. This suggests that a subset of UHGPS cases represent DDLPS despite lacking histological evidence of lipoblasts [19].

In this study, all five cases of previously diagnosed DDLPS showed positive reactions to all five MDM2, CDK4, calreticulin, FABP4, and stathmin antibodies. However, all four cases of other specific type of soft tissue sarcomas showed negative reactions to the five antibodies.

Immunohistochemical staining results for 'Set 1' and 'Set 2' displayed a strong correlation and MDM2/CDK4 positive cases showed more frequent positive results for calreticulin/FABP4/stathmin staining. This means that cases with positive reaction to the generally less verified antibodies calreticulin, FABP4, or stathmin should be regarded as candidates for DDLPS. Although definite diagnosis of DDLPS is impossible based on immunohistochemistry alone, these results allows us to detect possible candidates for DDLPS and narrow the pool for further studies, such as molecular analysis. Although 17 of the 46 US showed MDM2+/CDK4+ in this study, it is unreasonable to conclude that about 37% of US had a possibility of DDLPS, due to the limitation of sample size. Considering the somewhat nonspecific staining results, additional markers are needed. Based on results of this study, we can conclude that not only MDM2/CDK4, but also other markers such as calreticulin, FABP4, and stathmin, can be helpful in obtaining a more robust interpretation. With these markers, we can discriminate 11 (24%) cases as potential candidates of DDLPS from the 46 cases previously diagnosed as US.

DDLPS has a propensity for local recurrence whereas distant metastasis is rare. Its behavior is related to anatomic site and retroperitoneal neoplasms are known to have significantly worse prognosis [1, 20]. It has previously been described that the presence of metastasis alone can affect overall survival in high grade sarcoma [21]. DDLPS has been reported to

exhibit less aggressive clinical course than other types of high-grade pleomorphic sarcoma [1, 2]. In this study, survival analysis, based on staining pattern, showed significantly better survival in cases showing positive staining for MDM2 or CDK4 and positive for one of the other three 'Set 2' antibodies. However, histological grade, anatomic site, and presence of metastasis did not differ statistically between these DDPLS-suspicious cases and other US cases. When comparing survival according to IHC patterns, the positive groups in A, B, C, D, and E had a longer survival, however, only group E had a statistically significant difference. These findings suggest that, in addition to MDM2 or CDK4 positivity, any other positive IHC results for calreticulin, FABP4, or stathmin staining should raise the possibility of a DDPLS when making a diagnosis of high-grade sarcoma.

In summary, we can conclude that not only MDM2 and CDK4, but also other markers such as calreticulin, FABP4, and stathmin, can be helpful in obtaining a more robust interpretation of DDPLS. Based on immunohistochemical results of previously diagnosed DDLPS cases, we suggest that cases positive for at least one of 'Set 1' markers and at least one of 'Set 2' markers can be discriminated as DDLPS-suspicious. Morphologically, these cases displayed more frequent epithelioid features. When MDM2-positive or CDK4-positive cases showed any other positive IHC results for calreticulin, FABP4, or stathmin, the overall survival was significantly longer, raising the possibility of DDLPS in these cases. This allows us to detect possible candidates for DDLPS and narrow the pool for further studies such as molecular analysis for a definite diagnosis.

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Disclosure of conflict of interest

None.

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