A Case of Malignant Infantile Osteopetrosis Presenting with Irritability and Failure to Thrive

Huzursuzluk ve Kilo Alamama Şikayetleriyle Başvuran Bir Malign Infantil Osteopetroz Olgusu

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Abstract
Malignant infantile osteopetrosis (MIOP) is the autosomal recessively inherited form of osteopetrosis that usually presents within the first year of life. It is characterized by failure of osteoclasts to resorb bone. Bones are hyperdense and fragile. We presented this case because it is a rarely seen disease and the symptoms of presentation were nonspecific.

A 38-days old girl was admitted to our clinic with irritability and failure to thrive. She had macrocephaly, frontal bossing and hepatosplenomegaly in physical examination. She had anemia and thrombocytopenia. Serum LDH and ALP levels were elevated. Calcium and phosphorus levels were slightly decreased. Bone marrow aspiration was planned but could not be performed because of difficulty in aspiration. Osteopetrosis was suspected and whole body X ray radiographies were obtained. She had generalized osteosclerosis, mask like appearance around the orbita and fracture in humerus. Since she was very young and had typical radiological findings supporting the physical examination and laboratory findings, she was diagnosed as MIOP and steroid therapy was started at a dose of 2 mg/kg/day. Bone marrow transplantation (BMT) was planned however she died of infection while waiting for the appropriate donor.

Nonspecific presentation in MIOP can delay the diagnosis. Therefore MIOP has to be considered in case of abnormalities in craniofacial bones, together with organomegaly and cytopenias. Radiological findings are usually diagnostic. Drugs only help to decrease the symptoms. Bone marrow transplantation is the only curative treatment, tissue typing should be arranged and the patient has to be prepared for BMT as soon as possible. Turk Jem 2007; 11: 124-6

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Özet

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Introduction

Osteopetrosis, also called ‘marble bone disease’, is an autosomally inherited disease characterized by failure of osteoclasts to resorb bone. It was first described by Albers-Schönberg in 1904 (1). Bone modeling and remodeling is impaired and defect in bone turnover results in skeletal fragility despite increased bone mass and may cause insufficient hematopoietic activity. Abnormal remodeling of primary, woven bone to lamellar bone results in “brittle” bone that is prone to fracture (2,3). At least eight types of osteopetrosis have been described in humans (4). Autosomal dominant osteopetrosis (ADO) is the adult-onset form and more common than the other forms with good prognosis (5). It is observed in one of 20-500,000 children. Malignant infantile osteopetrosis (MIOP) is the autosomal recessively inherited form that usually presents within the first year of life, especially in first three months. It is observed in one of 200,000 children. This case is presented to emphasize that this rarely seen disease can present with nonspecific symptoms and has to be considered in differential diagnosis.

Case

A 38 days-old girl was admitted to our clinic with irritability and failure to thrive. She was taken to hospital by her parents when she was 11 days old with the complaint of failure to thrive and hepatosplenomegaly was detected in physical examination. She was referred to our hospital for further investigation. She was not prenatally followed-up and was born as a 2800 grams term baby by cesarean section. Parents were both at 23 years of age and there was no consanguinity between them. She had one healthy brother, 15 months old. Her weight (3100 gr.), height (52 cm.) and head circumference (35 cm.) were all at 3rd percentile. She was conscious, had pale appearance, frontal bossing, hyperteleorism, umbilical hernia and severe dermatitis in physical examination (Figure 1). Neurological examination was normal. She had 4 cm. of hepatomegaly and 2 cm. splenomegaly. Laboratory findings were as follows: Hb: 9.5 g/dl, Hct: 28.5 %, WBC: 12000/ mm3, PLT: 90000/ mm3, MCV: 82 fl, Ret: 0.9%, AST: 79 U/l, ALT 43 U/l, ALP: 676 U/l, GGT: 342 U/L, LDH: 2090 U/L, Ca: 8.2 mg/dl, P: 4.2 mg/dl. Parathyroid hormone level was slightly elevated and urine calcium/creatinin ratio was 0.3. For differential diagnosis of rickets, 1,25 OH vitamin D levels were checked and found to be slightly elevated and 25 OH vitamin D level was normal. She had bisitopenia. Peripheral blood smear revealed thrombocytopenia and prominent immature leucoerythroblastosis. There were morphological changes in erythrocytes. Other biochemical parameters, urinalysis, C-reactive protein and erythrocyte sedimentation rate were normal. No pathogen was detected in blood, urine culture and viral serology. Thyroid hormone levels, tandem mass and urine organic acid levels were also in normal limits.

Bone marrow aspiration was planned but several attempts were unsuccessful. Morphological features, hepatosplenomegaly, findings of ineffective hematopoiesis, bisitopenia and failure of bone marrow aspiration lead us to suspect of osteopetrosis. Whole body X-rays were obtained. She had generalized osteosclerosis. There was prominent increase in bone marrow density, ‘mephisto-mask’ appearance in craniography (Figure 2) and a fracture in humerus. Ophthalmologic examination was normal; there was no optic nerve compression. As the disease had appeared in early infantile period and she had progressive bisitopenia and typical radiological findings, she was diagnosed as malignant infantile osteopetrosis and allogeneic hematopoietic stem cell transplantation was planned. Methyl-prednisolone treatment was started at a dosage of 2mg/kg/day. There was an improvement in hematological parameters at 6th day of therapy. HLA-matched donor could not be found and the patient died of infection while she was waiting for the appropriate donor.

Discussion

Malignant infantile osteopetrosis is an autosomally recessively inherited disease characterized by abnormal bone formation due to dysfunction of osteoclasts. The incidence is 1/200000. It is diagnosed in early infantile period. Most common findings at presentation are macrocephaly, frontal bossing, abnormal craniofacial appearance, hyperteleorism, depression in nasal bridge, growth retardation, failure to thrive, nasal stuffiness, anemia and hepatosplenomegaly. Blindness and deafness can occur as a result of compression of cranial nerves (6). Laboratory findings are: anemia, thrombocytopenia, hypocalcaemia, hypophosphatemia, elevation in CPK, ALP, PTH, 1,25 dihydroxy vitamin D and acid phosphatase levels, normal 25 OH vitamin D3 levels and decrease in calcium/creatinin ratio. Progressive pancytopenia is seen as a result of bone marrow infiltration due to abnormal bone formation. There is compensatory extramedullary hematopoiesis. Radiological findings are usually diagnostic. Skeletal density is increased and bone looks solid on X-ray with metaphyseal modeling. Irregular conditions of the bone at the metaphyses may produce the appearance of parallel plates of dense bone at the end of long bones (7). Alternating sclerotic and lucent bands may be noted in iliac wings and near the ends of long bones (bone within the bone’ sign). Sclerosis is more prominent at the base of the skull and also around orbita defined as “Mephisto Mask”. Fractures are more commonly seen in long bones.

Our patient was brought to hospital because of irritability, nasal stuffiness and failure to thrive and she had findings of hepatosplenomegaly, anemia and thrombocytopenia together with growth retardation. Differential diagnosis is very important in this situation because these findings are nonspecific and may also exist in case of infectious diseases and congenital metabolic diseases. Therefore, blood and urine culture, acute phase reactants and viral serology were checked in our patient. She was also screened for metabolic diseases. There were morphological changes in erythrocytes, prominent immature leucoerythroblastosis and thrombocytopenia in peripheral blood smear. Since she had bisitopenia, organomegaly, elevated
LDH and abnormal peripheral smear findings, we had to make differential diagnosis of this ineffective erythropoiesis and rule out malignant hematological diseases. Therefore, bone marrow aspiration was planned and was tried several times but attempts were unsuccessful and bone marrow could not be aspirated. Osteopetrosis was suspected and whole body radiographies were obtained. The patient had generalized osteosclerosis, the typical “Mephisto-mask” appearance around orbita and a fracture in humerus (Figure 2).

Since the symptoms and findings are nonspecific in osteopetrosis, and the disease is rare, correct diagnosis may be delayed. In this situation, distinctive sclerotic bony changes have to alert the physician. The bones are hyperdense and fractures can be seen. If radiological appearances are supportive and the child has anaemia with compensatory erythropoietic hepatosplenomegaly and/or visual impairment, then the diagnosis is highly likely. A skeletal survey should be performed and reviewed by an experienced pediatric radiologist to confirm the diagnosis (6). A bone biopsy is not essential for diagnosis unless the disease has an atypical course.

In our case, radiological findings together with physical examination and laboratory findings lead us to diagnosis of MIOP. Differential diagnosis in this situation includes conditions that can result in diffuse osteosclerosis like hypoparathyroidism, pseudohypoparathyroidism, pyknodysostosis, osteomyelofibrosis, Gaucher’s disease, cranial tubular hyperostoses, renal osteodystrophy, chemical poisoning (fluoride, lead, beryllium), hypervitaminosis D, chronic hypervitaminosis A, Caffey’s disease, infantile cortical hyperostosis. Only a small number of these are associated with anaemia and visual impairment (6). Malignancies (leukaemia, myeloproliferative diseases) and sickle cell disease also have to be ruled out in differential diagnosis.

Since our patient had mild hypocalcaemia and elevated ALP levels, serum Parathyroid hormone and 1.25 OH and 25 OH Vitamin D levels were checked. 1.25 OH vitamin D was slightly elevated and 25 OH Vitamin D level was normal. There was no history of any drug intake or vitamin over-intake or exposure to any chemicals. She also had typical X-ray findings like ‘Mephisto-mask’ appearance and dysmorphic craniofacial features (Figure 1). Visual-evoked potentials (VEPs) were found to be in normal limits, there was no optic nerve compression. Prognosis in MIOP is poor without treatment as a result of bone marrow failure due to abnormal bone formation and insufficient hematopoiesis. Survival without treatment till 6 years of age is 30%, and most die until 10 years of age. Mortality rate is high in the first two years of life. Death ensues due to anaemia, bleeding and recurrent infections. Failure to thrive increases the morbidity. Corticosteroids, calcitriol (vitamin D3) and gamma-interferon can be used in its treatment. Drug therapies only decrease symptoms. Steroids at high doses only decrease bone density and bone marrow thickness (8). This is due to direct thinning effect of steroids on bone. These effects are transient and side effects can appear. Side effects are fewer at lower corticosteroid doses and need for transfusion is decreased to a great extent. Methyl prednisone treatment was started at a dose of 2 mg/kg/day in our patient.

Interferon gamma-1b slows down the progression of the disease. In some studies, it is shown to increase bone resorption and hematopoiesis and improve leukocyte functions (9). Calcitriol stimulates dormant osteoclasts and thus stimulate bone resorption however it is not the routine treatment modality. Usually modest improvement is seen and not sustained after cessation of therapy. Erythropoietin can be used to correct anaemia. Nutritional support and calcium supplementations are necessary to treat malnutrition.

The only curative treatment in patients with MIOP is bone marrow transplantation (BMT). In 1994, Gerritsen et al reported a 79% five year disease free survival in 19 patients with a HLA identical sibling donor (10). We observed an improvement in hematological parameters at 6th day of steroid therapy in our patient and the family was referred to Genetics Department of Istanbul University of Medicine for HLA investigations. However, they could not find an allogeneic HLA matched donor for our patient and she died of infection while she was waiting for an appropriate donor.

**Conclusion**

MIOP is a rarely seen disease and can present with nonspecific symptoms. Therefore it has to be considered in case of abnormalities in craniofacial bones, together with organomegaly and cytopenias. Radiological findings are usually diagnostic. Drugs only help to decrease the symptoms. Bone marrow transplantation is the only curative treatment. Tissue typing should be arranged and the patient has to be prepared for BMT as soon as possible. Genetic counseling should also be provided to the family members.

**References**