Intraarticular Osteoid Osteoma Associated with Synovitis: A Possible Role of Cyclooxygenase-2 Expression by Osteoblasts in the Nidus

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To clarify the condition of development of synovitis associated with intraarticular osteoid osteoma (OO), expressions of cyclooxygenase-2 (COX-2) protein and its messenger ribonucleic acid were investigated both in the nidus and the synovial tissue using immunohistochemical and reverse transcription-polymerase chain reaction analyses. Diffuse and strong COX-2 immunoreactivity was found in osteoblast-like tumor cells in the nidus of all six cases of OO (three of six cases were intraarticular OO associated with synovitis) and one case of osteoblastoma associated with synovitis. Expression of COX-2 messenger ribonucleic acid was demonstrated in one case of OO associated with synovitis, and was higher in the nidus than that in the inflamed synovial tissue. However, there were no significant difference between the nidus and synovium in the expression of cytosolic phospholipase A2, one of the enzymes involved in arachidonic acid metabolism, and inflammatory cytokines such as interleukin-1β and tumor necrosis factor alpha. Finally, as there was only one case in which the examinations of gene expression were performed, no definitive overall conclusions could be reached; rather it is suggested that COX-2 expressed primarily by osteoblasts in the nidus of intraarticular OO may play a role in activating the pathway of arachidonic acid metabolism, resulting in synovitis of the involved joint.

Osteoid osteoma (OO) that occupies 11% of all benign tumors (1, 2) is commonly located in the diaphysis of long bones in young patients. Its typical clinical feature is pain, which is relieved by non-steroidal anti-inflammatory drugs (NSAIDs). Attention has been directed to this unique clinical feature, and several hypotheses have been put forward to the cause of the pain. High levels of prostaglandins (PGs) and/or innervation in the nidus have been demonstrated (3, 4), but the essential character of this tumor remains disputable (5).

Intraarticular OO, characterized by its position inside the insertion of the joint capsule, can manifest a variety of non-specific symptoms such as pain, joint effusion, swelling, stiffness, local warmth, and muscle atrophy, which may further lead to joint dysfunction (2, 6, 7). Intraarticular OO within the joint capsule is rare and the incidence varies from 0 to 16% of OO cases (1, 5, 8). Cassar-Pullicino *et al.* (9) reported that synovitis in the involved joint occurred in 25% of tumors evaluated by surgical findings. Magnetic resonance imaging (MRI) showed pooling of joint effusion in all cases of intraarticular OO (10). Histologic examination further confirmed the presence of prominent non-specific chronic synovitis or lymphofollicular synovitis, resembling rheumatoid arthritis (RA), in the joint with intraarticular OO (11). However, the underlying mechanism of the development of synovitis is still unknown.

In 1973, Snarr *et al.* (11) hypothesized that a specific activating substance might induce inflammation of the synovium in intraarticular OO. Because Markley *et al.* (12) and Greco *et al.* (13, 14) demonstrated a higher level of PGs in the nidus of

OO, PGE2 has been suspected as a mediator that contributes to synovitis in the involved joint of intraarticular OO. As is well known, PGs are produced from phospholipids catalyzed by cytosolic phospholipase A2 (cPLA2) and cyclooxygenase (COX)-2 through arachidonic acid metabolism. COX consists of two isozymes; COX-1 and COX-2. COX-1 is a constitutive enzyme that is expressed at a fixed level throughout the cell cycle, whereas COX-2 is induced rapidly and transiently when stimulated by inflammatory cytokines. Siegle *et al.* (15) found that only COX-2 was induced to a high level in inflammatory joint diseases such as RA, ankylosing spondylitis and psoriatic arthritis but not in osteoarthritis, based on immunohistochemical examinations for both COX-1 and COX-2 expression.

We hypothesized that the production of PGs via COX-2 may play an important role in the development of synovitis in joints with intraarticular OO. In this study, we investigated the expressions of enzymes of arachidonic acid metabolism and inflammatory cytokines that stimulate the arachidonic acid metabolic pathway, both in the tumor and synovial tissues by immunohistochemical and molecular biological analyses.

MATERIALS AND METHODS

Tumor Samples

We retrieved and reviewed six cases of OO (three of six cases were associated with synovitis) and one case of osteoblastoma (OB) with synovitis in the involved joint. OB may induce pronounced inflammatory reactions in the surrounding soft tissue similar to reaction that occurs in OO (2). Table 1 shows the clinical features including sex, age, tumor location and size, and status of synovitis. In all three cases of intraarticular OO (Cases 1, 2, and 3) and one case of OB (Case 4) of the femoral neck, the lesions were located in the cortex of femoral neck within the joint capsule and the patients presented with pain, swelling, and joint effusion in the involved hip joint. Imagings in Case 1 are shown in Figure 1 as a representative case of intraarticular OO.
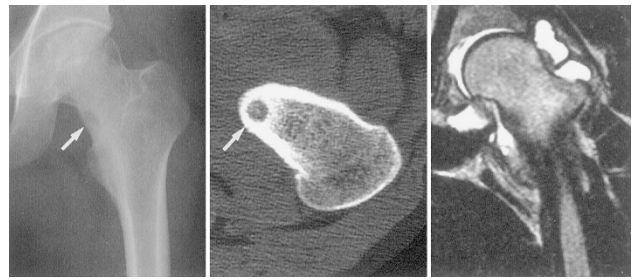
FIGURE 1. Imagings in Case 1. Conventional radiograph and computed tomography shows that nidus is located in the cortex of femoral neck within the joint capsule (**arrow**). T2 weighted image on MRI shows the pooling of the joint effusion indicating the presence of the synovitis.

Histologic and Immunohistochemical Examination

Tumor tissue (nidus) in all six cases of OO and one case of OB (Cases 1 to 7) and the adjacent synovial tissues in four cases complicated with synovitis (Cases 1, 2, 3, and 4) excised at surgery were fixed in 10% buffered formalin, routinely processed, and embedded in paraffin. Sections were cut in 4-mm thickness and stained with hematoxylin and eosin and processed for immunohistochemical examination.

Immunohistochemical staining was performed by the labeled streptavidin biotin (LSAB) method using a LSAB kit (DAKO, Capinteria, CA) and polyclonal antibodies for COX-2 (1:30; IBL, Fujioka, Japan). All sections were immersed in 10-mM citrate buffer (pH 6.0) and subjected to autoclaving at 121° C for 20 min for heat-induced epitope unmasking. Positive and negative controls were included in each batch of staining. For positive controls, colonic adenocarcinoma tissues known to be positive for COX-2 were used. For negative controls, the primary antibody was substituted with phosphate buffered saline in duplicate sections.

Reverse Transcription-Polymerase Chain Reaction (RT-PCR)

In Case 3, fresh tumor tissue of intraarticular OO and the adjacent synovium were frozen immedi-

TABLE 1. Summary of the Cases Studied

Case[a]	Age (yr)/Sex	Tumor Location	Size (cm)	Diagnosis	Synovitis	IC	RT-PCR
1	20/M	Femoral neck	1.5	OO	Present	N, S	ND
2	13/F	Femoral neck	1.5	OO	Present	N, S	ND
3	20/M	Femoral neck	1.0	OO	Present	N, S	N, S
4	19/F	Femoral neck	3.0	OB	Present	N, S	ND
5	9/M	Tibial diaphysis	1.6	OO	Absent	N	ND
6	10/M	Femoral diaphysis	0.6	OO	Absent	N	ND
7	21/M	Femoral diaphysis	1.0	OO	Absent	N	ND

IC, immunohistochemical analysis; RT-PCR, reverse transcription-polymerase chain reaction analysis; M, male; F, female; OO, osteoid osteoma; OB, osteoblastoma; N, nidus; S, synovium; ND, not determined.

[a] Cases 1 through 4 were intraarticular lesions associated with synovitis; Cases 5 through 7 were diaphyseal lesions unassociated with synovitis as controls.

ately and stored in liquid nitrogen. Each tissue weighing approximately 0.5 g was homogenized in an extraction buffer. The mRNA was reverse-transcribed to cDNA using an oligo dT17 anchored primer (5′-GGCCACGCGTCGACTAGTACTdT17–3′) (16) and RNase H-free reverse transcriptase at 37° C for 1 hour. Primers for PCR amplification are shown in Table 2. Design of the five pairs of primers was based on the originally constructed sequences of human COX-2 mRNA and on previously reported sequences for those of cPLA2, interleukin (IL)-1β, tumor necrotic factor (TNF)α, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (17–19). The specificity of the COX-2 primers was confirmed using RNA extracted from synovia of RA patients. The cDNA was amplified by PCR with *Taq* DNA polymerase as follows: (1) 94° C for 1 min; (2) 55° C for 1.5 min; (3) 72° C for 1.5 min, for 30 cycles using a Perkin Elmer Thermal Cycler (Perkin-Elmer, Norwalk, CT). The PCR products were electrophoresed on 1.5% agarose gels and visualized by ethidium bromide staining. To evaluate the intensity of the mRNA expression by each gene, the concentrations of the PCR-amplified DNA were translated into numerical data using NIH (National Institutes of Health) image. Numerical data of each band were expressed as ratios to GAPDH intensity to compare gene expression in different tissues.

The amplified COX-2 cDNA was ligated to PCRll Vector according to the manufacture's protocol. Plasmid DNAs with inserts were purified, and the nucleotide sequences were determined with ABI Model 373A DNA Sequencing System (PE Applied Biosystems, Forester City, CA). As a positive control, synovium of RA patient was processed by the same procedures. As a negative control, PCR amplification was conducted using each pair of primers and samples without reverse transcription.

RESULTS

Histologic Findings

In all seven lesions, the nidus was a well-demarcated osteoblastic mass and consisted of interlacing network of osteoid trabeculae with different levels of mineralization, rimmed by abundant, short-spindled or polygonal osteoblasts, and numerous osteoclast-like, multinucleate giant cells (Fig. 2). The bone surrounding the nidus was cancellous, frequently with thickened trabeculae and a stroma composed of rich vascular connective tissue. Prominent large blood vessels were also present in the loose connective tissues surrounding the nidus. In the four cases examined (Cases 1, 2, 3, and 4), the synovium was edematous and thickened with prominent chronic inflammatory cell infiltrate consisting of lymphocytes and plasma cells, forming multiple lymphoid follicles indistinguishable from those found in RA (Fig. 3). The synovial lining cells showed a mild degree of villous hyperplastic changes.

Immunohistochemical Findings

In all seven cases, nearly all short-spindled or polygonal osteoblasts within the nidus showed diffuse and intense immunoreactivity for COX-2 (Fig. 4), whereas osteoblasts that rimmed the surrounding thickened bone trabeculae and osteoclast-like, multinucleate giant cells completely showed absolutely no positive reactivity. In the synovial tissues examined (Cases 1, 2, 3, and 4), small numbers of subsynovial spindle and stellate cells in the edematous stroma exhibited positive reaction for COX-2 (Fig. 5).

RT-PCR Findings

COX-2 mRNA expression was examined in one case of OO (Case 3). Complementary DNA reverse-transcribed from the mRNA of tumor tissue and synovium was amplified by PCR with specific pairs of primers and electrophoresed on agarose gels (Fig. 6). DNA bands of expected sizes were observed in both tissues after amplification with primer pairs specific for the following genes: *COX-2, cPLA2, IL-1β, TNFα* and *GAPDH*. Numerical data of the quantities of the DNA amplified by PCR are shown in Table 3. COX-2 expression in the nidus was stronger than that in the synovium. Numerical data of

TABLE 2. Sequences of Primers Used to Identify Expression of COX-2, cPLA2, IL-1β, and TNFα and Genes

| mRNA	Primer Sequences	Length of PCR Product
COX-2	S:5′-GCAGGCAGATGATGAAATACCAGTC-3′	638bp
	AS: 5′-TATGACTCCTTTCTCCGCAACA-3′	
cPLA2	S: 5′-GAGCTGATGTTTGCAGATTGGGGTTG-3′	509bp
	AS: 5′-GTCACTCAAAGGAGACAGTGGATAAGA-3′	
IL-1β	S: 5′-ATGGCAGAAGTACCTAAGCTC-3′	810bp
	AS: 5′TTAGGAAGACACAAATTGCATGGTGAACTCCGT-3	
TNFα	S: 5′-GCACTGAAAGCATGATCCGG-3′	510bp
	AS: 5′-AGAGAGGGGAGGTTGACCTTGGT-3′	

S, sense; AS, anti-sense; COX-2, Cyclooxygenase-2; cPLA2, cytosol phospholipase A2; IL-1β, interleukin-1β; and TNFα, tumor necrosis factor alpha.
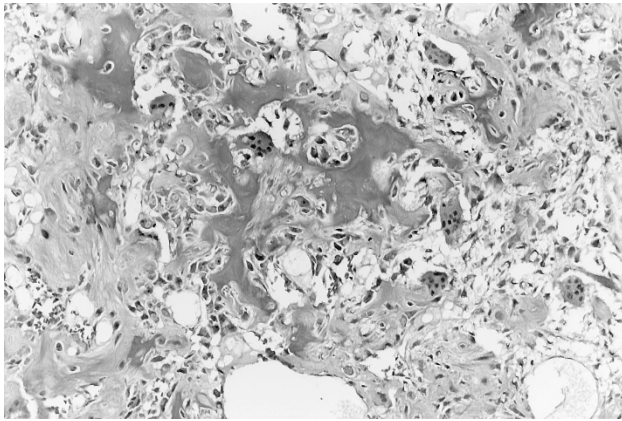
FIGURE 2. An intraarticular osteoid osteoma showing interlacing network of osteoid trabeculae with prominent osteoblastic rimming and numerous osteoclast-like, multinucleate giant cells in a richly vascular stroma (Case 3).
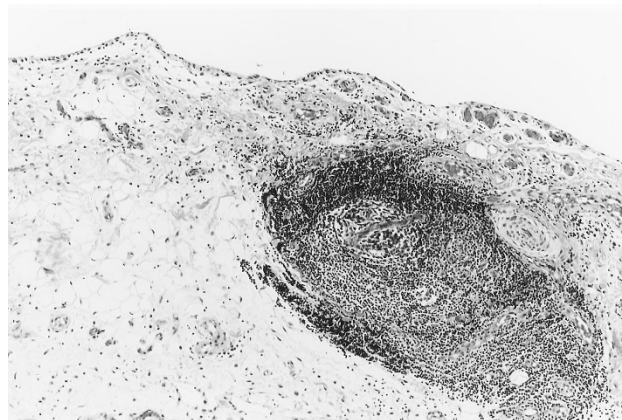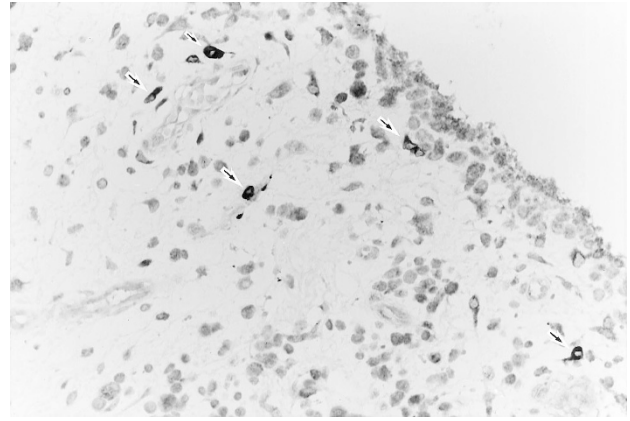

FIGURE 3. Synovium adjacent to the intraarticular osteoid osteoma in Figure 2, showing lymphofollicular synovitis with edematous stroma.
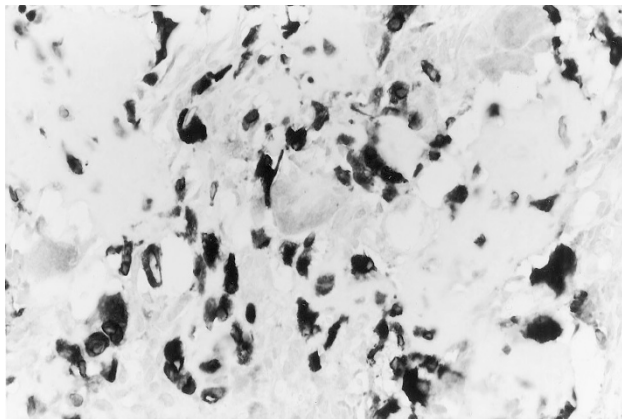
FIGURE 4. Immunohistochemical study of the nidus in a case of intraarticular osteoid osteoma (Case 3). COX-2 immunoreactivity is observed in the cytoplasm of many osteoblasts, but not in osteoclast-like, multinucleate giant cells within the nidus.

FIGURE 5. Immunohistochemical study of the synovium in the involved joint shown in Figure 3. COX-2 immunoreactivity is observed in the cytoplasm of a few subsynovial spindle and stellate cells (*arrows*).

FIGURE 6. Reverse transcription-polymerase chain reaction analysis of a case of osteoid osteoma (Case 3). *Lane 1* showing COX-2 in the nidus; *lane 2*, COX-2 in the synovium; *lane 3*, cytosol phospholipase A2 (cPLA2) in the nidus; *lane 4*, cPLA2 in the synovium; *lane 5*, interleukin-1β (IL-1β) in the nidus; *lane 6*, IL-1β in the synovium; *lane 7*, tumor necrosis factor alpha (TNFα) in the nidus; *lane 8*, TNFα in the synovium; *lane 9*, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in the nidus; and *lane 10*, GAPDH in the synovium (ethidium bromide staining, electrophoresed on 1.5% agarose gels).

TABLE 3. Numerical Data of Concentration of DNA Bands

mRNA	Tissue	Numerical Data	Versus GAPDH Ratio
COX-2	Nidus	3729	6.41 (3729/578)
COX-2	Synovium	643	0.98 (643/655)
cPLA2	Nidus	721	1.25 (721/578)
cPLA2	Synovium	734	1.12 (734/655)
IL-1β	Nidus	471	0.81 (471/578)
IL-1β	Synovium	687	1.05 (687/655)
TNFα	Nidus	519	0.89 (519/578)
TNFα	Synovium	432	0.66 (432/655)

COX-2, cyclooxygenase-2; cPLA2, cytosol phospholipase 2; IL-1β, interleukin-1 beta; TNFα, tumor necrosis factor alpha; GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

cPLA2, IL-1β, and TNFα were not significantly different between the nidus and synovium.

The cDNA from the nidus in Case 3 amplified by the primer pair specific for *COX-2* were cloned, sequenced, and identified by BLAST searches. BLAST searches revealed 100% similarity of the sequence to a partial sequence of exon 9 and exon 10 in human *COX-2* gene.

DISCUSSION

Since Jaffe (20, 21) first reported OO as "a particular lesion of probable neoplastic nature" in 1935, the tumor has been recognized as a benign bone tumor manifesting characteristic inflammatory symptoms such as nocturnal pain and marked aspirin responsiveness (22–24). Intraarticular OO was first described by Sherman *et al.* (25) in 1947, and

since then more than 50 cases have been reported (6). In intraarticular OO, pain is accompanied by other nonspecific arthritic symptoms such as local heat, swelling, and joint effusion (2, 6–8). Diagnostic imaging studies have reported synovitis, narrowing of the joint space, and other symptoms resembling osteoarthritis (7, 9, 26).

Many studies have been conducted to elucidate the mechanism of development of synovitis in intraarticular OO. No cases associated with synovitis in the adjacent joints have been reported in which the nidus is located in diaphysis of the long bones. Surgical removal of the nidus has been reported to result in remission of synovitis (10, 27). As previously reported, in our control Cases 5 to 7, diaphyseal lesions were not associated with synovitis. Also in Cases 1 to 4 associated with synovitis, synovitis disappeared in the early period after surgery, which were confirmed by MRI (data not shown).

In 1973, Snarr *et al.* (11) advocated a hypothesis that specific activated substances derived from the nidus induce inflammation of the synovial membrane. Later, Markley *et al.* (12), Greco *et al.* (13, 14, 28), and one of the authors of the present study (TH) (3) demonstrated an increase in PGE2 level in the nidus by radioimmunoassay (RIA) and immunohistochemical studies using anti-PGE2 antibodies. PG produced within the nidus has been proposed to be a mediator of synovitis in intraarticular OO (7, 23, 29). However, substances associated with PG metabolism have not been examined in OO.

In this study, expression of the arachidonic acid metabolic enzyme cPLA2, which induces COX-2 and inflammatory cytokines IL-1β and TNFα, was detected by immunohistochemical and molecular biological analyses. Cytosolic PLA2 is present in almost all cells and mediates the release of arachidonic acid from the lipid bi-layer of the cell membrane (30, 31). Inflammatory cytokines IL-1β and TNFα are stimulants for the activation of the arachidonic acid metabolic pathway. In our series, three cases of OO and one case of OB of the femoral head joint were all complicated by synovitis. OB when arises in the long bone bears a close resemblance to OO roentgenographically and histologically except for the size of the lesion. As in our cases, the nidus of OO is usually less than 1.5 to 2.0 cm, in contrast to OB, which is more than 2.0 cm in greatest diameter.

The histologic findings of the synovium were similar to those reported in the literature, partially showing lymphofollicular synovitis resembling RA (2, 11, 21). In the nidus of Case 3, semiquantitative RT-PCR demonstrated expression of COX-2 mRNA, and analysis of the NIH image of the amplified band showed a very large quantity. In the same patient, the COX-2 mRNA to GAPDH ratio was higher in the nidus than that in the synovium. This finding was supported by immunohistochemical

results of six cases of OO and one case of OB in which strong and diffuse staining of COX-2 was found in osteoblasts within the nidus. In the adjacent synovial tissues of three cases of OO and one case of OB, only a small number of subsynovial spindle and stellate cells in the inflamed stroma were positive for COX-2, but we have not seen an evidence of macrophage for these cells on a parallel section with a macrophage marker, CD68 (data not shown). In contrast, numerical data of the amplified DNAs for cPLA2, IL-1β, and TNFα were not significantly different in the nidus and synovium in Case 3. These findings indicate that the arachidonic acid metabolic pathway is activated in both the nidus and the synovium.

In RA, production of IL-1β and TNFα is increased in the inflamed synovial tissue, and these cytokines enhance cPLA2 secretion from fibroblasts, chondrocytes, and other cells in the synovium with increasing level of cPLA2 in the joint fluid (22, 32, 33). On the other hand, IL-1β and TNFα also induce COX-2 production in macrophages, fibroblasts, and synovial lining cells. The COX-2 produced in turn induces cPLA2-mediated release of arachidonic acid, with subsequent increase in PG. Masferrer *et al.* (34) reported that in the absence of arthritis, macrophages, fibroblasts, synovial cells, and chondrocytes did not express *COX-2*, and IL-1β and TNFα stimulated the expression of the *COX-2* gene when inflammation occurred.

Based on these findings, we propose the following mechanism of the development of synovitis in intraarticular OO. First, COX-2 expression in osteoblasts within the nidus primarily activates the arachidonic acid metabolic pathway and production of PGs, which might induce synovitis in the adjacent synovial tissue. As a result of inflammation, inflammatory cytokines such as IL-1β and TNFα further enhance COX-2 expression in the osteoblasts, which amplifies the inflammatory reactions. In the inflamed synovial tissue, the cytokine network between the infiltrated inflammatory cells and local cells further elicits secretion of cytokines. Although the definite pathway of transmission of inflammation from the nidus to synovium is not apparent, this study suggested that COX-2 expressed primarily by osteoblasts in the nidus may play a major role in activating the pathway of arachidonic acid metabolism, resulting in secondary synovitis of the involved joint in intraarticular OO. Further study is necessary to examine the significance of COX-2 expression in osteoblasts in tumor proliferation.

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