D-dimer Levels in the Differential Diagnosis Between Lipoma and Well-differentiated Liposarcoma

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Abstract. *Background: Lipoma and well-differentiated liposarcoma (WDLS) are two representative lipogenic soft tissue tumors that have similar clinical, radiological, and pathological characteristics. Accordingly, it is difficult to distinguish these tumors preoperatively. Plasma D-dimer levels are associated with the status of tumor progression, and we hypothesized that D-dimer levels could contribute to differential diagnosis. The D-dimer levels of these two entities have not yet been reported. Patients and Methods: We investigated 43 cases of lipoma and 14 cases of WDLS. We evaluated the utility of D-dimer levels and other clinicopathological factors for preoperative differential diagnosis between the two entities. Results: Receiver operating characteristic analysis revealed that the D-dimer level may contribute to differential diagnosis (area under the curve=0.73). Univariate and multivariate models demonstrated that plasma D-dimer levels (p=0.001 (univariate), and p=0.006 (multivariate)) and lower extremity location (p=0.006 (univariate), and p=0.03 (multivariate)) were independent risk factors for WDLS. Conclusion: The D-dimer level may be a helpful marker for preoperative differential diagnosis between lipoma and WDLS.*

Hypercoagulopathy is induced by several physiological and pathological conditions, including trauma, cardiovascular events, and surgery. Notably, a close association between the presence of a malignant tumor and hemostasis activation has been reported previously. Direct and indirect evidence suggest the involvement of pro-coagulant molecular mechanisms in malignancy, including the up-regulation of tissue factor expression (1, 2), the activation of the fibrinolytic pathway by up-regulated expression of fibrinolytic molecules (3, 4), and the secretion of various pro-inflammatory or pro-angiogenic cytokines, such as tumor necrosis factor-alpha, interleukin-1 beta, or vascular endothelial growth factor (VEGF) (5-7).

Plasma D-dimer, which is a degradation product of fibrinolysis, has been used in clinical practice to screen for venous thromboembolism. It is considered to be a marker of hypercoagulopathy. Because of the close relationship between malignancy and hypercoagulopathy, plasma D-dimer has also been considered as a marker for tumor progression. For example, plasma D-dimer was associated with tumor stage, the effectiveness of chemotherapy, and oncological outcomes (including prognosis) (8, 9). Indeed, we have previously established the close association of plasma D-dimer levels with malignancy and prognosis for malignant bone and soft tissue tumors. Particularly, preoperative and postoperative D-dimer levels were significantly higher in malignant musculoskeletal tumors than they were in benign musculoskeletal tumors (10). In addition, elevated D-dimer levels indicated poorer prognoses for patients with malignant musculoskeletal tumors (11).

Liposarcoma, one of the most frequent soft tissue sarcomas, has several subtypes: well-differentiated liposarcoma (WDLS), dedifferentiated liposarcoma, myxoid/round cell liposarcoma, and pleomorphic liposarcoma. Of these subtypes, WDLS is considered to have the best prognosis. Although cases of WDLS frequently include local recurrence (especially as a consequence of inadequate resection), the incidence of metastasis is quite low. The most important concern in cases of WDLS is the potential for dedifferentiation. WDLS presents clinical and radiological characteristics that resemble those of lipoma, which is a benign counterpart of liposarcoma. Accordingly, it is difficult to differentially diagnose the two entities based on clinical and radiological findings (12-15).

We hypothesized that the preoperative D-dimer level could be an indicator of the malignancy of lipogenic tumors. In this study, we sought to confirm the utility of preoperative D-dimer levels for preoperative differential diagnosis between lipoma and WDLS.

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Patients and Methods

We designed a retrospective uncontrolled study that employed data from medical records. We examined the records of a total of 89 patients who were pathologically diagnosed with lipoma, atypical lipomatous tumor, or well-differentiated liposarcoma and were treated between 2007 and 2012 at our Institution. Pathological diagnosis was based on the WHO classification system (16). Patients were excluded if any of the following were identified at the time of presentation: pre-existing hypercoagulopathy; recent anti-coagulant therapy, including prophylaxis of thromboembolic complications; recent trauma; inflammatory diseases; or another major surgery that recently performed. Patients with tumors less than 80 mm in diameter were also excluded, because this was the minimum size of WDLS in the present series. As a result, 32 cases were excluded. Finally, 43 cases of lipoma and 14 cases of WDLS were enrolled. There were 27 male patents and 30 female patients, with a mean age of 57 years.

The following risk factors were included in the present study: age, sex, anatomic site (lower extremity *vs*. trunk/upper extremity), tumor location (subcutaneous *vs*. deep), tumor diameter, D-dimer levels on referral, and magnetic resonance imaging (MRI) findings (including septation, nodule, and fat contrast). We selected these potentially independent variables based on previous reports of differential diagnosis between lipoma and WDLS (12-15, 17). The MRI protocols included a variety of sequences in the sagittal, coronal, and axial planes using T1-weighted spin-echo, T2-weighted fast spin-echo with fat suppression, and short tau inversion recovery sequences. Because patients were referred from a number of hospitals, which had different imaging protocols, contrast enhancement was not used for the majority of patients in this study, and was not evaluated in our analysis. Cases involving septal thickening to greater than 1 mm or an increase in the number of septations compared with adjacent fat were recorded as having septation (13) (Figure 1). Nodule findings were defined as the presence of single or multiple areas of non-fatty nodules of material within the lesion (13) (Figure 2). With respect to fat contents, the classification "solid/amorphous" was assigned to lesions that had amorphous, non-fatty areas within the lipomatous tumor, or even faint areas of hyperintensity on fluid-sensitive sequences (Figure 3). Otherwise, the lesions were classified as "completely fatty" (12). MR images were reviewed by a . radiologist and two orthopedic oncologists who were experienced with bone and soft tissue tumor MRI. Reviews were conducted without knowledge of the patient's history or the final pathological diagnosis. The images were viewed concurrently. If a unanimous consensus was not achieved, the final decision was based on the result that was shared by two reviewers.

Plasma D-dimer levels were assessed before performing any intervention for the tumor, including chemotherapy, radiotherapy, open biopsy, or tumor resection. To measure D-dimer levels, a latex agglutination assay (STA Liatest® D-Di; Roche Diagnostics AG, Rotkreuz, Switzerland) was performed on a STA-R® coagulation analyzer (Diagnostica Stago, Inc. New Jersey, USA) (10, 11). Based on the sensitivity of this assay, levels <0.20 μg/ml were treated as 0.20 μg/ml.

Receiver operating characteristic (ROC) curves were plotted to establish cut-off values for age, diameter, and D-dimer levels. To select risk factors, Fisher's exact test and logistic regression model were used for univariate and multivariate analyses, respectively. Statistical analyses were performed with JMP (version 8; SAS institute Inc., Cary, NC, USA).

The study was approved by the Institutional Review Board of the Authors' Institution (authorization number 471).

Results

Firstly, we plotted ROC curves to establish cut-off values for the continuous variables (Table I). The areas under the curves for age, diameter, and D-dimer levels were 0.61, 0.66, and 0.73, respectively. The greater area under the curve for D-dimer level shows its relatively greater usefulness for distinguishing between lipoma and WDLS, compared to age and diameter (Figure 4).

Secondly, we analyzed the between-group differences for each risk factor to identify the factors that were most significant for differential diagnosis between lipoma and WDLS. In univariate analyses, a D-dimer level more than 0.35 μg/ml (p=0.001), location in the lower extremity (p=0.006), the presence of thick septation on MRI (p=0.02), and the presence of nodule findings on MRI (p=0.03) were significant risks factors for the diagnosis of WDLS (Table II).

Finally, all these significant factors were entered into a multivariate model. Among the factors, D-dimer level (p=0.006) and lower extremity location (p=0.03) were thereby demonstrated to be independent risk factors for the diagnosis of WDLS (Table III).

Discussion

Large and well-differentiated lipogenic tumors (*i.e*. giant lipoma and WDLS) are among the most difficult entities for differential diagnoses based on clinical, radiological, and pathological findings. Indeed, the two entities sometimes have similar clinical courses, and MRI and histological findings. The prospect of preoperative differential diagnosis without pathological data has been especially controversial.

To date, several modalities have been considered for preoperative differential diagnosis between lipoma and WDLS. In general, the clinical characteristics that are associated with WDLS include large tumor size, acute progression, deep location, location in a lower extremity, and presentation in elderly patients (12, 14-16). However, none of these characteristics is specific, and each of them is controversial. Indeed, there was no case of WDLS less than 80 mm in diameter in the present study.

Similarly, several MRI and other radiological findings have been investigated as possible contributors to the differential diagnosis between giant lipoma and WDLS. On T1- and T2-weighted MRI of WDLS, non-fatty tumor components are often isointense to low-intensity components, such as thick septa (Figure 1), nodules (Figure 2), and other heterogeneous components (Figure 3). Such isointensity may result from elevated proportions of non-adipose tissue, including fat necrosis, fibrosis, hyperchromatic stromal cells, and fibrous septa (16).

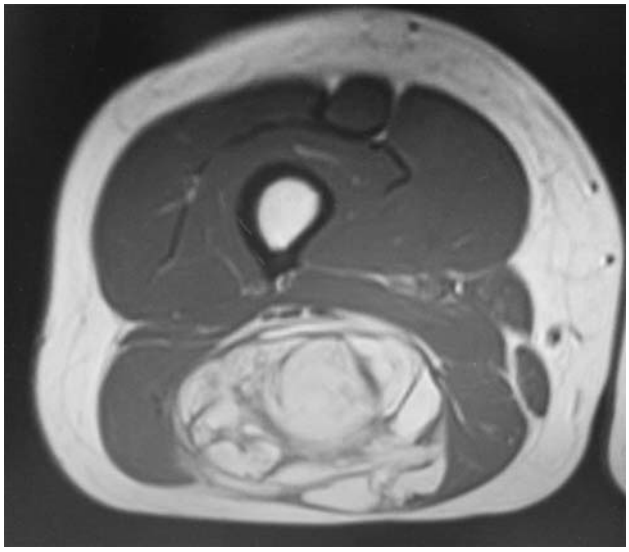

Figure 1. *Example of septation. The image presents a palpable mass in the posterior thigh of a 54-year-old female patient who was diagnosed with well-differentiated liposarcoma. The formation of multiple septa was detected in the T1-weighted image.*

Table I. *Results of receiver operating characteristic curve analyses of the continuous variables.*

	Cut-off	AUC	Sensitivity	Specificity
Age, years	60	0.61	92.7	50
Tumor diameter, mm	122	0.66	57.1	72.1
D-Dimer levels, μg/ml	0.35	0.73	78.6	69.8

AUC: Area under the curve.

It has also been reported that the presence of a thick septum in a homogeneous lipogenic tumor (as identified by MRI) is a useful clue for differential diagnosis between the two entities. Indeed, septa are a universal finding in both lipoma and WDLS. Several studies have reported that septa thicker than 2 mm are significant indicators of WDLS (17), although this conclusion is controversial (12). A second clue that may indicate WDLS is nodule formation, which is defined as single or multiple areas of non-fatty nodules of material within the lesion. Some studies have reported that nodule formation is useful for differential diagnosis (13, 17). Nodule size is also reported to be useful for differential diagnosis, but this conclusion is controversial. Brisson *et al*. reported that the presence of a nodule larger than 1 cm in diameter is useful for differential diagnosis, while the presence of a nodule itself is not significant (12).

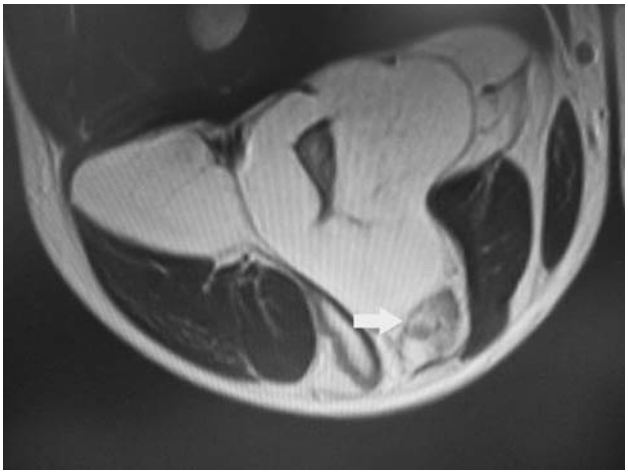

Figure 2. *Example of a nodule. The image presents a case of lipoma in the thigh of a 48-year-old male patient. A non-fatty nodule was detected in the T1-weighted image (white arrow).*

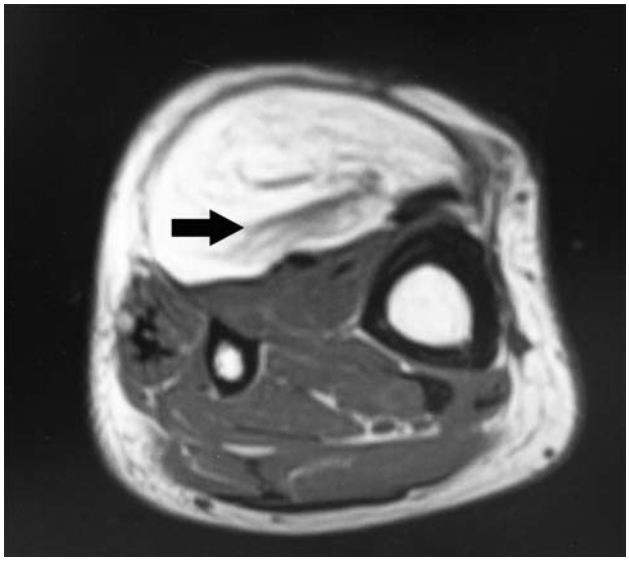

Figure 3. *Example of amorphous, non-fatty areas within the lipomatous tumor. The image presents a case of lipoma in the lower leg of a 67-year-old female patient. The amorphous, non-fatty areas were detected in the T1-weighted image (black arrow).*

Heterogeneity in homogeneous lipogenic components can be summarized as solid, amorphous, non-fatty areas (12), or hyper-intensity in fluid-sensitive MRI sequences (13). It appears that such heterogeneity indicates loss of fat tissue homogeneity, and can suggest WDLS. In some reports, this heterogeneity is described as being useful for differential diagnosis. However, it should be remembered that 28%-31%

Table II. *Characteristics of the cases, according to tumor subtype.*

Variables		Lipoma	WDLS	*p*-Value
Age, years	More than 60	29	7	0.34
	Less than 60	14	7	
Site	Trunk/upper extremity	34	5	0.006
	Lower extremity	9	9	
Location	Deep	28	12	0.19
	Subcutaneous	15	2	
Diameter	More than 122 mm	12	8	0.06
	Less than 122 mm	31	6	
D-Dimer level	More than 0.35 μg/ml	12	11	0.001
	Less than 0.35 μg/ml	31	3	
Septation	Thick	12	9	0.02
	Thin or absence	31	5	
Nodule	Absence	28	4	0.03
	Presence	15	10	
Fat contrast	Solid/amorphous	20	11	0.06
	Completely fatty	23	3	

WDLS: Well-differentiated liposarcoma.

Table III. *Multiple logistic regression model for differential diagnosis*

Variables	Odds ratio	95% Confidence interval	*p*-Value
D-Dimer			
Less than 0.35 μg/ml	Reference		
More than 0.35 μg/ml	3.08	1.45-7.68	0.006
Site			
Trunk/upper extremity	Reference		
Lower extremity	2.32	1.11-5.30	0.03

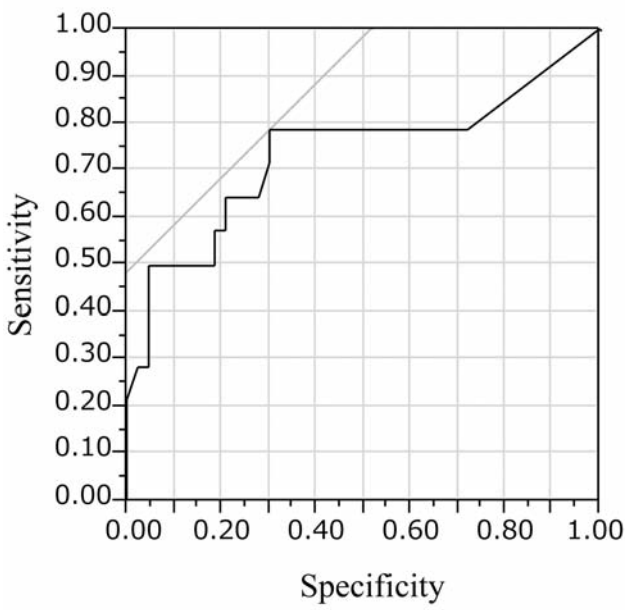

Figure 4. *Receiver operator characteristic curves of preoperative D-dimer levels for differential diagnosis between lipoma and well-differentiated liposarcoma. The area under the curve was 0.73, showing its usefulness for diagnosis.*

of cases of soft tissue lipomas have more complex appearances, including significant non-adipose elements, thick septa on CT and MRI, and nodular or globular regions of non-adipose tissue on CT and MRI (14).

In light of these findings, MRI may offer several clues for differential diagnosis, but there is no stand-alone modality that is sufficient for differential diagnosis. In contrast with clinical findings, such as age and tumor size, MRI findings can be biased by the investigators' skills and experience. Accordingly, the involvement of investigators with different levels of skill and experience may explain discrepancies in previous results on the value of MRI findings for differential diagnosis. In the present study, radiological factors (such as nodule formation and septation) were significant predictors in univariate analysis, but were not observed to be independent risk factors in multivariate analyses.

In this study, we have demonstrated the usefulness of D-dimer levels for the differential diagnosis between lipoma and WDLS. ROC analysis revealed that the D-dimer level was a more reliable indicator of the tumor type than other candidate factors, including age and tumor diameter. Indeed, it is easy to find reports that describe close relationships between D-dimer levels and tumor malignancy, progression, or prognosis for many different kinds of malignant tumors (8, 9). However, differences between the properties of soft tissue tumors and other malignancies should be considered carefully. In contrast to other malignancies, soft tissue tumors have a wide variety of sizes, sites, and progression rates. Production of D-dimer is directly associated with changes in the coagulation status, and location in a lower extremity, proximity to vessels, large size, and acute progression lead to hypercoagulopathy. Therefore, these characteristics would have greater effects on D-dimer levels than on enzymatic or chemical factors, including the activation of fibrinolysis, plasminogen production, and tissue factor production that are seen in other malignancies. Considering that the incidence of venous thromboembolism is higher in the lower leg than in the upper extremity, at least some of the up-regulation of D-dimer may simply result from weight effects, particularly through the compression and location effects that are dominant in the lower extremities. To clarify this hypothesis, future studies should analyze local conditions in the tumor specimen, such as the plasminogen activation system and expression levels of tissue factor in lipogenic tumors.

The elevated incidence of WDLS among elderly patients presents an additional bias in our analysis because D-dimer levels are generally elevated in elderly people (10). Indeed, the results of previous investigations and the present study suggest that there is a close relationship between the risk of WDLS and age (12, 15). In addition to human biases during the evaluation of MRIs, the limitations of the present study include biases that are involved in pathological diagnosis. Firstly, differential diagnosis between the two entities sometimes remains difficult when it is based on microscopic findings. Some cases are not clearly lipoma or WDLS (16). For example, a case may lack evident lipoblasts, but be diagnosed as WDLS based on significant variations in the adipocyte cell size. Moreover, this study lacked the input of genomic analyses, which are useful for differential diagnosis between the two entities (12).

In conclusion, we found that plasma D-dimer levels are more up-regulated in WDLS than in lipoma. Although not a stand-alone modality for differential diagnosis, the plasma D-dimer level may contribute substantially to the differential diagnosis between lipoma and WDLS.

Conflicts of interest

The Authors declare that they have no conflicts of interest.

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