

Liposarcoma with Meningothelial-like Whorls. Report of Four Cases Showing Diverse Histologic Findings and Behavior

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We report the clinicopathologic findings of four cases of liposarcoma with meningothelial-like whorls. Two cases occurred in the retroperitoneum and the remaining cases in the anterior mediastinum and scrotum. The whorls varied in terms of amount and morphology and the type tissue surrounding the whorls also varied in every case. One of the retroperitoneal cases with large areas of whorl coalescence recurred in the abdominal wall as an inflammatory malignant fibrous histiocytoma one year after primary resection of the tumor, and a metastasis to the cervical spines was detected twenty months later. The other retroperitoneal tumor recurred locally two years after the resection of the tumor and the amount and cellularity of the whorls as well as *p53* reactivity and Ki-67 labeling index were higher in the recurrent tumor. However, coalescence of the whorls was not present in the recurrent tumor in contrast to the primary tumor. The anterior mediastinal and scrotal cases have demonstrated neither local recurrence nor distant metastasis although the follow-up period has been less than one year. The cells comprising whorls showed positive reactions for CD10, CD56, CD99, factor XIII, and low-affinity nerve growth factor receptor in addition to vimentin and α -smooth muscle actin. Our results indicate that liposarcoma with meningothelial-like whorls is a heterogeneous group that shows wide variations in histologic findings and biologic behavior. The phenotypic transformation of the whorls to higher grade in two retroperitoneal tumors, which showed recurrence within two years of follow up, supports that a whorl is a sign of dedifferentiation. Although we demonstrate the expressions of several markers, such as CD10, CD56, CD99, factor XIII, and low-affinity nerve growth factor receptor, in

the spindle cells of the whorls for the first time, the lineage of the whorls still cannot be addressed due to the fact that these markers are lineage nonspecific.

Key Words: Liposarcoma, dedifferentiation, meningothelial-like whorls, immunohistochemistry

INTRODUCTION

Dedifferentiated liposarcoma (DDL) has been defined as a high-grade non-lipogenic sarcoma that arises in a background of well-differentiated liposarcoma (WDL). In contrast to the traditional concept that DDL is a high-grade sarcoma, which usually has morphologic features of malignant fibrous histiocytoma or high-grade fibrosarcoma, recent studies on the DDL illustrated a broad morphologic spectrum of dedifferentiation in terms of grade and type.¹⁻³ Therefore, nowadays low-grade dedifferentiation is also accepted as a pathway of dedifferentiation in WDL, and one that might have a similar prognostic meaning to high-grade dedifferentiation.^{2,3}

Recently, two papers described 26 cases of DDL showing peculiar meningothelial or neural-like whorling areas in DDL.^{4,5} Although these two papers described common characteristics of this subtype of DDL, such as a predominance in the retroperitoneum of elderly patients, there were several discrepancies particularly in the biologic behavior and in the interpretation of the nature of peculiar looking whorls. In this report, we describe the clinicopathologic findings of four additional cases of liposarcoma with meningothelial-

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like whorls to emphasize their diversity of histologic findings and biologic behavior. We performed immunohistochemical staining using antibodies not tried in the previous studies to investigate whorl lineage.

MATERIALS AND METHODS

We retrieved two cases (cases 1 and 2) of liposarcoma with meningothelial-like whorls from the archives of the Department of Pathology, Yonsei University College of Medicine. The remaining two cases were from Pundang Jesaeng General Hospital (case 3) and MizMedi Hospital (case 4). Histological sections were evaluated for all cases based on hematoxylin and eosin (H&E) staining; the section numbers taken varied from six to twelve per case.

Immunohistochemical stains were performed on paraffin-embedded tissue sections using an EnVision kit (Dako, Carpinteria, CA, USA). The primary antibodies, their dilutions, sources and pre-treatments are listed in Table 1. Clinical history and follow-up were obtained from medical records.

RESULTS

Clinical and gross features

A summary of the clinical findings is presented in Table 2. The ages of the patients ranged from 35 to 53 years (mean, 45 years). All patients were male. The primary tumors were situated in the anterior mediastinum (case 1), retroperitoneum (case 2 and 3), and scrotal area (case 4). The case histories and gross features of the tumors follow.

Case 1

A 45-year-old otherwise healthy man presented with dyspnea which started 3 months previously. An anterior mediastinal mass was detected by chest X-ray and CAT scan and the mass was excised. The excised specimen measured $16 \times 8 \times 6$ cm and was mainly comprised of fat tissue with a $5 \times 5 \times 4$ cm sized white-gray, rubbery nodule.

Case 2

A 47-year-old man complaining of vague abdominal pain was noted to have a huge retroperitoneal mass by abdominal CAT scan. The mass ($9 \times 7 \times 5$ cm) was excised and found to be a relatively well-demarcated rubbery trabeculated slightly myxoid tissue speckled with areas of a more yellowish tissue. Part of the external surface of the mass was covered by a small amount of fat. Follow up demonstrated a recurrent retroperitoneal tumor 2 years after the primary surgery and resection of the recurrent mass was performed. The specimen from the recurrent mass was composed of four fragments of tissue, $6 \times 5 \times 3$ cm in aggregation. Its cut surface was similar to that of the first specimen.

Case 3

A 53-year-old otherwise healthy man presented with a recently developed vague abdominal pain. Abdominal CAT scan demonstrated a poorly demarcated mass measuring 15 cm in greatest dimension. The mass was excised with attached right kidney, duodenum, pancreas, gallbladder, right colon and appendix. Grossly, the tumor was solid and friable with areas of necrosis and was of a friable yellow to gray appearance with discrete intratumoral calcified nodules. No further treatment was done. An abdominal wall mass measuring $9 \times 7 \times 3.5$ cm was noted 1 year later and it was excised. Twenty months after the second operation, the patient complained of neck pain and CAT scan revealed a destructive mass lesion involving the C7 and C8 vertebrae. Curettage and anterior fusion were performed.

Case 4

A 35-year-old otherwise healthy man presented with a right scrotal mass. Under the impression of lipoma, the mass was excised. The lipoma-like well demarcated mass was attached to the spermatic cord and measured 3.0 cm in greatest dimension. The cut surface was yellow with scattered grayish-white tiny nodules.

Histologic features

A summary of the histologic features is presented in Table 3.

Table 1. List of Primary Antibodies Used in This Study and Their Dilutions, Sources and Pre-treatment Methods

Antibody	Dilution	Source	Pre-treatment
Alpha-smooth muscle actin	1 : 50	Dako Carpinteria, CA, USA	None
CD10	1 : 30	Dako	Microwave
CD21	1 : 20	Dako	Trypsin
CD31 (JC/70)	1 : 30	Dako	Microwave
CD34	1 : 30	Becton Dickinson San Jose, CA, USA	Microwave
CD35	1 : 25	Dako	Trypsin
CD56	1 : 50	Novocastra Laboratories Ltd. Newcastle upon Tyne, UK	Microwave
CD57 (Leu-7)	1 : 30	Becton Dickinson	None
CD68 (PGM1)	1 : 50	Dako	Microwave
CD99		Dako	
c-kit		Dako	
Cytokeratin AE1/AE3	1 : 50	Dako	Trypsin
Desmin	1 : 100	Dako	Microwave
E-cadherin		Novocastra Laboratories Ltd.	Microwave
EMA	1 : 30	Dako	Microwave
Factor 13	1 : 50	BioGenex San Ramon, CA, USA	None
Low-affinity nerve growth factor receptor	1 : 50	Dako	Microwave
Muscle specific actin (HHF35)	1 : 100	Dako	None
S100 protein	1 : 500	Dako	None
Vimentin	1 : 100	Dako	Microwave
p53	1 : 50	Novocastra Laboratories Ltd.	Microwave
Ki-67	1 : 50	Novocastra Laboratories Ltd.	Microwave

Table 2. Clinical Features of 4 Cases of Liposarcoma with Meningothelial-like Whorls

Case	Age/ Sex	Primary site	Size of primary tumor (cm)	Treatment	Local recurrence (interval)	Metastasis (interval)	Patient status
1	45/M	Anterior mediastinum	16 × 8 × 6	Surgery	No		NED
2	47/M	Retroperitoneum	9 × 7 × 5	Surgery	Retroperitoneum (24 months)		NED
3	53/M	Retroperitoneum	15 × 12 × 7	Surgery	Rectus muscle (12 months)	Cervical spine (32 months)	AWD
4	35/M	Scrotal area	3 × 3 × 2.5	Surgery	No		NED

NED, no evidence of disease; AWD, alive with disease.

All primary tumors of these four cases had well differentiated liposarcoma (WDL) components of either the lipoma-like or sclerosing type. However, the amount of WDL varied greatly in the primary tumors of cases 1 and 2, and a recurrent tumor of case 2 had focal WDL components. The whorls formed a discrete mass well demarcated from the remainder in two cases (cases 1 and 2) while the other two cases (cases 3 and 4) demonstrated intermingling of whorls with WDL. The whorls occupied about from 5% to 60% of the total tumor volume and a conglomeration of the whorls was observed in all primary tumors, except case 4, while the recurrent tumor of case 2 showed no coalescence of the whorls. In the primary tumor of case 3, large areas of conglomeration of the whorls forming a solid mass with a histologic finding of low-grade spindle cell dedifferentiated liposarcoma was noted while the remaining cases demonstrated only focal areas of whorl coalescence. The whorls were composed of epithelioid or spindle-shaped cells and their cellularity varied even in the same case. The whorls in case 1 were predominantly composed of epithelioid cells (Fig. 1), whereas the whorls of the remaining cases were comprised of spindle cells (Fig. 2, 3, and 4). In case 1, thick walled blood vessels were present in the center of every whorl (Fig. 1). The type of tissue surrounding the whorls also varied in each case, as follows: loose connective tissue with many mast cells and lymphocytes

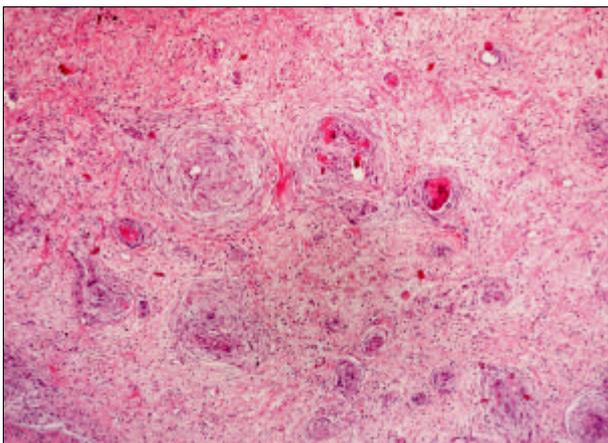


Fig. 1. The whorls in case 1, showing a prominent vessel in the center, a concentric cuff of epithelioid cells around the vessel and metaplastic bone formation. The whorl is surrounded by loose connective tissue with lymphocyte and mast cell infiltrates.

in case 1 (Fig. 1); collagenized fibrous tissue in case 2 (Fig. 2); collagenized fibrous tissue and WDL in case 3 (Fig. 3); WDL in case 4 (Fig. 4). Metaplastic bone formation within the whorls was prominent only in case 1 (Fig. 1) and metaplastic bones around the whorls were observed in the primary tumor of case 3 and in the recurrent tumor of case 2. Cuffing of lymphocytes around the whorls was noted in case 4 (Fig. 4). All the remaining cases demonstrated scattered lymphocytes without topographic relationship to the whorls. Many mast cells were also present in the loose connective tissue surrounding the whorls in case 1 (Fig. 1).

The primary and recurrent tumors of case 2 showed the same low-power pattern but the whorls became slightly more abundant, cellular and compact in the recurrent lesion (Fig. 2).

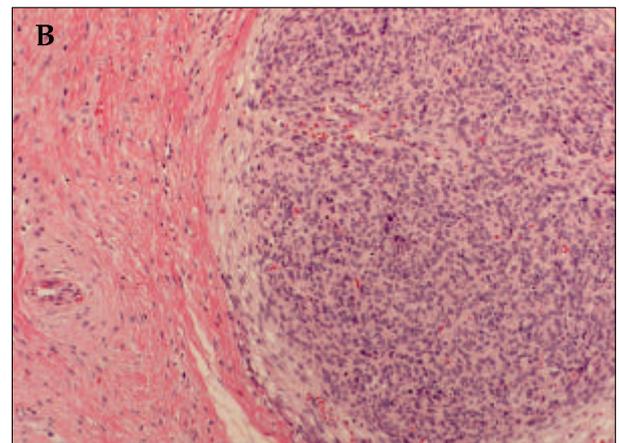
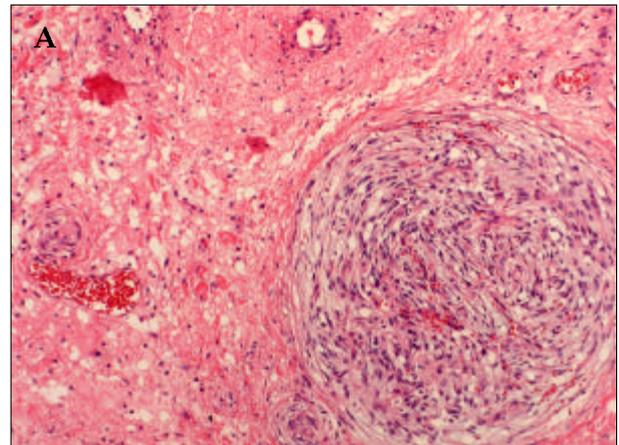


Fig. 2. The whorls in the primary (A) and recurrent lesion (B) of case 2, showing that the whorls of the recurrent lesion are more cellular and compact than the primary lesion. The whorls are surrounded by dense collagenized fibrous tissue.

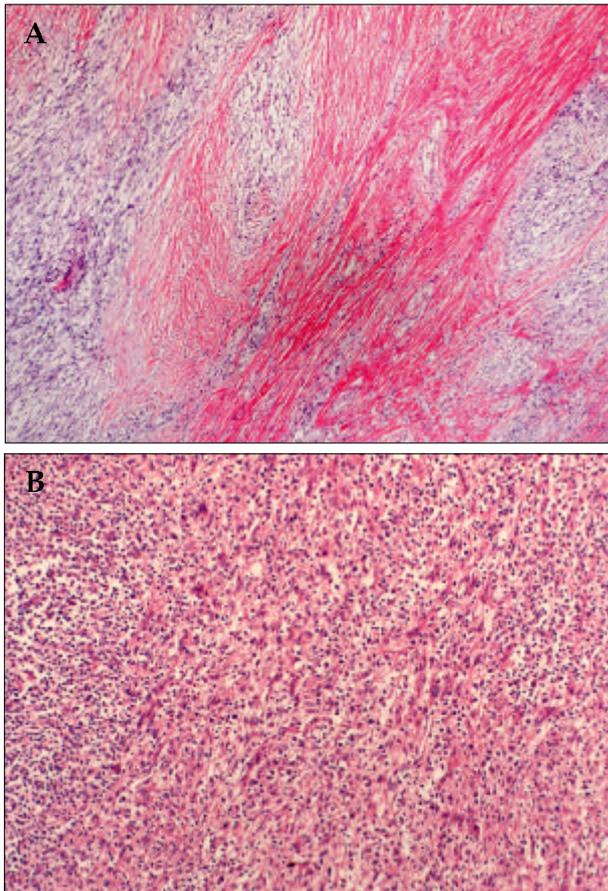


Fig. 3. The whorls and coalescence of the whorls forming solid growth of spindle cells in the primary tumor (A) of case 3. The abdominal wall recurrence (B) showing scattered plump pleomorphic tumor cells admixed with lymphohistiocytes.

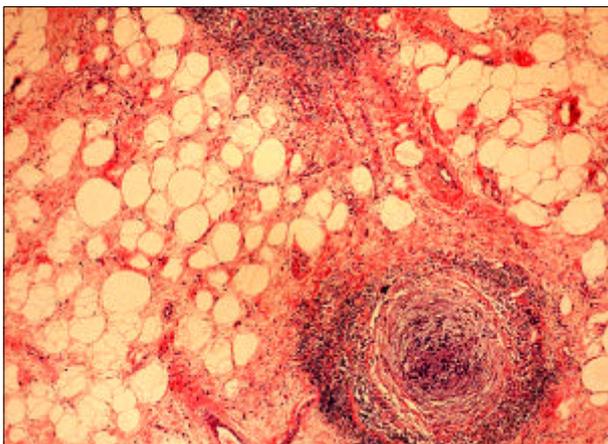


Fig. 4. The whorls in case 4, showing a concentric arrangement of spindle cells surrounded by well-differentiated liposarcoma. Cuffing of lymphocytes around the whorl is present.

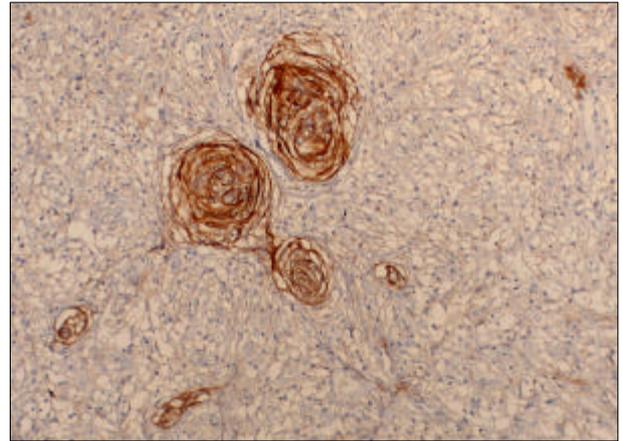


Fig. 5. The whorls in case 1 showing CD10 immunoreactivity.

However, coalescence of the whorls was not observed in the recurrent lesion. The recurrent tumor in the abdominal wall rectus muscle and metastatic tumor to cervical spines in case 3 were inflammatory malignant fibrous histiocytoma (MFH) (Fig. 3). No areas of liposarcoma including the whorls were present.

Immunohistochemical Features

The whorls showed positive reactions for vimentin, alpha-smooth muscle actin, CD10 (Fig. 5), CD56, CD99, factor XIII and low-affinity nerve growth factor receptor. All other markers, including CD21, CD31, CD34, CD35, CD57, CD68, c-kit, Cytokeratin AE1/AE3, desmin, E-cadherin, EMA, muscle specific actin, and S100 protein were not expressed in the whorls. P53 stain revealed no positive reaction in the whorls of all primary tumors but the whorls in the recurrent retroperitoneal tumor (case 2) demonstrated labeling some of the nuclei (Fig. 6). The Ki-67 labeling indices (case 2: 7%; case 3: 4%) of all primary tumors were low but the whorls in the recurrent tumors had higher Ki-67 labeling indices (case 2: 14%; case 3: 6%) than those of the primary tumors (Fig. 7).

DISCUSSION

In this report, we describe the histopathologic

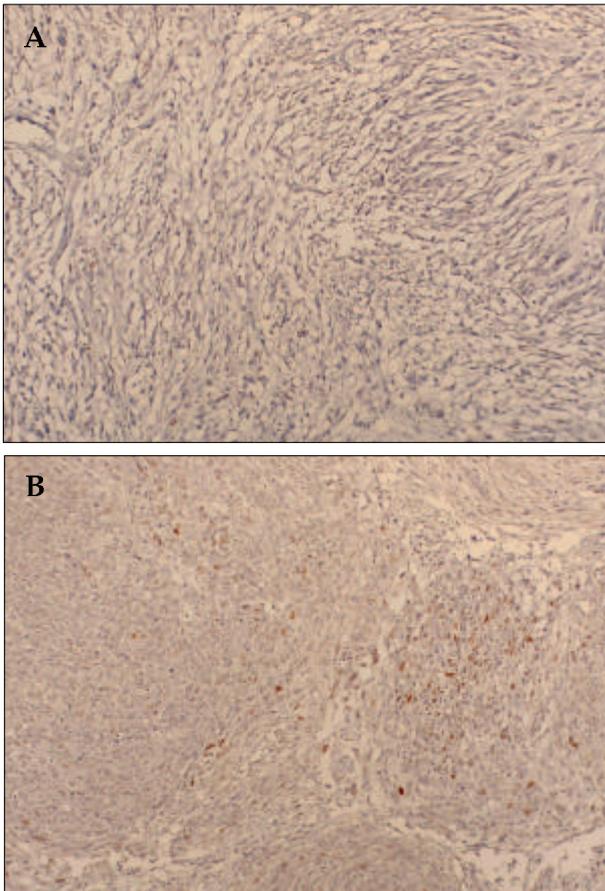


Fig. 6. The whorls in the primary (A) and recurrent lesion (B) of case 2, showing p53 nuclear labeling only in the recurrent tumor.

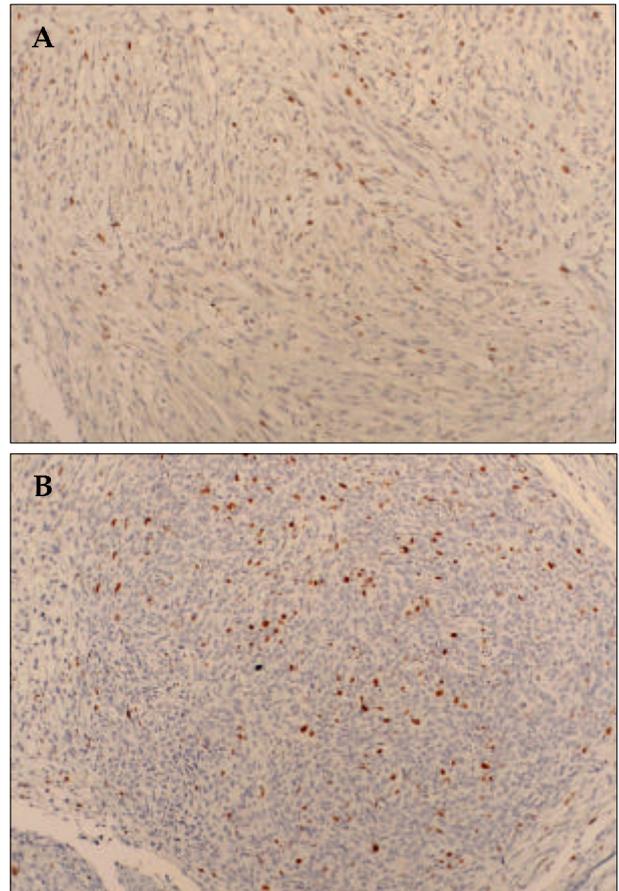


Fig. 7. The whorls in the primary (A) and recurrent lesion (B) of case 2, showing increased Ki-67 nuclear labeling index (7% → 14%) of the recurrent tumor.

findings and immunophenotypic profiles of four cases of liposarcoma with areas of meningothelial-like whorls. The presence of meningothelial-like whorls in DDL was briefly mentioned in two reports that the described clinicopathologic findings of DDLs.^{2,6} Subsequently, two separate articles drew our attention by describing 26 cases of DDL with meningothelial-like whorl as a distinct subgroup of DDL.^{4,5} According to the report by McCormick, et al.⁶ meningothelial-like whorls were noted in 3 of 32 cases of DDL and Hasegawa, et al.⁷ also described 2 cases of DDL with meningothelial-like whorls among 32 cases of the DDL of retroperitoneum and mesentery. So the actual incidence of this peculiar histologic subtype of DDL seems to be relatively high. This tumor demonstrates a predilection for the retroperitoneum of elderly patients as DDL and our 4 cases

also showed this tendency.

In addition to the peculiar meningothelial-like whorls, this entity is frequently accompanied by metaplastic bones and infiltrates of lymphocytes unlike DDL.^{4,5} However, there are wide variations in the histologic findings and grade in this peculiar group of liposarcoma. The nine cases reported by Nascimento, et al.⁴ were mostly low-grade, whereas varying histologic grade was reported by Fanburg-Smith, et al. in 17 cases.⁵ Our four cases also demonstrated a wide variation in the histologic findings (Table 3). The area occupied by the whorls formed a discrete mass demarcated from WDL in two cases (cases 1 and 2) and the whorls were scattered in the liposarcoma components without forming discrete mass lesions in the other two cases (cases 3 and 4). Only one of our cases that occurred in the retroperitoneum (case 3)

Table 3. Summary of Histologic Features of 4 Cases of Liposarcoma with Meningothelial-like Whorls

Case	Whorls				Components surrounding whorls	Metaplastic bones	Lymphocytes	WDL
	Amount	Cell type	Atypism	Coalescence				
Case 1	20%	Epithelioid	No	Focal	Loose connective tissue	Prominent Within whorl	Prominent No close topographic relationship to the whorls	Scanty Lipoma-like WDL
Case 2 Primary Lesion	30%	Spindle	Mild	Focal	Loose connective tissue	No	Minimal No close topographic relationship to the whorls	Scanty Lipoma-like WDL
Case 2 Recurrent Lesion	50%	Spindle	Moderate	No	Collagenized connective tissue	Focal Around the whorls	No	Scanty Lipoma-like WDL
Case 3 Primary Lesion	60%	Spindle	Moderate	Extensive	Collagenized connective tissue and WDL	Focal Around the whorls	Minimal No close topographic relationship to the whorls	WDL Sclerosing
Case 4	5%	Spindle	Mild	No	WDL	No	Prominent Around whorls	WDL Lipoma-like

showed large areas of low-grade DDL by coalescence of the whorls; coalescence of the whorls was not prominent in the remaining 3 cases. The morphologic findings of the whorls varied even in the same case. The whorls composed of epithelioid cells with metaplastic bones were present only in anterior mediastinal tumor (case 1). In this case, prominent thick-walled vessels were characteristically present in the center of every whorl. Slightly atypical spindle cells without metaplastic bones comprised the whorls in the remaining three cases. The histologic findings our 4 cases concur with the findings of Fanburg-Smith, et al.,⁵ with respect to the wide variation in histologic appearance and grade.

Fanburg-Smith, et al.⁵ suggested that the whorls may represent an early sign of liposarcoma dedifferentiation based on the significant proliferative activity, p53 reactivity and tendency to coalesce and associate with dedifferentiated liposarcoma. Nascimento, et al.⁴ tentatively suggested that liposarcoma with meningothelial-like whorls is a variant DDL due to the high cellularity associated

with the presence of the whorled zones. In our material, the retroperitoneal tumor (case 3) had large areas of conglomeration of the whorls with moderate atypia that corresponded to the histologic findings of low-grade DDL. The remaining three cases had only focal areas of whorl coalescence. However, the significant proliferative activity, as determined by the Ki-67 labeling index and p53 reactivity in the whorls, even in areas of coalescence was not observed in any whorls of the primary tumors. Only the recurrent tumor of case 2 demonstrated an apparently increased Ki-67 labeling index and p53 reactivity of the whorls. In this case, the whorls became more abundant, more cellular and thus more compact in the recurrent tumor than in the primary tumor and cells comprising the whorls were slightly more atypical than those of the primary tumor. However, the recurrent tumor of case 2 demonstrated no whorl coalescence, in contrast to the primary tumor. Therefore, case 2 illustrates the gradual transformation of the whorls into a more malignant phenotype in the recurrent tumor and coalescence of the whorls seems not to be a necessary step of

dedifferentiation.

A marked difference exists in the biologic behavior of DDL with meningothelial whorls within the two reports by Nascimento, et al.⁴ and by Fanburg-Smith, et al.⁵ The nine cases reported by Nascimento, et al.⁴ were mostly low-grade and pursued a less aggressive clinical course showing a high recurrence rate but no metastasis, whereas a significant proportion of the 17 cases reported by Fanburg-Smith, et al.⁵ demonstrated a grave clinical course. An analysis of the data summarized in Table 3 by Fanburg-Smith, et al.⁵ showed that at least nine cases in their series were high-grade DDLs with areas of MFH-like dedifferentiation. This difference in histologic grade explains the apparent difference in the biologic behavior of the tumors in these the two reports. There were no cases of high-grade DDL in our series and only two retroperitoneal tumors recurred. One of these (case 2) recurred two years after the resection of the primary tumor and the other (case 3) demonstrated a local recurrence in the abdominal wall 1 year after the primary resection of the tumor and a distant metastasis to the cervical spines 32 months after the first surgery. The remaining cases in our series presenting as an anterior mediastinal and a scrotal mass demonstrated neither recurrence nor metastasis although the follow-up has been less than 1 year. So the biologic behavior of the two retroperitoneal cases matches well the known grave prognosis of retroperitoneal liposarcomas in general.^{3,6-8} This tendency was also verified in the report by Nascimento, et al.,⁴ where four of six cases of retroperitoneal DDL with a follow-up of more than two years recurred. In our study, a retroperitoneal tumor that contained a large areas of whorl coalescence (case 3) transformed into inflammatory MFH one year after the primary surgery and metastasis developed 32 months after the primary surgery. So the grave outcome of this retroperitoneal tumor with large areas of whorl conglomeration and the gradual transformation of whorls into a more malignant phenotype, as observed in the recurrent tumor of case 2, support the suggestion that the whorl is an early sign of dedifferentiation. However, long-term evaluation of a large number of cases is needed to understand precisely the impact of the whorls on the biologic behavior of liposarcoma.

In this study, we performed immunohistochemical staining using antibodies not tried in previous studies to investigate the lineage of whorls. Nascimento, et al.⁴ suggested a follicular dendritic cell lineage based on light microscopic and ultrastructural findings, although they could not confirm their suggestion because follicular dendritic cell markers were not expressed in the whorls. Fanburg-Smith, et al.⁵ concluded that the whorls represented a mesenchymal proliferation which might undergo diverse differentiations. Our study also failed to demonstrate the expression of follicular dendritic cell markers in the whorls. We did observe a characteristic perivascular concentric proliferation of epithelioid cells in the whorls of case 1, which suggests a pericytic nature. However, this impressive histologic finding was not present in the remaining cases. No case expressed E-cadherins as well as cytokeratin and epithelial membrane antigen, though vimentin and alpha-smooth muscle actin were expressed in the whorls of all of our 4 cases. In contrast to the previous report by Nascimento, et al.,⁴ the whorls in our 4 cases did not express CD57, but CD56 and low-affinity nerve growth factor receptor were expressed in the whorls of all cases. In addition, we demonstrated the expression of CD10, CD99, and factor XIII factor receptor in the whorls. However all these markers are non-lineage specific markers expressed in various type of mesenchymal neoplasms,⁹⁻¹² and therefore we were unable to reach a conclusion on the nature of the whorls.

In summary, our results indicate that liposarcoma with meningothelial-like whorls is a morphologic variant of liposarcoma that shows wide variations in histologic findings and biologic behavior. The analysis of histologic transformation of our two retroperitoneal tumors, showing recurrences, indicates that the whorl is actively involved in the process of dedifferentiation and supports the suggestion that the whorl is an early sign of dedifferentiation. Although we demonstrate the expression of several markers, such as CD10, factor XIII, and CD56, in the spindle cells of the whorls for the first time, the lineage of the whorls cannot be addressed because these markers are lineage nonspecific.

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