The Use of Etidronate in Therapy-Resistant Hypercalcemia

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Hypercalcemia is one of the metabolic indicators of childhood malignancies; however, it is much more common in adults than in children (1). The rate of incidence has been reported to be as low as 0.4% to 0.7% in two of the largest studies carried out, one in France the other in the USA (1, 2). In 250 patients in our clinic the rate is 0.4%. Hypercalcemia is defined as serum calcium concentration greater than 3.24 mmol/L (13 mg/dl) and the symptoms, which begin to appear at this level, are generalized weakness, lethargy, nausea, vomiting, constipation, abdominal pain and polyuria. At greater levels, patients can go into coma (3). Although bisphosphonates are commonly used in the management of hypercalcemia in adults with certain types of malignancies (4, 5), these are relatively new agents for treating hypercalcemia in children (6–8). We report a case of cancer-associated hypercalcemia treated with etidronate.

Case report. A 15-year-old boy was admitted to another hospital complaining of nasal bleeding. Physical examination revealed lymphadenopathies on his neck. His Water's-graphy showed a mass in the maxiller sinus, and a paranasal and nasopharynx tomography was taken. The results of these tests revealed a tumoral mass in his nasal cavity spreading left maxiller sinus and nasopharenx. An operation was performed and the mass was resected immediately. The pathologic investigation showed an alveolar rhabdomyosarcoma (Fig. 1). Approximately 1 month after the operation, the patient was admitted to our hospital complaining of pain in the arm and general weakness. Physical examination revealed the presence of petechias, multiple masses on the head and chest, and multiple lymphadenopathies on the neck. Bone survey showed the lytic and destructive tumoral lesions in the distal part of the left and right arm as well as in the distal part of the femur and proximal part of the tibia (Fig. 1). The radionuclide bone scan showed multiple involvement, and bone marrow biopsy revealed diffuse infiltration of rhabdomyoblasts (Fig. 2). Abdominal and pelvic ultrasonograhy findings were normal. Laboratory evaluation demonstrated a CBC with a haemoglobin of 3.1 g/dl, a WBC count 11000/mm^3 with 42% lymphocytes, 2% monocytes, 56% PMN, and 18000/mm^3 with platelets. Serum calcium level was 15.4 mg/dl (the normal range is 8.1 mg/dl to 11.0 mg/dl). The results of other biochemical analyses were as follows: phosphorus 4.3 mg/dl, alkaline phosphatase 146 U/L, total protein 7.2 g/dl albumin 3.9 g/dl, uric acid 10.3 mg/dl, potassium 2.9 mEq/L. While the serum electrolytes, blood urea nitrogen and creatinine levels were within the normal range, the urinary calcium/creatinine ratio was 1.86; more than 9.3 times the normal. However, the urinary phosphorus level was found to be within the normal range. The bone marrow aspiration revealed a tumoral cell infiltration and a rosette formation as well as bone marrow biopsy. The tests resulted in an affirmative diagnosis of hypercalcemia and a regimen of hydration with saline infusion, furosemid 2 mg/kg, and prednisolone 2 mg/kg per day was administered. Within 12 h of the start of treatment the

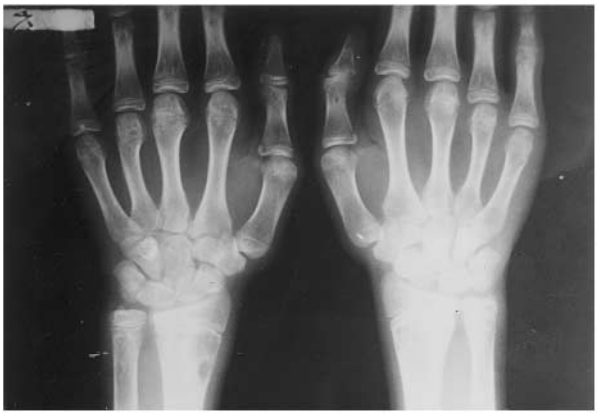

Fig. 1. Bone graphy demonstrating lytic and destructive lesions in the distal part of the arms.

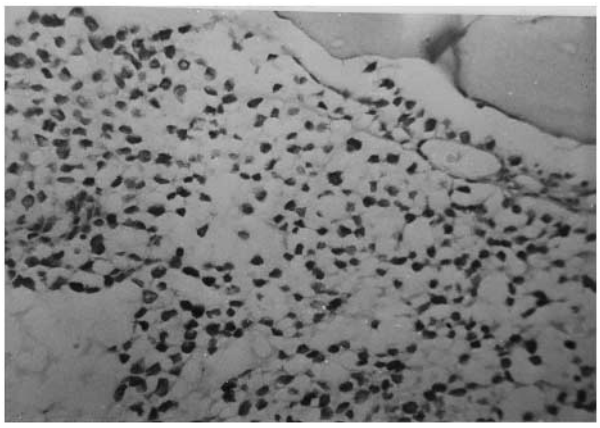

Fig. 2. Bone marrow was diffusely infiltrated by neoplastic cells with no apperent differentiation (H&E $\times$ 200).

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calcium levels had decreased to 14.5 mg/dl and remained stable for 24 h. Etidronate was given 10.0 mg/kg p.o. and the calcium levels dropped to 10.4 mg/dl on the third day of treatment; chemotherapy was administered for rhabdomyosarcoma.

Discussion. Hypercalcemia is a life-threatening disorder associated with malignancy. Although it occurs in approximately 10–20% of adult patients with malignancy, it is rarely seen in children (1, 2, 9). Bone metastases are seldom the cause of hypercalcemia during malignancy, especially in children. The elevation of calcium concentrations usually results from the effects of humoral mediators released by tumour. Many factors isolated from tumours have the potential to cause hypercalcemia, but the most important is parathyroid hormone-related protein (PTHrP), a peptide which mimics the effect of PTH (10). During a 29-year period, hypercalcemia was diagnosed and treated in only 25 children at St Jude's Children Research Hospital (1). Of 2400 children with solid tumours treated at the Institute Gustave Roussy, 17 had hypercalcemia. Seven patients had lymphoma and four of them had primary bone involvement (2). The types of malignancy associated with hypercalcemia are leukemias, rhabdomyosarcoma, malignant rhabdoid tumour, Hodgkin's disease, non-Hodgkin's lymphoma, hepatoblastoma, neuroblastoma, and Ewing sarcoma (1–4). Hypercalcemia in patients with solid tumours is more resistant to therapy. Seven patients in the St Jude and eight in the Institute Gustave-Roussy series, had bone involvement (1) fourteen had hypercalcemia associated with relapsed disease. Serum calcium levels were not detected routinely, so the true incidence of hypercalcemia in children was not known. Serum calcium levels in every patient with primary or secondary tumoral bone involvement, even without any symptoms of hypercalcemia, should be measured to establish the incidence of hypercalcemia in children with malignancy.

Bisphosphonates are new agents used in the treatment of cancer-associated hypercalcemia. The precise mechanism by which they inhibit osteoclasts is still unclear and may represent a combination of inhibition of osteoclast formation and, increased apoptosis in mature osteoclasts (11, 12). Three bisphosphonates are currently being used in clinical practice: etidronate, clodronate, and pamidronate (5, 6, 9, 11, 13–16). Etidronate disodium is the first bisphosphonate to be approved in the United States for the treatment of cancer-related hypercalcemia and, when used orally and intermittently, results in reduced bone loss. Several studies have demonstrated its efficacy in decreasing serum calcium levels (17–20). In children there are few reports on the use of bisphosphonates in malignancy-associated hypercalcemia and only one of these describes the treatment of hypercalcemia in a 10-year-old boy with leukemia (6). There are also few reports concerning the use of bisphosphonates in children with other disorders, including familial idiopathic hyperphosphatasia and immobilization-associated hypercalcemia (6, 7). Immediate management of cancer-related acute hypercalcemia to prevent death and provide symptomatic relief is warranted. Severity of the symptoms, calcium concentrations, and the overall status of the patient are important considerations in selecting the appropriate therapy. Although the specific role of individual agents may vary, hydration remains the cornerstone of therapy. A variety of medications used in the management of hypercalcemia include calcitonin, furosemide, gallium nitrate, glucocorticoids, NaC1 0.9%, and plicamycin and hemodialysis (9). It is known that hypercalcemia could be refractory to these treatments in patients with severe hypercalcemia (5). The bisphosphonates are recommended particularly for refractory disorders. For the present case, we first used the conventional approach for the treatment of hypercalcemia, but calcium levels did not decrease to a reasonable level. We therefore administrated etidronate, which can be used for palliative purposes in patients who have no hope of cure of underlying malignancies (21). A decrease in both calcium and phosphorus levels showed that etidronate was effective in the present case. We observed no side effects, such as renal malfunction, hypocalcemia or hypophosphatemia. The results of renal function tests were in the normal range in our case. We suggest that 10 mg/kg of etidronate as a single dose should be used to establish a normocalcemic state without resulting in hypocalcemia. We believe that etidronate can be used safely and effectively for malignancy-associated hypercalcemia in children. However, further studies are necessary to determine optimal dosages and toxic levels.

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