Activation of the arachidonic acid metabolic pathway and induction of sleep disturbance by sacral osteoblastoma: A case report

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Abstract. Osteoblastomas are benign bone tumors that produce prostaglandin and promote inflammation. The aim of the present study was to describe the clinical and radiological characteristics of a pediatric osteoblastoma case over an 8-month postoperative follow-up. The case involved an 11-year-old female patient with normal somatic development, presenting with a chief complaint of sleep disturbance. The patient had no spontaneous pain or other readily evident possible causes. Magnetic resonance imaging (MRI) revealed a neoplastic lesion in the sacrum, with peritumoral edema. Intraoperative fast-frozen biopsy raised the suspicion of osteosarcoma. However, the final diagnosis was osteoblastoma and a second operation was performed for total resection. The edematous peritumoral bone and muscle tissues were preserved. Following total removal of the tumor, the sleep disturbance resolved. Eight months after the surgery, MRI revealed no recurrence of the tumor and reduction of the peritumoral edema. On immunohistochemical examination, cyclooxygenase (COX)-1 and COX-2 were strongly positive, indicating that the tumor activated the arachidonic acid metabolic pathway and produced prostaglandin. The inflammatory process subsequently promoted the development of peritumoral edema and induced the sleep disturbance.

Introduction

Osteoblastomas are rare primary bone neoplasms, categorized as benign bone tumors mostly located in the spine (40%). Osteoblastomas typically affect the pediatric population, predominately children aged 10-15 years (1,2). These neoplasms often cause a diffuse, reactive prostaglandin (PG)-mediated inflammatory infiltrate in the surrounding soft tissues and bone marrow, referred to as the flare phenomenon (3).

Total removal is the standard treatment for osteoblastoma. Following subtotal resection, there is a high probability of local recurrence (1). The flare phenomenon, however, occasionally causes a misleading appearance, simulating a malignant process, with overestimation of the extent of the lesion (4). We herein report the case of a patient with sleep disturbance that resolved following total removal of a sacral osteoblastoma. Magnetic resonance imaging (MRI) revealed presence of the flare phenomenon, which had resolved on post-operative follow-up MRI. To the best of our knowledge, there has been no report on how this phenomenon varies on MRI post-treatment. The aim of the present study was to discuss the impact of the inflammatory process on the patient's clinical course.

Case report

The patient was an 11-year-old female who had experienced a weight loss of 5 kg within 1 year. The patient had also been a member of an athletics club, and her team members had noted a decline in her running performance. In addition, the patient was unable to sleep through the night, although she did not report spontaneous pain or any other symptoms. The patient was examined and followed up at the Department of Pediatrics of the Wakayama Medical University Hospital (Wakayama, Japan), and was referred to the Department of Neurological Surgery 8 months after the onset of symptoms. On physical examination, there was tenderness in the sacral area and neurological examination revealed a mild lateral rotation in the left leg while walking. There was no observed sensory disturbance or neurogenic bladder. Polysomnography revealed an increased frequency of micro-arousals over the normal upper limit (Fig. 1).

MRI studies of the sacral spine revealed a neoplastic lesion, located at the S3 level (Fig. 2A), which had doubled in size over a 6-month period. The vertebral body in S2, S3, S4 and the paraspinal muscles exhibited abnormal intensity (Fig. 2B and F). Gadolinium-enhanced T1-weighted images revealed mild and homogenous enhancement in the lesion (Fig. 2C and D). A computed tomography scan revealed bone deformation around the lesion and a potential spina bifida (Fig. 2E).

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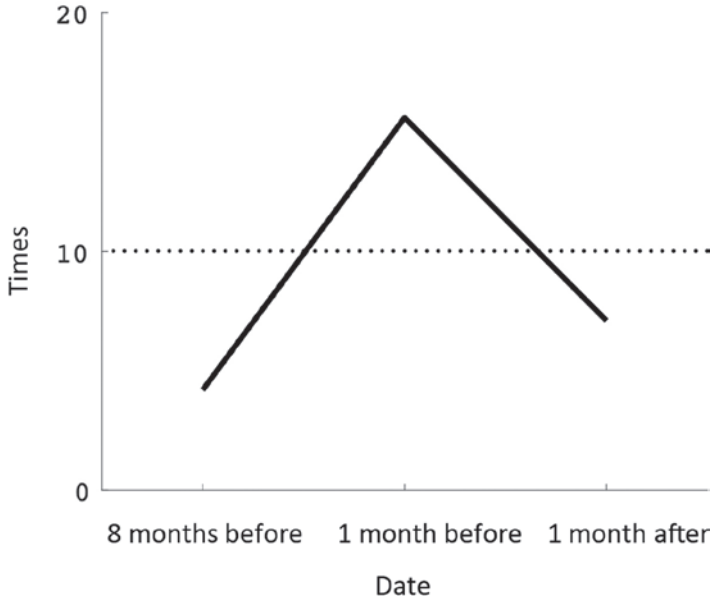

Figure 1. Polysomnography before and after surgery. This graph showed the times of micro-arousals overnight (vertical axis) at 8 months before, 1 month before and 1 month after surgery (horizontal axis). Dashed line, normal upper limit (10 times).

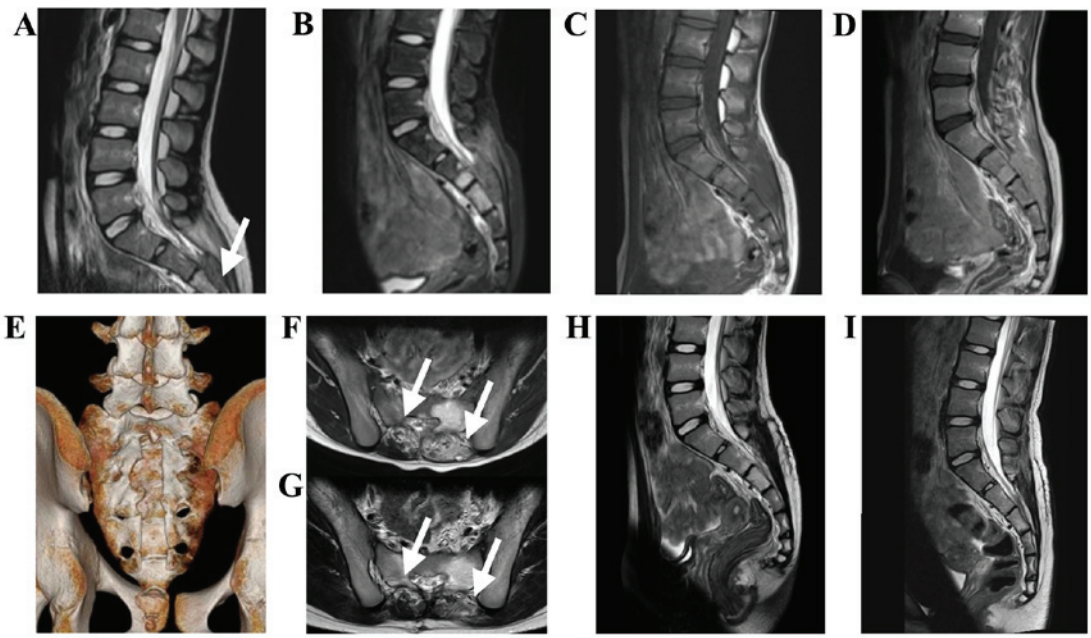

Figure 2. Imaging studies. (A) Magnetic resonance imaging (MRI) examination of the lumbar spine 6 months prior to surgery revealed a lesion (arrow) at the S3 level. The lesion doubled in size on MRI immediately prior to surgery: (B) T2-weighted imaging, (C) T1-weighted imaging and (D) T1-weighted imaging with gadolinium enhancement. (E) Computed tomography scan showing a preoperative 3D bone image. (F) T2-weighted axial image on MRI revealed abnormal intensity in the paraspinal muscles (arrows). (G and H) T2-weighted image on MRI showed no recurrence and reduced abnormal intensity area (arrows) at 3 months after the surgery. (I) T2-weighted image on MRI showed no recurrence and further reduction of the abnormal intensity area at 8 months after surgery.

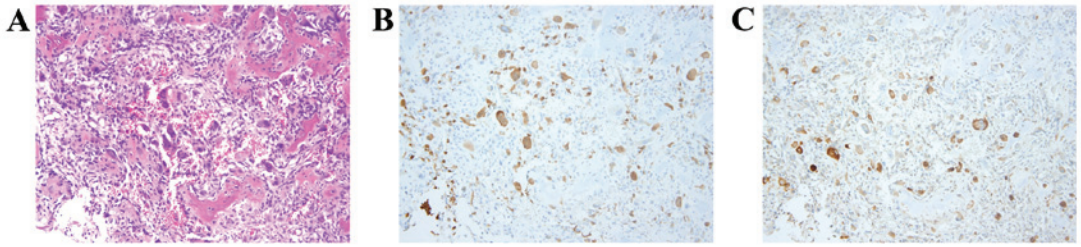

Figure 3. Photomicrographs of continuous tissue sections. (A) Hematoxylin and eosin staining. Immunostaining for (B) cyclooxygenase (COX)-1 and (C) COX-2. Original magnification, x20.

At first, schwannoma was suspected. Malignancy was also taken into consideration, as the patient exhibited a weight loss of 5 kilograms within 1 year, and the lesion had doubled in size over a period of 6 months. The surgical plan was decided upon depending on the intraoperative fast-frozen biopsy.

The patient had a potential spina bifida, and the lesion was detected following skin incision. The lesion exhibited a bleeding tendency and the suspected diagnosis following intraoperative fast-frozen biopsy was osteosarcoma. It was decided to interrupt the procedure and close the incision, due to the risk of dissemination if the lesion was malignant and resection was performed without safety margins, and revise the surgical plan following definitive pathological diagnosis. The final diagnosis was osteoblastoma, and a second operation was performed for total resection of the tumor. Although the lesion exhibited a bleeding tendency, the boundary from the surrounding tissue was clear and the sacral nerves were intact. The destructed and deformed bone tissues surrounding the tumor were removed and normal bone was identified underneath. Total macroscopic resection of the tumor was performed.

Postoperatively, there were no neurological deficits or tenderness in the sacrum. The sleep disturbance improved immediately after the operation and the frequency of micro-arousal on polysomnography was decreased (Fig. 1). At the 3-month follow up, MRI revealed no evidence of recurrence, and the area of abnormal intensity in the vertebral bodies of the sacrum and the paraspinal muscles was reduced (Fig. 2F-H). At the 8-month follow-up, there was no recurrence on MRI and the abnormal intensity area was further reduced in size (Fig. 2I).

On pathological examination, neoplastic bone trabeculae lined by osteoblasts with a loose and edematous fibrovascular stroma were observed. Although spindle cells were occasionally observed, the hyperplasia was not sufficient for the tumor to be diagnosed as osteosarcoma (Fig. 3A). On immunohistochemistry, large osteoblasts (double in size compared with normal osteoblasts), were strongly positive for cyclooxygenase-1 (COX-1; Santa Cruz Biotechnology, Inc., Dallas, TX, USA) (Fig. 3B), cyclooxygenase-2 (COX-2; Santa Cruz Biotechnology) (Fig. 3C), and PG synthetase. Immunohistochemistry was performed using Ventana Discovery XT Automated Immunostaining system (Ventana Medical Systems, Inc., Tucson, AZ, USA).

Discussion

In the present case, the flare phenomenon was observed on imaging, whereas COX-1 and COX-2 were strongly positive on immunohistochemistry, indicating activation of the arachidonic acid metabolic pathway and the production of PG; this subsequently activated the inflammation process that likely cause the patient's sleep disturbance.

In 1990, Crim *et al* reported a case of osteoblastoma causing a diffuse, reactive inflammatory infiltrate in the surrounding bone marrow and soft tissue; these findings were collectively referred to as the flare phenomenon (3). Osteoid osteoma, which is histologically similar to osteoblastoma in several aspects, also causes this inflammatory phenomenon, and in younger patients it tends to be associated with more extensive peritumoral edema (5,6). COX-2 expression, which is largely induced by inflammation, plays a key role in the activation of the arachidonic acid metabolic pathway and the production of PG (7,8). This finding on imaging is misleading and may cause overestimation of the tumor size and misdiagnosis of malignancy. However, the intensely reactive portion of the lesion is devoid of tumor cells (9). Total resection of the tumor is recommended to prevent recurrence (1,10). Yamamura *et al* measured the concentration of PGE2 by radioimmunoassay in two cases of osteoblastoma (11) and reported that osteoblastoma was associated with a relatively higher concentration of PG in primary bone tumors or tumor-like conditions, and that bone marrow and soft tissue edema were significantly associated with the PG levels. Mungo *et al* reported COX-1 and COX-2 expression in osteoid osteomas (8); however, in osteoblastoma, COX-1 was positive and COX-2 was negative, although only 1 case was reported. In the present case, the flare phenomenon was observed on imaging, and the findings resolved following total removal of the tumor. Moreover, immunohistochemical examination demonstrated that COX-1 as well as COX-2 were strongly positive. These findings suggested that the tumor activated the arachidonic acid metabolic pathway and the production of PG.

A number of previous studies have demonstrated an association between sleep and PG (12,13). PGD2 is an endogenous sleep-promoting substance that, together with PGE2, regulates sleep-wake behavior. PGD2 concentration in the cerebrospinal fluid possibly fluctuates with circadian rhythmicity in parallel with the sleep-wake cycle (13). The first step of PG synthesis is catalyzed by COX-1, which is constitutively expressed, and COX-2, which is generally induced by inflammation (8). COX-2 positivity on immunohistochemistry strongly supports the production of excess PG. To the best of our knowledge, this is the first case report on the association between sleep disturbance and osteoblastoma. Following gross total resection of the lesion, the patient's sleep disturbance improved and the abnormal intensity area of the vertebral bodies in the sacrum and the paraspinal muscles was reduced. This clinical course also indicates that the tumor was responsible for inducing the inflammatory reaction related to PG and disturbing the sleep pattern.

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