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Case Report

Malignant osteopetrosis in a child

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Osteopetrosis was first demonstrated in X-ray pictures by Albers-Schönberg in 1904.[1] Osteopetrosis is a heterogeneous group of heritable conditions, in which there is a defect in bone restoration by osteoclast,[2] leading to abnormal bone marrow cavity formation and clinically manifests as symptoms and signs of bone marrow failure.[3,4] The decrease of osteoclast activity also alters the bone remodeling capacity.[2]

Clinical manifestations of bone marrow failure usually present within the first year of life and frequently within the first three months. Impaired bone remodeling causes bony narrowing of the cranial nerve foramina which results in cranial nerve compression, especially optic nerve compression. Abnormality of primary remodeling woven bone to lamellar bone results in "brittle" bone that is prone to fracture. Thus, fractures, visual impairment, and bone marrow failure are the classical features of the disease.[3,4] We report a rare case of malignant osteopetrosis with special emphasis on the diagnosis and management.

The case

A 2-year-old boy came to the Emergency Department of Dr. Soetomo Hospital on July 1st, 2006 with pallor as the chief complaint. Pallor was noticed by his mother on the day of admission, preceded by gums and lips bleeding since 2 days before admission. He also suffered from fever for 3 days, and runny nose since 3 months ago. Poor eyesight and roving eyes movement were found since the age of one year. He could see light and people, but had difficulty in finding objects. Dentitions were irregular.

Previously, he had suffered from gum bleeding, and admitted twice to the pediatric ward because of anemia. The first admission was in May, 2006 for three weeks with pancytopenia and hemiparesis on the left extremities. The onset of hemiparesis was abrupt, and accompanied with speech disorder. Head CT-scan revealed chronic subdural and subarachnoid bleeding on the left side, with narrowing of the sulci, compressing the adjacent temporoparietal lobe to the right and causing right deviation of the midline structures (**Figure 1**). Hemiparesis was improved one week later. Abdominal ultrasonography revealed nonspecific hepatosplenomegaly. Bone marrow aspiration at that time revealed infective reactive marrow. Karyotyping revealed 46 XY.

The second admission was in June, 2006 for four days because of anemia and thrombocytopenia. Petechiae on the extremities were noted. CMV infection was suspected. IgG anti CMV was positive, IgM CMV was negative. Both blood and urine CMV antigenemia were negative.

Delivery history was normal. He was the only child of the family. His parents were third-degree-relatives

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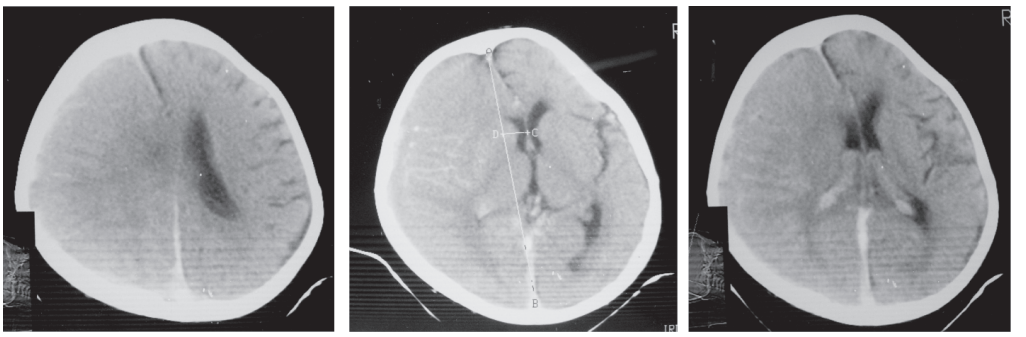

Figure 1. Head CT scan on May 1st 2006 showing chronic subdural and subarachnoid bleeding on the left side, with narrowing of the sulci, compressing the adjacent temporoparietal lobe to the right causing right deviation of the midline structures

(first-degree-cousins). No other family member has similar disease. Physical examination on admission revealed an alert boy with body weight of 11 kg (<5th percentile), height 83 cm (<5th percentile), and head circumference 50 cm (75th percentile). He looked pale, with the blood pressure of 90/60 mmHg, pulse rate 120/minute, respiratory rate 28/minute, and temperature 37.4^{0}C. There was esotropia and horizontal nystagmus on both eyes. Total dental caries was noted. Heart and lungs were normal. Abdominal examination revealed soft, hepatomegaly with the size of 5 x 4 x 4 cm, splenomegaly in Schuffner IV. Laboratory findings included hemoglobin 4.3 g/dl, white blood cells 16,000/mL, platelet 22,000/ mL, hematocrit 14.2 %. The child was considered had aplastic anemia and leukemia. Packed red cell and platelet transfusions were given.

Radiograph of the chest revealed normal heart and lung. Generalized sclerosis or increased bone density on thoracic vertebrae, costae, scapula, vertebra, and humerus were apparent (**Figure 2**). Alternating dense and lucent bands produce a sandwich-like-appearance of the all vertebral bodies. Osteopetrosis was suspected. Radiograph of the skull in anteroposterior and lateral projection revealed sclerotic on the right and left orbital ring and mastoid, showing an eyeglass image. The 2nd bone marrow aspiration was performed on 11th day of admissions, revealed hipocellular marrow. Lymphoblasts were found in less than 30%. The 3rd bone marrow aspiration performed 2 weeks later, revealed hipocellular marrow. Radiographs of hand-arm revealed bone-in-bone appearance on all of the metacarpals, generalized sclerosis or increased bone density on radius and ulna. Lack of differentiation between cortex and medullar cavity with widening of the metaphyseal of distal radius and ulna was noted.

Radiograph of the pelvis, femur and cruris in anteroposterior and lateral projection revealed generalized sclerosis or increased bone density on most of the pelvic bone and both distal femurs. Lack of differentiation between cortex and medullary cavity with widening of the metaphyseal region of both proximal femurs was noted. No abnormality on both hip and sacroiliac joints. All of the above bony changes above corresponded to osteopetrosis. The diagnosis of osteopetrosis was established.

During admission, gum bleeding and petechiae were found for the second times. Blood coagulation examinations revealed: Prothrombin Time (PT) was 10.9 second (control: 11.0 second), Activated Partial Thromboplastin Time (APTT) was 30.0 second (control: 30.2 second). No blasts cell was found on the peripheral blood smear. Numerous transfusions of red blood cells and thrombocyte concentrate were given as anemia, thrombocytopenia, and bleeding manifestation occurred. Nasal congestion was found perma-

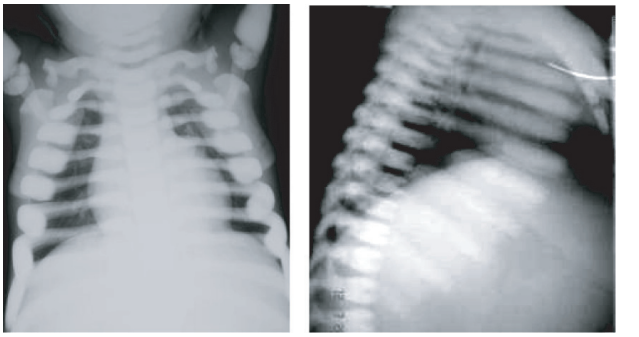

Figure 2. Radiograph of the chest showing generalized sclerosis or increased bone density on thoracic vertebrae, costae, scapula, vertebra, and humerus

nently. Fever was occurred. Cefotaxim was administered, and continued with cefixim.

Consultation to the ENT Department revealed chronic adenoiditis. There was no hearing impairment. Consultation to the Ophthalmology Department revealed papil atrophy, nystagmus, and estropia on both eyes. Consultation to the Pedodontist revealed total dental gangrene. Extraction with general anesthesia was planned.

On 31st day of admission, evaluation of parathyroid hormone, revealed 45 pg/mL (12–95 pg/mL). Serum electrolyte revealed sodium 136 mEq/L, potassium 4.7 mEq/L, calcium 10.1 mg/dL, chloride 97 mmol/L, Blood urea nitrogen 14.4 mg/dL, serum creatinin 0.2 mg/dL, ALT 13 U/L, AST 31 U/L, alkali phosphatase 282 U/L, albumin 4.0 g/dL. On the 35th day of admission, hematology and oncology division suggested to give erythropoietin 100 U/kgBW, 2 times weekly. On August 16th, 2006, the patient was discharged. The patient visited hematology clinic for erythropoietin administrations. However, after 4 weeks, there was no response. Erythropoietin was stopped. The patient persistently depends on blood transfusions.

On October 11th, 2006, gum bleeding and petechiae was noted. Peripheral blood count revealed hemoglobin 7.3 g/dL, white blood cells 13,500/mm, platelet 14,000/mm. The patient was admitted for blood transfusion. Post transfusion blood count revealed hemoglobin 11 g/dL, white blood cells 7,000/mm, platelet 22,000/mm.

Comment

Anemia, leukopenia, and thrombocytopenia occur alone or in combination as a common presenting signs for acute leukemia in childhood.[5,6] The initial diagnosis of ALL initial in our patient was based on the hematologic abnormality. However other physical findings and blast cells[7-10] were absent. Aplastic anemia was the second diagnostic consideration, but the presence of organomegly negate this diagnosis.[11]

The diagnosis of osteopetrosis depends mainly on radiographic examination.[12] If radiological appearances are supportive osteopetrosis and the child has features of anemia with compensatory erythropoietic hepatosplenomegaly and/or visual impairment, then the diagnosis is highly likely.[3] A skeletal survey should be performed and reviewed by an experienced pediatric radiologist to confirm the diagnosis. A bone biopsy is usually not required.[4]

Dysosteosclerosis is a very rare condition which can present with a very similar phenotype to osteopetrosis. These patients are usually not anemic; however, and while the initial x-ray changes may be indistinguishable from osteopetrosis, they later on develop the characteristic of irregularly coarse submetaphyseal trabecular pattern.[4] A bone within bone appearance is a characteristic and diagnostic for osteopetrosis. This finding differentiates osteopetrosis from other sclerosing dysplasias.[13] Pyknodystosis is an autosomal recessive bone dysplasia, presents in early childhood as short limbs, characteristic facieses, and an open anterior fontanel, a large skull with frontal and occipital bossing, and dental abnormalities. The hands and feet are short and broad, and the nails may be dysplastic. The sclera may be blue. Minimal trauma often leads to fractures. Skeletal radiographs show a generalized increase in bone density. In contrast to many disorders in this group, the metaphyses are normal. Other changes include wide sutures and wormian bones in the skull, a small mandible, and hypoplasia of the distal phalanges.[14]

In osteopetrosis, there is a defect in bone restoration by osteoclasts. The disease is associated with an increase of skeletal mass due to abnormally dense bone. The decrease of osteoclasts activity also affects the shape and structure of bone by altering its capacity to remodel during growth. The entire skull is thickened and dense, especially at the base. Sinuses are small and underpneumatized. The vertebrae are extremely radio dense. They may show alternating bands, known as the rugger-jersey sign. Radiographs may show evidence of fractures or osteomyelitis.[15]

The incidence of autosomal recessive 'malignant' osteopetrosis is very rare in most populations (less than 1:200,000 births). In Costa Rica, Saudi Arabia, and some other countries the incidence is higher, likely as the result of a high degree of consanguinity.[3,16] Inheritance pattern in congenital osteopetrosis is autosomal recessive.[17,18] Thus there is a 1 in 4 (25%) risk of having another affected child with each subsequent pregnancy.[3] In our case, the patient is an offspring of a consanguineous marriage. His parents are third-degree-relatives (first-degree-cousins).

Osteopetrosis presents in one of three forms: benign osteopetrosis (osteopetrosis tarda), malignant osteopetrosis (osteopetrosis congenital) and "marble bone" disease. Osteopetrosis tarda, the benign form, presents in adulthood, while the two more malignant variants, osteopetrosis congenital and marble bone disease, present in infancy and childhood, respectively. In all three forms, the main features are pathologic alteration of osteoclastic bone restoration and thickening of cortical and lamellar bones. Benign osteopetrosis is usually discovered accidentally on routine radiographs and is often asymptomatic. Malignant osteopetrosis results in bone marrow failure and is almost always fatal. Marble bone disease is not characterized by bone marrow failure. Patient with marble bone disease are usually of short stature, and present with cerebral calcification and mental retardation.[17,18]

In our patient, the first symptom was visual impairment and nystagmus, noted at the age of one year. Papil atrophy and estropia on both eyes was also noted. Hearing is less commonly affected than vision, with approximately a third of patients having some degree of hearing loss. The impairment usually manifest within the first year of life. The pathology of deafness is unclear, but probably secondary to a combination of bony compression of the nerve, sclerosis of the middle ear ossicles, and/ or chronic middle ear effusion. [18] In our case, consultation to ENT department revealed no hearing loss.

Fractures are common and are one of the classical features of osteopetrosis. The susceptibility is variable and in some children recurrent fractures are most debilitating part of disease. Children with osteopetrosis often have an abnormal head shape. Macrocephally and frontal bossing are common.[3] In our case, fracture, macrocephally and frontal bossing was not found. Children frequently have dental problems: failure of tooth eruption, recurrent caries, and abnormal dentinogenesis.[3] In our case, total gangrene of the teeth was found. Extraction with general anesthesia has not been performed yet, because the patient always has nasal congestion.

Infants with malignant osteopetrosis also suffer from recurrent infections as a result of defect in macrophage function.[14] Neutrophil responses to stimulation was significantly reduced.[19] Cerebrovascular complications so far described include intracerebral hemorrhage, subdural hematoma, cerebral venous thrombosis, and subarachnoid hemorrhage.[20] In our case, hemiparesis accompanied with speech disorder was found. Head CT scan revealed chronic subdural and subarachnoid bleeding.

Failure to thrive is seen in many osteopetrotic children and is a result of the chronic anemia, feeding problems caused by bulbar nerve involvement, nasal congestion, and recurrent infections.[3,4] In our case, failure to thrive was noted. Both body weight and height was under 5th percentile.

Hypocalcaemia, low serum phosphorous level, and elevated serum alkaline phosphates levels are known to occur in osteopetrosis. Hypocalcaemia is related to decrease in osteoclastic activity and cause seizures occasionally.[13] Parathyroid hormone (PTH) is often elevated (secondary hyperparathyroidism).[15]

Corticosteroid, high dose calcitriol, and interferon gamma have all been reported to be helpful in the treatment of osteopetrosis. Corticosteroid has been used to stimulate bone restoration and treat anemia. The effect on blood cells is due to reduce destruction in reticuloendothelial system.[15] Several children with severe osteopetrosis were treated with 1,25-dihydroxy vitamin D in an effort to provoke nonresorbing osteoclasts to resorb bone or to cause a differentiation of mononuclear cell precursors into mature normal osteoclasts. This therapy is still considered experimental.[17] The recombinant interferon gamma has been reported in increasing bone restoration, hematopoiesis, and leukocyte function was seen in the small number of patient studied.[21,22] The experience with the drug in early onset severely affected group of patient is disappointing.[3] The initial promise of steroid and calcitriol has proved unwarranted although there are may be some initial short term benefit. [3]

Erythropoietin was found to correct anemia and thrombocytopenia in a 22-year-old female with adult osteopetrosis. Anemia and thrombocytopenia were corrected.[23] Bone marrow transplantation is the only treatment that has been proven to significantly alter the course of disease.[3] Allogeneic bone marrow transplant (BMT) has been reported to provide curative therapy.[24] Anemia, thrombocytopenia, and leukoerythroblastosis corrected within 12 weeks of transplantation. Serial x-ray studies revealed bony remodeling and new nonsclerotic bone formation. Osteoclast ac-

tively desorbing bone, and medullary cavities contained normal bone marrow.[25] While successful recipients may continue to have minor orthopedic and dental problems and their vision rarely significantly improved, their hemopoietic potential is restored and long term prognosis is favorable. [3] The infant transplanted with marrow from a Human Leukocyte Antigen (HLA)-identical sibling or volunteer donor has an actuarial five year survival with a functioning graft of 50-70%.[26]

In our case, both serum calcium and PTH were normal. Calcitriol was not administrated. Erythropoietin has no effect in our patient. Unfortunately, bone marrow transplantation can not be performed in our hospital.

The prognosis is poor; mostly die in the first decade, especially in children with early visual and hematological impairment. The causes are bone marrow failure, septicemia, intracranial hemorrhage, and neurodegeneration. The natural course of the disease results in survival of about 30% of patients at 6 years of age. Although life expectancy in some cases was superior, the quality of life mostly was poor. [20]

In conclusion, the diagnosis of osteopetrosis was suspected based on chest x ray that revealed increased bone density. Skeletal radiological survey confirmed the diagnosis. The critical feature in this patient was bone marrow failure.

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