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Vertebral Compression Fractures at the Onset of Acute Lymphoblastic Leukemia in a Child

M. Beatriz Oliveri, MD,* Carlos A. Mautalen, MD,† Carlos A. Rodriguez Fuchs, MD,* and M. del Carmen Romanelli, MD*

A child with acute lymphoblastic leukemia, spinal osteoporosis with vertebral compression fractures, and hypercalcemia appearing early in the course of the hematologic disease was followed for two and a half years. Bone mineral density (BMD), measured by single photon absorptiometry at the radial shaft, was within normal limits for age and sex. However, x-rays of vertebrae and vertebral BMD, measured by dual photon absorptiometry, showed marked demineralization. Despite leukemic remission, the spinal osteoporosis became worse and the patient required aggressive treatment for eight months. Treatment included 50 units of calcitonin subcutaneously every other day, 1,000 mg/day of oral calcium, and 3,000 IU/day of vitamin D. The back pain disappeared quickly, and laboratory controls showed a significant diminution of bone turnover. No new compression fractures occurred. Eighteen months later, the patient continued in remission and menarche had occurred. Dual photon absorptiometry revealed a significant “catch up” of the lumbar spine BMD. X-ray examination showed a marked remodeling of the vertebral bodies. BMD measurements in this child indicate that bone loss affected the trabecular bone compartment or occurred only at active bone marrow sites. The rapid clinical amelioration and objective biochemical, densitometric, and radiologic evidence of bone improvement warrant further clinical trials on similarly affected patients. (Henry Ford Hosp Med J 1991;39:45-8)

Skeletal radiologic studies in children with acute leukemia have shown many abnormalities: radiolucent metaphyseal bands, generalized osteoporosis, osteolytic lesions, periosteal infiltration with new bone formation, osteosclerotic new bone formation, and vertebral compression fractures (1,2). The frequency of these abnormalities has varied from 21% to 70% (3-6). Although the axial skeleton can be affected (2,5,7-9), lesions occur more frequently in the peripheral bones (5,7,9-11).

The following case describes a child with acute lymphoblastic leukemia (ALL), hypercalcemia, back pain, and axial osteoporosis with vertebral compression fractures. Measurements of the axial and peripheral density and the effect of calcitonin treatment are reported. Fifteen other ALL cases (aged 3 to 16 years) with severe axial osteoporosis are reviewed (5,12-18, C. A. R. Fuchs, unpublished observations).

Case Report

A 9-year-old white girl was well until two months prior to admission when she developed intermittent fever, weight loss (5.5 kg [12.1 lb]), general malaise, lumbar and abdominal pain, and muscular aches. Physical examination on admission revealed hepatosplenomegaly and inguinal adenopathies. The patient was pale and febrile. Laboratory data showed a WBC count of 3.5 10^9/L (3,500/μL) with 72% blast cells. The hematocrit was 0.33 (33%) after a blood transfusion performed in the emergency room. Bone marrow examination showed a massive infiltration of blast cells. The back pain was not specifically investigated, and skeletal x-rays were not taken at that time.

ALL (French-American-British classification type L1) was diagnosed and treatment begun according to the GATLA 1-LLA-84 protocol. Chemotherapy induction was initiated with prednisone (60 mg daily during one month), vincristine, daunorubicin, and L-asparaginase. She received two intrathecal doses of methotrexate (12 mg) and dexamethasone (4 mg). Hematologic remission was achieved after 20 days of treatment. However, the patient continued to complain of lumbar pain. X-rays taken seven weeks after admission revealed compression fractures of T10, T12, and L1, with generalized diminution of bone density. Laboratory studies performed at that time revealed a serum calcium of 2.87 mmol/L (11.5 mg/dL), phosphate 1.65 mmol/L (5.1 mg/dL), alkaline phosphatase 1.4 μkat/L (83 U/L), serum creatinine 44.2 μmol/L (0.50 mg/dL), and parathyroid hormone 20 pg/mL (normal 20 to 90 pg/mL). The urinary excretion of calcium was 76 mg/24 hrs (2.5 mg/kg/day) (Table 1).

One and a half months later, despite the hematologic remission and diminution of serum calcium levels into the normal range, x-rays showed new compression fractures of T7 and T8 (Fig 1A). No peripheral skeletal abnormalities were noted. In addition to the biochemical determinations of mineral metabolism, the bone mineral density (BMD) was measured at the radial shaft by single photon absorptiometry (19) and at the lumbar spine by dual photon absorptiometry (20). The bone mineral content of the radial shaft was 0.509 g/cm, width 0.99 cm, and BMD 0.515 g/cm^2 (105% of normal values according to sex

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†Submitted for publication: September 18, 1989.
Table 1
Laboratory Data

<table>
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<th>Serum</th>
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<tr>
<td></td>
<td>Total Calcium (mg/dL)</td>
<td>Phosphate (mg/dL)</td>
<td>Alkaline Phosphatase (U/L)</td>
<td>Hydroxyproline/Creatinine Ratio (mg/kg/d)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*</td>
<td>11.5</td>
<td>5.1</td>
<td>83.4</td>
<td>2.5</td>
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<tr>
<td>+</td>
<td>9.5</td>
<td>4.5</td>
<td>72.3</td>
<td>3.4</td>
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<tr>
<td>Two weeks‡</td>
<td>10.0</td>
<td>3.9</td>
<td>137.0</td>
<td>3.0</td>
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<td>Four weeks‡</td>
<td>10.5</td>
<td>3.6</td>
<td>101.0</td>
<td>0.20</td>
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<td>Six weeks‡</td>
<td>10.4</td>
<td>3.6</td>
<td>29.0</td>
<td>3.4</td>
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<td>Five months‡</td>
<td>10.0</td>
<td>3.7</td>
<td>90.0</td>
<td>2.0</td>
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<td>Normal range</td>
<td>9.1-10.8</td>
<td>3.8-5.8</td>
<td>47-134</td>
<td>4.0</td>
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</table>

*Patient in hematologic remission with severe back pain.
†Patient in hematologic remission but worsening of osteoporosis; treatment with 50 IU of calcitonin every other day and daily calcium and vitamin D was started.
‡After onset of calcitonin therapy.

Discussion

This patient had back pain, vertebral compression fractures, and hypercalcemia early in the course of ALL. The clinical, radiologic, and laboratory data on this child resemble findings of other ALL cases reported in literature (Table 2) (5,12-18, C. A. R. Fuchs, unpublished observations). Back pain was present 10 days to 5 months prior to ALL diagnosis in 11 cases; evidence of back pain in the remaining four cases was not clearly reported.

In our patient, back pain was present at initiation. Although vertebral compression fractures were not documented until seven weeks later, after a course of chemotherapy, the early appearance of back pain supports the concept that symptoms specific to ALL were the cause of axial osteopenia.

Skeletal pain in children with acute leukemia ranges from 25% as initial manifestation to 42% to 59% during the course of eight months later. At that time, x-rays of the spine revealed bands of remineralization in the upper and lower plates of most vertebrae with remodeling of the bodies resembling the "bone within bone" image (Fig 1B).

Calcitonin was discontinued based on clinical, radiologic, and bone density improvements. Shortly thereafter, the patient's family discontinued her calcium and vitamin D oral treatments. Menarche occurred at 10 years, 11 months of age. During the following 18 months the patient continued in hematologic remission, and her clinical course was uneventful.

A new evaluation of the mineral and skeletal status disclosed BMD of L2-L4 at 0.835 g/cm² (96% of normal values) and radial shaft 0.569 g/cm² (104.4% of normal values). The increments of the BMD from the initial assessment were 29% for the lumbar spine and 10% for the radial shaft (Fig 2). Radiologic examination of the spine revealed a marked remodeling of the affected vertebral bodies (Fig 1C). Laboratory values were within normal limits.

Fig 1—Lateral x-rays of the spine: A) several compression fractures and generalized osteopenia three months after onset of the disease despite hematologic remission; B) remodeling and remineralization of vertebral bodies eight months later; C) remodeling and remineralization of vertebral bodies 30 months later (arrows indicate T12).
the disease (4,22). Skeletal pain in children is reported more of­
ten in the lower extremities and less frequently in the spine (1.3-
5.7,22).

The initial hematologic examination in cases previously re­
ported (Table 2) showed diminished or normal WBC counts in
all but one (13). The number of blasts in the majority was low or
undetectable. Enlargement of the liver, spleen, or lymph nodes
was seldom reported. In most cases, the clinical features were
similar to those of patients with a low leukemic burden reported
by Blatt et al (15). A high incidence of hypercalcemia was de­
tected in this group (64% of the cases whose serum calcium was
reported). The hypercalcemia appeared early in the disease and
was well controlled with antileukemic treatment. Conversely,
most patients with acute leukemia seldom develop hypercalce­
mia (2% to 4%). However, in such cases hypercalcemia is usu­
ally of late onset and is indicative of a poor prognosis (23,24).

Of special interest in our case is the dissociation between loss
of bone mineral content in the peripheral and axial skeleton. Ra­
diologic studies and BMD measurements showed severe demin­
eralization of the spine, whereas the BMD of the peripheral skel­
eton was within normal limits. Whatever the factor implicated in

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**Table 2**

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>Age/Sex</th>
<th>Initial Symptom</th>
<th>WBC (µL)</th>
<th>Peripheral Blasts (%)</th>
<th>Serum Calcium (mg/dL)</th>
<th>Spine X-rays</th>
<th>Evolution</th>
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<tr>
<td>Lightwood et al (5)</td>
<td>3/F</td>
<td>Lumbar pain</td>
<td>WNL</td>
<td>0</td>
<td>NR</td>
<td>VAW</td>
<td>*</td>
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<td>Newman &amp; Melhorn (12)</td>
<td>8/F</td>
<td>Back/abdominal pain</td>
<td>WNL</td>
<td>0</td>
<td>14.6</td>
<td>VCF</td>
<td>NR</td>
</tr>
<tr>
<td>deCastro et al (14)</td>
<td>9/M</td>
<td>Ankle/wrist/hand/back pain</td>
<td>3,250</td>
<td>0</td>
<td>8.8</td>
<td>VCF</td>
<td>No improvement</td>
</tr>
<tr>
<td>Blatt et al (15)</td>
<td>6/M</td>
<td>Back pain</td>
<td>WNL</td>
<td>0</td>
<td>11.4</td>
<td>VCF</td>
<td>Improved</td>
</tr>
<tr>
<td>Infante &amp; David (16)</td>
<td>5/M</td>
<td>Limb pain</td>
<td>WNL</td>
<td>0</td>
<td>11.0-12.6</td>
<td>VB</td>
<td>NR</td>
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<tr>
<td>Leheup et al (17)</td>
<td>6/M</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Elevated Spinal osteoporosis</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Tsuji et al (18)</td>
<td>12/M</td>
<td>Lumbar/abdominal pain</td>
<td>4,600</td>
<td>0</td>
<td>11.4</td>
<td>VCF</td>
<td>Improved</td>
</tr>
<tr>
<td>C.A.R, Fuchs (Unpublished data)</td>
<td>12/M</td>
<td>NR</td>
<td>2,900</td>
<td>3</td>
<td>9.8</td>
<td>VCF</td>
<td>Improved</td>
</tr>
<tr>
<td>Present study</td>
<td>9/F</td>
<td>Intermittent fever, lumbar/abdominal pain</td>
<td>3,500</td>
<td>72</td>
<td>11.5</td>
<td>VCF</td>
<td>Upper &amp; lower bands of remineralization; vertebral remodeling</td>
</tr>
</tbody>
</table>

*Poor response to treatment.
†Back pain disappeared with hematologic remission.
‡Recurrence of back pain with leukemic relapse.
§Back pain disappeared with calcitonin, calcium, and vitamin D therapy.
WNL = within normal limits, NR = not reported, VAW = vertebral anterior wedging, VCF = vertebral compression fractures, VB = vertebral biconcavity.
the genesis of this bone alteration in association with ALL, it affected the trabecular compartment or occurred only at sites of active bone marrow.

Several factors have been implicated as the cause of hypercalcemia and bone rarefaction in hematologic diseases: osteoclast activating factor, colony stimulating factor, 1,25(OH)₂ vitamin D, prostaglandins (18,25,26), lymphokines, transforming growth factors, tumoral necrosis factor, and interleukin-1 (18,25-27). Tumoral hypercalcemia may be mainly multifactorial which makes it difficult to identify one factor in the genesis of this change (25,28-30). Some of the drugs administered to our patient, such as corticosteroids (31,32) and methotrexate (33,34), could have affected the skeleton, but this usually occurs after a more prolonged treatment period.

Calcitonin, calcium, and vitamin D were given to our patient because of worsening of the osteoporosis despite the hematologic remission. This treatment induced a prompt amelioration of the clinical symptoms and a significant but transient decrease in bone turnover. Eight months later, a 5.5% increment of the vertebral bone mineral content and a marked improvement in radiologic appearance were observed.

Eighteen months after the interruption of treatment with calcitonin, vitamin D, and calcitonin, the BMD evaluation showed a significant “catch up” over the lumbar spine. Since menarche occurred between the last two measurements, it might have had a strong influence on the marked increment of the vertebral BMD. However, during this time the BMD of the radial shaft increased 10% from the initial measurement and the augmentation was 29% over the lumbar spine. The average increments in a normal population during the same age interval are approximately 11% for the radial shaft and 14% for the lumbar spine.

The benefit of antioestiolysis therapy in our patient is uncertain as similar changes have occurred as a result of leukemic remission. However, the rapid clinical amelioration and the objective biochemical, densitometric, and radiologic evidence of bone improvement after a short time warrant further clinical trials in similar ALL cases.

Acknowledgments

We thank Dr. Susana Barreiro for allowing us to study this patient and Sandoz Argentina for supplying the calcitonin for treatment.

References