Prostaglandin Levels of Primary Bone Tumor Tissues Correlate with Peritumoral Edema Demonstrated by Magnetic Resonance Imaging

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BACKGROUND. Several reports have shown peritumoral edema accompanying primary bone tumors demonstrated by magnetic resonance imaging (MRI). However, the mechanism of this inflammatory reaction is still unclear. The authors postulated that the reaction was caused by some chemical mediators including prostanoids, because several investigators have observed that some types of bone tumors synthesize prostanoids. Therefore, the authors compared MRI findings and tumor prostaglandin (PG) levels.

METHODS. The subjects were 29 patients with primary bone tumor or tumor-like conditions: chondroblastoma (n = 5); chondrosarcoma, including rare variants (n = 8); giant cell tumor (n = 6); osteochondroma (n = 5); osteoblastoma (n = 2); Ewing's sarcoma (n = 2); and eosinophilic granuloma (n = 1). T1- and T2-weighted spin echo images were obtained in all but one patient before surgery. The tumor concentration of prostaglandin E_2, 6-keto-$PGF_{1\alpha}$, and thromboxane B_2 were measured by radioimmunoassay.

RESULTS. MRI distinctly showed bone marrow edema in 9 and soft tissue edema in 12 of the 28 patients examined. These findings were significantly correlated with the PG levels. Moreover, the PG levels were correlated with the histologic classifications ($P < 0.001$). In particular, the chondroblastomas showed prominent concentrations of PGs compared with other cartilaginous tumors or giant cell tumors.

CONCLUSIONS. Although peritumoral edema accompanying benign and malignant bone tumors is not necessarily related to one single pathophysiologic mechanism, these results suggest that PG production was an important cause of the inflammatory reaction that was revealed by MRI. Recognition of this phenomenon is advantageous not only for strict diagnostic purposes but also for understanding the characteristic features of individual primary bone tumors. ***Cancer* 1997; 79:255–61.**

KEYWORDS: magnetic resonance imaging, bone neoplasms, prostaglandin, edema.

It is well known that magnetic resonance imaging (MRI) reveals bone marrow and soft tissue edema in musculoskeletal sarcomas.[1–4] These inflammatory reactions on MRI were also recently observed in some benign bone tumors and tumor-like lesions, such as osteoid osteoma,[5] osteoblastoma,[6], chondroblastoma,[7,8] and eosinophilic granuloma.[9] Knowledge of this phenomenon is especially important to avoid the overestimation of the size of the lesion or biopsy sample error, and to make a precise diagnosis in the preoperative evaluation, as well as for detecting residual tumors and recurrent lesions in follow-up studies.[8,10,11]

Increased levels of prostaglandins (PGs), which mediate inflammation, pain, and vasodilatation, were found in the tumor tissues

TABLE 1
Concentration of Prostaglandins

		ng/g wet weight tissue			Clinical findings		MRI	
Case no.	Diagnosis	PGE_2	6-keto-$PGF_{1\alpha}$	Thromboxane B_2	Local warmth	Spontaneous pain	Bone marrow edema	Soft tissue edema
	Normal bone (n = 5)	1–10	2–7	5–73				
1	Osteochondroma	3	6	21	No	No	No	No
2	Osteochondroma	2	1	2	No	No	No	No
3	Osteochondroma	1	1	2	No	No	No	No
4	Osteochondroma	1	1	1	No	No	No	No
5	Osteochondroma	1	1	3	No	No	No	No
6	Chondrosarcoma	3	1	2	No	No	No	No
7	Chondrosarcoma	1	2	4	No	No	No	No
8	Chondrosarcoma	14	11	4	No	No	No	Yes
9	Chondrosarcoma	10	5	3	No	No	No	No
10	Chondrosarcoma	49	8	10	No	Yes	No	Yes
11	Chondrosarcoma	19	4	6	No	Yes	No	Yes
12	Chondroblastoma	226	104	185	No	No	Yes	No
13	Chondroblastoma	1850	489	583	Yes	Yes	Yes	Yes
14	Chondroblastoma	216	195	996	Yes	Yes	Yes	Yes
15	Chondroblastoma	175	1320	336	Yes	Yes	Yes	Yes
16	Chondroblastoma	40	159	21	No	No	No	Yes
17	Giant cell tumor	36	16	21	No	No	Yes	No
18	Giant cell tumor	11	18	22	No	No	No	No
19	Giant cell tumor	3	5	12	Yes	No	No	No
20	Giant cell tumor	5	8	56	No	No	Not done	Not done
21	Giant cell tumor	14	6	59	No	No	No	No
22	Giant cell tumor	18	17	121	No	Yes	No	No
23	Eosinophilic granuloma	561	39	802	No	Yes	Yes	Yes
24	Ewing's sarcoma	6	60	36	Yes	Yes	No	Yes
25	Ewing's sarcoma	2	2	95	No	No	No	Yes
26	Osteoblastoma	203	167	69	No	Yes	Yes	Yes
27	Osteoblastoma	31	78	76	No	Yes	Yes	Yes
28	Clear cell chondrosarcoma	33	9	15	No	Yes	No	Yes
29	Mesenchymal chondrosarcoma	24	2	31	Yes	Yes	No	Yes

PG: prostaglandin; MRI: magnetic resonance imaging.

of patients with various carcinomas,[12–14] and there are a few reports of high level PG synthesis in some primary bone tumors, particularly osteoid osteoma.[15–17] Although the biologic significance has not been clearly established, it has been suggested that tumor cell production of PGs is associated with cell growth, mutagenesis and promotion, immune suppression, and even metastasis.[18] However, in primary bone tumors the concentration of PGs does not necessarily represent malignant potential. In this article, the authors report on the correlation between peritumoral edema and PG levels. To their knowledge, this is first report describing the PG levels of primary bone tumors in comparison with their MRI findings of bone marrow and soft tissue edema.

PATIENTS AND METHODS

MRI

The subjects were 29 patients with primary bone tumors or tumor-like conditions who underwent surgery at the study institution between April 1993 and December 1995. The histologic diagnoses are listed in (Table 1). The clinical data were based on the records of the first consultation to the study institution. MRI studies were performed using a Signa 1.5-tesla (T) (General Electric Medical Systems, Milwaukee, WI) in 13 patients, a Resona 0.5-T (GE-YMS, Tokyo, Japan) in 5 patients, and a Visart 1.5-T (Toshiba, Tokyo, Japan) in 10 patients. T1-weighted spin echo images (repetition times/echo times = 450-500/15-20 milliseconds [ms]) and T2-weighted spin echo images (4000-1800/120-80 ms) were obtained in all but 1 patient before surgery. Gadopentetate dimeglumine (Gd-DTPA)-enhanced T1-weighted images were obtained in 17 patients. Fat-saturated Gd-DTPA-enhanced T1-weighted images, which might be expected to highlight the edema, were available in six patients. All MRI examinations were reviewed by two radiologists unaware of patient identity, who were experienced in

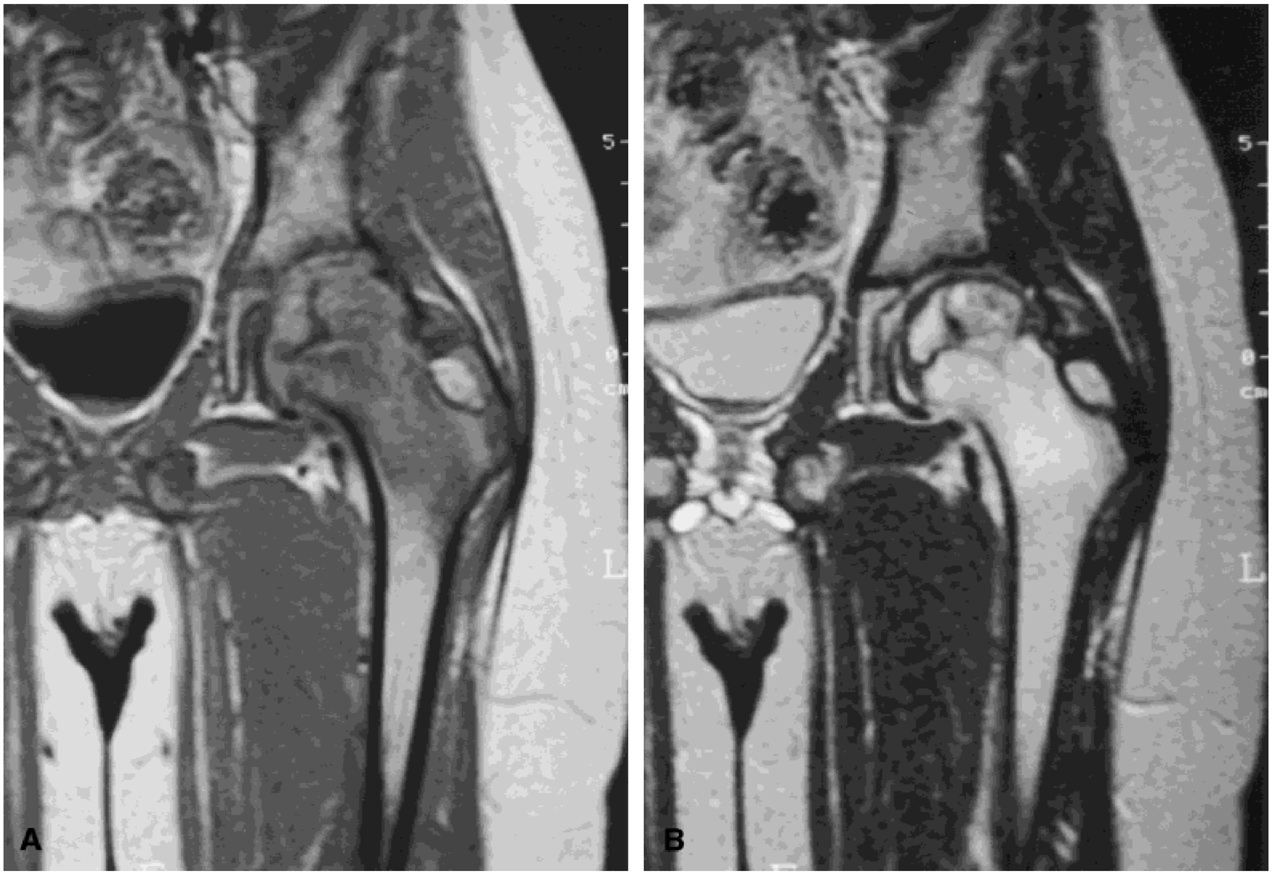


FIGURE 1. Case 12. Chondroblastoma of the capital femoral epiphysis. (A) A coronal T1-weighted image showed widespread bone marrow edema as an area of low signal intensity beyond the epiphyseal line. (B) A coronal T2-weighted image showed widespread edema as an area of high signal intensity.

musculoskeletal MRI interpretation. Bone marrow and soft tissue edema on MRI were defined as follows: bone marrow edema was considered to be present when the peritumoral area showed low signal intensity (SI) on T1-weighted images and intermediate or high SI on T2-weighted images compared with the normal bone marrow. Soft tissue edema was defined as a poorly delineated area showing high SI on T2-weighted images in adjacent muscle or other soft tissue. Gd-DTPA-enhanced T1-weighted images (with or without fat saturation) were used to certify the above findings.

Prostaglandin Determinations

The resected tumor specimen without surrounding bone marrow or soft tissues was immediately frozen in liquid nitrogen and stored at -80 °C in an ultracold freezer until it was assayed. The frozen tissue (0.5-1 g) was homogenized with methanol. The homogenate was dissolved with chloroform (6 mL) and centrifuged at 1600 revolutions per minute for 30 minutes at 4 °C. Supernatant fluid from the centrifugation was pooled and evaporated at 55 °C under a stream of nitrogen. The dried residue was reconstituted with methanol (0.5 mL) and distilled water (1.5 mL). PGs were then extracted and fractionated by Jaffe's method with organic solvent and column chromatography.[19] The concentration of PG E_2, 6-keto-$PGF_{1\alpha}$, and thromboxane B_2 were measured by radioimmunoassay (RIA Kit; Amersham, Buckinghamshire, United Kingdom). Iliac bone marrow obtained during bone grafting was used as the control.

Statistical Analysis

The Kruskal-Wallis nonparametric test was used for multiple group comparison, and the Mann-Whitney U test was used for two group comparisons. Significance was set at $P < 0.05$.

RESULTS

Tumor PG levels and clinical data for each patient are summarized in Table 1. MRI distinctly showed bone

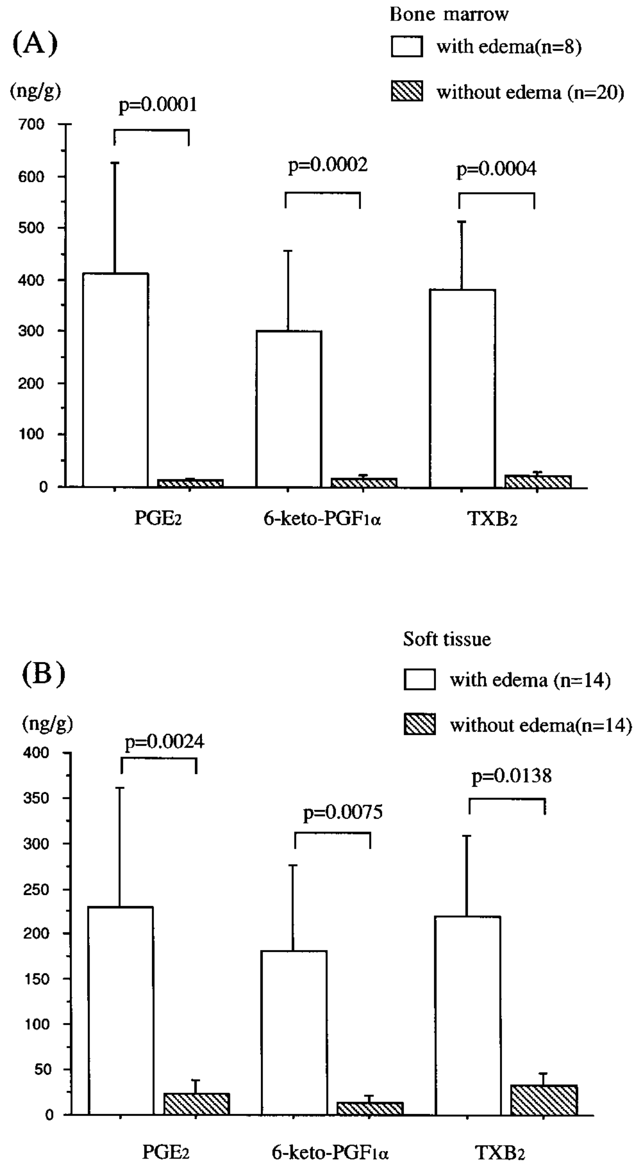


FIGURE 2. Correlations between prostaglandin level and the magnetic resonance imaging findings in (A) bone marrow edema and (B) soft - tissue edema. Significance tested using the Mann-Whitney *U* test. Columns: mean; bars: standard error of the mean.

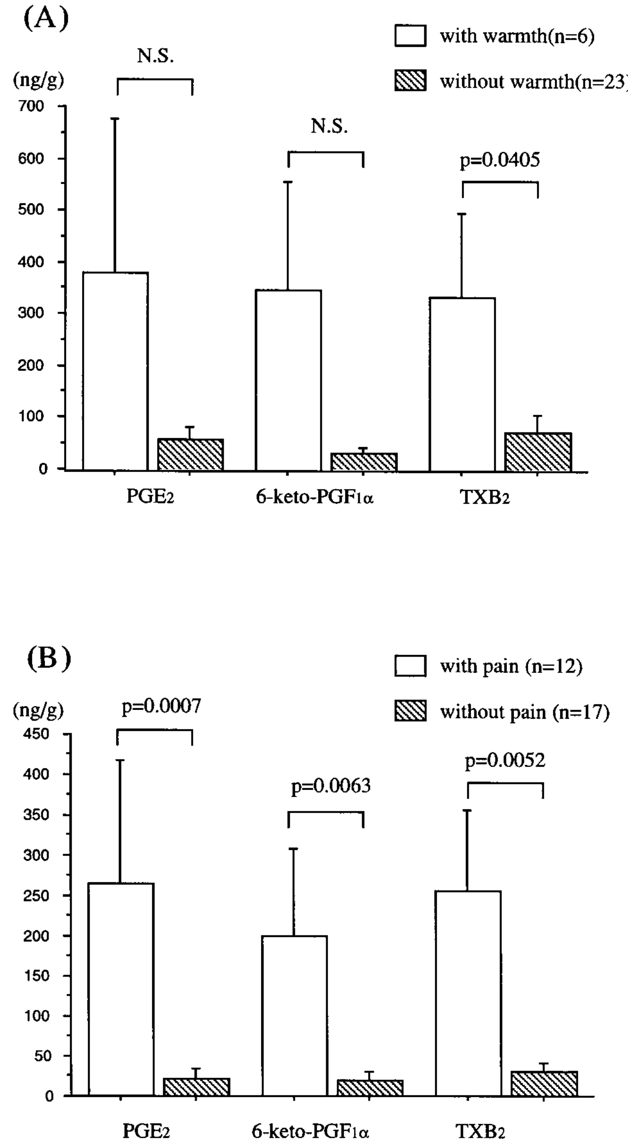


FIGURE 3. Correlations between prostaglandin level and the clinical findings of (A) local warmth and (B) spontaneous pain. Significance tested using the Mann-Whitney *U* test. Columns: mean; bars: standard error of mean.

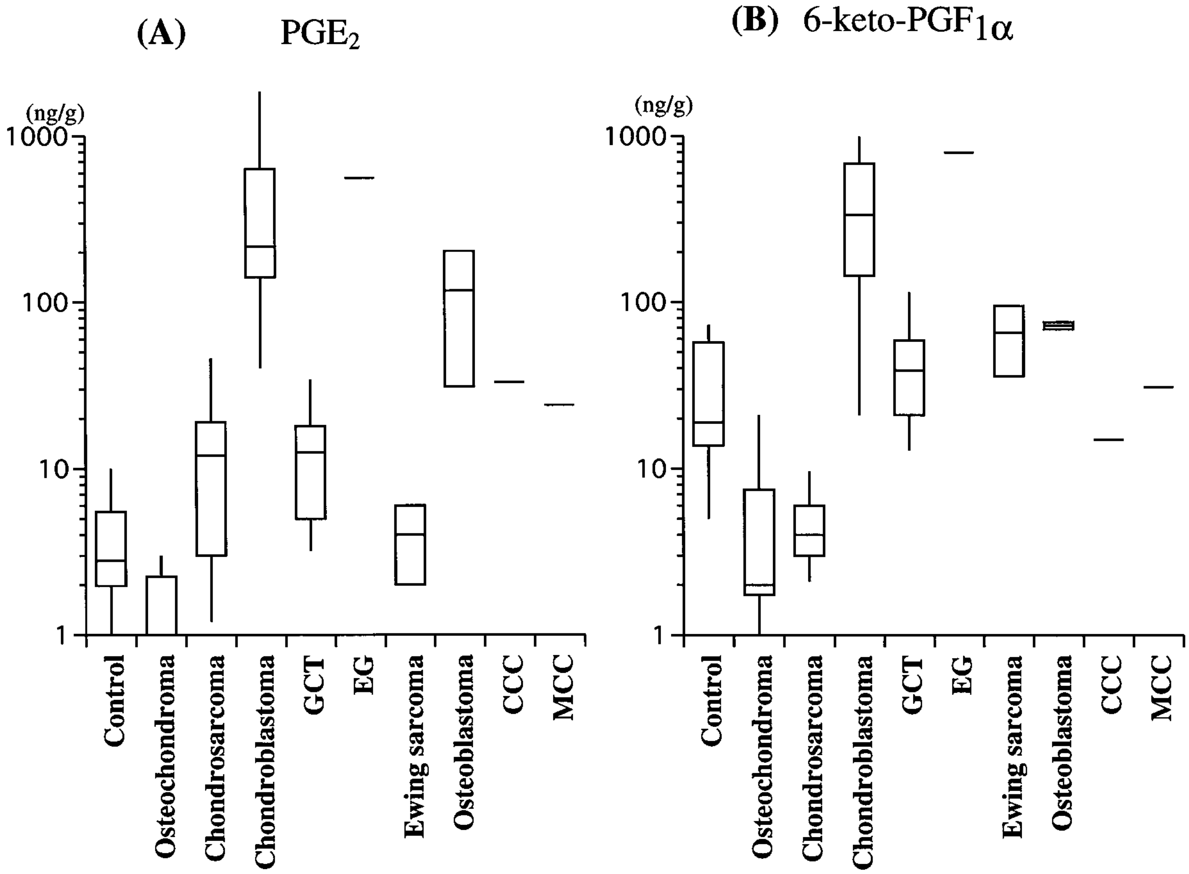
marrow edema in 8 and soft tissue edema in 14 of the 28 patients examined (Fig. 1). These findings of inflammation were significantly correlated with each PG level (Fig. 2).

Swelling and warmth were observed in 6 patients, and spontaneous pain occurred in 12 of the 29 patients. The thromboxane B_2 level of the tumor was significantly higher in these patients. PGE_2 and 6-keto-$PGF_{1\alpha}$ were also increased in the patients with spontaneous pain (Fig. 3).

In the current series, chondroblastoma, osteoblastoma, and eosinophilic granuloma showed high PG levels (Fig. 4). Of the cartilage tumors, giant cell tumors, and normal bone (which were sufficient in number for statistic analysis), the PG level was significantly different among the histologic classifications (Kruskal-Wallis analysis: PGE_2, $P = 0.0011$; 6-keto-$PGF_{1\alpha}$, $P = 0.0009$; and thromboxane B_2, $P = 0.0008$). The PG level of the chondroblastomas was higher than that of any other group (Table 2).

DISCUSSION

Bone marrow and soft tissue edema are observed with MRI in many skeletal lesions, such as those resulting



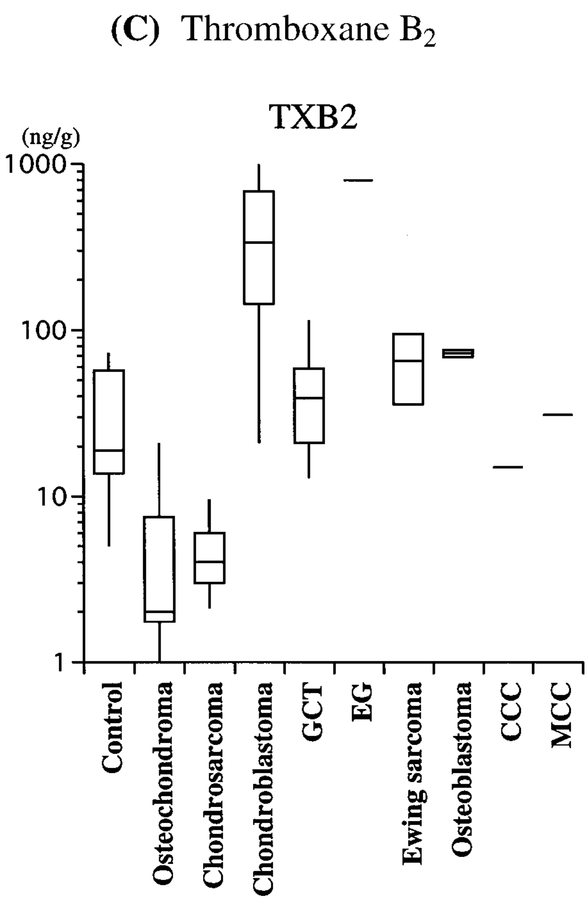


FIGURE 4. Box plot graph of prostaglandin level in the tumor tissues (A) PGE_2, (B) 6-keto-$PGF_{1\alpha}$, and (C) thromboxane B_2. GCT: giant cell tumor; EG: eosinophilic granuloma; CCC: clear cell chondrosarcoma; MCC: mesenchymal chondrosarcoma.

TABLE 2
Prostaglandin Comparison by Histologic Classification

	P value		
	PGE_2	6-keto-$PGF_{1\alpha}$	Thromboxane B_2
Control, chondroblastoma	0.009	0.0088	0.0283
Control, osteochondroma	NS	NS	0.0465
Control, chondrosarcoma	NS	NS	0.0174
Control, GCT	0.0285	0.0270	NS
Chondroblastoma, osteochondroma	0.0082	0.0071	0.0117
Chondroblastoma, chondrosarcoma	0.0106	0.0062	0.0061
Chondroblastoma, GCT	0.0062	0.0062	NS
Osteochondroma, chondrosarcoma	0.0394	NS	NS
Osteochondroma, GCT	0.0074	0.0114	0.0133
Chondrosarcoma, GCT	NS	NS	0.0039

GCT: giant cell tumor; NS: not significant.
The Mann–Whitney *U* test was employed to compare pairs of groups.

from trauma,[10] acute osteomyelitis,[20,21] and some neoplasms.[1] In malignant bone tumors especially, the disappearance of the inflammatory reaction has been investigated as an indicator of chemotherapeutic responses.[22–24] The reaction has recently been observed more dramatically in some benign bone tumors rather than malignant tumors.[5–7,9] However, the mechanism that results in edema is still obscure. To the authors' knowledge, the current study is the first time a close relationship has been shown between peritumoral edema demonstrated by MRI and primary bone tumor PG levels. These results offer a possible explanation of why MRI discloses the edema around some particular tumors, and also clearly shows one of the characteristic features of these neoplasms.

Increased levels of PGs in tumor tissues have been found in patients with various carcinomas.[13] These levels were suggested to be associated with malignancy or aggressiveness.[18] However, with regard to skeletal tumors, previous studies have shown that the levels are increased in benign tumors such as osteoid osteoma and osteoblastoma.[15,17] The results of the current study support the latter findings, and suggest that the production of PGs does not necessarily correlate with malignancy. PGs are important mediators of normal bone metabolism;[25] therefore, it might be natural that bone-forming tumors synthesize a large amount of PGs as a consequence of the absence of regulation.

In the current series, chondroblastoma showed prominent peritumoral edema and a high level of PG concentration, which might be characteristic of this rare cartilaginous tumor. Radiographically, periosteal reaction is a well recognized manifestation of this tumor.[26] However, its pathophysiology has long remained a mystery. The authors now postulate that the PGs, especially PGE_2, may cause inflammation of the subperiosteal region with resulting elevation of the periosteum, which is demonstrated radiographically as periosteal reaction. Keller et al investigated the effect of local PGE_2 on the periosteum in rabbits, and showed a primitive periosteal-woven bone with thin trabeculae in a richly vascularized connective tissue after local PGE_2 infusion.[27]

There are some diagnostic problems with cartilaginous tumors. For example, the differentiation between entirely benign and low grade malignant lesions may be extremely difficult based on radiologic or even histologic study.[28] Occasionally, chondroblastoma, a benign cartilaginous tumor, has radiologic and histologic features mimicking other tumor classifications such as giant cell tumor or clear cell chondrosarcoma. Therefore, it is very important for diagnostic purposes to recognize that chondroblastoma alone shows a prominent inflammatory reaction.

One of the current osteoblastoma cases (Case 27) showed a lower PG concentration compared with that of a previous study.[17] The reason might be that this patient had taken nonsteroidal antiinflammatory drugs for a long time before undergoing surgery. Another discrepancy between MRI and PG level was observed in the Ewing's sarcoma and mesenchymal chondrosarcoma cases. In spite of marked soft tissue edema, the tumor PG levels were relatively low. This suggested that other chemical mediators or cytokines might have caused the reaction in these tumors.

Local warmth as a clinical finding did not correlate well with the PG level, except for that of thromboxane B_2. The reason might be that local warmth could be easily detected by the physician when the tumor was superficial, but could not be detected when it was deeper. In other words, the anatomic location of the tumors made a difference in the degree of the clinical sign.

In conclusion, the peritumoral edema demonstrated by MRI was significantly correlated with the tumor PG level. In the current series, bone marrow and/or soft tissue edema was observed in chondroblastoma, osteoblastoma, eosinophilic granuloma, mesenchymal chondrosarcoma, and Ewing's sarcoma cases. Of these lesions, benign bone tumors and tumor-like lesions correlated well with tumor PG level. These findings are important to make a precise diagnosis as well as to understand the characteristic features of individual primary bone tumors. The biologic significance of these findings will be studied further.

REFERENCES

1. Beltran J, Simon DC, Katz W, Weis LD. Increased MR signal intensity in skeletal muscle adjacent to malignant tumors: pathologic correlation and clinical relevance. *Radiology* 1987;162:251–5.
2. Golfieri R, Baddeley H, Pringle JS, Leung AW, Greco A, Souhami R, et al. Primary bone tumors. MR morphologic appearance correlated with pathologic examinations. *Acta Radiol* 1991;32:290–8.
3. Hanna SL, Fletcher BD, Parham DM, Bugg MF. Muscle edema in musculoskeletal tumors: MR imaging characteristics and clinical significance. *J Magn Reson Imaging* 1991; 1:441–9.
4. Seeger LL, Widoff BE, Bassett LW, Rosen G, Eckardt JJ. Preoperative evaluation of osteosarcoma: value of gadopentetate dimeglumine-enhanced MR imaging. *AJR Am J Roentgenol* 1991;157:347–51.
5. Yamamura S, Sato K, Sugiura H, Asano M, Takahasi M, Iwata H. Magnetic resonance imaging of inflammatory reaction in osteoid osteoma. *Arch Orthop Trauma Surg* 1994;114:8–13.
6. Crim JR, Mirra JM, Eckardt JJ, Seeger LL. Widespread inflammatory response to osteoblastoma: the flare phenomenon. *Radiology* 1990;177:835–6.
7. Weatherall PT, Maale GE, Mendelsohn DB, Sherry CS, Erdman WE, Pascoe HR. Chondroblastoma: classic and confusing appearance at MR imaging. *Radiology* 1994;190:467–74.
8. Yamamura S, Sato K, Sugiura H, Iwata H. Inflammatory reaction in chondroblastoma. *Skeletal Radiol* 1996;25:371–6.
9. Beltran J, Aparisi F, Bonmati LM, Rosenberg ZS, Present D, Steiner GC. Eosinophilic granuloma: MRI manifestations. *Skeletal Radiol* 1993;22:157–61.
10. Hayes CW, Conway WF, Sundaram M. Misleading aggressive MR imaging appearance of some benign musculoskeletal lesions. *Radiographics* 1992;12:1119–34.
11. Kroon HM, Bloem JL, Holscher HC, van der Woude H, Reijnierse M, Taminiau AH. MR imaging of edema accompanying benign and malignant bone tumors. *Skeletal Radiol* 1994;23:261–9.
12. Nigan S, Becker R, Rosendahl U, Hammerstein J, Benedetto C, Barbero M, et al. The concentrations of 6-keto-PGF_{1a} and TXB_2 in plasma samples from patients with benign and malignant tumors of the breast. *Prostaglandins* 1985; 29:513–28.
13. Heinonen PK, Metsä-Ketelä T. Prostanoids and cyclic nucleotides in malignant and benign ovarian tumors. *Med Oncol Tumor Pharmacother* 1988;5:11–5.
14. McLemore TL, Hubbard WC, Litterst CL, Liu MC, Miller S, McMahon NA, et al. Profiles of prostaglandin biosynthesis in normal lung and tumor tissue from lung cancer patients. *Cancer Res* 1988;48:3140–7.
15. Makley JT, Dunn MJ. Prostaglandin synthesis by osteoid osteoma. *Lancet* 1982;2:42.
16. Gebhardt MC, Lippiello L, Bringhurst FR, Mankin HJ. Prostaglandin E_2 synthesis by human primary and metastatic bone tumors in culture. *Clin Orthop* 1984;196:300–5.
17. Wold LE, Pritchard DJ, Bergert J, Wilson DM. Prostaglandin synthesis by osteoid osteoma and osteoblastoma. *Mod Pathol* 1988;1:129–31.
18. Ara G, Teicher BA. Cyclooxygenase and lipoxygenase inhibitors in cancer therapy. *Prostaglandins Leukot Essent Fatty Acids* 1996;54:3–16.
19. Jaffe BM, Behrman HR, Parker CW. Radioimmunoassay measurement of Prostaglandins E, A, and F in human plasma. *J Clin Invest* 1973;52:398–405.
20. Modic MT, Feiglin DH, Piranino DW. Vertebral osteomyelitis: assessment using MR. *Radiology* 1985;157:157–66.
21. Erdman WA, Tamburro F, Jayson HT, Weatherall PT, Bond Ferry K, Peshock RM. Osteomyelitis: characteristics and pitfalls of diagnosis with MR imaging. *Radiology* 1991;180:533–9.
22. Pan GP, Raymond AK, Carrasco CH, Wallace S, Kim EE, Shirkhoda A, et al. Osteosarcoma: MR imaging after preoperative chemotherapy. *Radiology* 1990;174:517–26.
23. Fletcher BD. Response of osteosarcoma and Ewing sarcoma to chemotherapy: imaging evaluation. *AJR Am J Roentgenol* 1991;157:825–33.
24. Holscher HC, Bloem JL, Vanel D, Hermans J, Nooy MA, Taminiau AH, et al. Osteosarcoma: chemotherapy-induced changes at MR imaging. *Radiology* 1992;182:839–44.
25. Kawaguchi H, Pilbeam CC, Harrison JR, Raisz LG. The role of prostaglandins in the regulation of bone metabolism. *Clin Orthop* 1995;313:36–46.
26. Brower AC, Moser RP, Kransdorf MJ. The frequency and diagnostic significance of periostitis in chondroblastoma. *AJR Am J Roentgenol* 1990;154:309–14.
27. Keller J, Schumacher B, Lind M. Effect of local prostaglandin E2 on periosteum and muscle in rabbits. *Acta Orthop Scand* 1992;63:623–7.
28. Mirra JM, Picci P, Gold RH. Bone tumor: clinical, radiologic and pathologic correlations. Philadelphia: Lea & Febiger, 1989:532–46.