

## Case Report

## Osteoporosis in Acute Lymphoblastic Leukemia

Lestry Fibriani<sup>1</sup>, Eka Agustia Rini<sup>2</sup>

### Abstrak

Leukemia merupakan keganasan yang paling banyak terjadi pada anak, melibatkan sumsum tulang dan organ lain seperti sistem saraf pusat, tulang dan sendi. Abnormalitas skeletal yang berhubungan dengan leukemia antara lain osteoporosis, reaksi periosteal, sklerosis reaktif. Osteoporosis dapat terjadi sebagai manifestasi klinis awal atau lanjutan pada anak leukemia. Tatalaksana osteoporosis tepat sangat penting karena dapat mempengaruhi kualitas hidup, dan dapat berdampak negative pada kemampuan aktivitas anak. Dilaporkan kasus leukemia dan osteoporosis pada anak perempuan usia 7 tahun dan 5 bulan, berdasarkan manifestasi klinis, pemeriksaan laboratorium, dan radiologi. Pasien ditatalaksana dengan pemberian vitamin D dan kalsium dengan luaran perbaikan klinis.

**Kata kunci:** leukemia, osteoporosis, vitamin D

### Abstract

*Leukemia is the most common malignancy in childhood, affected primarily bone marrow and other organ such as central nervous system, bone and joint. Skeletal abnormalities associated with leukemia is osteoporosis, periosteal reaction, reactive sclerosis. Osteoporosis could happen as initial presentation or late effect in survivors of childhood cancer. The treatment is important because affecting quality of life and has negative effect on the survivors ability to perform developmentally appropriate activities. Reported a case of 7 years and 5 months girl with leukemia and osteoporosis, diagnosed by clinical manifestation, laboratory examination and radiology. Patient given vitamin D and calcium and got clinical improvement.*

**Keywords:** leukemia, osteoporosis, vitamin D

**Affiliasi penulis:** 1. Program Pendidikan Dokter Spesialis-1 Ilmu Kesehatan Anak Fakultas Kedokteran Universitas Andalas Padang (FK Unand), 2. Ilmu Kesehatan Anak FK Unand

**Korespondensi:** rini\_ea@yahoo.co.id Telp: 081267337323

### INTRODUCTION

Osteoporosis is a major public health problem worldwide and its prevalence is increasing. This morbidity burden has considerable medical, social and financial implications due to the fractures associated with the disease. Osteoporosis is a well-established clinical worldwide problem for adults. On the other hand, osteoporosis in children and adolescents is rather new and increasingly recognized with certain unique diagnostic and clinical challenges.<sup>1</sup>

Leukemias as the most common malignant neoplasms in childhood, accounting for approximately 31% of all malignancies that occur in children younger

than 15 yr of age. Although it is primarily a disease of bone marrow and peripheral blood, many other organ could be infiltrated by leukemic cells., such as genitourinary tract, central nervous system, cardiac, skin, gastrointestinal, bone and joint. Bone pain is one of the initial symptoms in 25% of patients. Skeletal abnormalities have been described in association with ALL, including osteoporosis, periosteal reaction, reactive sclerosis, lytic defects and vertebral compression fractures. It may result from direct leukemic infiltration of the periosteum, bone infarction, or expansion of marrow cavity by leukemic cells.<sup>2,3</sup>

Osteoporosis is currently receiving an increasing attention as an important initial presentation or late effect in survivors of childhood cancer and its treatment because of their quality of life and its negative effect on the survivors ability to perform

developmentally appropriate activities. Physician should aware of osteoporosis as one of skeletal manifestation occurs in leukemic patient.

## CASE

Reported a 7 years and 5 months old girl, hospitalized at Pediatric Ward of M.Djamil Hospital with chief complain lower extremities could not be moved since 10 months prior admission. She had been diagnosed with Acute Lymphoblastic Leukemia (ALL) L3, and still had chemotherapy. She fell down from bicycle 10 months prior admission, and her lower extremities could not be moved since then. Intermittent pain was felt on back and knees, but there was no swollen on knees either her back. History of fractures prior to this was unknown. There was no uncontrolled miction nor defecation. Both micturition and defecation were normal.

On physical examination, general appearance was moderately ill, she was alert. Pulse rate at 100 bpm regular, respiratory rate at 24 bpm, and body temperature at 37<sup>0</sup> C. Body weight 16 kg, body height at 119 cm. Nutritional status based on CDC was undernourished. The conjunctiva was anemic, sclera was not icteric. Lymph nodes sized 0,3x0,3x0,3 was palpable on submandibula region. Chest symmetrical shape, no retraction, and no wheezing and rales. Regular heart rhythm, no murmur. Abdominal was supple, liver palpable ¼-¼, flat surface, sharp edge, chewy consistency. Spleen was not palpable. Bowel sound (+) normal. Puberty state was A1M1P1. Peripheral acral was warm, and good capillary refilling time. Deformity on lumbar region was (-). Genu dextra and sinistra range of movement was 45<sup>0</sup>. Laboratory examination result; hemoglobin 9.2 g/dl, white blood cell was 4750/mm<sup>3</sup>, erythrocyte was 3,4 millions/mm<sup>3</sup>, platelet was 406.000/mm<sup>3</sup>, differential count 0/1/2/25/72/0, Blast was not found, hematocrit 31%, reticulocyte 16 ‰, MCH 27 pq, MCV 91,17 fl, MCHC 29,6%. Peripheral blood smear result; normochrome, anisocytosis, polychromacy, nuclear erythrocyte was found 4/100 white blood cell. Sodium 145 mmol/l, potassium 3,9 mmol/l, calcium 9,8 mg/dl. Calcium ion 1,13 mmol/l. Vitamin D-25 OH 15,6 ng/ml.

Bone survey result was osteoporosis with multiple thoracolumbal vertebrae compression fractures. Patient diagnosed as ALL L3 with osteoporosis. Treatment on this patient; vitamin D 1x1000 IU/day 8-12 weeks, calcium lactate 3x500 mg/day, continue chemotherapy. Patient was consulted to Orthopedic Department and Medical Rehabilitation. After appropriate therapy, vitamin D was reevaluated. Vitamin D-25 OH was 30 ng/ml. Patient got improvement, she could walk by herself.

## DISCUSSION

Patient diagnosed as acute lymphoblastic leukemia L3 with osteoporosis. Acute lymphoblastic leukemia was established based on clinical sign and several examination, such as peripheral blood examination and bone marrow puncture. Patient felt intermittent backache. Bone pain is one of the initial symptoms in 25% of patients, as in this case. It may result from direct leukemic infiltration of the periosteum, bone infarction, or expansion of marrow cavity by leukemic cells.<sup>3</sup> About two-thirds of children with ALL will have had signs and symptoms of disease for less than 4 weeks at the time of diagnosis. However, a history of some months is also compatible with the diagnosis of ALL. The first symptoms are usually nonspecific and include lethargy, unrelenting fatigue, bone pain or loss of appetite. Acute leukemia of childhood may present with various manifestations that mimic orthopedic conditions. Haddy et al reported a boy with spontaneous fractures as an initial symptoms of leukemia.<sup>4</sup>

Bone survey showed there was compacted fracture on spine and osteoporosis. Radiographic abnormalities in childhood ALL have been described in the literature for over 80 years. Radiologic changes occasionally seen include: Osteolytic lesions involving medullary cavity and cortex; transverse metaphyseal radiolucent bands; transverse metaphyseal lines of increased density (growth arrest lines); subperiosteal new bone formation.<sup>3</sup> As noted by Halton et al the prevalence of severe vertebral compression fractures in children with newly diagnosed ALL is as high as 16%.<sup>5</sup> Riccio *et al* reported fifty-five (75.3%) patients

showed radiographic abnormalities, mostly osteoporosis in 22 patients (40%).<sup>6</sup> Although back pain is a recognized complaint in children with vertebral fractures at ALL diagnosis, a significant proportion of these fractures (45 %) are asymptomatic, despite identified vertebral fractures on lateral spine imaging.<sup>4</sup>

Laboratory examination revealed low calcium ion 1,13 mmol/l (Reference range 1,17-1,29 mmol/L), low Vitamin D-25 OH 15,6 ng/ml (Reference range 30-100 ng/ml). There was several classification of Vitamin D deficiency according to each consensus as shown in Table 1.

**Table 1.** Vitamin D status based on calcidiol concentrations<sup>7</sup>

Vitamin D status	Calcidiol (ng/ml)			
	AAP 2008, IOM	Endocrine Society	KDOQI	Adult-NEJM 2007
Severe Deficiency	< 5	-	<5	-
Mild to moderate deficiency	5-15	<20	5-15	<20
Insufficiency	16-20	21-30	16-30	20-30
Sufficiency	21-100	31-60	>30	31-60
Excess	101-149	-	-	-
Intoxication	>150	-	-	>150

AAP, American Academy of Pediatrics; IOM, Institute of Medicine; KDOQI, Kidney Disease Outcomes Quality Initiative; NEJM, New England Journal of Medicine

In a vitamin D deficient patient, the intestinal absorption of calcium and phosphorus is decreased. The parathyroid gland recognizes the low serum calcium concentrations and releases PTH to increase the serum calcium back into an adequate range. PTH increases the calcium reabsorption in the kidneys and the excretion of phosphorus, therefore decreasing the risk of complication from an elevated calcium phosphate product (e.g., kidney stones). While this reduction is protecting the body, it is also decreasing bone mineralization at the same time. Over weeks to months, osteomalacia, stunted growth, and rickets may develop.<sup>7</sup>

The 2 major forms of Vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamins D2 and D3 are produced by photolysis with UVB (wavelength 280–315 nm) from sterol precursors. Certain plants and fungi produce vitamin D2, whereas vitamin D3 is synthesised by animals (eg, fish, birds, vertebrates) and within the human skin. Dietary vitamin D2 and D3 are absorbed in the small intestine. Absorption is dependent on the presence of dietary fats in the intestine to stimulate the production of pancreatic lipase and bile acids. Excretion of vitamin D metabolites takes place mainly through the bile, and to a much lesser extent through the urine.<sup>8</sup>

Vitamins D2 and D3 are both inactive prohormones that bind to the vitamin D-binding protein to be transported to the liver, where they are converted to 25-hydroxyvitamin D (25(OH)D) by the enzyme 25-hydroxylase. 25(OH)D undergoes further hydroxylation by the enzyme 1 $\alpha$ -hydroxylase in the kidney to become the active metabolite 1,25-dihydroxyvitamin D (1,25(OH)D). This second hydroxylation step is regulated by calcium and phosphate concentrations via parathyroid hormone (PTH). 1,25(OH)D is the active metabolite that is involved in many physiological processes, mainly, but not exclusively in calcium and phosphate metabolism.<sup>8</sup>

Dietary sources of vitamin D are scarce and include mainly fatty fish (wild salmon, mackerel, eel, anchovy, sardines, swordfish, tuna), and to a lesser extent, egg yolk and certain fungi. In some European countries, certain foods are fortified with vitamin D. These include milk, dairy products, margarine, breakfast cereals, and fruit juices.<sup>8</sup> In addition to dietary sources, children and adults obtain vitamin D through exposure to ultraviolet B sunlight. As little as 10 to 15 minutes of direct sunlight can generate 10,000 to 20,000 IU of vitamin D. Many factors influence vitamin D synthesis, such as skin pigmentation, latitude, and amount of skin exposed, making it difficult to assess how much vitamin D will be converted from sunlight exposure.<sup>9</sup> Patient consumed milk, egg, fish, and egg routinely. She also lived in area near the beach where sun exposure was quite high.

In efforts to achieve and maintain the target vitamin concentrations, the AAP recommends all infants, children, and adolescents should receive a minimum daily intake of 400 international units of vitamin D to prevent rickets and to maintain vitamin D concentrations at  $> 20$  ng/mL (50 nmol/L). Term infants should be supplemented with 400 to 800 units daily to account for the insufficient transfer of maternal vitamin D stores and ensure calcidiol concentrations of  $> 20$  ng/mL (50 nmol/L). Vitamin D dose for prevention and treatment of vitamin D deficiency are listed in Table 2. In addition to dietary sources, children and adults obtain vitamin D through exposure to ultraviolet B sunlight. As little as 10 to 15 minutes of direct sunlight can generate 10,000 to 20,000 IU of vitamin D. Many factors influence vitamin D synthesis, such as skin pigmentation, latitude, and amount of skin exposed, making it difficult to assess how much vitamin D will be converted from sunlight exposure. Infants and children who have darker pigmentation require five to 10 times the length of sunlight exposure to reach the same levels of 25-hydroxyvitamin D when compared with children who have lighter pigmentation. However, the AAP recommends that infants younger than six months be kept out of direct sunlight.<sup>9</sup>

**Table 2.** Vitamin D dosing for prevention and treatment of nutritional vitamin D deficiency in children.<sup>9</sup>

Vitamin D supplementation (Cholecalciferol)	
Prevention	400 IU/day
Treatment	< 1 month : 1000 IU/day for 2-3 months
	1-12 months: 1000-5000 IU/day for 2-3 months
	>12 months : 5000 IU/day for 2-3 months

The Endocrine Society Guideline recommend that infants and children aged 0–1 yr require at least 400 IU/d (IU=25ng) of vitamin D and children 1 yr and older require at least 600 IU/d to maximize bone health. Whether 400 and 600 IU/d for children aged 0–1 yr and 1–18 yr, respectively, are enough to provide all the potential nonskeletal health benefits associated with vitamin D to maximize bone health and muscle function is not known at this time. However, to raise

the blood level of 25(OH)D consistently above 30 ng/ml (75 nmol/liter) may require at least 1000 IU/d of vitamin D.<sup>10</sup> Patient was given vitamin D 1000 IU given once daily for 8-12 weeks, and calcium 500 mg given 3 times daily.

Every child who has risk factor of developing osteoporosis should be done examination of Dual X Ray Absorptiometry (DXA) to define bone mass density. Even in child diagnosed with cancer, DXA should be done prior or off therapy, as stated in the algorithm above. We could not do DXA examination in this patient, because currently it is not available in Padang.

Other treatment of osteoporosis is weight bearing exercise. Weight-bearing exercises can include aerobics, circuit training, jogging, jumping, volleyball and other sports that generate impact to the skeleton. There is evidence to suggest that the years of childhood and adolescence represent an opportunity period during which bone adapts particularly efficiently to such loading. Patient was done extremities traction to improve the contracture, but it lasted for a while, as patient could not bear the pain caused by traction. Medical rehabilitation suggested to do exercise on bilateral hip, that could be done at home by her mother.

## CONCLUSION

Osteoporosis could occur in malignancy such as leukemia. Vitamin D and calcium have a big role in maintaining bone density. Every leukemia should be considered having osteoporosis, regarding natural disease and chemotherapy.

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