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Pain in Soft Tissue Tumors: A Comprehensive Retrospective Study

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Background: In the field of orthopedics, few studies have examined pain associated with soft tissue tumors. To accurately and promptly diagnose soft tissue tumors and provide appropriate treatment, it is necessary to have a comprehensive understanding of the relationship between soft tissue tumors and pain.

Methods: We analyzed data from patients with mass lesions in the extremities or trunk diagnosed by biopsy or surgery in our department and patients with ganglion cysts diagnosed by puncture between October 1, 2005, and September 30, 2011. Using medical records, we retrospectively investigated the clinical data.

Results: Data from 473 patients with 482 lesions were analyzed. Pain was observed in 204 of the 482 lesions (42.3%). So-called painful tumors accounted for approximately half of the painful lesions (45.0%). Logistic regression indicated that pain was significantly associated with so-called painful tumors (odds ratio [OR]: 5.64; $P < 0.001$), inflammatory nodules (OR: 3.42; $P = 0.007$), and sites with strong physical stimulation (OR: 2.45; 95% confidence interval [CI]: 1.58-3.81; $P < 0.001$) but not with long diameter (OR: 0.90; $P = 0.001$) or malignancy (OR: 1.78; $P = 0.144$).

Conclusion: Our findings suggest that so-called painful tumors account for approximately half of soft tissue mass lesions requiring surgery, biopsy, or puncture in orthopedics. It is thus important to have a clear understanding of such tumors. Inflammatory nodules are also important in the differential diagnosis of painful soft tissue lesions. Lesions at sites exposed to strong physical stimulation can cause pain. (J Nippon Med Sch 2025; 92: 80–87)

Key words: painful tumor, soft tissue tumor, pain, physical stimulation, radiating pain

Introduction

On July 16, 2020, the International Association for the Study of Pain revised its definition of pain to "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". In addition, six notes were added, including "pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors", "pain and nociception are different phenomena and pain cannot be inferred solely from activity in sensory neurons", and "through their life experiences, individuals learn the concept of pain"[1]. These definitions show that pain is difficult to evaluate objectively. However, in clinical practice, pain prompts patients to seek medical care and is one of the most important clinical symptoms in medical treatment.

X-ray examinations are extremely useful for objectively diagnosing bone tumors; however, X-ray examinations provide little information about soft tissue tumors. Thus, diagnosis is often based on clinical findings alone. Pain is a useful symptom for diagnosing soft tissue tumors. There are many "so-called painful tumors", including schwannomas, angioleiomyomas, venous malformations, glomus tumors, and angiolipomas[2–6]. Ganglion cysts can cause nerve entrapment syndrome[7,8]. MRI scans to identify the reason for pain sometimes reveal that small tu-

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mors are the cause. However, physicians may delay diagnosis to investigate other causes of the pain because they feel that the tumor is too small to be the cause of pain[9–12].

Cohen et al.[2] developed an acronym to describe painful cutaneous and subcutaneous masses as a memory aid for clinicians: "CALM HOG FLED PEN AND GETS BACK". In orthopedics, a report was published in 1987 stating that "one-third of all soft tissue tumors cause pain or discomfort". However, few studies have comprehensively examined pain associated with soft tissue tumors[13].

To accurately and promptly diagnose soft tissue tumors and provide appropriate treatment, the relationship between soft tissue tumors and pain must be better understood.

Patients and Methods

This study was approved by the relevant Institutional Review Board (No. F-2024-119) and was conducted in accordance with the principles of the Declaration of Helsinki.

Between October 1, 2005, and September 30, 2011, patients with mass lesions in the extremities or trunk diagnosed by biopsy or surgery in our department and patients with ganglion cysts diagnosed by puncture were included. Recurrent lesions were excluded. If multiple lesions were identified, only data for the main lesion were analyzed.

Using medical records, we retrospectively investigated clinical data, including pain at first visit, age at first visit, sex, disease duration before first visit, and lesion size (long diameter), site, and histological type. In addition, the proportion of painful lesions for each clinical variable was calculated, and the relationship between each clinical variable and pain was investigated. We compared pain findings for upper extremities, lower extremities, and trunk; for proximal and distal extremities; and for sites with strong physical stimulation and others. We arbitrarily defined the distal upper extremity as the forearm to the fingers, and the distal lower extremity as the leg to the toes. Additionally, multivariate analysis was used to compare five clinical factors putatively associated with pain: size (long diameter), sites with strong physical stimulation, so-called painful tumors, malignant tumors, and inflammatory nodules.

Presence of pain was defined as spontaneous pain, tenderness, pain on movement, or radiating pain. Radiating pain was defined as pain radiating to areas innervated by peripheral nerves related to the lesion. Pain spreading in nonspecific directions was excluded. Sites with strong physical stimulation were defined as the hands, feet, buttocks, and joints (if any part of the lesion was contained within the joint). So-called painful tumors were designated by using criteria from previous reports[2–5] (**Table 1**).

Statistical Analysis

The Mann-Whitney U test was used to analyze associations between presence of pain and age, and between presence of pain and lesion size. Differences in pain in relation to site were analyzed using the chi-square test, followed by Bonferroni correction, for post-hoc analysis for comparisons among the three groups. To analyze clinical factors associated with pain, logistic regression models were used to calculate adjusted odds ratios (ORs) and their 95% confidence intervals (CIs). A two-sided p value of <0.05 was considered significant. All statistical analyses were performed with an Excel statistical software package (BellCurve for Excel, ver. 2.15, 2017; Social Survey Research Information Co., Ltd., Tokyo, Japan).

Results

The subjects were 473 patients with 482 lesions. Pain was observed in 204 of the 482 lesions (42.3%) (**Table 1**). Spontaneous pain was observed in 56 lesions, tenderness in 170 lesions, pain on motion in 83 lesions, and radiating pain in 42 lesions. Painful lesions included schwannomas, epidermal cysts, angioleiomyomas, ganglion cysts, inflammatory lesions, malignant tumors, and venous malformations (deep) (**Table 1**). So-called painful tumors, such as schwannoma, angioleiomyoma, venous malformation, glomus tumor, neurofibroma, and angiolipoma, accounted for 92 of 204 (45%) of painful lesions (**Table 1**).

Pain was observed in 13 of 46 (28.3%) malignant tumors, including liposarcoma, undifferentiated pleomorphic sarcoma, and malignant lymphoma (**Table 2**). Inflammatory lesions, such as infection and hematoma, were associated with pain in 14 of 24 cases (58.3%) (**Table 3**). Among painful lesions, 20.6% (42/204) had radiating pain, of which schwannomas and ganglion cysts were the most common (**Table 4**). The nerves involved were the median nerve, tibial nerve, and cutaneous nerve (six lesions); peroneal nerve (five lesions); radial nerve, ulnar nerve, and digital nerve (four lesions); sciatic nerve and sural nerve (three lesions); and saphenous nerve (one lesion) (**Table 4**). Among mass lesions with radiating pain, 52% were schwannomas. Among all schwannomas, 51% of lesions had radiating pain. Of the six ganglion cysts in which radiating pain was observed, four lesions caused nerve entrapment syndrome (**Table 4**).

Table 1 Lesions with pain

Diagnosis	Pain (+)	Pain (–)	Rate[a] (%)	Location
Schwannoma[b]	31	12	72.1	Forearm (5), Upper arm (4), Leg (4), others (18)
Epidermal cyst	21	31	40.4	Foot (9), Hand/finger (5), others (3)
Angioleiomyoma[b]	19	0	100.0	Forearm (5), Foot/toe (3), Ankle (3), others (8)
Ganglion cyst	15	9	62.5	Foot/toe (5), Ankle (3), Hand/finger (3), others (5)
Inflammatory lesions	14	10	58.3	Hand/finger (4), others (9)
Malignant tumors[c]	13	33	28.3	Thigh (4), Buttock (3), others (6)
Venous malformation (deep)[b]	11	2	84.6	Thigh (5), others (8)
Lipoma (deep)	9	43	17.3	Thigh (3), others (6)
Lipoma (superficial)	9	60	13.0	Foot/toe (2), others (7)
Venous malformation (superficial)[b]	8	6	57.1	Hand/finger (5), others (3)
IPEH[d]	6	1	85.7	Hand/finger (4), others (2)
SOD[e]	6	3	66.7	Knee (3), others (3)
TGCT[f]	6	17	26.1	Hand/finger (3), Foot/toe (3)
Glomus tumor[b]	4	0	100.0	Hand/finger (2), Foot/toe (2)
Neurofibroma[b]	4	0	100.0	Leg (2), others (2)
Meniscal cyst	3	0	100.0	Knee (3)
EADT[g]	3	1	75.0	Upper arm (2), other
Nodular fasciitis[b]	3	6	33.3	Thigh (2), Forearm
Thrombus (organizing)[b]	2	2	50.0	Hand/finger, Foot/toe
PVS[h]	2	3	40.0	Ankle, Foot/toe
Angiolipoma[b]	2	3	40.0	Upper arm, Forearm
Calcifying epithelioma	2	3	40.0	Neck, Forearm
Others	11[i]	33	21.2	Foot/toe (4), other (7)
Total	204	278	42.3	

[a] pain association rate. [b] so-called painful tumors. [c] including epithelioid hemangioendothelioma[b]. [d] intravascular papillary endothelial hyperplasia. [e] synovial osteochondromatosis. [f] tenosynovial giant cell tumor. [g] extra-abdominal desmoid tumor. [h] pigmented villonodular synovitis. [i] including heterotopic endometriosis[b], Morton neuroma[b], calcinosis cutis[b], eccrine spiradenoma[b], and dermatofibroma[b].

Table 2 Malignant tumors with pain

Diagnosis	With pain	Without pain	Rate[a] (%)
Liposarcoma	3	12	20.0
Well-differentiated	*2*	*4*	*33.3*
Myxoid	*1*	*7*	*12.5*
Dedifferentiated	*0*	*1*	*0.0*
Malignant lymphoma	2	5	28.5
Undifferentiated pleomorphic sarcoma	2	6	25.0
Epithelioid hemangioendothelioma	1	0	100.0
Epithelioid sarcoma	1	0	100.0
Extraskeletal myxoid chondrosarcoma	1	0	100.0
Pleomorphic rhabdomyosarcoma	1	0	100.0
Myxofibrosarcoma	1	3	25.0
Soft tissue metastasis	1	4	20.0
Clear cell sarcoma	0	1	0.0
Solitary fibrous tumor, malignant	0	1	0.0
Synovial sarcoma	0	1	0.0
Total	13	33	28.3

[a] pain association rate.

Table 3 Inflammatory lesions with pain

Diagnosis	With pain	Without pain	Rate[a] (%)
Infection	6	1	85.7
Hematoma	3	1	75.0
Arthritis	2	0	100.0
Rheumatoid arthritis	2	0	100.0
Sarcoidosis	1	1	50.0
Panniculitis	0	1	0.0
Tophus	0	1	0.0
Lymphadenitis	0	2	0.0
Bursitis	0	3	0.0
Total	14	10	58.3

[a] pain association rate.

Table 4 Lesions with radiating pain

Diagnosis	RP[a] (+)	RP (–)	Rate[b] (%)	Associated nerve (n)
Schwannoma	22	21	51.2	Median N (4), Radial N (4), Peroneal N (4), Ulnar N (3), Cutaneous N (3), Sural N (2), Saphenous nerve, Tarsal tunnel syndrome
Ganglion cyst	6	18	25.0	Tarsal tunnel syndrome (3), Sural N, Carpal tunnel syndrome, Peroneal N
Malignant tumors	3	43	6.5	Sciatic N (3)
Neurofibroma	2	2	50.0	Tibial N, Cutaneous N
Angioleiomyoma	2	17	10.5	Digital N, Cutaneous N
Lipoma	2	67	2.9	Carpal tunnel syndrome, Digital N
Morton neuroma	1	0	100.0	Digital N
Angiolipoma	1	4	20.0	Cutaneous N
VM[c] (deep)	1	12	7.7	Sciatic N
VM[c] (superficial)	1	13	7.1	Digital N
Epidermal cyst	1	51	1.9	Ulnar N
Total	42	248	14.5	

[a] radiating pain. [b] pain association rate. [c] venous malformation.

The overall median age of the patients was 53.0 years (interquartile range [IQR] 38.0-65.0) (**Table 5**). Patients with painful lesions were significantly younger (median 48.5 years, IQR 34.8-64.0) than those with painless lesions (median 57.0 years, IQR 40.0-67.0) (P = 0.002) (**Table 5**). There were 237 men and 245 women. The proportion of painful lesions was higher in women (46.1%, 113/132) than in men (38.4%; 91/146); however, the difference was not significant (P = 0.086) (**Table 5**). The median disease duration before the first visit for all lesions was 12 months (IQR 2.0-48.0). There was no significant difference in disease duration for painful lesions (median 12.0 months, IQR 3.0-36.0) and painless lesions (median 12.0 months, IQR 1.0-60.0) (**Table 5**). The median long diameter of all lesions was 3.0 cm (IQR 1.6-6.0). Long diameter was significantly shorter for painful lesions (median 2.1 cm, IQR 1.2-4.0) than for painless lesions (median 4.2 cm, IQR 2.3-7.4) ($p < 0.001$) (**Table 5**).

The number of painful lesions, by site, was 115 in the lower extremities, 76 in the upper extremities, and 13 in the trunk (**Table 5, 6**). The proportion of painful lesions at each site was significantly higher in the lower extremities (51.1%, 115/225) than in the upper extremities (40.4%, 76/188, P = 0.03) and trunk (18.8%, 13/69, P < 0.001), and significantly higher in the upper extremities than in the trunk (P = 0.013), using Bonferroni correction (**Table 5**). The number of painful lesions was significantly higher in the distal extremities (56 upper limbs, 73 lower extremities) than in the proximal extremities (20 upper extremities, 42 lower extremities), and the proportion of painful lesions was significantly higher in the distal extremities (50.9%, 56/110 upper extremities, 69.5%, 73/105 lower extremities) than in the proximal extremities (25.6%, 20/78 upper extremities, 35.0%, 42/120 lower extremities) (upper extremities, P < 0.001; lower extremities, P < 0.001) (**Table 5**). The proportion of painful lesions at

Table 5 Presence of pain, by clinical variable

		All lesions	Painful lesions	Painless lesions	Rate[a] (%)	P-value
Age, median (IQR[b])		53.0 (38.0-65.0)	49.0 (34.8-64.0)	57.0 (40.0-67.0)		0.002
Sex	Male	237	91	146	38.4	0.086
	Female	245	113	132	46.1	
Disease duration[c], median (IQR)		12.0 (2.0-48.0)	12.0 (3.0-36.0)	12.0 (1.0-60.0)		0.96
Long diameter, median (IQR)		3.0 (1.6-6.0)	2.1 (1.2-4.0)	4.2 (2.3-7.4)		<0.001
Location						
Trunk vs. Extremities	Trunk	69	13	56	18.8	<0.001[d]
	UE.[e]	188	76	112	40.4	
	LE.[f]	225	115	110	51.1	
Proximal vs. Distal	UE. prox.[g]	78	20	58	25.6	<0.001
	UE. dist.[h]	110	56	54	50.9	
	LE. prox.	120	42	78	35.0	<0.001
	LE. dist.	105	73	32	69.5	
Sites with stimulation[i]	Yes	181	102	79	56.4	<0.001
	No	301	102	199	33.9	
So-called painful tumor	Yes	123	88	35	72.7	<0.001
	No	359	116	243	32.1	
Malignant tumor	Yes	46	13	33	28.3	0.042
	No	436	191	245	43.8	
Inflammatory nodule	Yes	24	14	10	58.3	0.10
	No	456	190	268	41.7	

[a] pain association rate. [b] interquartile range. [c] disease duration until the first visit. [d] upper extremity and lower extremity are significantly different from trunk (P = 0.013 and P<0.001 respectively, Bonferroni correction) and lower extremity is significantly different from upper extremity (P = 0.03 Bonferroni correction). [e] upper extremity. [f] lower extremity. [g] proximal. [h] distal. [i] sites with strong physical stimulation.

sites exposed to strong physical stimulation was significantly higher (56.4%, 102/81) than those not exposed strong physical stimulation (33.9%, 102/301) (P < 0.001) (**Table 5**).

Logistic regression revealed that pain was significantly associated with so-called painful tumors (OR: 5.64; 95% CI: 3.44-9.24; P < 0.001), inflammatory nodules (OR: 3.42; 95% CI: 1.40-8.33; P = 0.007), and sites with strong physical stimulation (OR: 2.45; 95% CI: 1.58-3.81; P < 0.001), but not with long diameter (OR: 0.90; 95% CI: 0.84-0.96; P = 0.001) or malignancy (OR: 1.78; 95% CI: 0.82-3.85; P = 0.144) (**Table 7**).

Discussion

The most important finding of this study was that among painful mass lesions diagnosed by surgery or biopsy and ganglion cysts diagnosed by puncture during orthopedic surgery, approximately half were so-called painful tumors. There have been several reports in the field of dermatology, and many so-called painful tumors have been described[2,3,6]. Among them, schwannomas, angioleiomyomas, venous malformations (deep and superficial), and glomus tumors are common in orthopedics. A thorough understanding of so-called painful tumors is thus essential for treating soft tissue tumors.

The characteristics of typical painful tumors are described below. Schwannomas are characterized by radiating pain and limited mobility along the nerve. The tumor is enveloped by the epineurium and grows eccentrically along the long axis of the nerve, compressing the nerve fibers. Angioleiomyomas are subcutaneous tumors that are usually less than 2 cm in size and most frequently develop in the lower extremities. Although small, such tumors often cause severe pain. Caution is required, as they may remain undiagnosed because the pain is disproportionate to the size of the lesion[14]. Pain may be mediated by the nerve fibers, especially those located within the tumor parenchyma[15]. Venous malformation is a congenital disorder that is often diagnosed in childhood or adolescence and may be accompanied by changes in skin color. Pain is often intermittent, but if the lesion is located in muscle, pain often occurs with movement. Plain X-rays may show phleboliths. Pain may be caused by intralesional thrombosis or localized intravascular coagulation due to blood stagnation in the venous malformation[16,17]. Glomus tumors often occur under the nail. They

Table 6 Sites of painful and painless lesions

Location	With pain	Without pain	Rate[a] (%)
Upper extremity	76	112	40.4
Shoulder	*3*	*27*	*10.0*
Axilla	*1*	*6*	*14.3*
Upper arm	*6*	*14*	*30.0*
Elbow	*10*	*11*	*47.6*
Forearm	*12*	*11*	*52.2*
Wrist	*4*	*3*	*57.1*
Hand	*10*	*8*	*55.6*
Finger	*30*	*32*	*48.4*
Lower extremity	115	110	51.1
Buttock	*9*	*14*	*39.1*
Inguinal	*1*	*5*	*16.7*
Thigh	*20*	*39*	*33.8*
Knee	*12*	*20*	*37.5*
Leg	*18*	*6*	*75.0*
Ankle	*11*	*6*	*64.7*
Foot	*31*	*14*	*68.9*
Toe	*13*	*6*	*68.4*
Trunk	13	56	18.8
Neck	*1*	*17*	*5.6*
Chest	*5*	*8*	*38.5*
Upper back	*3*	*24*	*11.1*
Abdomen	*1*	*5*	*16.7*
Lower back	*3*	*2*	*60.0*
Total	204	278	42.3

[a] pain association rate.

Table 7 Factors related to pain

Factors	OR[a]	95% CI[b]	P-value
Long diameter	0.90	0.84-0.96	0.001
Sites exposed to frequent stimulation[c]	2.45	1.58-3.81	<0.001
So-called painful tumors	5.64	3.44-9.24	<0.001
Malignant tumors	1.78	0.82-3.85	0.144
Inflammatory nodules	3.42	1.40-8.33	0.007

[a] odds ratio. [b] confidence interval. [c] sites with strong physical stimulation.

are often less than 1 cm in size but are very painful. Plain X-rays may reveal erosion of the distal phalanx. Love's, Hildreth's, and cold sensation (cold water or alcohol) tests are useful for diagnosis[18]. Pain may be related to substance P and cyclooxygenase-2 found in such tumors[19]. Angiolipomas are spherical tumors, usually less than 2 cm in diameter, that most frequently develop on the forearm. It is not uncommon for multiple lesions to occur. In 20-30% of cases, pain or tenderness is present, particularly during tumor growth, and tends to subside after the tumor reaches its maximum size. Histologically, thrombi, which are found in large numbers in areas where blood vessels are concentrated, are believed to be the cause of pain[20]. When these painful tumors are difficult to diagnose by history or physical findings, MRI scans can be useful[21–25].

In the present study, the presence of a lesion at a site with strong physical stimulation, such as the hands, feet, buttocks, and joints (if any part of the lesion was contained within the joint), was significantly associated with pain. In daily life, the hands are frequently subjected to mechanical pressure during grasping, holding, lifting, and other actions. When standing and walking, mechanical pressure is applied to the soles of the feet, and pressure from shoes applies mechanical pressure to parts of the foot other than the soles. When sitting, the buttocks

are constantly subjected to strong localized mechanical pressure. Strong mechanical pressure is applied to joints during weight bearing and exercise. Epidermal cysts and lipomas in the hands and feet, and meniscal cysts in the knee joint, are thought to be typical examples of lesions that cause pain because of their presence at sites with strong physical stimulation.

The present study showed no association between lesion size and pain. Moreover, there was no association between malignancy and pain. Iida et al.[26] reported in a study of soft tissue sarcomas less than 2 cm in diameter that all seven patients with lesions in the hands and feet had pain, but only two of 10 patients with lesions at other sites had pain. Rooser et al.[27] reported that seven of 10 patients with high-grade tumors had pain at rest and an intratumoral pressure of 65 mmHg or higher; the other three patients had no pain at and an intratumoral pressure less than 65 mmHg. There was no pain at rest in low-grade tumors or benign tumors, all of which had intratumoral pressures less than 46 mmHg. Their findings suggested that increased intratumoral pressure in tumors with a fast growth rate may be related to pain at rest. There was no correlation between pain and tumor size in their report.

We found that 52% of mass lesions with radiating pain were schwannomas. Thus, when radiating pain is present in a patient with a soft tissue mass, it is important to consider that, in addition to schwannoma, it could be a variety of other tumors, including ganglion cyst. Furthermore, we found that the proportion of lesions with radiating pain among all schwannomas was 51%; thus, when removing a mass that does not have radiating pain, it is important to consider that it may be a schwannoma, to avoid damage to peripheral nerves that could potentially be spared[28]. In a study of 99 patients with extremity schwannoma who underwent surgery, 45% had radiating pain[29]. El Sayed et al.[30] reported that among 150 patients with extremity schwannoma who underwent surgery, Tinel-like signs were observed in 55.7%. Rockwell et al.[28] reported that of 21 patients with schwannomas of the hand or wrist that underwent surgery, only four schwannomas were diagnosed preoperatively and eight were diagnosed as ganglion tumors.

This study has several limitations. First, sampling bias is a concern because the study was limited to lesions in patients who underwent biopsy or surgery, or ganglion cysts diagnosed by puncture. Second, the study was retrospective. Third, pain is subjective, which results in bias. Despite these limitations, we believe this study is the first to carefully examine the association between soft tissue tumors and pain. Furthermore, this study is clinically based and applicable to everyday practice.

In summary, we found that so-called painful tumors account for approximately half of painful soft tissue mass lesions that require surgery, biopsy, or puncture in the field of orthopedics. Thus, our findings highlight the necessity of a clear understanding of such tumors in clinical orthopedics practice. Lesions at sites with strong physical stimulation, such as the hands, feet, buttocks, and joints, may cause pain, especially if part of the lesion is contained within a joint. However, there is no association between malignancy and pain or between lesion size and pain. Only about half of tumors with radiating pain are schwannomas, and only about half of schwannomas are associated with radiating pain. When resecting a tumor without radiating pain, it is important to consider that the tumor may be a schwannoma, to avoid damage to peripheral nerves that could be spared.

Conflict of Interest: The authors declare no conflicts of interest.

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