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**Remarkable response of juvenile diffuse sclerosing osteomyelitis of mandible to pamidronate**

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## **ABSTRACT**

We report a juvenile case of diffuse sclerosing osteomyelitis of the mandible that showed a favorable response to pamidronate, a bisphosphonate derivative. Although conventional treatments had been ineffective for five years, pamidronate administration brought about conspicuous improvement both clinically and radiographically. Severe adverse reaction was not found except for low-grade fever and lassitude only on the day following administration. During the course of the treatment, however, nonsuppurative osteomyelitis of the right humerus also occurred, leading to the established diagnosis of chronic recurrent multifocal osteomyelitis. Then, pamidronate therapy was again performed successfully with almost disappearance of clinical symptoms. Both bone-specific alkaline phosphatase (bone formation marker) and pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICPT) (bone resorption marker) showed a marked decrease with pamidronate therapy, which suggested that pamidronate is useful for the treatment of chronic recurrent multifocal osteomyelitis with inhibitory effect on bone turnover.

Diffuse sclerosing osteomyelitis (DSO) of the mandible has been considered an intractable disease of unknown etiology, characterized by recurrent pain, swelling and trismus in the absence of pus formation, fistula or sequestration.<sup>1,2</sup> Radiographically, DSO shows intermingled sclerotic and osteolytic lesions with solid periosteal reaction or external bone resorption.<sup>3</sup> Histologically, nonspecific chronic inflammation change of bone is shown. Mandibular symptoms tend to recur after conventional therapy with antibiotics, anti-inflammatory drugs, hyperbaric oxygen or surgery.<sup>1,2,4</sup>

Bisphosphonates, potent inhibitors of osteoclast-mediated bone resorption,<sup>5</sup> have been widely used in the management of patients with advanced cancer involving skeletal metastasis and hypercalcemia of malignancy.<sup>6,7</sup> Recently, a few studies have reported that bisphosphonates are useful for the treatment of the recurrent pain of DSO.<sup>8-11</sup>

We herein report a juvenile case of DSO of the mandible with a favorable response to pamidronate therapy.

## **CASE REPORT**

A 9-year-old boy was referred to our clinic with a 5-month history of recurrent swelling of the left lower face in June 2000. After extraction of the left lower second deciduous molar in January 2000, he had been referred to an oral surgery clinic because of pain and swelling around the region. There he underwent administration of multiple courses of antibiotics and curettage of the mandibular lesion twice, but these treatments were not effective. On clinical examination, low-grade fever, left mandibular swelling

and trismus were found, but his teeth and gingiva appeared normal. Computed tomography (CT) revealed widespread periosteal bone formation and cortical bone resorption from the left mandibular ramus to the right premolar region, together with thickening of the overlying soft tissues. Bone scintigraphy showed high uptake in the corresponding area. The histological finding from biopsy specimens led to a diagnosis of osteomyelitis, but microbiological culture of bone fragments was negative. In the laboratory data, the erythrocyte sedimentation rate was elevated to 58mm/h (range of normal pediatric value 0-10mm/h), but the value of C-reactive protein and leukocyte count were normal. Alkaline phosphatase was elevated to 568 IU/l (range of normal adult value 104-338 IU/l). He received long-term antibiotic (imipenem/cilastatin sodium and clarithromycin) and corticosteroid treatment (prednisolone). However, symptoms were improved only transiently, and swelling and trismus frequently recurred. Because of severe enlargement and deformity of the mandible with intermingled sclerotic and osteolytic lesions extending from the left condyle to the right angle (Fig. 1), decortication of the mandible along with hyperbaric oxygen therapy and irrigation-perfusion treatment with antibiotics, was performed three times. Postoperatively, he received the nonsteroidal anti-inflammatory drug diclofenac sodium (50mg/day) for a long-term period. Histopathological examination revealed the same result as the previous biopsy, and microbiological culture was negative again. These findings led to the diagnosis of diffuse sclerosing osteomyelitis. Although the treatments resulted in the transient disappearance of symptoms, they recurred repeatedly at monthly intervals. Two years after the last decortication, osteolytic changes in the

sclerotic lesions extended to the bilateral condylar processes (Fig. 2, A~C), and marked resorption of the alveolar bone with absence of the lamina dura was observed (Fig. 3A). In December 2004, we decided to administer pamidronate to him with the approval of the Ethical Committee of Hokkaido University. A 30-mg dose of pamidronate was diluted with 500 ml of saline and infused intravenously for 4 hours. He became slightly febrile and complained of slight lassitude only the following day. Following the second infusion 3 months after the first administration, conspicuous improvement was brought about both clinically and radiographically. The dose of diclofenac sodium for the relief of symptoms was decreased from 50mg every day to 25 mg/day every other day, osteolytic changes of the mandible were decreased (Fig. 2, D~F), and reappearance of the lamina dura and alveolar bone with normal density were observed (Fig. 3B). However, 3 months after the second infusion, he noticed painful swelling of the right upper arm. Bone scintigraphy showed slight uptake in the mandible and high uptake in the right humerus in which there had been no uptake before the first infusion (Fig. 4). Open biopsy of the humerus revealed nonsuppurative osteomyelitis, consistent with the findings of the mandibular lesion. At this point the diagnosis of chronic recurrent multifocal osteomyelitis (CRMO)<sup>12</sup> was established. He underwent the third pamidronate therapy (30mg) 7 months after the second infusion. Humerus pain almost disappeared in a few days. The mandibular lesion remained being under control. Bone-specific alkaline phosphatase, which is a marker of bone formation, decreased with pamidronate therapy (from 134.7 to 84.7 IU/l). Moreover, pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICPT)<sup>13</sup>, which is a marker

of bone resorption, also demonstrate drastic reduction with it (from 25.2 to 13.5 ng/ml) (Table 1).

## **DISCUSSION**

We reported a marked response of juvenile diffuse sclerosing osteomyelitis to the intravenous administration of pamidronate. Until now, there have been only four reports on the effectiveness of bisphosphonates (pamidronate,<sup>8,10</sup> clodronate<sup>9</sup> and alendronate<sup>11</sup>) for mandibular diffuse sclerosing osteomyelitis. Among these pamidronate and alendronate had immediate effects (within 72 h) for pain relief.<sup>8,10,11</sup> However, their continuous effects could not be estimated because of short follow-up periods. Although Wright et al.<sup>14</sup> reported that risedronate therapy resulted in a dramatic response for diffuse sclerosing osteomyelitis of the femur, the symptoms reoccurred after its discontinuation. In the present case, a single infusion of pamidronate had a dramatic effect resulting in radiographical improvement, and the second infusion brought about a discontinuation of diclofenac sodium for symptom relief, but mandibular swelling and trismus reoccurred 2 months later. Recently, there have been reports of osteonecrosis of the jaw in cancer patients who receive anticancer therapy and an intravenous long-term bisphosphonate concomitantly.<sup>15,16</sup> Although a causal relationship between them has not been established, bisphosphonate should be strongly responsible. These results suggest that small dose of bisphosphonate may be effective for diffuse sclerosing osteomyelitis, but a large dose for patients receiving supportive cancer therapy may induce osteomyelitis. Therefore, frequent intravenous

administration of bisphosphonates should be avoided.

We identified nonsuppurative osteomyelitis of the right humerus five years after the first visit that developed after the second pamidronate therapy. We believe the newly developed lesion in humerus is unrelated to the drug-use (side effect), because only the two infusions of pamidronate with considerably low dose (only 30 mg per infusion) had been administered. Hence, this case should be diagnosed as chronic recurrent multifocal osteomyelitis (CRMO)<sup>12</sup>, which affects multiple bone lesions, most commonly involving the long bone metaphyses in younger persons. Swei et al.<sup>17</sup> reported that diffuse sclerosing osteomyelitis is an expression of chronic recurrent multifocal osteomyelitis, since there are no distinguishing features between them. Moreover, they mentioned that multiple bone lesions might have been found in previous reports of diffuse sclerosing osteomyelitis if bone scintigraphy had been done. However, in our case, at the time of bone scintigraphy (first admission, just before the first debridement and the first pamidronate infusion), no humerus lesion was detected. Therefore, whole body investigation using bone scintigraphy should be done in diffuse sclerosing osteomyelitis cases not only at the first examination but also during the follow-up.

Bisphosphonate therapy can be a new treatment strategy for patients with diffuse sclerosing osteomyelitis when conventional treatments are not effective. In our case, we administered 30mg of pamidronate not only for the mandibular lesion but also for the humerus lesion, leading to dramatic improvement. Moreover, both bone formation (bone-specific alkaline phosphatase) and resorption markers (ICPT) drastically



decreased with pamidronate therapy. These findings obviously supports the usefulness of pamidronate to chronic recurrent multifocal osteomyelitis with the inhibitory effect on bone turnover. Therefore, with this therapy, particular attention should be paid to the low dose (30mg) and appropriate interval of the administration (at least 3 months), and long-term follow-up examination with bone scintigraphy is essential.

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### Figure Legends

**Fig. 1** A~C, Axial CT scans taken before the first decortication showing enlargement, sclerotic and osteolytic lesions of the mandible. **D**, 3-D CT reconstruction showing enlargement and deformation of the mandible.

**Fig. 2** A~C, Axial CT scans before the first pamidronate infusion showing advanced osteolytic changes in the sclerotic lesions extending to the bilateral condylar processes of the mandible (*arrowheads*). **D~F**, Axial CT scans taken 3 months after the first pamidronate infusion showing apparent regression of the osteolytic changes of the mandible.

**Fig. 3** **A**, Intraoral radiograph of the mandibular alveolar region taken before the first pamidronate infusion showing marked osteolytic destruction with loss of lamina dura (*arrowheads*). **B**, Intraoral radiograph of the mandibular alveolar region taken 3 months after the first pamidronate infusion showing remineralization and reappearance of the lamina dura.

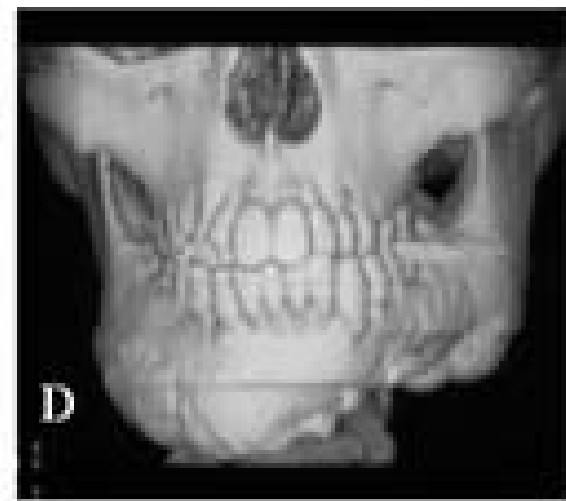
**Fig 4.** **A**, Bone scintigraphy taken before the first pamidronate infusion showing excessive uptake only in the entire mandible. **B**, Bone scintigraphy taken 5 months after the second pamidronate infusion showing reduction of the activity in the mandible and excessive uptake in the right humerus.

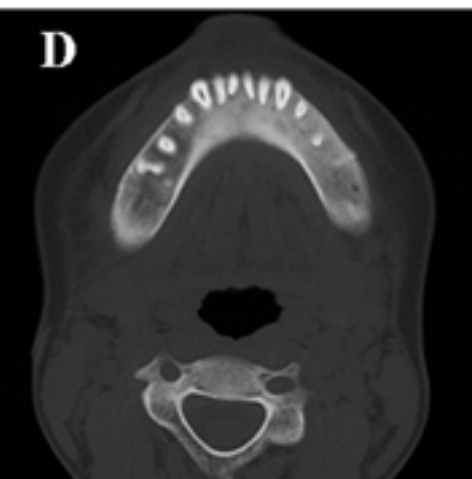
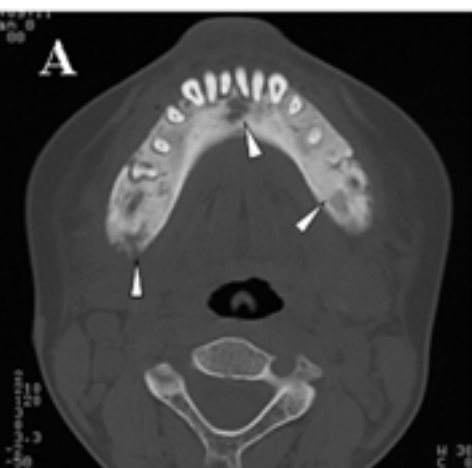
**Table I.** Changes of bone turnover markers with pamidronate infusion

	Bone formation marker	Bone resorption marker
	Bone-specific ALP	ICTP
Time of pamidronate infusion	( 13.0-33.9 IU/l )*	( 4.5 >ng/ml )*
Before pamidronate infusion	134.7	25.2
After the third pamidronate infusion	84.7	13.5

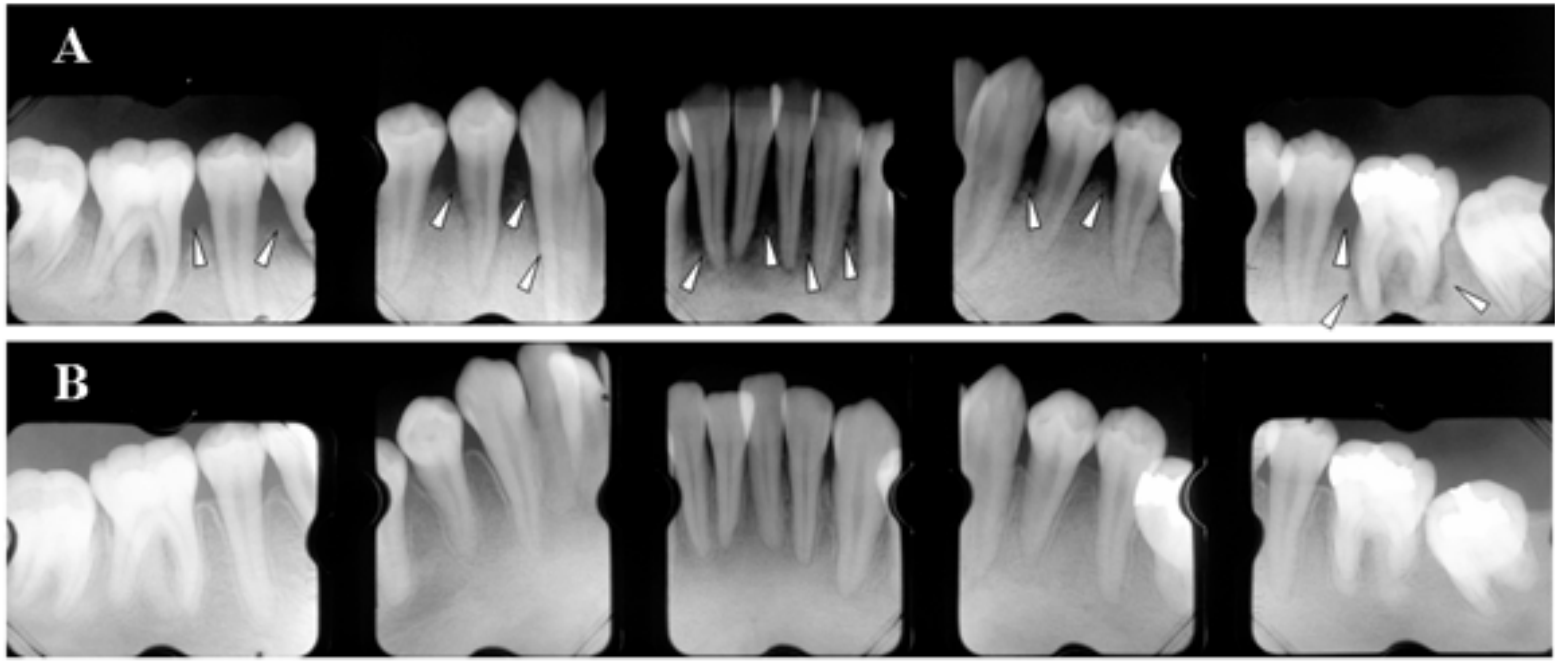
*ALP*, alkaline phosphatase; *ICTP*, pyridinoline cross-linked carboxyterminal telopeptide of type I collagen.

\* range of normal adult value

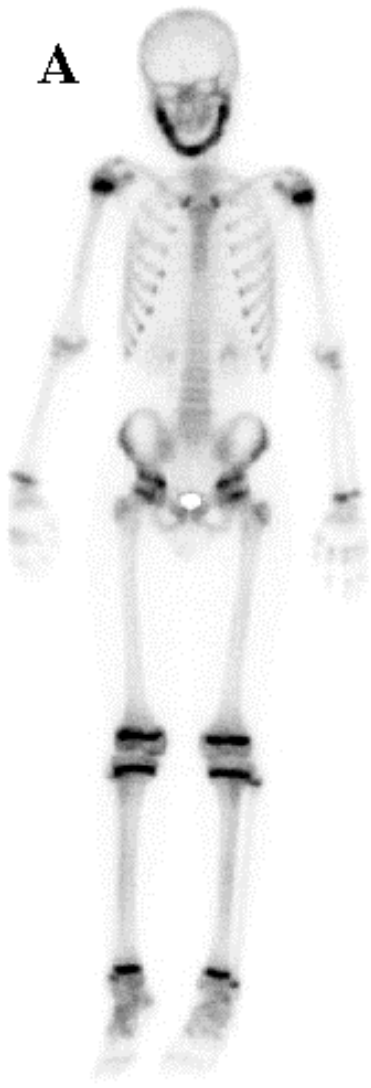








**A**



**B**

