**INTRODUCTION**

Acute lymphoblastic leukemia is a malignancy of the blood and bone marrow that progresses rapidly, creating immature blood cells rather than mature ones that affect lymphocytes. It accounts for approximately 75% of leukemia cases in children <15 years of age, with the peak incidence occurring at 3 to 5 years of age. 

Bone pain occurs in 20-30% of children with ALL. Although bone pain is common, a non-traumatic fracture is rare, occurring in about 16% of newly diagnosed ALL, and only half of the patients complained of back pain. Infiltration of leukemic cells to periosteal can cause microthrombus and causing osteocyte death and manifest as osteonecrosis. Bone pain also occurs during treatment because chemotherapy can cause a reduction in bone density. During chemotherapy, 10-40% of patients developed osteonecrosis. This case report described vertebrae compression fracture due to osteonecrosis as the initial sign of childhood acute lymphoblastic leukemia.

**CASE REPORT**

An 8-year-10-month girl was referred from secondary health care to the Orthopedic Department of our Hospital and diagnosed with low back pain due to suspected spondylitis tuberculosis and severe constipation. The patient's chief complaint was low back pain 1 month ago that worsened 3 days before admission. The patient was unable to walk or stand due to pain. History of trauma was denied. The patient had a fever 2 days before being admitted to the hospital, with the highest temperature reaching 38.5°C. Her appetite was decreased since the patient got sick. The patient had 1 kg of weight loss since 1 month ago. Family history with prolonged var. 

**ABSTRACT**

**Background:** Acute lymphoblastic leukemia (ALL) is the most common cancer in children. Manifestations of ALL vary from pallor, organomegaly, fever, and pancytopenia. Bone pain caused by vertebrae fracture is an uncommon manifestation of ALL, approximately only 16% of all bone pain occurrences. Fractures in ALL could occur at diagnosis and following treatment initiation. This case report described vertebrae compression fracture due to osteonecrosis as the initial sign of childhood acute lymphoblastic leukemia.

**Case:** An 8-year-10-month girl was referred to an orthopedic because of worsened low back pain since 1 month before, with no history of trauma. The pain was throbbing and radiated to the lower extremities. The patient was non-ambulant due to the pain. Physical examination revealed the visual analog scale was 8, tenderness in the spine, decreased strength, and range of movement in the lower extremities. There was no organomegaly in this patient. Serial laboratory examination revealed mild pancytopenia (leukopenia, mild normochromic normocytic anemia, mild thrombocytopenia) with dominancy of lymphocytes (68.1-81.9%). No blast was found in the peripheral blood smear. Magnetic Resonance Imaging of the spine revealed compression of the vertebral corpus with a pincer fracture and bone infarction. Bone marrow aspiration showed ALL-L2 with lymphoblast 50%. The patient started chemotherapy with ALL standard risk protocols and got zoledronic acid during the treatment. The patient's condition gradually improved, and able to undergo chemotherapy protocol. No side effects of zoledronic acid occurred.

**Conclusion:** Vertebral compression fracture without trauma and pancytopenia can be an early symptom of ALL. Zoledronic acid can be given concurrently with chemotherapy for bone mineralization.

**Keywords:** vertebral compression fracture, acute lymphoblastic leukemia, osteonecrosis, case report.


**CASE REPORT**

An 8-year-10-month girl was referred to the Orthopedic Department of our Hospital and diagnosed with low back pain due to suspected spondylitis tuberculosis and severe constipation. The patient's chief complaint was low back pain 1 month ago that worsened 3 days before admission. The patient was unable to walk or stand due to pain. History of trauma was denied. The patient had a fever 2 days before being admitted to the hospital, with the highest temperature reaching 38.5°C. Her appetite was decreased since the patient got sick. The patient had 1 kg of weight loss since 1 month ago.
cough or anti-tuberculosis treatment was denied. History of nosebleeds, bleeding gums, pallor, and malignancy in the family was denied.

During hospitalization, the pain was reduced with intravenous pain medication but still had difficulty standing up. Recurrent fever was denied, but the patient routinely got paracetamol for her pain. The patient was consulted by Pediatric Division on day 7th of hospitalization. On physical examination, there was skin pallor and anemic conjunctiva. Lymph node enlargement was absent. The liver and spleen were not palpable. On the back, there was no gibbous. No deformities were seen at the spine. The pain scale was 8 using a visual analog score (VAS). The patient was overweight in nutritional status.

Serial blood examination continuously showed pancytopenia with leukopenia (WBC 2.03-2.49x10^3/uL), mild normochromic normocytic anemia (Hb 8.50-10.75 mg/dL, MCV 81.3 fl, MCH 26.28 pg, MCHC 32.29 g/dL), and mild thrombocytopenia (PLT 101.6-118.4x10^3/uL). There was a dominance of lymphocytes (68.17-81.90%). Peripheral blood smear showed normochromic normocytic anemia with relative leukopenia, neutropenia, and thrombocytopenia. Serum calcium level was 10.2 mg/dL, alkaline phosphatase was 163 U/L, and an-organic phosphate 3.87 mg/dL. Bone marrow aspiration results in hypercellular, decreased activity in the erythroid system, decreased activity in the myeloid system, decreased activity in megakaryocytes, non-hemopoietic cell infiltration resembling 50% lymphoblast, heterogeneous morphology, multiple lymphoblasts with clefts in the nucleus. The conclusion of the bone marrow aspiration (BMA) was following ALL-L2 (Figure 1).

Cervicothoracic x-ray showed an impression of compression on Th.8-12. The results of the MRI were compression of the vertebral corpus Th.7 accompanied by a pincer fracture (AO subtype 2) and compression of the vertebral corpus Th. 8-12; according to the image of bone infarction in the vertebral corpus V Th.7 to S1 were suspected as blood disorders; paracervical muscle spasm; no visible picture of spondylitis tuberculosis (Figure 2). Bone Mineral Densitometry examination obtained bone density following the patient’s age with a total body score of 0.73 g/cm^2, a z-score total body 0.1.

Management for the patient was pain management, chemotherapy protocol, and supportive therapy, for the pain management patient was given ketorolac and paracetamol. The patient was given cefixime as a prophylaxis antibiotic for severe neutropenia. The patient was staged as ALL standard risk and had chemotherapy using Standard Risk Indonesian Childhood ALL 2018 Protocol. The supportive therapy patient was
consulted by Rehabilitation Department for corsage usage and range of movement exercise with the physiotherapist.

The patient started intravenous chemotherapy and got evaluated for radiology at the end of the consolidation phase. No new fracture appeared and no fracture at the location for intrathecal; the patient started intrathecal chemotherapy. The patient got zoledronic acid for her vertebrae fracture. The patient’s condition gradually improved, and able to have chemotherapy according to the protocol. There was no side effect of zoledronic acid occurred.

**DISCUSSION**

In this case, the patient’s chief complaint was severe low back pain with no other specific complaint. Leukemia was suspected from complete blood count findings, which showed pancytopenia. The patient had BMA and was diagnosed with ALL-L2 (50% lymphoblasts). Initial symptoms in ALL may present as nonspecific complaints and are found incidentally with pancytopenia on a complete blood count (CBC). One of 10,000 children and adolescents present with musculoskeletal pain as the primary symptom of cancer. Children with manifesting symptoms of musculoskeletal pain such as arthralgia, limping, or pathologic fracture only 1% was diagnosed with malignancy, with ALL being the most common diagnosis. Alarm signs that require prompt further examination are signs of trauma or mechanical injury (swelling, joint/bone dislocation, and limp), signs of acute infection, signs of chronic or systemic disease (pallor, fever, malaise, signs of poor growth, organomegaly, lymphadenopathy, and muscle weakness), signs of inflammatory autoimmune disease, and intense progressive pain that restrain daily activities and ambulation.

Bone pain in children at diagnosis of ALL is due to pressure applied to the periosteaum by leukemic-cell infiltration. Infiltration of leukemic cells to the bone will cause a decrease in blood flow due to microthrombus and cause osteocyte death (apoptosis). Apoptosis can destroy bone architecture. During revascularization, bone resorption by osteoclasts resulting demineralization. Defective mineralization and reduced bone formation caused by cytokines released from leukemic cells. Cytokines can trigger osteoclast-mediated bone resorption, causing bone pain and osteopenia. Uncontrolled osteoclastic activity can cause altered sympathetic nerve fiber regulation and neuropeptide release and infiltration of leukemic cells in bone. Manifestation bone morbidity are low bone mass (<40%), periosteal reaction (<19%), and fractures (<10%). Most common sites of vertebral fractures in children with ALL occur at the thoracolumbar (31%) and midthoracic (26%). Fractures are more commonly seen in vertebrae than non-vertebrae because vertebrae have more active trabecular tissue than in cortex bone.

Besides bone morbidity due to ALL itself, chemotherapy also affected bone morbidity. Toxicity of certain chemotherapy developed in 10-40% of children with ALL who received chemotherapy. Osteotoxic drugs are glucocorticoids, methotrexate, L-asparaginase, daunorubicin, and vincristine. Effects of osteotoxic drugs on bone morbidity mostly happened within 6-8 months of therapy and ceased after discontinuation. Glucocorticoids also affect demineralization and osteoclastogenesis by increasing bone resorption, inducing apoptosis of osteoclasts and osteoblasts, and decreasing bone formation and density that cause bone remodeling and loss of bone volume. Loss of bone volume increased the risk of fracture. Glucocorticoids can reduce osteoblast precursors by directly targeting osteoblasts and osteocytes. Prednisone cumulative dosage of more than 9 g/m² increases the risk of decline in BMD.

The vertebral fracture can occur asymptptomatically. Only 55% of children with vertebral fractures complained of back pain, while only 20-45% of children with osteonecrosis develop symptoms. Symptomatic osteonecrosis occurs in 1-8% of children with ALL. Every 1-standard deviation reduction in BMD Z-score at baseline showed an 89% increase in vertebral fracture (HR 1.89; 95%CI 1.68-2.12;p<0.01). Similar findings in another study, every reduction in lumbar spine BMD Z-score increased the odds of fracture by 80%, and the presence of back pain had an OR 4.7 (95%CI 1.5-4.5). Osteonecrosis can be seen on MRI by detecting chemical changes in the bone marrow, it can show the earliest stages before it is seen on x-ray. Some studies recommend identifying patients at high risk for osteonecrosis for further evaluation for potential therapeutic adjustments. Risk factors are older age at ALL diagnosis (>13 years), high-risk ALL group, T-cell immunophenotype, female gender, and bone pain at the time of leukemia diagnosis.

Biphosphonate is a choice of therapy for osteonecrosis in ALL besides weight-bearing restriction using crutches or wheelchairs, physiotherapy, and surgery. Biphosphonate administration and supplementation with adequate vitamin D (400 IU/day) and calcium (200-1100 mg/day) can benefit bone minerals in patients with ALL. Benefits of bisphosphonate are pain relief, increased mobility of the patient and prevention progressivity of bone destruction. The safety of bisphosphonate in ALL is still not well known. There are no well-defined criteria for bisphosphonates treatment in pediatric patients, therefore, biphosphonate administration should be given when the benefit outweighs the risk. If osteonecrosis is untreated, most patients will experience severe pain and limitation in movement within 2 years. Biphosphonate for vertebral fracture or low BMD or long bone fracture more than 2 sites is 0.05-1 mg/kg/year in 2-4 dosages. From other literature, bisphosphonate dosage can be given 0.015-0.05 mg/kg every 3-6 months. Biphosphonate is effective in reducing bone density loss when initiated early or late during chemotherapy. Bisphosphonates had effect on direct deposit to the bony matrix and reduce bone resorption which may strengthen bone structural integrity and reduce the development of osteonecrosis. Biphosphonate inhibits osteoclast activity and reduces bone resorption, prevention of osteoclast and osteocyte apoptosis increases their survival. Side effects of bisphosphonate are flulike symptoms in 1-2 days following the first or second course of treatment and hypocalcemia. Hypocalcemia can occur due to a failure to release calcium due
to osteoclast inhibition. Monitoring of bisphosphonate administration should be clinical assessment (measurement of linear growth, dental examination, complete eye examination, calcium intake examination), biochemical measurements (complete blood count, electrolytes, total alkaline phosphatase, hepatic and renal function test, vitamin D status, and parathyroid hormone, urine analysis and urinary calcium excretion), and imaging examinations (x-ray of wrist and knees, and bone mineral status). There has not been any consensus regarding the optimal duration or discontinuation of therapy. There is also a recommendation to give zoledronic acid in ALL patients which showed that zoledronic acid may prevent osteonecrosis if begun with chemotherapy and showed no benefit when administered later in therapy.

Vertebral deformity might happen if there is no intervention regarding vertebral fracture. In some studies, about 25% of children had persistent vertebral deformity following vertebral fracture that has not interfered. Deformity of bone is seen in 20% of patients with ALL in 10-38 years after an untreated fracture.

CONCLUSION
This patient showed vertebral compression fracture without trauma and pancytopenia which then diagnosed as ALL. Zoledronic acid can be given concurrently with chemotherapy for bone mineralization.

DISCLOSURE
Funding None.

Ethical Consideration
The patient’s parents signed the informed consent and agreed that the medical data would be published as a case report in medical scientific journals.

Conflict of Interests
The author reports no conflicts of interest in this work.

Author contribution
All authors contributed equally.

REFERENCES