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Characteristics of Patients with Giant Cell Tumor of Bone and High Serum Tartrate-Resistant Acid Phosphatase 5b Levels: Comparison of Tumor Volume and Clinical Factors

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Background: Serum tartrate-resistant acid phosphatase 5b is well known to be increased in giant cell tumors of bone. However, there are only a few studies that analyzed the association with tartrate-resistant acid phosphatase 5b expression in those patients. Therefore, we analyzed the characteristics of patients with giant cell tumors of bone and high tartrate-resistant acid phosphatase 5b expression.

Methods: This retrospective study included 26 patients with giant cell tumors of bone. The correlation between tartrate-resistant acid phosphatase 5b before initial treatment and tumor volume was evaluated. Patients were divided into two groups according to tartrate-resistant acid phosphatase 5b level. Statistical analysis was performed between the two groups.

Results: Tartrate-resistant acid phosphatase 5b was elevated in 17/26 patients, and the mean value was 852 mU/dL. There was no correlation with tumor volume (r = 0.034, P = 0.86). The mean age of 34.5 years in the HT group was significantly younger than the mean age of 47.4 years in the LT group (P = 0.040). Pathologically, 19/26 cases showed at least one focal area with features of typical giant cell tumor of bone. Although 11/18 patients in the LT group exhibited relatively noticeable secondary changes, all patients in the HT group exhibited typical features (P = 0.0074).

Conclusions: Tartrate-resistant acid phosphatase 5b levels were not elevated in some giant cell tumors of bone. This study suggested that tartrate-resistant acid phosphatase 5b may be elevated in younger patients and in cases with fewer pathological secondary changes, regardless of tumor volume.

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Key words: tartrate-resistant acid phosphatase 5b, TRACP 5b, giant cell tumor of bone, GCTB

Introduction

Serum tartrate-resistant acid phosphatase 5b (TRACP 5b) is a unique and clinically relevant biomarker of osteoclasts in metabolic and pathologic bone diseases[1]. The relationship between serum TRACP 5b and systemic osteoclast number was recently confirmed in vivo and clinical studies[2–4]. Serum TRACP 5b is known as a bone resorption marker for bone metastasis, such as that from breast cancer[5,6], lung cancer[7], and prostate cancer[8]. Some studies have reported an association with serum TRACP 5b and primary bone tumors, including osteosarcoma and giant cell tumor of bone (GCTB)[9–12].

GCTB is a primary bone tumor that occurs predominantly in the epiphyses of long bones and presents with locally aggressive osteolysis[13]. GCTB comprises spindle-like stromal cells and multinucleated giant cells that exhibit many of the properties of osteoclasts[14]. Giant cells express characteristics similar to osteoclasts such as TRACP, cathepsin K, and receptor activator of nuclear factor-kB ligand (RANKL)[14]. Due to the nature of

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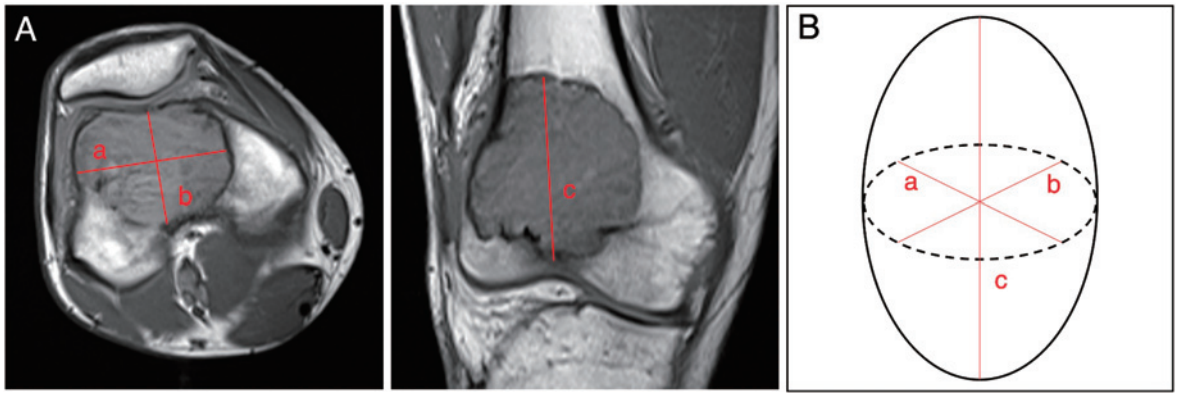

Fig. 1 Tumor volume measurement in this study. A. We measured the major axis (a), the minor axis (b) at the largest cross-section, and the maximum diameter of the orthogonal axis (c). B. Tumor volume was calculated as 4/3×π×a/2×b/2×c/2.

osteoclast-like giant cells, it has been suggested that serum TRACP 5b may become a specific marker for GCTB[10–12].

In the previous work, Hayashida et al. reported high TRACP 5b levels with an average of 1,077 mU/dL in pretreatment GCTB samples[15]. With respect to the mean, TRACP 5b levels were considerably elevated in some cases, while they were not elevated in the other cases. It is well known that GCTB shows a wide variety of morphological and imaging features, especially in younger or older patients[16,17]. Because these features have a risk of leading to misdiagnosis, establishing an indicator for evaluating GCTB is important. Although TRACP 5b may be applied to assess the status of GCTB less invasively and objectively, it is still unclear what factors affect TRACP 5b.

Previous studies have focused on changes in serum TRACP 5b levels with treatment and local recurrence, suggesting that TRACP 5b may sensitively reflect GCTB status[11,12,15]. It has been reported that TRACP 5b increases with the number of systemic osteoclasts[3,4], so it is expected that TRACP 5b will be higher if the tumor volume is large. However, contradictory results have been reported regarding the association between tumor size and serum TRACP 5b levels[10,11]. Therefore, we evaluated serum TRACP 5b levels before treatment for GCTB and examined their association with tumor volume. Furthermore, to clarify the factors that influence serum TRACP 5 b levels, we divided the patients into two groups according to the TRACP 5b level and analyzed the clinical factors.

Materials and Methods

The Institutional Review Board of our university approved the study design (Approval number: B200600056). All patients who were referred to our clinic due to suspicion of osteolytic bone tumors and diagnosed with histologically confirmed GCTB during April 2014 - March 2021 were included in this study. We retrospectively reviewed the medical records of 26 patients (13 male and 13 female) with a mean age of 45.5 (15-78) years who had serum TRACP 5b levels measured before treatment. All patients underwent plain radiography, magnetic resonance imaging (MRI), blood tests including serum TRACP 5b, and fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) before treatment. Only one patient could not be evaluated by FDG-PET/CT due to the schedule of biopsy. Intralesional curettage with high-speed burring was performed in 24 patients. Tumor resection and replacement with megaprosthesis were performed in one patient. Patients who were not evaluated for serum TRACP 5b before treatment and who were treated with medication that affected bone metabolism, such as bisphosphonates, selective estrogen receptor moderators (SERMs), denosumab, human parathyroid hormone, and anti-sclerostin antibodies, were excluded.

Tumor size and tumor volume were measured by MRI in all cases. The maximum diameter on the largest cross-section was considered the tumor size. We considered all tumor lesions ellipsoidal, and tumor volume was approximated with the standard mathematical formula for ellipses[18]. We measured the major axis (a), the minor axis (b) at the largest cross-section, and the maximum diameter of the orthogonal axis (c). Tumor volume was calculated as 4/3×π×a/2×b/2×c/2 (**Fig. 1**). The correlation between tumor volume and TRACP 5b expression was evaluated using Pearson's product-moment correlation

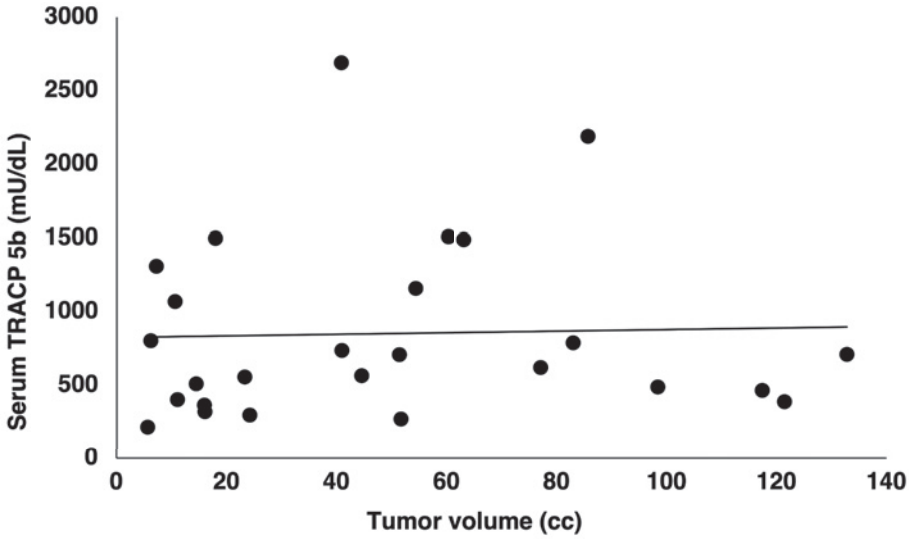

Fig. 2 Correlation with regression lines of tartrate-resistant acid phosphatase 5b (TRACP 5b) and tumor volume. No significant correlation was found between tumor volume and TRACP 5b (r = 0.034, P = 0.86).

analysis.

We divided patients into two groups according to serum TRACP 5b level. Considering metabolic factors such as osteoporosis, 8 patients with serum TRACP 5b greater than 852 mU/dL, the median of this study, were classified into the high TRACP 5b group (HT group), and 18 patients with serum TRACP 5b less than 852 mU/dL were classified into the low TRACP 5b group (LT group). We analyzed clinical characteristics, including age, sex, tumor location, Campanacci classification, tumor size, tumor volume, pathological secondary change, maximum standard uptake value (SUVmax) of FDG-PET/CT, pathological fracture, denosumab administration, and local recurrence. Cases in which denosumab was administered even once during the follow-up period were considered to be treated with denosumab.

We retrospectively reviewed the pathological reports in our institution for pathological evaluation. Hematoxylin and eosin (H&E) staining and immunohistochemistry for anti-histone H3.3 G34W (G34W; a specific marker of GCTB) were performed on the specimens obtained by biopsy and operation. The primary antibody used was anti-histone H3.3 G34W (rabbit monoclonal, clone RM 263, 31-1145-00, dilution 1:400; RevMAb Biosciences, San Francisco, CA, USA). Secondary changes were assessed according to the histological features of H&E staining. G 34W immunostaining was performed for diagnosis in 23 of 26 cases.

We compared clinical factors between the two groups and performed a statistical analysis. In the univariate analysis, Student's t test and Mann-Whitney U test were performed for continuous variables, and Fisher's exact test was performed for categorical variables. P values less than 0.05 were considered to indicate significance in all statistical analyses. All statistical analyses were performed using R (R Core Team (2020); R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

Serum TRACP 5b increased in 17/26 cases (65.4%), with a mean value of 852 (215-2,690) mU/dL. Mean tumor volume was 42.6 (5.6-132.7) cc. No significant correlation was found between tumor volume and TRACP 5b level (r = 0.034, P = 0.86. **Fig. 2**). The profile of the HT group is summarized in **Table 1**. Eight patients with a mean age of 34.5 (15-66) years included 3 males and 5 females. The mean serum TRACP 5b level in the HT group was 1,615 (1,070-2,690) mU/dL. Four of 8 cases occurred in the distal radius. Campanacci stage II and III were identified in 4 patients each. Local recurrence was observed in 5 patients, and denosumab was administered in 8 patients. The profile of the LT group is summarized in **Table 2**. Eighteen patients with a mean age of 47.4 (29-77) years included 10 males and 8 females. The mean serum TRACP 5b in the LT group was 512 (215-803) mU/dL. Nine of 18 cases occurred in the distal femur. Statistical analysis of both groups is summarized in **Table 3**. Campanacci stages I, II, and III were identified in 4, 7 and 5 patients, respectively. Local recurrence was observed in 6

Table 1 Characteristic of the high tartrate-resistant acid phosphatase 5b (TRACP 5b) group

Patient No.	Age	Sex	Location	Campanacci classification	Tumor size (mm)	Tumor volume (cc)	Serum TRACP 5b[a] (mU/dL)	Secondary change	SUVmax of FDG-PET/CT[b]	Pathological fracture	Denosumab administration	Local recurrence
1	17	F	radius	II	25.7	7.2	1,310	–	11.6	–	+	+
2	39	F	radius	II	63.0	54.2	1,160	–	9.8	–	+	+
3	35	M	femur	II	57.0	63.4	1,490	–	8.2	–	+	+
4	35	M	radius	III	36.2	10.6	1,070	–	8.9	–	+	+
5	26	M	femur	II	54.8	60.1	1,510	–	10.2	–	+	–
6	15	F	radius	III	37.4	17.9	1,500	–	8.5	–	+	+
7	43	F	tibia	III	70.4	85.9	2,190	–	9.4	–	+	–
8	66	F	sacrum	III	54.8	40.7	2,690	–	9.4	–	+	–

[a]TRACP 5b: tartrate-resistant acid phosphatase 5b, [b]SUVmax of FDG-PET/CT: maximum standard uptake value of (18) fluro-deoxyglucose positron emission tomography with computed tomography

Table 2 Characteristic of the low tartrate-resistant acid phosphatase 5b (TRACP 5b) group

Patient No.	Age	Sex	Location	Campanacci classification	Tumor size (mm)	Tumor volume (cc)	Serum TRACP 5b[a] (mU/dL)	Secondary change	SUVmax of FDG-PET/CT[b]	Pathological fracture	Denosumab administration	Local recurrence
1	45	F	radius	III	41.9	23.2	556	+	9.5	–	+	+
2	52	M	femur	II	65.3	121.4	790	+	6.1	–	+	–
3	43	M	ulna	II	32.2	16.0	803	–	8.2	–	+	+
4	62	F	radius	II	35.6	83.2	510	–	7.6	–	+	+
5	38	F	femur	III	57.4	6.2	709	–	7.1	–	+	–
6	30	F	femur	III	72.9	14.4	489	+	8.5	+	+	–
7	37	F	femur	II	59.5	51.2	622	–	9.4	–	+	+
8	51	M	tibia	II	71.9	11.0	711	–	8.8	–	–	–
9	78	M	femur	II	52	24.1	738	+	9.1	–	–	–
10	49	M	tibia	III	68.1	117.4	389	+	7.8	–	+	+
11	33	M	tibia	I	40.1	98.5	320	+	10.2	–	+	+
12	46	F	tibia	I	32.3	77.3	403	–	8.7	–	–	–
13	45	F	femur	I	36.5	51.5	298	+	11.6	–	–	–
14	29	M	femur	III	59.6	15.9	465	+	8.5	+	+	–
15	54	M	femur	II	50.1	132.7	270	+	8.5	+	–	–
16	58	M	radius	II	34.0	44.4	366	+	4.8	–	–	–
17	42	M	femur	I	57.1	40.8	566	–	6.9	–	–	–
18	62	F	fibula	II	23.6	5.6	215	+	NE[c]	–	–	–

[a]TRACP 5b: tartrate-resistant acid phosphatase 5b, [b]SUVmax of FDG-PET/CT: maximum standard uptake value of (18) fluro-deoxyglucose positron emission tomography with computed tomography, [c]NE: not evaluated

patients, and denosumab was administered to 10 patients. Plain radiographs showed a radiolucent zone with a distinct margin in 23 cases, while 3 cases showed destruction in the cortex with soft tissue infiltration. MRI showed cystic changes in more than 50% of the tumors in 9 cases.

According to the pathological findings, all cases in the HT group and 11 of 18 cases in the LT group mainly showed classic features of GCTB, which included round mononuclear cells within a background of evenly spaced osteoclast-like giant cells. Pathological secondary changes were widely observed in 7 patients in the LT group. Fibrohistiocytic changes, foamy macrophages, reactive bone formation, xanthogranulomatous changes and aneurysmal bone cyst changes were observed as secondary changes. G34W immunostaining was performed in 23 of 26 cases and positively stained in some stromal cells in all cases. In one case, xanthogranulomatous changes were predominant, and no classic morphological features of GCTB were found. The case was diagnosed as GCTB by imaging findings, clinical course, and G34W immunostaining.

Table 3 Statistical analysis of both groups

Variables		Case number or mean value		Univariate analysis
		HT[a] group (n = 8)	LT[b] group (n = 18)	p-value
Age (years old)		34.5 (17 - 66)	47.4 (29 - 78)	0.040
Sex	Male	3	10	0.67
	Female	5	8	
Location	Femur/tibia	3	13	0.19
	Others	5	5	
Campanacci stage	III	4	5	0.38
	I or II	4	13	
Tumor size (mm)		49.9 (25.7 -70.4)	49.5 (23.6 - 72.9)	1
Tumor volume (cc)		47.5 (7.2 – 85.9)	42.6 (5.6 – 132.7)	0.85
Serum TRACP 5b[c] (mU/dL)		1,615 (1,070 - 2,690)	512 (215 - 803)	NE[f]
Pathological	Yes	0	11	0.0074
secondary change	No	8	7	
SUVmax of FDG-PET/CT[d]		9.5 (8.2 - 11.6)	8.3 (4.8 - 11.6)	0.058
Pathological fracture	Yes	0	3	0.53
	No	8	15	
Denosumab administration	Yes	8	10	0.031
	No	0	8	
Local recurrence	Yes	5	6	0.22
	No	3	12	
Observation period (month)[e]		10 (n = 5)	18 (n = 6)	0.053

P values less than 0.05 were considered to indicate significance. [a]HT: high tartrate-resistant acid phosphatase 5b, [b]LT: low tartrate-resistant acid phosphatase 5b, [c]TRACP 5b: tartrate-resistant acid phosphatase 5b, [d]SUVmax of FDG-PET/CT: maximum standard uptake value of (18) fluro-deoxyglucose positron emission tomography with computed tomography, [e]Observation period: period from initial treatment until local recurrence, [f]NE: not evaluated

A comparison of the two groups revealed significant differences in age, secondary changes, and denosumab administration (P = 0.040, 0.0074, 0.031, respectively). The mean age was lower in the HT group, and secondary changes were more common in the LT group. The SUVmax of FDG-PET/CT was 9.5 in the HT group and 8.3 in the LT group, but no significant difference was observed (P = 0.058). Local recurrence was observed in 5/8 patients in the HT group and 6/18 patients in the LT group, but there was no significant difference (P = 0.22). The mean maximum tumor diameter and tumor volume were 49.9 mm and 47.5 cc in the HT group and 49.5 mm and 42.6 cc in the LT group, respectively.

Representative cases with high serum TRACP 5b values and small tumor volumes and cases with low serum TRACP 5b values with secondary changes are shown in **Figure 3** and **Figure 4**. A case of a 15-year-old female with GCTB in the distal radius is shown **Figure 3**. Serum TRACP 5b was high at 1,500 mU/dL, but the tumor volume was 17.9 cc, which was much smaller than the average. A case of a 42-year-old male with GCTB in the distal femur is shown **Figure 4**. No classic features of GCTB (a mixture of mononuclear cells and osteoclast-like giant cells) were observed in the entire tumor, but approximately half of the spindle-shaped cells were positive for G34W immunostaining. The tumor was diagnosed as GCTB with secondary changes. The tumor volume was 40.8 cc, and the serum TRACP 5b level was 566 mU/dL.

Discussion

We investigated the characteristics of serum TRACP 5b in GCTB. TRACP 5b is secreted into the circulation by osteoclasts; thus, serum TRACP 5b is useful as a marker of osteoclast activity and bone resorption. The normal ranges for TRACP 5b are 170-590 mU/dL for men and 120-420 mU/dL for women. This study showed that serum TRACP 5b was in the normal range in approximately 1/3 of patients with GCTB. In addition, there was no significant correlation between tumor volume and serum TRACP 5b level. This result suggests that serum TRACP 5b is influenced by the nature of tumors rather than the size of the entire lesion. To clarify the factors associated with TRACP 5b, we divided the patients into two groups. It has been reported that serum TRACP 5b

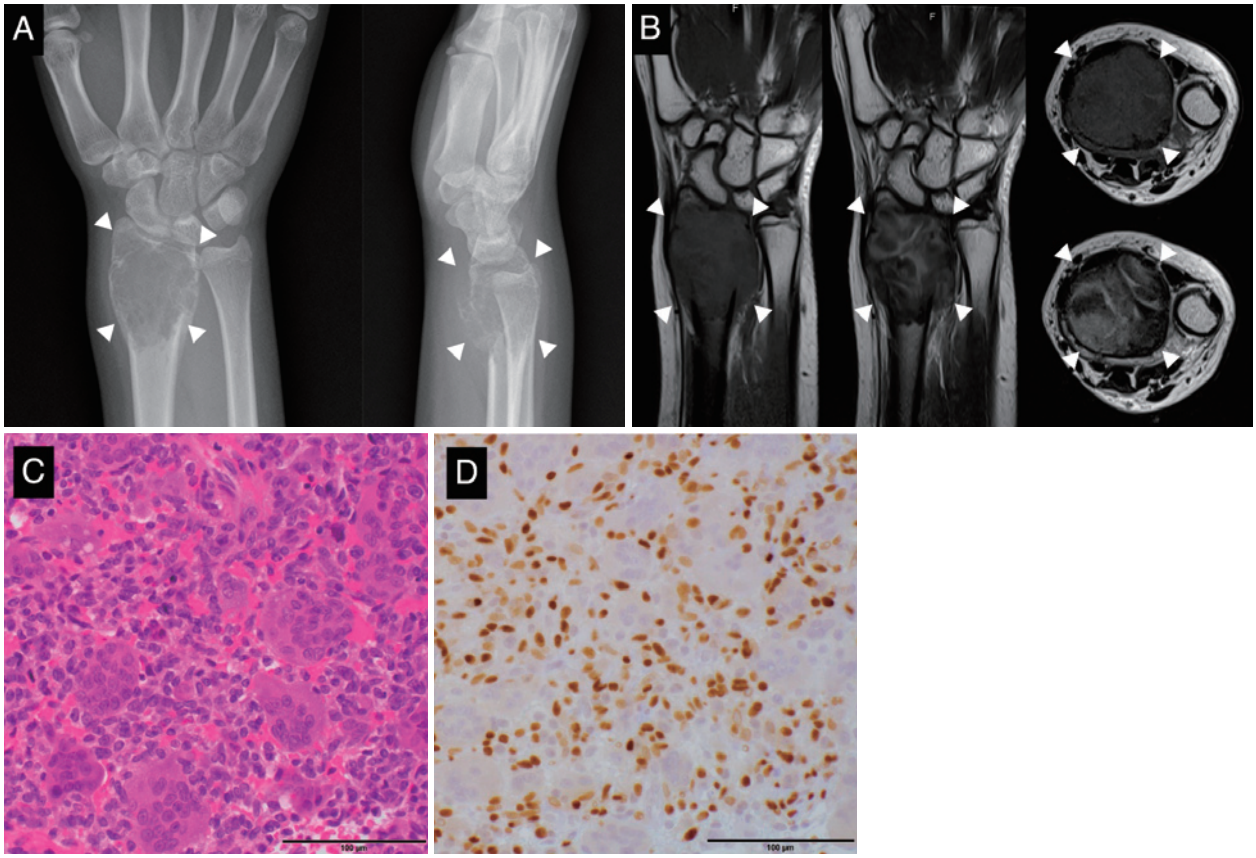

Fig. 3 Representative case with high tartrate-resistant acid phosphatase 5b and small tumor volumes. Radiographs (A) and MRI (B) showed a lytic lesion with cortical destruction in the distal radius (white arrows). H&E staining (C) and G34W immunostaining (D) revealed typical features.

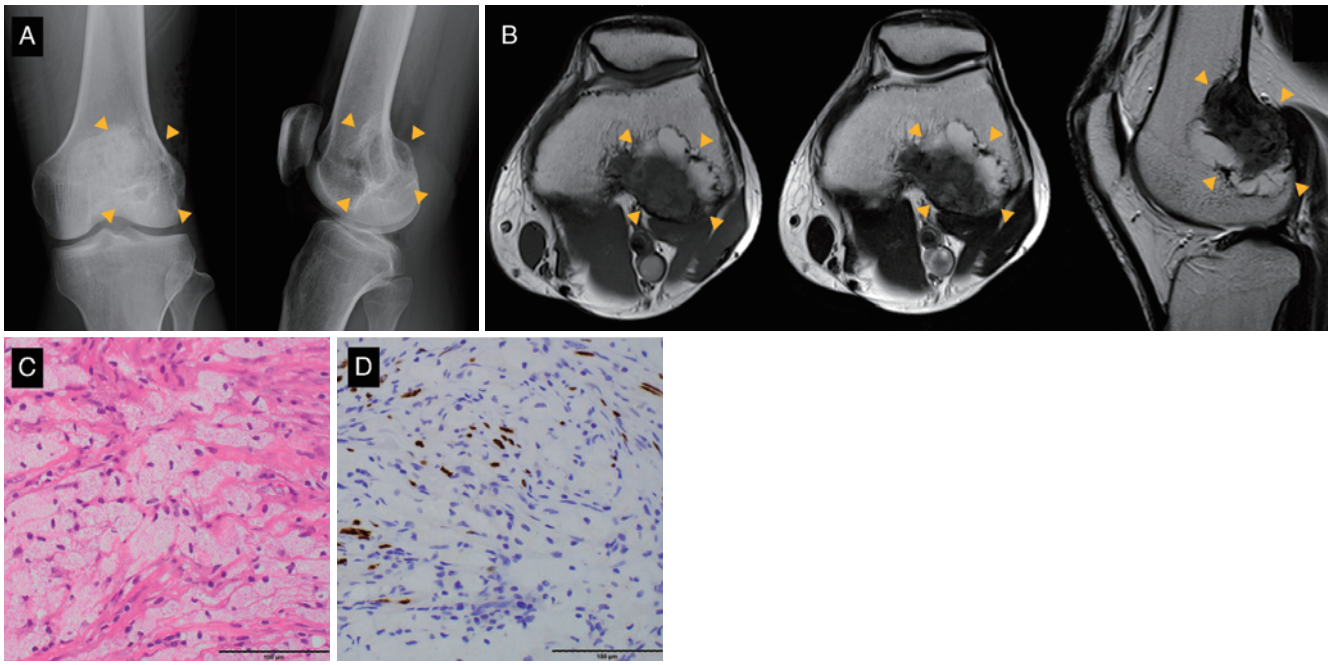

Fig. 4 Representative case with morphological secondary changes. Radiographs (A) and MRI (B) showed a lytic lesion with marginal sclerosis in the distal femur (yellow arrows). H&E staining (C) revealed almost only xanthogranulomatous change without typical features, but G34 immunostaining was positive (D).

has a significant negative correlation with bone mineral density[19]. Considering metabolic factors such as osteoporosis, cases exceeding 852 mU/dL were classified into the HT group.

GCTB predominantly occurs in early to middle adulthood[13,20–22]. Cases in skeletally immature children and adolescents account for less than 10% of all GCTBs[13,16,20,23]. The clinical behavior of the disease is similar to that seen at the predominant age, with no significant age-related differences reported[23]. In this study, the HT group was over 10 years younger on average than the LT group, suggesting that age is a factor influencing TRACP 5b level. However, in some cases, serum TRACP 5b increases markedly even in old age, so age is not considered to be the most important factor.

GCTB is a primary bone tumor with local osteolysis[13]. The radiological features of GCTB are an excentric radiolucent zone remaining within the physiological borders of the bone with a distinct margin[22,23]. Some GCTBs show destruction in the cortex and aggressive periosteal bone formation along with soft tissue mass in plain radiographs and need to be distinguished from osteosarcoma[16]. The MRI findings of GCTB are reported to be low to isointense with respect to muscle on T1-weighted images and heterogeneously higher signal than the signal intensity of muscle on T2-weighted images, but the signals are nonspecific[24]. The MR signal reflects hemosiderin deposition[24,25]. The patients in this study presented with typical features on radiographs and MRI, and it was difficult to identify factors influencing TRACP 5b from these imaging findings. FDG-PET/CT, which detects glucose uptake, may allow the qualitative evaluation of GCTB. In this study, there was no significant difference in SUVmax, but a higher tendency was observed in the HT group.

It is widely known that mononuclear stromal cells are a truly neoplastic cell population and recruit secondary multinucleated osteoclastic giant cells[14,26]. However, GCTB often presents morphological secondary changes, and most GCTB is diagnosed from partial typical features. Due to these pathologic features, differential diagnosis is necessary to distinguish GCTB from some bone tumors having a lesion with giant cells, such as aneurysmal bone cyst (ABC), osteoblastoma, and giant cell-rich osteosarcoma. In cases in which pathologically secondary changes are predominant, it may be difficult to diagnose from morphological findings. Testing for G34W mutations is reported to be useful in differentiating between cellular ABC versus GCTB with secondary ABC-like changes[27]. Undetected GCTB in previous reports may be included by using the result of G34W immunostaining in this study.

The relationship between GCTB and serum TRACP 5b has been reported in a few studies[10–12]. Shinozaki et al. suggested that the size of osteolytic lesions in the high serum TRACP 5b primary group had no relation with serum TRACP 5b, but no details were mentioned[10]. On the other hand, Chen et al. reported that the serum levels of N-terminal telopeptide of type I collagen (NTx) and TRACP 5b were significantly higher in GCTB $\geq$ 5 cm than in GCTB < 5 cm[11]. To better clarify this discrepancy, we performed an assessment by tumor volume calculated as an ellipsoid. Serum TRACP 5b was high in cases with histologically prominent typical findings, indicating that the serum TRACP 5b level was influenced by the presence of pathological secondary change rather than the size of the entire lesion. Since GCTBs were suggested to interact between osteoclast-like giant cells and stromal tumor cells, a relationship between serum TRACP 5b levels and clinical activity was expected. However, other clinical variables, such as Campanacci grading, pathological fractures, and local recurrence, had no significant effect on serum TRACP 5b. The denosumab administration rate was significantly higher in the HT group. The reason may be that the HT group showed clinically aggressive behavior and required adjuvant treatment for local control. However, denosumab was administered to all patients from 2014 to 2018, and it is necessary to consider the bias for this variable. Serum TRACP 5b is a useful and less invasive marker to evaluate GCTBs subjectively. In interpreting serum TRACP 5b levels, it should be kept in mind that it does not increase in all GCTBs.

There are several limitations to this study. First, the number of patients was small. It is possible that this contributed to the lack of a significant difference in some variables. In addition, some statistical analyses could not be performed. Second, there was no quantitative evaluation of osteoclast-like giant cells. Secondary changes were evaluated by a pathologist specializing in musculoskeletal tumors. Third, to exclude the influence of osteoporosis and other metabolic diseases, the serum TRACP 5b value was conveniently set at 852 mU/dL to divide the patients into two groups. It is desirable to increase the number of cases in the future and determine the cut-off value of serum TRACP 5b for the diagnosis of GCTB. Further studies need to investigate the relationship between osteoclast-like giant cell activity and serum TRACP 5b levels.

In conclusion, serum TRACP 5b is not associated with the tumor volume of GCTB, suggesting that the presence of pathological secondary change in the tumor has a significant effect. In addition, younger patients tend to have higher serum TRACP 5b levels, and in one-third cases, serum TRACP 5b level was not elevated.

Conflict of Interest: None.

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