The rapid correction of hypercalcemia at presentation of acute lymphoblastic leukemia using high-dose methylprednisolone

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Hypercalcemia is a well-recognized complication of neoplastic disorders. Herein, we report a hypercalcemic pediatric acute lymphoblastic leukemia case at presentation refractory to hydration, furosemide, pamidronate and calcitonin. Normal serum calcium levels were achieved with the initiation of chemotherapy protocol including vincristine, daunomycin and high-dose methylprednisolone. The impact of high-dose methylprednisolone in the correction of severe hypercalcemia in steroid-responsive tumors as an initial treatment approach or for cases refractory to other measures may be life-saving.

Key words: hypercalcemia, acute lymphoblastic leukemia, children, methylprednisolone.

Hypercalcemia is the most common life-threatening metabolic disorder associated with neoplastic diseases, occurring in 10-20% of all adults with cancer. It also occurs in children with cancer, but with much less frequency (approximately 0.5%-1%)\(^1\)\(^-\)\(^3\). Solid tumors, as well as certain hematologic malignancies, are most frequently associated with hypercalcemia\(^4\). Among hematopoietic malignancies, multiple myeloma and T-cell leukemia lymphoma (human T-lymphotropic virus 1-associated) have a high incidence of hypercalcemia, whereas only a few cases of acute lymphoblastic leukemia (ALL) with this complication have been recorded in adult cases. On the other hand, in a series of 6,055 childhood tumors (3,239 solid tumors and 2,816 leukemias and lymphomas), hypercalcemia at diagnosis was seen in 11 cases, 7 (0.2%) of which were ALL. The authors concluded that hypercalcemia at diagnosis occurs more frequently in ALL and that solid tumors are more likely to present hypercalcemia later, being also more resistant to therapy\(^1\).

Herein, we report a three-year-old male patient with ALL who presented with severe hypercalcemia refractory to hydration, diuretics and bisphosphonates. The calcium level decreased dramatically with the initial dose of chemotherapy including vincristine, daunomycin and high-dose methylprednisolone (HDMPE) (20 mg/kg/day). The hypocalcemic effect of glucocorticoids is well-known in conventional doses; however, HDMPE in steroid-responsive malignancies with resistant hypercalcemia may have beneficial impact and must be further investigated.

Case Report

A three-year-old boy with no remarkable personal history, who presented initially with the complaints of fatigue, anorexia, weight loss and vomiting, was found to have serum calcium level of 19 mg/dl and was referred from another center to Hacettepe University, Pediatric Intensive Care Unit; at that time, three-dose pamidronate treatment was transiently successful in lowering the serum calcium level. The physical examination revealed lethargy, general skeletal tenderness, painful movement of left arm, left submandibular lymphadenopathy (2x1 cm), and hepatomegaly and splenomegaly palpable 4 cm and 2 cm, respectively, below the costal margins. A complete blood count showed a hemoglobin concentration of 10.1, and a white blood cell count of 11.2x10\(^9\)/L with 15% blasts and platelets of 536x10\(^9\)/L.
Serum chemistry values were as follows: blood urea nitrogen (BUN) 15.6 mg/dl, creatinine 0.41 mg/dl, and uric acid 13.1 mg/dl. Serum calcium and phosphate concentrations were initially 22.2 and 3.1 mg/dl, respectively. The ionized calcium was measured as 2.79 (0.9-1.3 mmol/L). The concomitantly studied serum vitamin D and parathyroid hormone (PTH) levels were 46.2 (20-120 µg/L) and 6.6 (12-95 ng/ml). The PTH–related protein (rP) and urinary cyclic adenosine monophosphate levels were not determined. A skeletal radiographic examination revealed bilateral proximal diaphyseal fractures in humeri, bilateral distal diaphyseal fractures in femurs and metaphyseal radiolucent bands compatible with leukemic involvement (Fig. 1). No mediastinal mass was detected in radiologic evaluation. The bone marrow aspiration showed 85% L1 blasts according to French-American-British (FAB) classification and the immune phenotyping revealed a diagnosis of T-cell ALL.

The patient was treated initially with 3000 ml/m$^2$ saline infusion, furosemide (1 mg/kg/dose, q12h), pamidronate (0.5 mg/kg/dose by the 4th hour of admission and 1 mg/kg/dose by the 24th hour of admission) and calcitonin (the initial dose applied concomitantly with the onset of hydration in admission, 4 Unit/kg/dose, q8h, for a total of 7 doses). These measures were able to lower serum calcium level from 22.2 mg/dl to 17.1 (ionized calcium 1.99 mmol/L) by the 44th hour of admission. We initiated modified St. Jude Total XIII remission-induction chemotherapy protocol by the 44th hour of admission and the first day agents including vincristine (1.5 mg/m$^2$), daunomycin (25 mg/m$^2$) and MP (20 mg/kg/day) were given. After the onset of chemotherapy, saline hydration and furosemide were continued and one last dose of calcitonin was also applied three hours after the onset of chemotherapy regimen. By the 15th hour of the chemotherapy regimen, serum calcium level decreased from 17.1 to 12.7 mg/dl, and by the 24th hour we achieved a level of 8.94 mg/dl (Fig. 2 and Table I).

**Discussion**

Bone lesions in ALL are well-recognized and are present in 21% of childhood cases of leukemia at diagnosis\(^5\). These lesions include transverse metaphyseal bands, osteopenia and periosteal...
**Table I. Serum Biochemical Parameters During Follow-Up of the Patient**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>On admission</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (8.1-10 mg/dl)</td>
<td>22.28</td>
<td>16.32</td>
<td>17.1</td>
<td>8.14</td>
<td>8.98</td>
<td>9.1</td>
<td>9.59</td>
</tr>
<tr>
<td>Ionized calcium (0.9-1.3 mmol/L)</td>
<td>2.79</td>
<td>2.22</td>
<td>1.99</td>
<td>0.80</td>
<td>0.93</td>
<td>0.94</td>
<td>1.10</td>
</tr>
<tr>
<td>Phosphorus (3.4-4.7 mg/dl)</td>
<td>3.17</td>
<td>3.01</td>
<td>3.90</td>
<td>4.98</td>
<td>6.43</td>
<td>3.46</td>
<td>3.01</td>
</tr>
<tr>
<td>BUN (5-18 mg/dl)</td>
<td>15.6</td>
<td>18.7</td>
<td>12.6</td>
<td>42.6</td>
<td>69.5</td>
<td>59</td>
<td>38.5</td>
</tr>
<tr>
<td>Creatinine (0-1.3 mg/dl)</td>
<td>0.41</td>
<td>0.53</td>
<td>0.41</td>
<td>0.84</td>
<td>0.86</td>
<td>0.77</td>
<td>0.53</td>
</tr>
<tr>
<td>Uric acid (2.4-5.7 mg/dl)</td>
<td>13.1</td>
<td>9.2</td>
<td>5.1</td>
<td>6.7</td>
<td>7.6</td>
<td>5.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Vitamin D (20-120 µg/L)</td>
<td>46.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PTH (12-95 ng/ml)</td>
<td>6.6</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tr>
</tbody>
</table>

BUN: Blood urea nitrogen. PTH: Parathyroid hormone.

reactions. Unexplained hypercalcemia should prompt a possible diagnosis of malignancy especially in the presence of pathologic fractures, as in this case. The presence of pathologic fractures in the presented case designates a later stage of disease that is different from the previously described pediatric ALL cases with hypercalcemia. It is also interesting that the vital signs and the electrocardiographic evaluation were normal, although the serum calcium level was as high as 22.2 mg/dl.

Two types of cancer-induced hypercalcemia have been described: osteolytic and humoral hypercalcemia. Osteolytic hypercalcemia results from direct bone destruction by primary or metastatic tumor. Humoral hypercalcemia is mediated by circulating factors secreted by malignant cells such as PTHrP or -peptide. PTHrP is homologous to normal PTH, binds with the same receptors on skeletal and renal target tissues, and affects calcium and phosphate homeostasis, as does PTH. Increased blood levels of PTHrP have been found in patients with solid tumors; however, results in hematologic malignancies with hypercalcemia are variable. Three cases of adult leukemia with hypercalcemia (1 B-cell ALL and 2 T-cell ALL) were reported to show an increase in serum PTHrP concentration accompanied by leukemic cell proliferation. In a report describing four cases of pediatric ALL with hypercalcemia from a single institution, all four cases showed elevated serum PTHrP. On the other hand, some reports indicated the lesser importance of PTHrP in hematologic malignancies. Circulating growth factors including transforming growth factor-α and -β, interleukin-1 and -6, and tumor necrosis factor (TNF)-α may also mediate hypercalcemia.

Although hydration together with moderate doses of furosemide is the classical approach for the treatment of hypercalcemia, these measures may be inadequate in malignancy-associated cases and may require addition of bisphosphonates, calcitonin or plicamycin. Bisphosphonate treatment reduces the number of osteoclasts in sites undergoing active bone resorption and may prevent osteoclast expansion by inhibiting differentiation from their monocyte-macrophage precursors. Calcitonin rapidly inhibits calcium and phosphorus resorption from bone and decreases renal calcium reabsorption. Plicamycin (also referred to as mithramycin) is an inhibitor of osteoclast RNA synthesis. It has been shown to inhibit bone resorption in vitro and is clinically effective in the presence or absence of bone metastases. Calcitonin and plicamycin have a more rapid hypocalcemic effect than bisphosphonates; however, bisphosphonates reduce serum calcium concentrations to normocalcemic ranges more frequently. Glucocorticoids have efficacy as hypocalcemic agents primarily in steroid-responsive tumors (e.g., lymphomas and myeloma) and in patients whose hypercalcemia is associated with increased vitamin D synthesis or intake (sarcoidosis and hypervitaminosis D). Glucocorticoids increase urinary calcium excretion and inhibit vitamin D-mediated gastrointestinal calcium absorption. The hypocalcemic response of glucocorticoids, however, is typically slow and one to two weeks may elapse before serum calcium concentrations decrease. Glucocorticoid is known to prolong the calcium-lowering effect of calcitonin.
In the presented case, the hypercalcemia was quite refractory to conventional treatments of hydration, furosemide, pamidronate and calcitonin, and the initiation of chemotherapy protocol resulted in a rapid normalization in serum calcium levels. Although the pamidronate treatment may have a sustained decreasing effect on calcium levels and the tumor lysis effect may also have contributed to that decrease, the response to vincristine, daunomycin and HDMP is dramatic. Previous studies have shown that the effect of steroid on leukemic cell death is related to glucocorticoid receptor occupation, the presence of non-functional receptor protein and lineage-specific differences in glucocorticoid receptor levels. The use of glucocorticoids for hypercalcemia seen in steroid-responsive malignancy cases is well known; however, the recommended pediatric dose of prednisone is orally 1-2 mg/kg/day. Glucocorticoids exhibit hypocalcemic effect slowly at these doses, but at higher doses, such as applied in our case, the hypocalcemic effect may be more rapid. In our center, we apply modified St. Jude Total XIII protocol. The use of HDMP (20 mg/kg/day) in this regimen was found to have a statistically significant beneficial effect on eight-year event-free survival rates when compared to conventional-dose glucocorticoid (60 mg/m²/day) (66% vs 53%).

In conclusion, hypercalcemia may be an initial finding of ALL patients at presentation. In the present case, although pamidronate has the cumulative continuing effect on calcium decrease, the impact of HDMP in the correction of severe hypercalcemia in steroid-responsive tumors as an initial treatment approach or as an addition in cases refractory to other measures may be life-saving. Further clinical observations supporting the beneficial effect are required for the treatment of this fatal association.

REFERENCES


