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RESEARCH ARTICLE Open Access

D-dimer levels as a prognostic factor for determining oncological outcomes in musculoskeletal sarcoma

Takeshi Morii*, Kazuo Mochizuki, Takashi Tajima, Shoichi Ichimura and Kazuhiko Satomi

Abstract

Background: Plasma d-dimer levels have been associated with the status of tumor progression or oncological outcomes in cancer. Although there are many evidences suggesting the involvement of procoagulant trend in musculoskeletal sarcoma, no clinical data on d-dimer levels and oncological outcome of musculoskeletal sarcoma has been reported.

Methods: In this study, we included a total of 85 patients who were diagnosed with musculoskeletal sarcoma and treated at our institute. Plasma d-dimer levels were determined before performing any clinical intervention, including open biopsy, chemotherapy, radiotherapy or tumor resection. We evaluated the effect of d-dimer levels and other clinicopathological factors on oncological outcomes of patients.

Results: Upregulation of plasma d-dimer levels proved to be an independent risk factor for metastasis and lethal outcome of patients with musculoskeletal sarcoma.

Conclusions: Upregulation of plasma d-dimer levels were indicated poor oncological outcome in metastasis and total survival rate of musculoskeletal sarcoma patients. Hence d-dimer levels may be a helpful marker for evaluating the tumor progression status and prognosis of musculoskeletal sarcoma.

Background

Deterioration in the hemostatic status is one of the significant physiological changes induced by malignant condition. The close relationship between cancer and thrombosis has been clinically well established. Indeed, the risk of venous thromboembolism is higher in cancer patients than in non-cancer patients [1].

Various kinds of procoagulant factors such as malignant condition itself, chemotherapy, long rest period, pathological fracture, orthopedic surgery, and reconstruction by prosthesis or plastic surgery, have been associated with musculoskeletal sarcoma. Indeed, the incidence of venous thromboembolism caused by systemic activation of clotting-fibrinolytic system in musculoskeletal sarcoma patients is considerably high [2-5].

Direct or collateral evidences suggested the involvement of procoagulant molecular mechanisms in musculoskeletal sarcoma. Some examples are as follows. (1) Tissue factor (TF) is a key factor in thrombin generation/fibrin formation and regulates procoagulant activity in many cancer tissues [1,6,7]. This molecule has been reported to be upregulated in a human osteosarcoma cell line [8]. (2) Fibrinolytic molecules that regulate fibrinolytic pathway in tumor tissue include urokinase type plasminogen activator, urokinase type plasminogen activator receptor, and plasminogen activator inhibitors [1]. The expression of these fibrinolytic molecules was reported to be changed in musculoskeletal malignancy [9,10]. (3) Tumor cells secrete various proinflammatory or proangiogenic cytokines such as tumor necrosis factor-alpha, interleukin-1 beta or vascular endothelial growth factor (VEGF), which may affect the anticoagulant system [1]. There is a close relation in the expression and function between VEGF and TF [11,12]. Upregulation of VEGF has been widely reported in musculoskeletal malignancy [13].

D-dimer, a degradation product of cross-linked fibrin blood clots, is an indicator of fibrin concentration.

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Upregulation of plasma d-dimer levels has been reported in several procoagulant pathophysiological conditions, including cancer. Recent studies revealed that plasma d-dimer levels could be used to determine tumor stage/grade [2,14-17], disease progression/response to treatment [18,19], or oncological outcome [17,20,21]. However, the relevance of d-dimer levels as a prognostic factor of musculoskeletal sarcoma has not yet been established thus far. On the basis of the abovementioned data, we hypothesized that plasma d-dimer levels in musculoskeletal sarcoma patients were indicators of tumor progression and oncological outcome, and we analyzed the effect of d-dimer levels on metastasis and lethal outcome in order to establish the clinical significance of d-dimer levels as a prognostic marker.

Methods

We designed a retrospective uncontrolled study based on data obtained from medical records. The inclusion criteria for this study were as follows: (1) musculoskeletal sarcoma diagnosed and treated at our institute between 2006 and 2010; (2) patients who had undergone standard oncological resection [22]; (3) adequate clinical information in the records; and (4) at least 12 months follow-up, except in the case of death before that time. Patients were excluded if the presence of any of the following was identified at the time of presentation: (1) evident metastases; (2) pathological fracture; (3) pre-existing hypercoagulopathy; (4) recent anticoagulant therapy including prophylaxis of thromboembolic complications; (5) recent trauma; (6) inflammatory diseases; and (7) other major surgery recently performed. Finally, 85 patients who met these criteria were included in this study. Clinicopathological and demographic variables of this cohort are summarized in Table 1.

Adjuvant and neoadjuvant systemic chemotherapy were performed in less than 65 years old patients with high grade sarcoma. The treatment regimens were selected based on the histological findings of the patients [23-25]. Radiotherapy was performed postoperatively only for 6 patients in whom postoperative pathological evaluation suggested microscopic residual tumors. Histological grade and surgical margin was determined as previously described [22]. Tumor relapse was detected by physical examination of the tumor site and regional lymph node and by computed tomography

Table 1 Characteristics of the patients

Age (year)		Mean	55.7	
		Range	9-95	
Sex		Male	38	(44.7%)
		Female	47	(55.3%)
Location		Upper extremity	14	(16.5%)
		Lower extremity	47	(55.3%)
		Trunk	24	(28.2%)
Extension		Intracompartmental	36	(42.4%)
		Extracompartmental	49	(57.6%)
Tumor size (mm)		Mean	87.0	
		Range	20-308	
Diagnosis	Bone		19	
		Osteosarcoma	10	(11.8%)
		Chondrosarcoma	8	(9.4%)
		Others	1	(1.2%)
	Soft tissue		67	
		Liposarcoma	23	(27.1%)
		Undifferentiated pleomorphic sarcoma	14	(16.5%)
		Leiomyosarcoma	7	(8.2%)
		Malignant peripheral nerve sheath tumor	5	(5.9%)
		Others	17	(20.0%)
Grade		High	48	(56.5%)
		Low	37	(43.5%)
Surgical margin		Adequate	74	(87.1%)
		Inadequate	11	(12.9%)
Follow up period (months)		Mean	23.0	
		Range	6-50	

scan of lungs by the standard procedure. Mean follow up period was 23.0 (6-50) months.

Plasma d-dimer levels were assessed before performing any kind of intervention for tumor, including chemotherapy, radiotherapy, open biopsy, or tumor resection. For the measurement of d-dimer levels, a latex agglutination assay (STA Liatest® D-Di (Roche Diagnostics AG, Rotkreuz, Switzerland), which was performed on the STA-R® coagulation analyzer) was peformed [2,3]. On the basis of the sensitivity of this assay, levels < 0.20 μg/ml were considered as 0.20 μg/ml.

The endpoints of this study were local recurrence, metastasis, and total survival. The independent risk factors in the present study were patient' age, sex, anatomic site, tumor origin (bone vs soft tissue), histological grade, extracompartment extension, tumor size, surgical margin, and d-dimer levels on referral.

Statistical analysis was performed using the receiver operating characteristic (ROC) curve analysis, Kaplan-Meier methods, log-rank tests, and Cox proportional hazards model with JMP (version 7; SAS institute Inc., North Carolina, USA). The differences were considered significant when $p < 0.05$. For multivariate analysis, covariates with a p value of less than 0.05 were retained in the final model. The study was approved by the institutional review board of the authors institution.

Results

The d-dimer levels ranged from 0.2 to 8.3 μg/ml (mean, 0.84 μg/ml; median, 0.42 μg/ml). In order to determine the cut off value of d-dimer levels in this analysis, we performed ROC curve analysis (Figure 1). The areas under the curve (AUC) were 0.437 for local recurrence, 0.712 for metastasis and 0.749 for total survival, suggesting that there was no evident difference in the levels of d-dimer in patients with and without local recurrences; hence, local recurrence was deleted from the endpoints of this study. The optimal cut off value of d-dimer was determined at the point on ROC curve at which (sensitivity+specificity-1) was maximized (Youden index). For metastasis, optimal cut off value of d-dimer was 0.41 μg/ml with which sensitivity and specificity were 0.83 and 0.57, respectively. In a similar way for total survival, optimal cut off value of d-dimer was 0.80 μg/ml with which sensitivity and specificity were 0.80 and 0.75, respectively.

Next, the effect of independent variables, including d-dimer levels, on the 2 endpoints, namely, metastasis and total survival, was analyzed by using survival analysis model. The result of univariate analysis suggested that elevated d-dimer levels ($p = 0.002$) (Figure 2A) and histological grade ($p = 0.009$) were the significant risk factors for metastases (Table 2); further, elevated d-dimer levels ($p = 0.0004$) (Figure 2B), histological grade ($p = 0.03$), and extracompartmental extension of the tumor ($p = 0.04$) were the significant risk factors for lethal outcome (Table 3). Multivariate analysis results suggested that both elevated d-dimer levels ($p = 0.003$) and histological grade ($p = 0.01$) were the independent risk factors for metastases, and elevated d-dimer levels ($p = 0.004$) and extracompartmental extension of the tumor ($p = 0.04$) were the independent risk factors for lethal outcome.

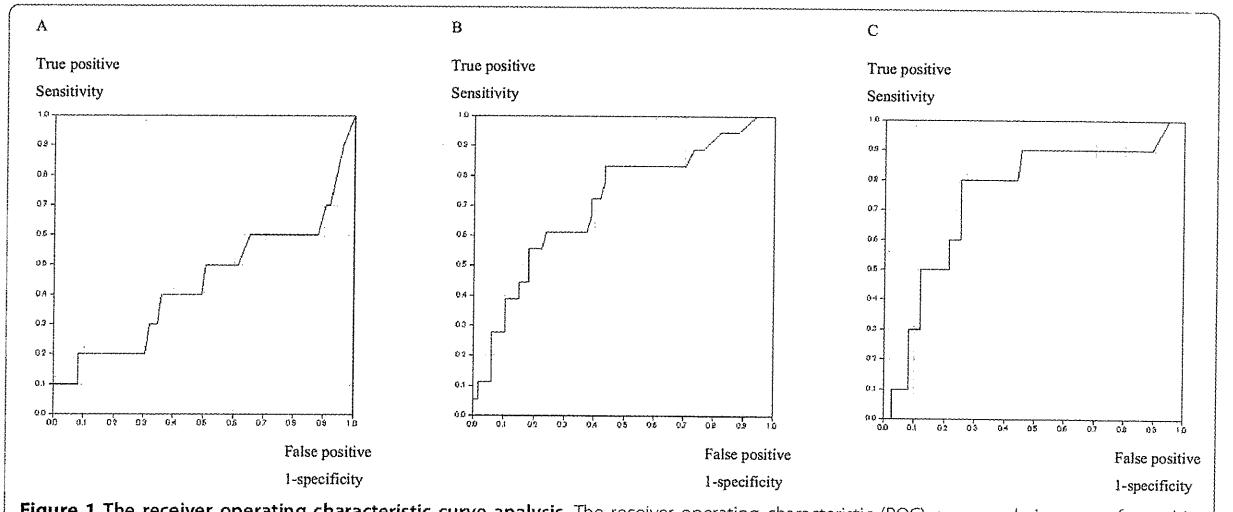

Figure 1 The receiver operating characteristic curve analysis. The receiver operating characteristic (ROC) curve analysis was performed in order to determine the cut off value of d-dimer levels. **A.** Local recurrence. **B.** Metastasis. **C.** Tumor specific death. The optimal cut off value of d-dimer was determined at the point on ROC curve at which (sensitivity+specificity-1) was maximized (Youden index). For metastasis, optimal cut off value of d-dimer was 0.41 μg/ml with which sensitivity and specificity were 0.83 and 0.57, respectively. In a similar way for total survival, optimal cut off value of d-dimer was 0.80 μg/ml with which sensitivity and specificity were 0.80 and 0.75, respectively.

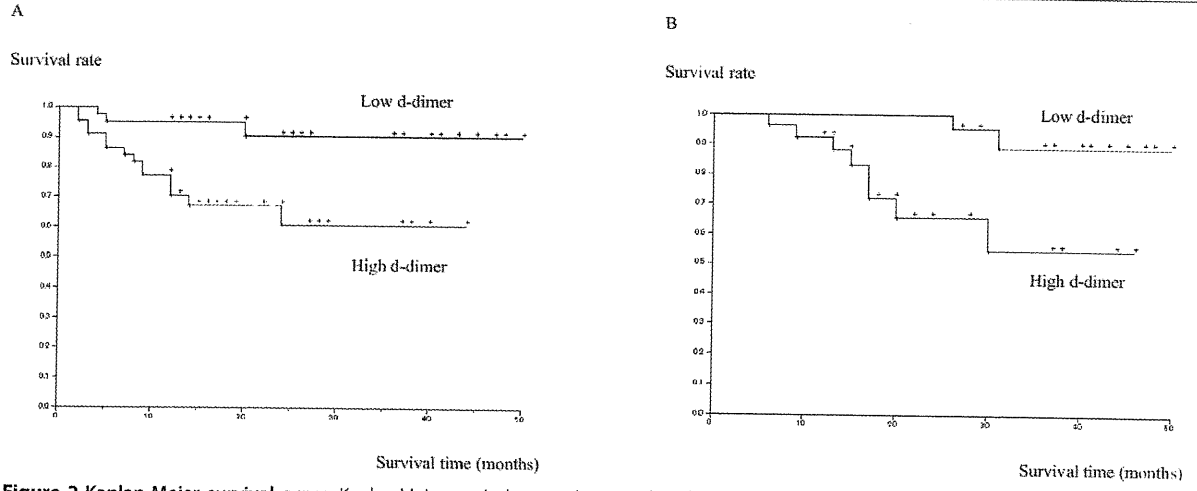

Figure 2 Kaplan-Meier survival curve. Kaplan-Meier survival curve showing the effect of d-dimer level on metastasis (**A**) and the total survival rate (**B**).

Discussion

Musculoskeletal sarcoma is a group of rare heterogeneous tumors of the mesenchymal lineage. Innovation in treatment modality, including theory in determining safety margin, limb salvage procedure and systemic chemotherapy have improved oncological outcomes of musculoskeletal sarcoma over the past 3 decades [22]. Accumulated clinical data suggested that several clinicopathological factors, including histological grade, tumor size, surgical margin, tumor extension, and age are prognostic factors of oncological outcome [22,26,27]. In order to evaluate the biological properties of musculoskeletal sarcoma, additional markers are being intensively investigated.

D-dimer is a degradation product of cross-linked fibrin blood clots and indicates fibrin concentration. We have previously shown that plasma d-dimer levels were closely related to the histological grade of musculoskeletal tumor

Table 2 Risks for metastasis

Variables	Subclass	Event	Cases	Univariate analysis	Multivariate analysis		
				p	p	Hazard ratio	95% Confidence interval
Age	≧ 56 years	8	42	0.54			
	< 56 years	10	43				
Sex	Male	12	47	0.24			
	Female	6	38				
Site	Upper extremity	2	14	0.72			
	Lower extremity	11	47				
	Trunk	5	24				
Origin	Bone	6	19	0.20			
	Soft tissue	12	66				
Histological grade	Low	3	37	0.009	0.01	3.9	1.2-16.9
	High	15	48				
Extracompartment extension	No	5	36	0.15			
	Yes	13	49				
Tumor size	≧ 50 mm	13	57	0.58			
	< 50 mm	5	28				
Surgical margin	Adequate	15	74	0.56			
	Inadequate	3	11				
D-dimer levels	≧ 0.41 μg/ml	15	44	0.002	0.003	5.0	1.6-21.7
	< 0.41 μg/ml	3	41				

Table 3 Risks for lethal outcome

Variables	Subclass	Event	Cases	Univariate analysis	Multivariate analysis		
				p	p	Hazard ratio	95% Confidence interval
Age	≧ 56 years	4	42	0.42			
	< 56 years	6	43				
Sex	Male	7	47	0.34			
	Female	3	38				
Site	Upper extremity	1	14	0.54			
	Lower extremity	6	47				
	Trunk	3	24				
Origin	Bone	4	19	0.14			
	Soft tissue	6	66				
Histological grade	Low	1	37	0.03	0.01	3.9	1.2-16.9
	High	9	48				
Extracompartment extension	No	1	36	0.04	0.04	5.9	1.1-110
	Yes	9	49				
Tumor size	≧ 50 mm	8	57	0.29			
	< 50 mm	2	28				
Surgical margin	Adequate	7	74	0.12			
	Inadequate	3	11				
D-dimer levels	≧ 0.8 μg/ml	8	44	0.0004	0.004	7.3	1.8-49
	< 0.8 μg/ml	2	41				

[2]. However to date, there has been no report indicating the prognostic relevance of plasma d-dimer levels in musculoskeletal sarcoma. This is the first report showing a close relation between d-dimer levels and oncological outcomes in musculoskeletal sarcoma. In contrast to the result of our previous study, multivariate analysis in this study revealed that d-dimer levels and tumor grade were independent factors. However we were not able to precisely determine the mechanism underlying this result. We believe that d-dimer levels might represent the state of disease progression itself rather than tumor properties represented by genetic changes or morphologic findings.

Musculoskeletal malignancy is characterized by heterogeneity in tumor site and patients age, which may be independent from its biological properties that are regulated by genetic change. Our previous data [2] and analysis of the present cohort (data not shown) suggested that d-dimer levels were significantly upregulated in the elder patient group or downregulated in upper extremity cases. If d-dimer level was significant prognostic factor and the abovementioned close relations between the factors were true, patient age and tumor site might indeed be the prognostic factors in this cohort. Hence, these factors were entered into the independent variables in the present model, which confirmed that these factors had little effect on oncological outcome than the d-dimer levels.

In this study, chemotherapy was indicated strictly on the basis of grade/histological subtype of the tumor and patient age. The results of preliminary statistical analysis suggested a strong association between tumor grade and indication of adjuvant chemotherapy ($p = 0.001$, Fisher's exact test) and between age and indication of adjuvant chemotherapy ($p = 0.0002$, Mann-Whitney *U* test), suggesting that the application of chemotherapy might serve as a confounding bias. Thus, we did not include application of adjuvant chemotherapy as independent risk factor in survival analysis. In addition, limited number of patients received radiotherapy, and thus, indication of radiotherapy was not considered as risk factor.

The merits of the application of d-dimer levels for predicting oncological outcome in clinical practice was previously shown [17] as being not time and cost efficient, requirement of only small plasma aliquots, and less invasive technique. Thus, we proposed the usage of this modality in evaluation of musculoskeletal sarcoma patients. The limitations of this study are considerably small sample size and candidate bias caused by procoagulant factors, for example, smoking or obesity, which were not evaluated in this study. In addition, it is necessary to validate the cut off value of d-dimer. Thus, accumulation of data from prospective study with a large sample might be needed in the future.

Conclusions

Upregulation of plasma d-dimer levels indicated poor oncological outcome in metastasis and total survival rate of musculoskeletal sarcoma patients. D-dimer levels may

be a helpful marker for evaluating the tumor progression status and prognosis of musculoskeletal sarcoma.

Fundings

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Authors' contributions

TM collected the data, performed the statistical analysis and drafted the manuscript. KM collected the data and helped to draft the manuscript. TT collected the data. SS and KS helped to draft the manuscript. All authors have read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

Surgical site infection in malignant soft tissue tumors

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Abstract
Background Postoperative wound complications, including surgical site infections, which frequently occur in the course of management of musculoskeletal sarcomas, sometimes necessitate repeat surgeries, including amputation, and may result in a prolonged healing time, prolonged hospital stay, or fatal outcome. A comprehensive understanding of surgical site infections associated with specific diseases is needed to reduce the risk.
Methods This series comprised 84 patients with malignant soft tissue tumors treated at our institute. The occurrence rate, management modality and clinical course of surgical site infections, impact of surgical site infections on the length of hospitalization, risk factors for the development of surgical site infections, and the impact of surgical site infections on the oncological outcomes were analyzed. Surgical site infection was defined according to Centers for Disease Control and Prevention guidelines.
Results Surgical site infections occurred in 7 cases (8.3%). Although successful clinical cure was achieved in all cases, surgical site infection was identified as one of the independent risk factors for prolongation of hospitalization. Both univariate and multivariate analyses identified larger intraoperative blood loss and a trunk location as risk factors associated with deep infections. No association was detected between age, tumor grade, chemotherapy, tumor volume, or plastic surgery and the risk of surgical site infections. Although the differences were not statistically significant, patients with surgical site infections showed worse oncological outcomes in terms of local recurrence and total survival.
Conclusion The incidence rate of surgical site infection was larger than that associated with conventional orthopedic surgeries, such as osteosynthesis, spine surgery, or arthroplasty. Surgical site infections remain a critical and frequent complication of surgical treatment of soft-tissue malignancies and often result in prolongation of hospital stay. Although practical options to prevent surgical site infections seem quite limited, the present data provide a rationale for perioperative evaluation in patients at a high risk of surgical site infections.

Introduction

With innovations in operation planning with systematic application of the definition of surgical margin, and also in chemotherapy and radiotherapy for soft-tissue sarcomas over the last 3 decades, improvements of the limb salvage rate and oncological outcomes have been acquired. However, surgeries for soft-tissue sarcomas are associated with several candidate risk factors for surgical site infections (SSIs), such as prolonged operation time, large incisions, large defects of soft tissues resulting from the need to secure adequate safety margins, perioperative radiotherapy, and immune deficiency associated with perioperative chemotherapy, some of which are indispensable for obtaining better oncological outcomes. Indeed, the wound complication rate and infection rate are much higher than those associated with conventional orthopedic surgery. In fact, the infection rate reported to be associated with conventional orthopedic surgery has been reported to be as low as less than 1% [1], whereas that associated with surgeries for soft-tissue sarcomas is in the range of 6–15% [2–5].

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The advantages of surveillance for SSIs in a specific disease group include classification of the operations or of patients with risk factors for infection in order to reduce the rate of SSIs [6]. Considering that accumulation of data on the status of SSIs associated with specific diseases may be imperative, we conducted a detailed review of the data on SSIs in patients with soft tissue sarcomas at our institute in the present study. Our aims were to: (1) present an overview of the situation regarding SSIs associated with oncological resection of malignant soft-tissue tumors, (2) identify the impact of SSIs on the length of hospital stay, (3) identify perioperative risk factors for SSIs, and (4) identify the impacts of SSIs on the oncological outcomes.

Methods

We designed a retrospective uncontrolled study based on data obtained from medical records. The inclusion criteria for this study were patients with: (1) malignant soft tissue tumors treated at our institute; (2) treatment between 2006 and 2010; (3) standard oncological resection [7, 8]; (4) adequate recording of clinical information; (5) at least 12 months' follow-up, except in the case of death before that time; (6) cases operated on or supervised by the first author (T.M). There were 84 subjects who met these criteria. Forty-two patients were male, and the remaining 42 were female. Mean age at first operation was 58.5 years (range 12–95 years). Tumor location in the upper extremity was defined as tumor in the region extending from the medial border of the scapula to the fingers and that in the lower extremity in the region extending from the iliac crest to the toes [9]. The tumor site was the lower extremity in 44 patients, upper extremity in 13 patients, and trunk in 27 patients. There were 53 and 31 patients with deep and subcutaneous locations of the tumors, respectively. The histological diagnosis was liposarcoma in 27 patients, pleomorphic malignant fibrous histiocytoma/undifferentiated pleomorphic high-grade sarcoma in 18 patients, leiomyosarcoma in 6 patients, malignant peripheral nerve sheath tumor in 5 patients, synovial sarcoma in 4 patients, myxofibrosarcoma in 4 patients, and other subtypes in the remaining 20 cases. Tumor grade in this study was defined as previously described [7]. A total of 15 patients received preoperative systemic chemotherapy. The VDC-IE regimen was used for high-grade round cell tumors such as Ewing's sarcoma [10]. For the remaining high malignant grade sarcomas, doxorubicin- and ifosfamide-based regimens were used [11]. Preoperative radiotherapy was used for only one case of Ewing's sarcoma in the forearm, in which an adequate margin could not be determined for limb salvage. Postoperative radiotherapy was employed for 4 patients in whom microscopic residual tumors were suggested by postoperative pathological examination. Preoperative antibiotics were given within 2 h prior to the operation. For all cases, postoperative antibiotics were administrated for more than 72 h. Diabetes mellitus was detected in 7 patients. Other candidate risk factors for infection included lymphedema, otitis, and urinary tract infection in 1 patient each. Oncological resection was undertaken in all cases; among them, reconstruction by plastic surgery was performed in 29 cases. Postoperative wound drainage was performed until the daily volume of drainage was less than 30 ml. The duration of the operation and intraoperative blood loss were determined from the operation records. The approximate tumor volume was calculated by multiplying the length, width, and depth of the tumors as measured in preoperative radiological images. The clinical status of the patients was continuous-disease-free (CDF) in 57 patients, no evidence of disease (NED) in 9 patients, alive with disease (AWD) in 7 patients, and dead of the disease (DOD) in 11 patients. The 5-year local-recurrence-free survival rate, metastasis-free survival rate, and total survival rate were 85.1, 70.0, and 77.6%, respectively.

Then, the SSI rate, clinical course and management of the SSIs, risk factors for SSI, risk factors for prolonged hospitalization, and impact of SSI on the oncological outcomes were analyzed for the study population. Surgical site infection was defined according to CDC guidelines [6]. Clinical cure of infection was defined according to Hardes, as follows: (1) no clinical signs of inflammation; (2) normal CRP [12]. The hospitalization period in this study was defined as the period between the day of admission and the day of discharge. At our institute, the date of admission is usually the day before the operation. If the patients received postoperative adjuvant therapy, such as chemotherapy or radiotherapy, patients were usually discharged from the hospital after completion of the postoperative management and then re-admitted for the adjuvant therapy. Thus, the hospitalization period in this study did not include the hospitalization period for adjuvant therapy. For the statistical analysis, the Kaplan-Meier method, log-rank tests, Fisher's exact test, Mann-Whitney's U test, Spearman's rank-correlation coefficient, multiple linear regression analysis, and logistic regression were used. Differences were considered significant when values of p were <0.05. For multivariate analysis, covariates with a p value of less than 0.05 were entered in the final model. The study was conducted with the approval of the institutional review board of the first author's institution.

Results

SSIs were detected in a total of 7 patients (8.2%) at a mean of 16 days (range 4–30 days) after the initial surgery (Table 1).

Table 1 Demographic data of the cases with surgical site infection

Case	Age	Sex	Site	Diagnosis	Culture results	Treatment	Surgical procedure	Treatment duration (days)
1	75	F	Back	Myxofibrosarcoma	Coryneform gram-positive rods	Antibiotics, vacuum-assisted closure therapy	No	47
2	85	F	Groin	MFH	MSSA	Antibiotics, irrigation	No	10
3	41	M	Chest wall	Fibrosarcoma	MRSA	Antibiotics (VCM), globulin preparations, hydrogen peroxide, irrigation	No	19
4	42	M	Groin	Liposarcoma	*E. coli*, Coryneform gram-positive rods	Antibiotics, debridement, skin grafting	Yes	61
5	64	M	Back	MFH	MRSA	Antibiotics (VCM), globulin preparations	No	30
6	70	M	Buttock	Liposarcoma	MRSA	Antibiotics (VCM)	No	28
7	52	F	Thigh	MPNST	*Pseudomonas aeruginosa*	Antibiotics, debridement	Yes	28

MFH malignant fibrous histiocytoma, *MSSA* methicillin-sensitive *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*, *VCM* vancomycin, *MPNST* malignant peripheral nerve sheath tumor

Four of these patients were male, while the remaining three were female. The patients ranged in age from 41 to 85 (mean 61.3) years old. Wound dehiscence was found in 4 cases. In 2 of the remaining 3 cases, fluid accumulation with local heat and redness was detected at the site of the surgery, and in the remaining 1 case, discharge from the skin covered with the mesh graft was the initial symptom. In all cases, pathogens were detected by culture of the discharge fluid, including methicillin-resistant *Staphylococcus aureus* (MRSA) (3 cases), a combination of *Corynebacteria* and *E. coli* (1 case), *Corynebacteria* (1 case), methicillin-sensitive *Staphylococcus aureus* (MSSA) (1 case), and *Pseudomonas aeruginosa* (1 case). The treatment modalities used are summarized in Table 1. For all cases, antibiotics to which the pathogens were found to be sensitive were applied. In addition, various kinds of conservative therapies, including vacuum-assisted closure therapy, globulin preparations, and hydrogen peroxide application, were adopted. However, 2 of the patients finally required surgical procedures, including debridement (cases 4 and 7) and skin grafting (case 4). Clinical cure was achieved in all cases. The interval to clinical cure from the diagnosis for SSI ranged from 10 to 61 (mean 32) days.

An attempt was made to identify the risk factors for prolonged hospitalization (Table 2). Univariate analysis identified age, tumor grade, operation duration, intraoperative blood loss, drainage duration, and SSI as significant risk factors for prolonged hospitalization. When analysis was conducted after entering these factors into a multivariate model, SSI together with tumor grade, operation duration, and drainage period were identified as independent risk factors for prolonged hospitalization (Fig. 1).

Next, we analyzed the risk factors for the development of SSIs. Age, sex, diabetes mellitus, tumor grade, depth of tumor, tumor volume, radiotherapy, chemotherapy, reconstruction by plastic surgery, operation time, and the postoperative drainage period were identified as not being risk factors for SSIs. In addition, SSI did not occur in any of the patients with candidate risk factors for the development of infection, such as lymphedema, otitis, and urinary tract infection. Among the independent variables, tumor site (trunk vs. extremity) ($p = 0.004$) and intraoperative blood loss ($p = 0.043$) were revealed as risk factors for SSIs (Table 3). Independent variables identified as candidate risk factors for SSI by univariate analysis were entered into a multivariate analysis model. Both of these risk factors identified by univariate analysis proved to be independent risk factors for SSIs (tumor site, $p = 0.02$; intraoperative blood loss, $p = 0.03$).

The impact of SSI on the oncological outcomes was also analyzed. Although not statistically significant, worse oncological outcomes in terms of the total survival ($p = 0.08$) and local recurrence ($p = 0.07$) were detected in the patients who developed SSI. Development of SSI did not affect the risk of development of metastases ($p = 0.96$).

Discussion

Because postoperative wound complications, including surgical site infections, encountered in the course of management of musculoskeletal sarcomas sometimes necessitate repeated surgical procedures, including amputation [4, 13], and may result in a prolonged healing time [2], prolonged hospital stay [2], or fatal outcome [4], the status of occurrence of complications associated with soft-tissue sarcoma surgeries has been intensively studied. Wound complications include wound dehiscence, infection, seroma,

Table 2 Risks for prolonged hospital stay

Variables	Mean hospital stay (days) (mean ± SD)	*p*	
		Univariate analysis	Multivariate analysis
Age		0.006	0.06
Sex			
Male	27.1 ± 19.0	0.98	
Female	24.2 ± 11.8		
Diabetes mellitus			
No	25.3 ± 15.4	0.56	
Yes	32.2 ± 21.9		
Tumor grade			
Low	20.5 ± 16.2	0.0008	0.04
High	28.9 ± 14.7		
Tumor site			
Trunk	28.4 ± 20.1	0.50	
Extremity	24.4 ± 13.3		
Tumor location			
Subcutaneous	25.8 ± 13.9	0.62	
Deep	25.6 ± 16.9		
Tumor volume		0.24	
Radiotherapy			
Not done	26.1 ± 16.1	0.46	
Done	19.2 ± 5.6		
Chemotherapy			
Not done	23.5 ± 12.3	0.19	
Done	34.2 ± 24.8		
Amputation			
Not done	25.2 ± 15.9	0.16	
Done	31.0 ± 13.3		
Plastic surgery			
Not done	25.2 ± 17.2	0.23	
Done	26.7 ± 12.9		
Operation duration		0.001	0.03
Intraoperative blood loss		0.0004	0.09
Drainage duration		0.003	0.01
Surgical site infection			
No	23.7 ± 13.8	0.001	0.03
Yes	47.5 ± 20.9		

SD, standard deviation

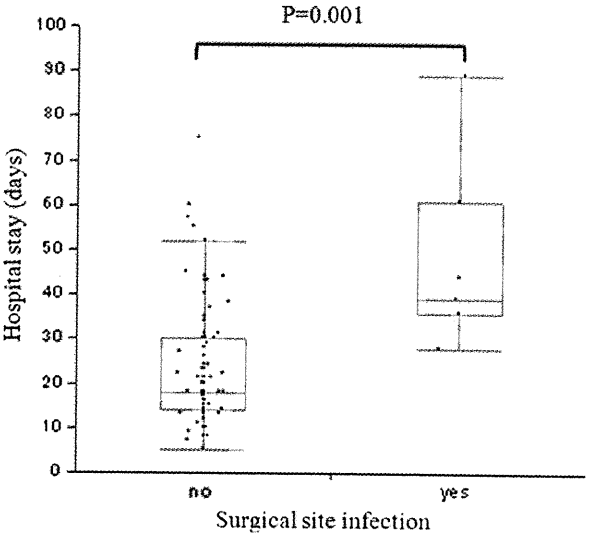

Fig. 1 The *box*-and-*whisker* plot shows that the hospital stay was significantly longer in patients with surgical site infection (SSI) than in those without SSI

skin graft breakdown, and hematoma [4, 13, 14], and many authors have focused not on "infection" itself, but on "wound complications," including infection. According to the results of these studies, the reported wound complication rates in soft-tissue sarcoma series range from 16 to 40% [2–5, 9, 13–17]. Our primary goal in the present study was to evaluate the wound complication status in a consecutive series of patients with soft-tissue sarcomas at our institute. Although in some cases we found a combination of infection and dehiscence, seroma or skin necrosis, we did not detect such complications in the absence of infection in the present series, and we set the primary endpoint of our study as SSI, the rate of which was considered as the wound complication rate in the present study. Assuming that the above-mentioned interpretations were true, the incidence of SSIs (i.e., wound complication rate) in the present study was lower than that reported from most previous studies. In addition, the previously reported "postoperative infection" rates ranged from 6 to 15% [2–5], which were equal to or higher than that in the present study. Moreover, in the present study, only 2 out of 7 cases (28.6%) with infection could not be controlled successfully by conservative therapy, whereas in previous reports, the percentage of patients needing surgical procedures ranged from 44.6 to 65% [4, 13, 15]. This considerably low wound complication rate and good response to conservative therapy in our study were perhaps due to the lack of use of perioperative radiotherapy in most patients in our series. In fact, in the previous study, the application rate of radiotherapy ranged from 40 to 100% [4, 5, 9, 13–17], whereas in the present study, only 5 patients (6%) received postoperative radiotherapy. The data presented here should therefore be interpreted taking this striking difference from the previously reported data into consideration.

The causative pathogens for the infections were generally not specified in previous reports. To the best of our knowledge, only Saddegh et al. [2], who analyzed 103 consecutive soft-tissue sarcoma cases and determined the infection rate (15.5%), reported the isolated organisms;

Table 3 Risk factors for SSI

Variables	SSI (+)	SSI (−)	Univariate analysis	Multivariate analysis		
			p	*p*	Odds ratio	95% Confidence interval
Age (years old) (mean ± SD)	61.3 ± 16.8	58.2 ± 19.3	0.79			
Sex						
Male	4	38	0.99			
Female	3	39				
Diabetes mellitus						
No	7	72	0.99			
Yes	0	5				
Cardiovascular comorbidities						
No	6	70	0.52			
Yes	1	7				
Tumor grade						
Low	2	30	0.7			
High	5	47				
Tumor site						
Trunk	6	21	0.004	0.024	14.4	1.4–17.8
Extremity	1	56				
Tumor location						
Subcutaneous	2	29	0.99			
Deep	5	48				
Tumor volume (cm^3) (mean ± SD)	493 ± 621	427 ± 848	0.57			
Radiotherapy						
Not done	7	72	0.99			
Done	0	5				
Adjuvant chemotherapy						
Not done	5	64	0.6			
Done	2	13				
Amputation						
Not done	7	69	0.99			
Done	0	8				
Plastic surgery						
Not done	5	50	0.99			
Done	2	27				
Operation duration (min) (mean ± SD)	378 ± 240	218 ± 118	0.083			
Intraoperative blood loss (ml) (mean ± SD)	858 ± 909	229 ± 381	0.043	0.028	1.002	1.001–1.003
Drainage duration (days) (mean ± SD)	7.7 ± 5.5	4.6 ± 3.8	0.15			

SSI surgical site infection, *SD* standard deviation

they reported that *Staphylococcus aureus* and *S. epidermidis* were the most commonly isolated organisms, supporting our data as to the incidence of SSI caused by *Staphylococcus aureus* (57.1%). The trend of the predominance of *Staphylococcus aureus* infection complicating proximal wounds that they pointed out also supported our data, because all of the wounds with *Staphylococcus aureus* infection in the present study were proximal site wounds. These data would seem to be useful for the selection of antibiotics, and further accumulation of data in the future is desirable.

Previous reports have suggested that wound complications result not only in prolonged hospital stays, but also in delayed wound healing [3, 13]. The median wound healing

times were 3 and 6 times longer in patients who developed complications after resection of superficial and deep tumors, respectively [13]. We showed that SSI was one of the independent risk factors for prolonged hospital stay, with the average hospital stay expected to double in patients with SSIs as compared to those in patients without SSIs, underscoring the clinical importance of the prevention and control of SSIs in the management of soft-tissue sarcoma.

Risk factors for wound complication have been extensively reported by previous studies. Radiotherapy, especially preoperative radiotherapy, has been reported as being a strong risk factor for the development of wound complication [5, 9, 14, 16]. Perhaps because of the small number of patients who received radiotherapy in our series, we failed to extract this factor as a risk factor. Our policy in regard to the application of radiotherapy is to apply it only for they patients with an inadequate surgical margin as revealed by postoperative pathological examination, so as to avoid an unacceptably high wound complication rate. We did take into consideration the importance of strict evaluation of the merits and demerits of radiotherapy in the management of soft-tissue sarcomas, not only for obtaining better local control and total survival [9], but also for obtaining a minimal wound complication rate.

Other risk factors reported so far include diabetes mellitus [14], smoking [14], trunk or lower extremity location of the tumors [2–4, 9, 17], older age [2–4, 17], large tumor or resected specimen size [2, 3, 5, 9, 14], high intraoperative blood loss [2–4], longer operation time [2], and longer duration of drainage [2], partially supporting the present data. We think that among these factors, controllable variables by the surgeons in clinical practice are quite limited. Complete hemostasis during the operation, resulting in lower intraoperative blood loss, shorter operation time, and lesser duration of drainage, might reduce the wound complication rate, although none of these may be direct causal factors.

The results of this study suggested a trend towards the existence of a close relationship between worse oncological outcomes and the occurrence of SSI. Although confounding factors, including large tumor size, prolonged operation time, and increased blood loss associated with advanced tumors, could easily be pointed out, further accumulation of data might be warranted for better understanding of the relationship between SSI and oncological outcome.

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Conflict of interest The authors declare that they have no competing interests.

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母指末節骨に発生した骨内グロムス腫瘍の 1 例*

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[Key words：intraosseous glomus tumor（骨内グロムス腫瘍），bone tumor（骨腫瘍），digit（指）]

骨内グロムス腫瘍の最初の報告は，1939 年の Iglesias de la Torre らによるとされる比較的稀な腫瘍である[2]．われわれは，母指末節骨に発生したグロムス腫瘍の 1 例を経験したので報告する．

症　例

患者：55 歳，女性．

主訴：左母指の疼痛．

既往歴：2003 年春，右腎細胞癌のため右腎摘出術を受けている．

現病歴：2003 年秋，特に誘因なく左母指末節部の圧痛を自覚したため，近医を受診した．単純 X 線像で左母指末節骨の異常陰影を指摘され，半年ごとに経過観察されていた．その後，異常陰影が増大し，疼痛が軽減しないため，2006 年 8 月当科に紹介され受診した．

入院時現症：左母指爪甲の中央部に自発痛と圧痛を認めた．爪甲の変形や寒冷刺激による疼痛の増悪はなかった．血液生化学検査では明らかな異常はなかった．

画像所見：単純 X 線像では，左母指末節骨内に径約 8 mm，辺縁の硬化を伴う骨透亮像を認めた（図 1）．同部は MRI では T1 強調画像で低信号，T2 強調画像で高信号を示し，脂肪抑制像では抑制されなかった（図 2）．以上より，内軟骨腫，類骨骨腫，骨髄炎，骨内グロムス腫瘍などを鑑別すべき疾患とし，確定診断を兼ねて切除生検を施行した．

手術所見：抜爪したのち，背側より末節骨を展開すると，背側の皮質は一部菲薄化していた以外，明らかな骨外病変はなかった．骨内に白色の病巣を確認し（図 3），掻爬した．なお，骨内病変の周囲には骨硬化がみられた．爪床を縫合し，爪を元の部位に再縫着し，手術を終了した．

病理組織学的所見：腫瘍細胞は過色素性で，軽度の大小不同を示す核とやや好塩基性な胞体を持ち，時に境界明瞭な細胞がシート状に配列していた．豊富な小血管がみられる以外に myxoid な間質を認めた（図 4a）．免疫組織化学的染色においては，smooth muscle actin（SMA）が腫瘍細胞に陽性であった（図 4b）．以上の所見より，本症例を母指末節骨内に発生したグロムス腫瘍と診断した．

術後経過：術直後より，すみやかな疼痛の消失が確認された．術後 2 年の現在，単純 X 線像上，骨融解像の修復がみられ，再発はみられない（図 5）．

考　察

グロムス腫瘍は円形から類円形の核を持ち，皮膚に存在する動静脈吻合部の温度調節に関わる Sucquet-Hoyer 管を取り囲む，グロムス細胞に類似する細胞からなることを特徴とする良性腫瘍である[5]．本疾患は 1812 年 Wood による painful subcutaneous tubercle とした報告を嚆矢とする[8]．1924 年 Masson は，組織所見が皮膚の末梢循環を調節する glomus body に似ていることから，グロムス腫瘍と命名した[5]．

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* A case of intraosseous glomus tumor in the distal phalanx of the thumb.

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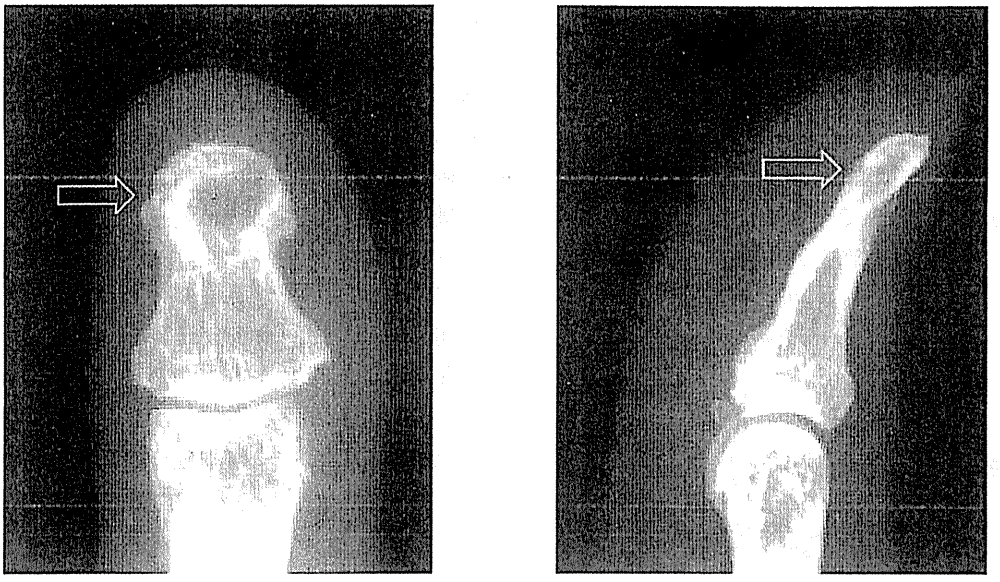
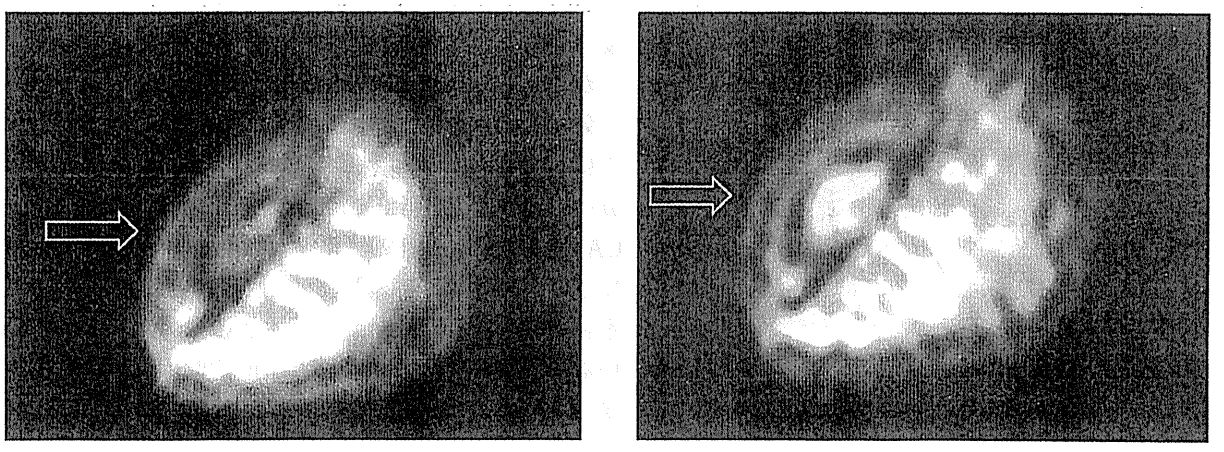
（受稿　2010 年 6 月 21 日）



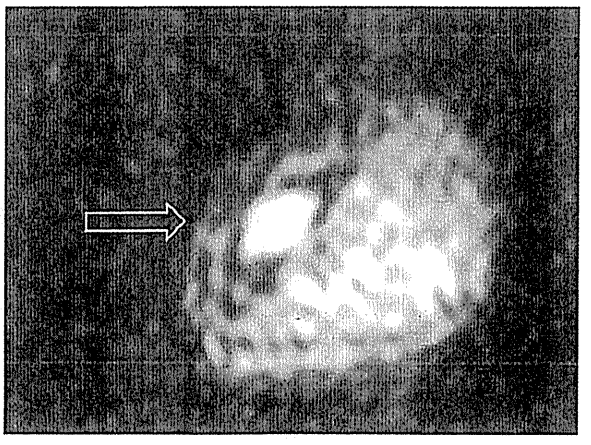
(a) 正面像 (b) 側面像

図 1 左母指末節骨単純 X 線像．末節骨内に骨融解像を認めた．



(a) T1 強調画像．病巣部はで低信号．

(b) T2 強調画像．病巣部は高信号．



(c) 脂肪抑制像．病巣部は抑制されず高信号を呈する．

図 2 左母指 MRI (axial)

本腫瘍は青壮年層の女性に好発する．グロムス器官の分布する部位に発生するため，好発部位は手爪下部，指腹部，などの軟部組織である．

また，グロムス器官は骨髄内にも存在するため，稀ではあるが骨内にもグロムス腫瘍は発生し，渉猟しえた限りでは 25 例であった（表 1）．発生部位は手指の末節骨が 14 例と過半数を占め，他の部位では中節骨，仙尾骨，脊椎，尺骨などである．女性に多く，20 ～ 40 歳台に好発する点では，骨外発生の本腫瘍と同様であった．骨外グロムス腫瘍に一般にみられる自発痛，圧痛，寒冷時痛の三徴は，骨内発生例では自発痛と圧痛はほぼ全例に認めるものの，寒冷時痛は約 10％のみであった．自験例でも寒冷時痛はなかった．

単純 X 線像上，本腫瘍の多くは自験例と同様に溶骨性の mass を形成するが，時に骨全体を破壊して浸潤することがある．一方，骨に隣接する軟部組織に発生し，骨変化を伴う場合には骨内よりの発生と誤診されることがあり，注意を要する．骨内グロムス腫瘍の診断には，腫瘍の周囲すべてに皮質骨が存在したことを術中所見で確認することが必要である[7]．自験例での主病変は骨内であった．

臨床像および単純 X 線像が類似する鑑別疾患として，内軟骨腫，類骨骨腫，慢性骨髄炎，骨転移癌などがある．各腫瘍ともそれぞれ画像上の特徴があるが，確定診断には病理組織学的診断が必要である．自験例では腎細胞癌の既往を有していたが，転移を示す X 線像や組織像はなかった．

免疫組織化学的染色では，自験例で見られたようにα-SMA あるいはビメンチンなど筋分化マーカーが陽性となる．一方，上皮系マーカーである CAM5.2 および AE1/AE3，神経系マーカーの NSE や S-100 蛋白などは陰性となる．これは，本腫瘍が平滑筋への分化を示す腫瘍と考えられているためであり[6]，病理組織学的診断上で参考とすべきである．

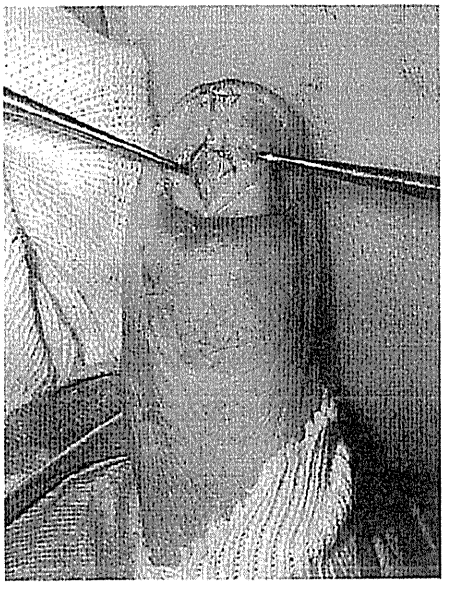
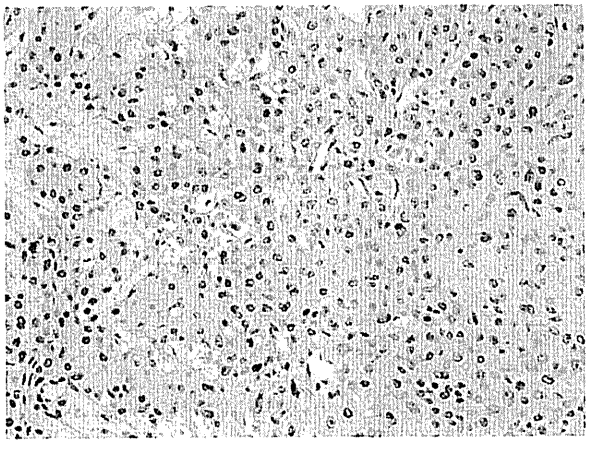
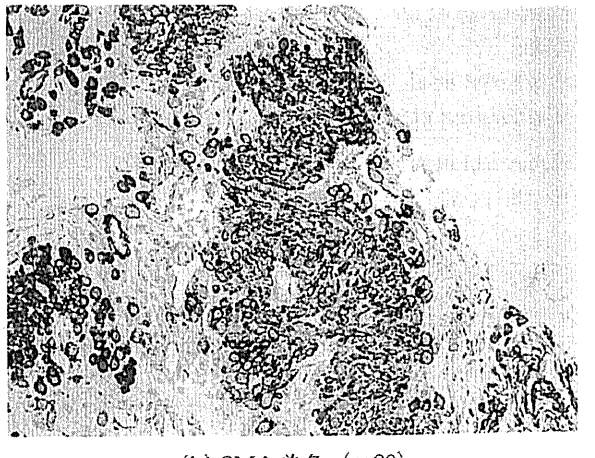


図 3　術中所見．骨皮質は菲薄化していたが，残存していた内部の白色病巣を掻爬した．

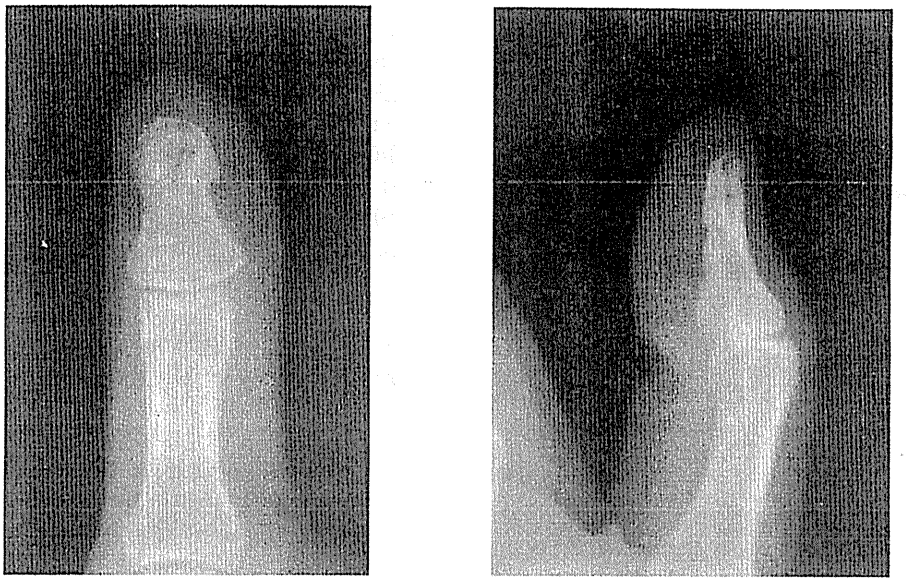


(a) HE 染色（×20）



(b) SMA 染色（×20）

図 4　病理組織像



(a) 正面像 (b) 側面像

図 5 術後 2 年の単純 X 線像．骨融解はほぼ修復されており再発像はない．

表 1 過去の骨内グロムス腫瘍報告例

報告者	報告年	年齢	性別	部位	症状期間	Radiographs	治療
Iglesias de la Torre et al	1939	32	女性	左環指末節骨	4 年	cystic	関節離断術
Lattes et al	1948	28	女性	右母指末節骨	4 年	honeycomb area	掻爬
Leshman et al	1949	48	女性	左小指末節骨	6 年	punch out	掻爬
Leshman et al	1949	36	女性	右母指末節骨	14 カ月	circumscribed radiolucent	切除術
Mackenzie	1962	30	女性	左小指末節骨	2 年	circular cystic	切断術
Mackenzie	1962	61	女性	左母指末節骨	6 年	cystic	切除術
Siegel	1967	24	男性	左示指末節骨	10 カ月	round smooth walled osteolytic	掻爬
Ishii et al	1973	60	男性	左小指末節骨	不詳	round radio lucent	掻爬骨移植
Sugiura	1976	33	女性	左小指末節骨	2 年	well defined radiolucent area	掻爬
Ho et al	1980	27	女性	尾骨	不詳	NA	不詳
Pambakian et al	1981	14	女性	尾骨	1 カ月	erosion	切除術
Pambakian et al	1981	35	女性	尾骨	12 年	negative study	切除術
Chan	1981	42	女性	左環指末節骨	20 年	osteolytic	切断術
Rozmaryn et al	1986	24	女性	右尺骨	24 年	lytic defect	掻爬
Bjorkengren et al	1986	68	男性	右小指中節骨	5 年	radiolucent	掻爬
Kobayashi et al	1990	22	女性	仙骨	1 年	radiolucent	掻爬
Bessho et al	1991	49	男性	第 2 胸椎	不詳	NA	不詳
Simmons et al	1992	30	男性	左母指末節骨	2 年	radiolucent destructive	切断術
Johnson et al	1993	28	男性	右母指末節骨	18 カ月	destruction	切断術
Robinson et al	1996	45	女性	第 1 腰椎	4 年	lytic expansion	掻爬
Bahk et al	2000	34	女性	腓骨	1 カ月	lytic expansion	切除術
Settakorn et al	2001	53	女性	左示指末節骨	3 年	osteolytic	切除術
Kawasaki et al	2004	53	女性	右中指中節骨	3 年	osteolytic	掻爬骨移植
Urakawa et al	2008	25	女性	右尺骨	4 カ月	osteolytic	掻爬骨移植
Ishii et al	2009	54	女性	左中指末節骨	10 年	osteolytic	掻爬骨移植

治療は，骨外グロムス腫瘍と同様に骨内グロムス腫瘍も良性腫瘍であるため，切除または掻爬術で十分であるが，時に骨全体を破壊し浸潤する症例では切断に至る場合もある[1,3,4]．過去の骨内グロムス腫瘍報告例における治療法では，掻爬術がほぼ半数と最多であり，次に切除術，切断術が施行されている．自験例では掻爬術を施行し，再発はなく予後良好であった．

結　語

比較的稀な骨内グロムス腫瘍を経験し，報告した．

（患者は，得られた写真やデータが掲載されることについて説明を受け，その内容について同意した．）

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第19回日本小児整形外科学会学術集会

足関節部に発生したDysplasia epiphysealis hemimelicaの1例

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要　旨　2年にわたる右足関節部の腫瘤と足関節の可動域制限を主訴とする，6歳男児に発生した比較的まれなdysplasia epiphysealis hemimelicaの1例を経験した．右足関節部に直径5 cm大の骨性隆起と，関節可動域制限があり，単純X線像とCTでは脛骨遠位端および距骨と連続する2か所の病変を認めた．

確定診断と関節可動域制限の改善を目的に切除術を施行した．病理組織学的には骨軟骨腫に類似していたが，距骨および脛骨遠位骨端部から発生していたことから，dysplasia epiphysealis hemimelicaと診断した．術後関節可動域制限と歩容の改善が得られた．

はじめに

Dysplasia epiphysealis hemimelica(以下，DEH)は一般的に片側肢の長管骨の骨端部・関節内や距骨など扁平骨に発生する骨軟骨の過形成である．発症年齢は大部分が幼少期で，男児の足部に多く見られる．病理組織学的には軟骨帽を有する良性疾患であり，骨軟骨腫に一致する．今回，切除術によって足関節の良好な機能回復を得た比較的稀なDEHの1例を経験したので報告する．

症　例

症　例：6歳，男児

主　訴：右足関節前方の腫瘤と可動域制限

現病歴：4歳頃から母親は主訴に気付いていたが経過を見ていた．しかし，腫瘤は次第に増大し，歩行中にしばしば転倒するようになったため平成19年に当科を受診した．

既往歴：特記すべきことなし

初診時所見：全身状態に明らかな異常はなかった．右足関節前方には，可動性のない直径約5 cmの辺縁不整な球状の骨性隆起を認めた．自発痛，圧痛はなく，局所に発赤，熱感もなかった(図1)．足関節の可動域は自動運動，他動運動ともに背屈−15°であった．

画像所見：X線正面像(図2-a)では脛骨内側遠位骨端部に，側面像(図2-b)では距骨前方に骨化を思わせる異常陰影を認めた．CT(図3)では距骨前方に石灰化を伴う異常陰影を認めた．両側膝関節や左足関節に，単純X線像では異常所見はなかった．

臨床検査：特に異常所見はなかった．

以上により良性の骨軟骨性病変を疑って切除術を行った．

手術所見：約12 cmの足関節前方縦切開にて進入し，右足関節を展開した．関節包内には距骨に連続した直径約40 mm×40 mm，厚さ15 mm，表面が軟骨様の辺縁不整な球状の骨性病変を認めた(図4)．これとは別に足関節内側にも脛骨と連続する同じ性状の直径約10 mmの骨性隆起を認めた．関節包との癒着はなく，滑膜は軽度茶褐色に変色していた．関節軟骨を損傷しないように注意

Key words：dysplasia epiphysealis hemimelica(片肢性骨端異形成症)，bone tumor(骨腫瘍)，ankle joint(足関節)
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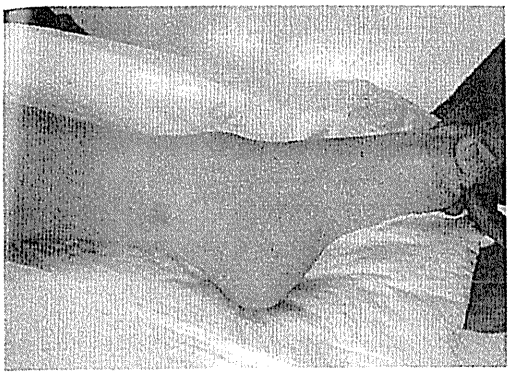

図 1. 肉眼所見
右足関節の前方および内側に骨性隆起を認めた.

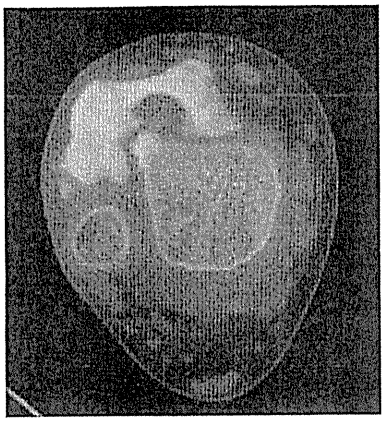

図 3. CT
脛骨および腓骨前方に骨性の異常陰影を認めた.

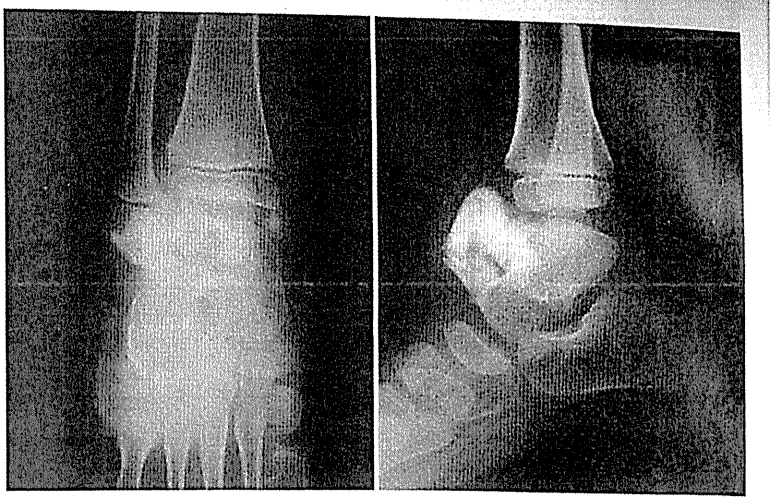

図 2. 単純 X 線像
a：正面像では脛骨内側遠位骨端部に骨化を思わせる小円形の異常陰影を認めた.
b：側面像では距骨前方に直径約 4 cm の骨化を思わせる異常陰影を認めた.

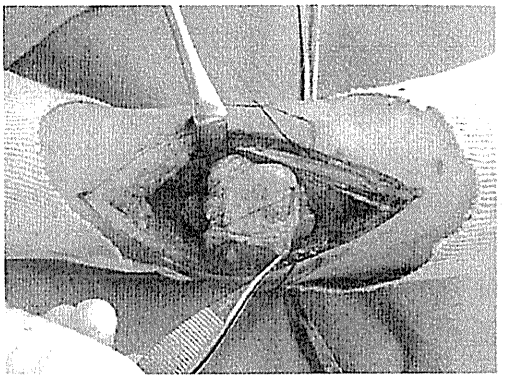

図 4. 術中所見
関節包を切開すると，既存骨と連続性した腫瘤があり腫瘤表面は白濁し軟骨帽様であった．関節包との癒着はなく，滑膜は軽度茶褐色に変色していた.

しつつ腫瘤を切除した.

病理組織学所見：腫瘤の表層は硝子軟骨からなる軟骨帽を有し，既存の骨梁と連続する内軟骨性骨化を呈する病変であり，骨軟骨腫と一致した(図 5-a，b).

腫瘤が骨端部より発生していたことから DEH と診断した.

術後経過：術後 1 年の現在，右足関節前方の骨性腫瘤は消失した．可動域は背屈 10° と改善し，歩容は改善された．転倒することはなくなり局所に疼痛もなく，再発もない(図 6-a，b).

なお，ヘルシンキ宣言にのっとり，両親に本症例を発表する事について，承諾を得ている.

考　察

DEH は 1926 年，Mounchet と Belot が tarso-megalie として報告したのを嚆矢とし，1956 年 Fairbank が DEH と命名し今日に至っている．DEH は一般的には片側肢の長管骨の骨端部・関節内や距骨などの扁平骨に単発あるいは多発する骨軟骨の過剰発育を示す骨系統疾患であり，病理組織診断学には骨軟骨腫像を示す[6]．発生頻度は 100 万人に 1 人と稀であり[2]，本邦では現在までに約 75 例が報告されているにすぎない[5]．遺伝性は未だ不明である．多くは 10 歳以下の小児期に発生し，男女比は 3 対 1 と男児に多い[6]．今日まで報告された症例の 2/3 が多発性である．発生部位は大腿骨遠位内側，脛骨近位内側および足関節が好発部位とされており[6]，自験例は 6 歳男子の