

## Hypercalcemia and Extensive Osteolytic Lesion with Increased Plasma Prostaglandin E<sub>2</sub> Level in a Child with Acute Lymphoblastic Leukemia

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In this report, we present a rare case of childhood ALL with hypercalcemia and extensive osteolytic lesions. The case was a 7-year-old girl presenting with vomiting and aggravating bone pain. Radiologic examinations showed severe osteolytic lesions of the skull and extremities. Laboratory findings revealed low hemoglobin, normal WBC count with absent circulating blasts, and an increased serum calcium level. Serum intact PTH and 1,25-(OH)<sub>2</sub> vitamin D<sub>3</sub> levels were below the normal ranges and parathyroid hormone-related peptide (PTHrP) was not detected, whereas serum levels of prostaglandin E<sub>2</sub> were elevated. The hypercalcemia resolved with specific antileukemic chemotherapy along with supportive care. The elevated plasma prostaglandin E<sub>2</sub> levels decreased slightly after complete remission with induction chemotherapy. These findings suggest that increased plasma prostaglandin E<sub>2</sub> levels may be one of the pathogenetic mechanisms responsible for the occurrence of hypercalcemia in this patient. (*Korean J Hematol* 2007;42:433-438.)

**Key Words:** Acute lymphoblastic leukemia, Prostaglandin E<sub>2</sub>, Hypercalcemia, Osteolytic lesion

### INTRODUCTION

Hypercalcemia is a rare complication in childhood acute lymphoblastic leukemia (ALL), although it often presents with adult hematologic malignancies, such as multiple myeloma or adult T-cell leukemia/lymphoma.<sup>1,2)</sup> This presentation also commonly coincides with lytic bone lesions and absent circulating blasts.<sup>3)</sup> The underlying mechanism for hypercalcemia in malignancies is associated with paraneoplastic production of humoral factors, mainly parathyroid hormone-re-

lated peptide (PTHrP),<sup>4)</sup> or local osteolytic hypercalcemia.<sup>5)</sup>

Here, we describe a case of childhood ALL presenting with hypercalcemia and extensive osteolytic lesions, which are probably mediated by increased plasma prostaglandin E<sub>2</sub> levels.

### CASE REPORT

A 7-year-old girl was admitted to the pediatric hematology-oncology service at our institution for evaluation of hypercalcemia and multiple osteo-

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lytic lesions. She presented at another hospital with generalized ache for 4 weeks and vomiting with aggravating pain on the shoulder and hip for 5 days, where hypercalcemia and multiple osteolytic lesions were noted.

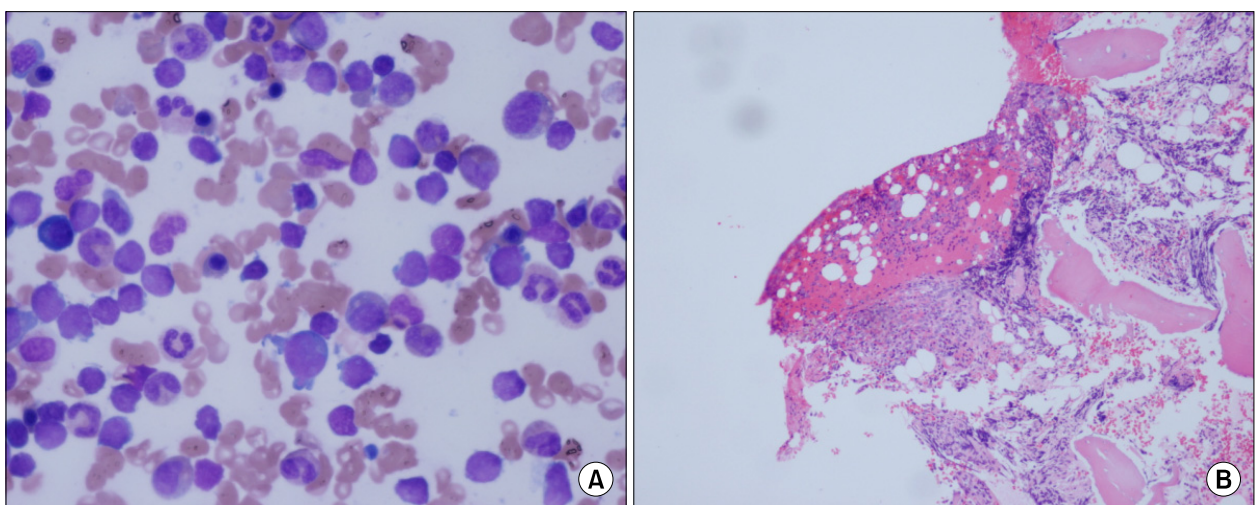
On admission to our institution, she was pale and appeared ill. Physical examination revealed limitation of motion with tenderness on the up-

**Table 1.** Laboratory findings at diagnosis and upon complete remission (CR) of ALL

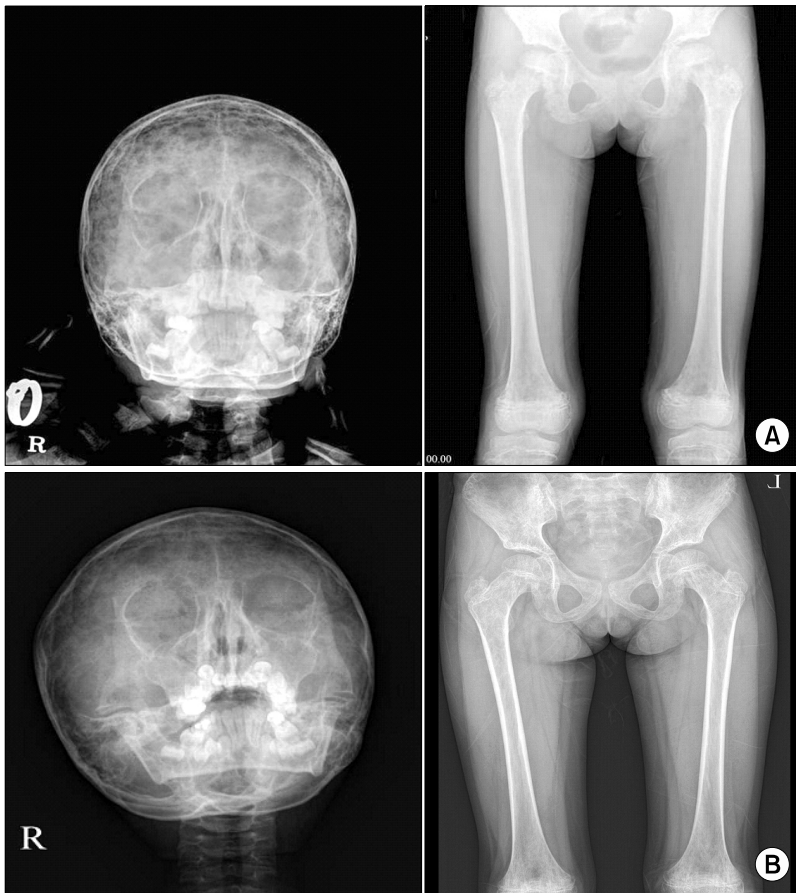
	At diagnosis	At CR
Leukocyte count (/ $\mu$ L)	6,100	7,100
Platelet (/ $\mu$ L)	228,000	160,000
Hemoglobin (g/dL)	9.3	8.8
Serum calcium (mg/dL)	18.4	8.5
Serum phosphorus (U/L)	127	2.2
Serum uric acid (mg/dL)	6.3	2.8
Serum LDH (U/L)	182	287
Serum creatine (mg/dL)	0.5	0.4
Serum alkaline phosphatase (U/L)	127	154
Serum PTH-intact (pg/mL)	9.07	46.2
PTHrP (pmol/L)	<1.0 (<1.0)	<1.0
Calcitonin (pg/mL)	3.9 (2~17)	1.5
1,25-hydroxy vitamin D (pg/mL)	4.8	35.4
Prostaglandin E <sub>2</sub> (pg/mL)	166 (<4.4)	124

Abbreviations: LDH, lactate dehydrogenase; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide.

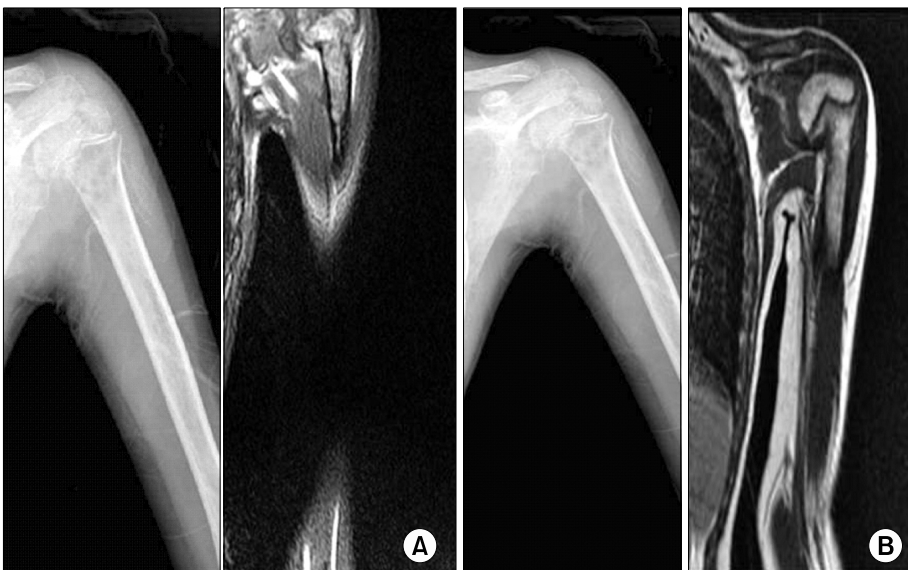
per extremities and no hepatosplenomegaly/lymphadenopathy. Laboratory studies on admission disclosed the following values: hemoglobin 9.3g/dL, WBC 6,100/ $\mu$ L (differential count; segmented 65%, no blast), platelet 228,000/ $\mu$ L, AST 17U/L, ALT 6U/L, alkaline phosphatase 127U/L, lactate dehydrogenase 182U/L, blood urea nitrogen 26 mg/dL, creatinine 0.5mg/dL, uric acid 6.3mg/dL, calcium 18.4mg/dL, and phosphorus 3.2mg/dL (Table 1). We performed bone marrow aspiration and biopsy (Fig. 1), which showed that nearly 30% of all hematopoietic cells were immature cells. These cells were medium to large in size with a high nuclear/cytoplasmic ratio, and a scanty bluish cytoplasm with fine nuclear chromatin. The bone marrow section was hypocellular (40%) for her age and had more immature cells than those in the aspirate. The immunohistochemical staining was positive for CD45 and CD10, but negative for CD3, CD20, CD68, and CD79a. Cytogenetic study showed a normal female karyotype (46,XX). The skeletal survey revealed multiple, extensive osteolytic lesions on the skull, upper and lower extremities, and pelvis (Fig. 2). MR imaging revealed a pathologic fracture on the metaphysis of the proximal humerus



**Fig. 1.** Bone marrow aspiration (A: Wright stain, X1,000) and biopsy (B: H&E stain, X100). Nearly 30% of all hematopoietic cells were immature cells. The bone marrow section was hypocellular (40%) for her age and there were more immature cells than those in the aspirate. Immunophenotypic analysis was positive for CD45 and CD10, but negative for CD3, CD20, CD68, and CD79a. Cytogenetic analysis showed a normal female karyotype (46,XX).



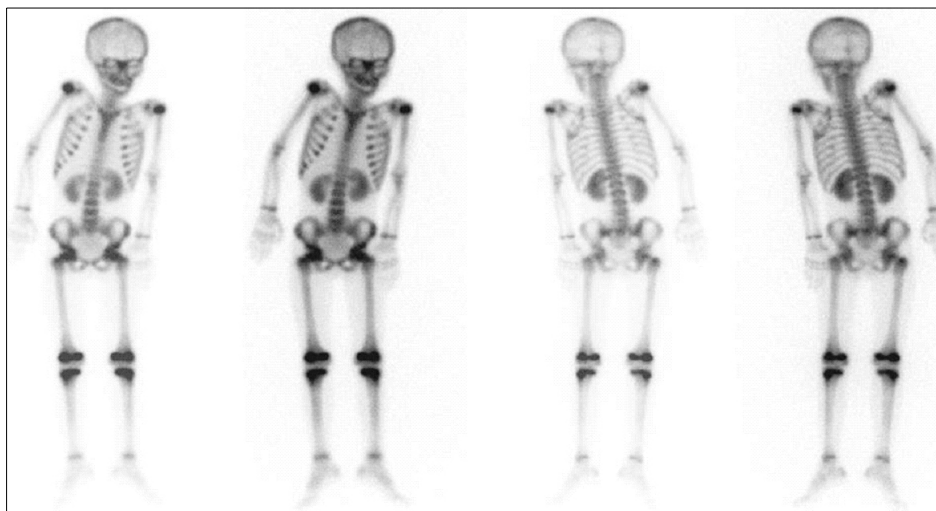
**Fig. 2.** Multiple osteolytic lesions at diagnosis (A) and after CR (B). At diagnosis, multiple osteolytic lesions were seen in the skull, pelvic bone, both femurs, and both tibias (A), but after CR, the multiple osteolytic lesions were improved, but the osteoporotic change remained (B).



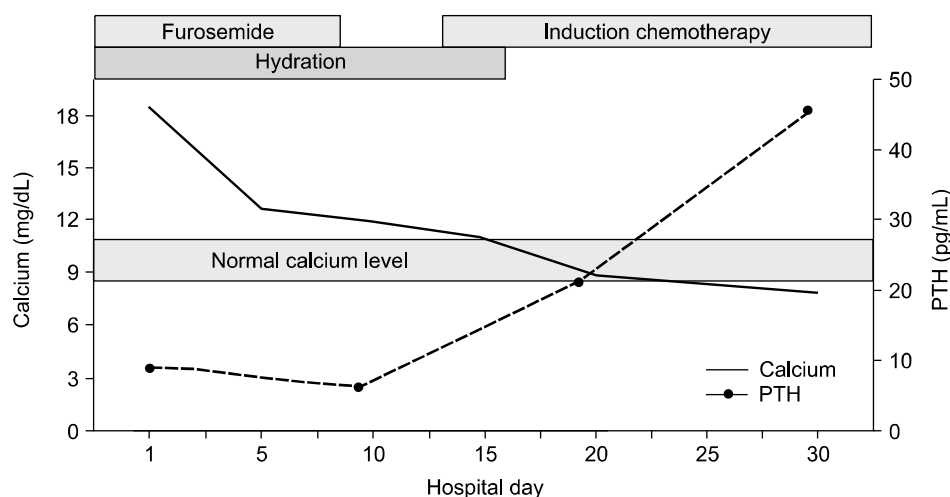
**Fig. 3.** Simple x-ray and MR image of the left proximal humerus at diagnosis (A) and after CR (B). At diagnosis, a simple X-ray revealed an osteolytic lesion of the left proximal humerus metaphysis. On MR imaging, an ill-defined low-signal intensity mass lesion was noted at the same level of the T1-weighted image coronal scan (A). However, simple x-ray and MR images of this lesion showed improvement after CR (B).

(Fig. 3). A whole body bone scan showed an overall decrease in activities of the growth plates, which were more severe at the left femoral head, right knee, and left humeral head (Fig. 4).

Further investigations to clarify the etiology of the hypercalcemia revealed the following (Table 1): 6.1pg/mL (9~65) of intact parathyroid hormone (PTH), <1.0pmol/L (<1.0) of PTHrP, 3.9



**Fig. 4.** Whole body bone scan shows overall decreased activities of the growth plates, which were more severe at the left femoral head, right knee, and left humeral head.



**Fig. 5.** Clinical courses. The elevated calcium level was normalized after supportive care with the initiation of induction chemotherapy.

pg/mL (2~17) of calcitonin, 4.8pg/mL (25~45) of 1,25-(OH)<sub>2</sub> vitamin D<sub>3</sub>, and 166pg/mL (<4.4) of prostaglandin E<sub>2</sub>.

Aggressive fluid therapy with furosemide and allopurinol slowly reduced the calcium and uric acid level. Immediately after the diagnosis of ALL, we started chemotherapy according to the standard risk protocol of the Children Cancer Group (CCG-1952), and the calcium and uric acid levels were rapidly normalized (Table 1, Fig. 5). The elevated plasma E<sub>2</sub> level decreased slightly, yet not to normal after complete remission.

## DISCUSSION

Hypercalcemia in childhood ALL is a rare

complication occurring at frequencies ranging from 0.6% to 4.8%.<sup>1,2,6)</sup> Hypercalcemia of malignancy is divided into two subgroups according to the underlying mechanisms for the elevated serum calcium levels. The first mechanism is local osteolytic hypercalcemia with osteolytic skeletal metastases and possible cytokine involvement.<sup>5)</sup> In multiple myeloma or adult T cell leukemia/lymphoma, the primary mechanism for hypercalcemia is increased osteoclastic bone resorption by tumor cells. The second subgroup of humoral hypercalcemia of malignancy is due to paraneoplastic production of humoral factors, mainly parathyroid hormone-related peptide and some other factors such as vitamin-D-like sterols,<sup>7)</sup> prostaglandin E<sub>2</sub>,<sup>8)</sup> tumor necrosis factor alpha

(TNF- $\alpha$ ),<sup>9)</sup> and interleukin (IL)-6.<sup>10)</sup> TNF- $\alpha$  and IL-6 are known to promote osteoclastic bone resorption, but PTHrP-independent hypercalcemia with increased proinflammatory cytokines is rarely seen in childhood ALL.<sup>1,2)</sup> Osteoclasts are differentiated from hematopoietic progenitor cells in response to these bone-resorbing factors including prostaglandin E<sub>2</sub>, IL-6, and 1,25-(OH)<sub>2</sub> vitamin D<sub>3</sub>, and increased osteoclasts results in increased bone resorption.

For our patient, serum intact PTH and 1,25-(OH)<sub>2</sub> vitamin D<sub>3</sub> levels were below the normal ranges and PTHrP was not detected, whereas serum levels of prostaglandin E<sub>2</sub> were elevated before treatment and then decreased after chemotherapy. Based on these observations, we can speculate that the systemic overproduction of prostaglandin E<sub>2</sub>, probably produced directly or indirectly by leukemic cells, may be the cause of the severe osteolytic lesions and hypercalcemia in our case. This suggests that hypercalcemia in our patient is associated with increased humoral factor and prostaglandin E<sub>2</sub>, and is PTHrP-independent, which is rarely seen in childhood ALL. In acute leukemia, some blasts can produce prostaglandin E<sub>2</sub>,<sup>11)</sup> while in at least some in vitro systems prostaglandin E<sub>2</sub> appears to upregulate renal tubular 1-hydroxylation of 25-hydroxyvitamin D.<sup>12)</sup> Intravenous infusion of prostaglandin E<sub>2</sub> was found to raise plasma calcium concentrations in rats.<sup>13)</sup>

The clinical features of our patient, such as multiple osteolytic lesions with hypercalcemia and a normal white blood cell count without lymphoblasts in the peripheral blood, are very similar to other reported cases.<sup>3,14)</sup> In our case, the hypercalcemia disappeared after chemotherapy.

In conclusion, we experienced a case of childhood ALL with hypercalcemia and extensive osteolytic lesions, which rapidly responded after the initiation of induction chemotherapy. The elevated plasma prostaglandin E<sub>2</sub> levels, possibly related to the hypercalcemia and bone lesions, decreased after complete remission.

## 요 약

저자들은 구토와 골 통증을 주소로 내원한 7세 된 여자 환자에서 심한 골용해성병변과 고칼슘혈증을 동반한 급성림프모구백혈병의 경우를 경험하였기에 보고하는 바이다. 두개골과 사지의 방사선 소견상 심한 골용해성 병변이 있었다. 검사소견상 혈색소치가 감소되어 있었고 백혈구수는 정상이면서 말초혈액에 모세포는 발견되지 않았다. 혈청 칼슘은 증가되어 있었으며, 부갑상선호르몬과 비타민 D<sub>3</sub> 농도는 약간 감소되어 있었으나 부갑상선관련단백은 검출되지 않았고, 프로스타글란딘 E<sub>2</sub>의 농도는 증가되어 있었다. 항암제치료와 함께 보존적 치료로서 고칼슘혈증은 호전되었으며, 프로스타글란딘 E<sub>2</sub>의 농도도 약간 감소되었다. 본 증례에서 고칼슘혈증의 원인은 증가된 프로스타글란딘 E<sub>2</sub>의 농도가 관련이 있을 수 있다는 것을 시사한다.

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