A child presenting with hypercalcemia

Emre Çelik¹, Gül Nihal Özdemir², Gülen Tüysüz², Yücel Taştan³, Halit Çam^{3,4}, Tiraje Celkan²

¹Department of Pediatrics, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

²Division of Pediatric Hematology-Oncology, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

³Division of Pediatric Emergency, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

⁴Division of Pediatric Intensive Care, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

Case

A 6-year old boy presented to our emergency department with complaints of vomiting and abdominal pain which had been continuing for 2 days. On physical examination, he appeared pale, his lips were dry, turgor of his skin was reduced, he had sunken eyeballs and lymphadenopathy smaller than 1 cm in both sides of his neck. Laboratory investigations revealed no pathology in complete blood count: hemoglobin 11.4 g/dL, WBC: 10 430/mm³, neutrophils: 7 610/mm³, platelets: 157 000/mm³; no atypical cell was observed on peripheral blood smear. Blood biochemistry tests were as follows: calcium: 16.2 mg/dL (reference range 8.4-10.5), phosphorous: 6 mg/dL (reference range 2.3-4.7), sodium: 136 mEq/L (reference range 135-145), serum urea: 113 mg/dL (reference range 10-50), creatinine 1.7 mg/dL (reference range 0.9-1.3), uric acid: 13.7 mg/dL (reference range 3.4-7), alkaline phosphatase: 92 U/L (reference range 40-300). The patient was internalized in the emergency ward with prediagnoses of fluid loss, hypercalcemia and renal failure and hydration treatment was initiated. In the follow-up urine output was normal and the creatinine value decreased to 1.1 mg/dL with hydration. The uric acid level was found to be 4.8 mg/dL following hydration and allopurinol treatment. The calcium level was reduced from 16.2 mg/dL to 15.5 mg/dL with hydration, but later increased to 17.2 mg/dL. 1 mg/kg furosemide was administered on the second and fifth days of hospitalization. When hypercalcemia continued on the fourth day of treatment, pamidronate at a dose of 0.25 mg/kg/day was initiated and the calcium level was found to be 9.6 mg/dL on the second day of pamidronate treatment. The parathormone level which was measured in terms of the etiology of hypercalcemia was found to be 6 pg/mL (suppressed) (reference range 15-65 pg/mL). Thyroid function tests were found to be normal. Osteolytic lesions were observed in the frontal and temporal regions on direct cranium graphy (Figure 1). On abdominal ultrasonography, the sizes of both kidneys were found to be increased. There was no finding in favour of calculus.

Figure 1. Osteolytic lesions on plain cranium graphy of the patient

Address for Correspondence: Gül Nihal Özdemir, Division of Pediatric Hematology-Oncology, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey. E-mail: gnozdemir@hotmail.com

Received: 02.01.2013 **Accepted:** 26.02.2013

©Copyright 2014 by Turkish Pediatric Association - Available online at www.turkpediatriarsivi.com

DOI:10.5152/tpa.2014.661

Diagnosis-acute lymphoblastic leukemia

One atypical cell was observed on peripheral blood smear which was repeated in the follow-up and bone marrow aspiration was performed. 86% blasts were found on the smear which was compatible with acute lymphoblastic leukemia (ALL)-L1. Flow cytometry revealed positive CD10 and CD19 antigene expression and a diagnosis of common B ALL was made. Cytogenetic analysis revealed t (12:21) positivity (indicator of good prognosis). TRALL-BFM-2000 method treatment was started in the patient. The patient's treatment was completed, but isolated bone marrow recurrence occurred in the follow-up. During treatment for recurrence, the patient was lost because of intracranial hemorrhage.

Discussion

Although hypercalcemia is observed less frequently in children compared to adults, its significant clinical effects are more prominent. It may lead to life-threatening effects including cardiac arrhythmia, renal failure, acidosis, hypertension, fluid loss and coma. In the childhood, vitamin D intoxication, primary hyperparathyroidism, immobilization and malignancy are the main causes of hypercalcemia (1). In addition, hypercalcemia may also be observed in granulomatous diseases including sarcoidosis, cat scratch disease and tuberculosis.

In adults, hypercalcemia related with malignancies is observed frequently in breast cancer, multiple myeloma, non-Hodgkin lymphoma, T cell leukemia, renal cell carcinoma and squamous cell carcinomas of the lung (2, 3). Malignancy-related hypercalcemia is explained by two main mechanisms (1):

1. Bone invasion of tumor cells: The most common cause of hypercalcemia is bone destruction due to osteoclasts activated by tumor cells which metastasize to the bone.

2. The effect of osteoclastic factors released from tumor cells: The most important factor which activates osteoclastic bone destruction is parathyroid hormone (PTH)-like protein. The main tumors which cause to hypercalcemia by releasing parathyroid hormone-like protein include squamous cell tumors of the lung, head and neck, renal cell carcinoma, adult type T cell leukemia and disgerminoma (1). Parathyroid hormone-like protein activates osteoclastic bone destruction like PTH and increases calcium reabsorption in the distal tubules (4). Other factors originating from tumors which lead to hypercalcemia include calcitriol, interleukin 1 and 6, TGF- β and tumor necrosis factor (1, 4). Vitamin D analogues like calcitriol cause to hypercalcemia especially in lymphomas (5).

Hypercalcemia is a rare finding of childhood cancers in contrast to adults and it is observed in less than 1% of children with cancer at the time of diagnosis. Malignancies related with hypercalcemia in children include leukemia, lymphoma, rhabdomyosarcoma, Hodgkin and non-Hodgkin lymphoma, brain tumors and neuroblastoma (5-9). Hypercalcemia has been reported in a small number of patients in children with leukemia (9-12). In the largest series published so far, hypercalcemia was shown in only 11 of 2816 children with leukemia followed up in St. Jude

hospital (4). 10 of these patients had ALL and only one had acute myeloid leukemia. In a recent study conducted in Japan, hypercalcemia was reported in 22 children with ALL in a follow-up period of 15 years (11). In half of these patients, PTH-like protein was found to be high in serum or immunohistochemical study. It is thought that PTH-like protein is directly released from the blasts in acute lymphoblastic leukemia. In our series, we found hypercalcemia at the time of diagnosis only in one of 241 patients with ALL who were followed up between 1995 and 2012 and for whom sufficient information could be reached from patient files (0.4%).

It is noted that the median age at presentation is 8 years, most patients have a normal complete blood count at presentation and the majority have no blast on peripheral blood smear, when the ALL patients presenting with hypercalcemia reported in the literature are examined. Similarly, our patient had a completely normal complete blood count at the time of diagnosis and one suspicious cell was observed on peripheral blood smear in the follow-up. The diagnosis was made by bone marrow aspiration. Among the patients published in the literature, the diagnosis was delayed especially in the ones who had normal complete blood count. A significant question discussed in studies performed is if presence of hypercalcemia at the baseline affects prognosis. In the study performed by Inukawi et al. (10), no difference was shown between the patients with and without hypercalcemia in terms of prognosis, but t (17, 19) positivity was found in five of the patients with hypercalcemia and the disease recurred in all of these patients. We could not study this translocation in our patients, but recurrence was observed in our patient, although good prognosis translocation was present.

Another common accompanying finding in ALL patients presenting with hypercalcemia is osteolytic lesions (9, 12-14). In our patient, osteolytic lesions were found interestingly on plain cranium graphy. Osteolytic lesions are observed rarely in leukemia patients, although bone pain and pathological fractures are observed frequently. The importance of osteolytic lesions in prognosis is not known. However, most of the patients published in the literature had recurrence in the early period.

Untreated asymptomatic hypercalcemia is a condition which is life-threatening and requires urgent intervention. Severe hypercalcemia usually leads to marked hypovolemia. The first step in treatment is intravenous fluid therapy. Serum calcium should be measured with frequent intervals. Urinary excretion of calcium increases with furosemide treatment. Forced diuresis can be provided with serum and urinary electrolyte monitoring. Bisphosphonates prevent bone destruction which occurs with osteoclastic effect (15). The most commonly used bisphosphonates in treatment of hypercalcemia related with malignancy include pamidronate and zoledronic acid. Clinical response occurs in approximately 12-24 hours. In our patient, the calcium level regressed to the normal limits with intravenous fluid, furosemide and pamidronate treatment.

In children presenting with hypercalcemia, malignancies should be kept in mind in differential diagnosis. Malignancy should be

primarily considered especially in cases with suppressed PTH. In children with a completely normal complete blood count and peripheral blood smear, bone marrow aspiration should be performed, if no other underlying cause can be found. Bone scintigraphy, lung graphy and abdominal ultrasonography may be ordered in terms of differential diagnosis of solid tumors.

Informed Consent: Written informed consent was obtained from patients' parents who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Literature Review - G.N.Ö.; Writer - G.N.Ö., E.Ç.; / Critical Review - Y.T., H.Ç., T.C.; Other - G.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Lietman SA, Germain-Lee EL, Levine MA. Hypercalcemia in children and adolescents. *Curr Opin Pediatr* 2010; 22: 508-15. [\[CrossRef\]](#)
2. Halfdanarson T, Hogan W. Oncologic emergencies: diagnosis and treatment. *Mayo Clin Proc* 2006; 81: 835-48. [\[CrossRef\]](#)
3. Strewler GJ, Nissenson RA. Hypercalcemia in malignancy. *West J Med* 1990; 153: 635-40.
4. Rankin W, Grill V, Martin TJ. Parathyroid hormone-related protein and hypercalcemia. *Cancer* 1997; 80: 1564-71 [\[CrossRef\]](#)
5. Seymour JE, Gagel RE. Calcitriol: the major humoral mediator of hypercalcemia in Hodgkin's disease and non-Hodgkin's lymphomas. *Blood* 1993; 82: 1383-94.
6. McKay C, Furman WL. Hypercalcemia complicating childhood malignancies. *Cancer* 1993; 72: 256-60. [\[CrossRef\]](#)
7. Kawasaki H, Takayama J, Nagasaki K, Yamaguchi K, Ohira M. Hypercalcemia in children with rhabdomyosarcoma. *J Pediatr Hematol Oncol* 1998; 204: 327-9. [\[CrossRef\]](#)
8. Leblanc A, Caillaud MI, Hartman O, et al. Hypercalcemia preferentially occurs in unusual forms of childhood non-Hodgkin's lymphoma, rhabdomyosarcoma and Wilms'tumor: A study of 11 cases. *Cancer* 1984; 54: 2132-6. [\[CrossRef\]](#)
9. Shimonodan H, Nagayama J, Nagatoshi Y, et al. Acute lymphocytic leukemia in adolescence with osteolytic lesions and hypercalcemia mediated by lymphoblast-producing parathyroid hormone-related peptide: a case report and review of the literature. *Pediatr Blood Cancer* 2005; 45: 333-9. [\[CrossRef\]](#)
10. Trehan A, Cheetham T, Bailey S. Hypercalcemia in acute lymphoblastic leukemia: An overview. *J Pediatr Hematol Oncol* 2009; 31: 424-7. [\[CrossRef\]](#)
11. Inukai T, Hirose K, Inaba T, et al. Hypercalcemia in childhood acute lymphoblastic leukemia: frequent implication of parathyroid hormone-related peptide and E2A-HLF from translocation 17;19. *Leukemia* 2007; 21: 288-96. [\[CrossRef\]](#)
12. Türker M, Oren H, Yilmaz S, Cakmakçi H, Demircioglu F, Irken G. Unusual presentation of childhood acute lymphoblastic leukemia: a case presenting with hypercalcemia symptoms only. *J Pediatr Hematol Oncol* 2004; 26: 116-7. [\[CrossRef\]](#)
13. Soni P. Hypercalcemia and multiple osteolytic lesions in childhood acute lymphoblastic leukaemia. *Postgrad Med J* 1993; 69: 483-5. [\[CrossRef\]](#)
14. Ganesan P, Thulker S, Gupta R, Bakhshi S. Childhood aleukemic leukemia with hypercalcemia and bone lesions mimicking metabolic bone disease. *J Pediatr Endocrinol Metab* 2009; 22: 463-7. [\[CrossRef\]](#)
15. Body JJ, Baril R, Burckhardt P, et al. Current use of bisphosphonates. *J Clin Oncol* 1998; 16: 3890-9.