Infantile Malignant Osteopetrosis: Delay in Diagnosis Eliminates Chance of Cure

Nazan SARPER, Kadir BABAOĞLU, Metin AYDOĞAN, Gülcan TÜRKER, Hülya AKAÇ, Ayşe S. GÖKALP

Department of Pediatrics, Medical Faculty, University of Kocaeli, Kocaeli, TURKEY

ABSTRACT

A 4.5 year-old girl presented with abdominal distention, failure to thrive, visual and hearing loss. In her medical history there was meningitis in the neonatal period, convulsions, enlargement of her head, nistagmus and exophtalmus at the tenth month. When she was 15 month-old, she had ventriculoperitoneal shunt and surgical transection of the filum terminale due to tethered cord. When she was 3 year-old she had headaches and swallowing difficulties and she underwent suboccipital craniectomi and C1 laminectomi. On admission to our Center she had normal mental and motor development, high arched palate, only three teeth, hepatosplenomegaly, weight and height below 3 percentile, leukoerythroblastic anemia and thrombocytopenia. Roentgenograms of bones showed sclerosis and no medullary tissue could be obtained in bone marrow biopsy. Diagnosis was infantile malignant osteopetrosis but the patient can not be referred to bone marrow transplantation due to delay in diagnosis and irreversible visual and hearing loss and lack of medullary space for marrow engraftment.

Key Words: Infantile malignant osteopetrosis, Tethered cord, Hydrocephalus.

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INTRODUCTION

Infantile malignant osteopetrosis (marble bone disease) is an autosomal recessive disease encoded on chromosome 11. It is characterized by dense, sclerotic, radyoopaque bones and associating hematologic and neurologic disorders[1,2]. Osteopetrosis is the result of dysfunction of osteoclasts, leading defective resorption of bone and mineralised cartilage[3,4]. Defective osteoclastic activity, in the presence of normal bone formation by osteoblasts results restriction of medullary spaces, pancytopenia, extramedullary hematopoesis and hypersplenism. Encroachment on cranial nerve foramina leads to cranial nerve palsies, optic atrophy with blindness and deafness[5]. The only curative procedure is the allogeneic bone marrow

transplantation. Diagnosis beyond infantile ages, eliminates chance of cure, because neurologic complications are irreversible. Early diagnosis is also important for genetic counselling.

CASE REPORT

A 4.5 year-old white girl admitted to our Center with abdominal distention, paleness, failure to thrive, progressive blindness and deafness. She was born 2 kg at term and had menengitis in the neonatal period. She had progressive failure in sucking and swallowing and had convulsion when she was ten-month-old. Her head enlarged, abnormal eye movements started, she had exophtalmus and visual defects. She underwent operation for tethered cord and hydrocephalus. When she was three-year-old she again had difficulty in swallowing and had headaches. She underwent suboccipital craniectomy and laminectomy at the level of first cervical vertebra due to increased pressure on the brain stem. She was followed by neurosurgeons until then.

Parents were first-degree-cousins. Parents and two siblings were healthy.

On admission she was a pale, ambulatuar patient with atypical features but with normal mental and motor developement (Figure 1). Her axillar temperature was 37.5°C, respiratory rate was 36/min., pulse rate was 148/min. and blood pressure was 100/60 mmHg. Her body weight was 12 kg (< 3rd percentile) and height was 90 cm (< 3rd percentile). She had macrocephaly with a head circumference of 50 cm. She had bilateral exophthalmus, horizantal nistagmus, high-arched-palate and only one central incisor on mandibula and two on maxilla. Ventriculoperitoneal shunt was palpated on the parieto-temporal region. Ophtalmoscopic examination revealed bilateral atrophy of the fundus. There was 2/6 systolic ejection murmur on cardiac oscultation. Extremities were thin but there was a distended abdomen. There was splenomegaly and hepatomegaly, 6 and 5 cm below costal margins respectively. She had bilateral complete blindness and auditory defects. There was no pathologic reflexes.

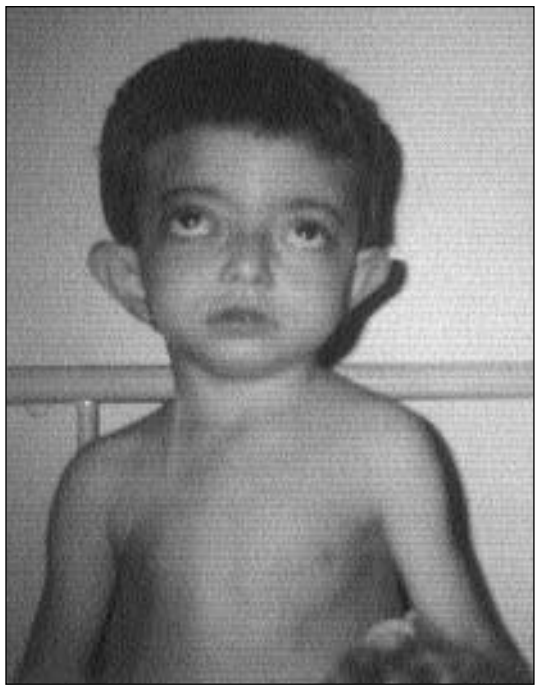

Figure 1. Patient with macrocephaly and exopthalmus.

Laboratory investigations: Hb 3.64 g/dL, RBC 6.55 milion/mm^3, WBC 8.9 x 10^9/L, PLT 96 x 10^9/L, ANC 5.9 x 10^9/L, MCV 77 fl. In the peripheral blood smear RBC showed normocromia, 52% neutrophil, 35% lymphocyte, 10% metamyelocyte, 3 myelocyte, a few platelets and normoblasts. Reticulocyte count was 12%, D. Coombs test was negative and erythrocyte sedimentation rate was normal. Hemoglobin electrophoresis showed Hb A 92.3%, Hb A_2 4% and Hb F 2.6%. Serum iron was 91 µg/dL, iron binding capacity was 306 µg/dL, transferrin saturation was 29.4% and ferritin was 62.8 ng/mL. Blood urea was 21 mg/dL, creatinin was 0.9 mg/dL, gluco- se was 102 mg/dL, Na was 137 mEq/L, K was 4.4 mEq/L, AST was 15 U/L, ALT was 4 U/L, T. Protein was 6.9 g/dL, albumin was 3.7 g/dL, globulin was 3.2 g/dL, Ca was 8.9 mg/dL, P was 3 mg/dL, alkaline phosphatase was 194 U/L, T. bilirubin was 1 mg/dL. Blood picture showed leukoerythroblastic anemia. Bone marrow aspiration showed hypocellularity; similar to blood smear there were a few normoblasts, lymphocytes and neutrophils. In bone marrow biopsy, no medulary tissue could be seen. Roentgenograms of the cranium, extremities, vertebra and ribs revealed homogenoeously dense sclero-

sis and clubbing of metaphyses which were characteristic for osteopetrosis (Figures 2,3,4).

Brain stem auditory and visual potentials showed abnormally prolonged latencies.

The patient can not be referred to bone marrow transplantation due to irreversibility of the neurologic defects and lack of enough marrow space for engraftment. She was transfused once with packed red cells. The patient was lost to follow-up after parents were informed about poor prognosis and genetic transmission. We learned that the patient died at home at the sixth month of diagnosis.

DISCUSSION

Although diagnosis in infantile malignant osteopetrosis is easy and depends mainly on radiographic examination, it is often delayed due to rarity of the disease and lack of clinical suspicion. Patients may present with failure to thrive, macrocephaly, frontal bossing, delay in dentition, exophtalmus, nistagmus, visual and hearing loss, anemia, thrombocytopenia, leukoerythroblastosis, hepatosplenomegaly, osteomyelitis of the mandibula and hypocalcemic convulsions[6,7].

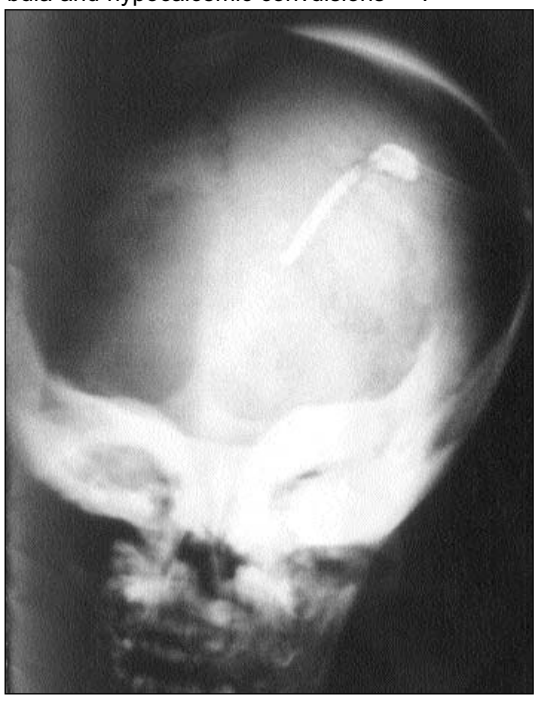

Figure 2. Increased bone density in cranium, showing an eyeglass image.

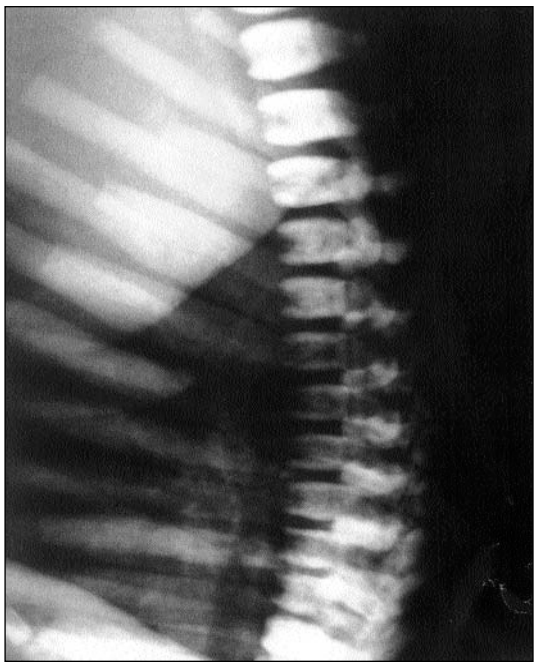

Figure 3. Alternating dence and lucent bands produce a sandwich appearence of vertebral bodies. Ribs also show sclerosis.

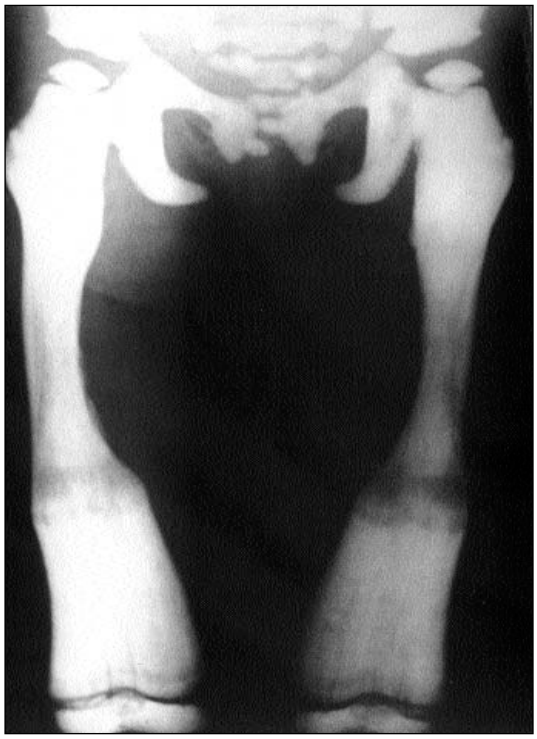

Figure 4. Symmetrical sclerosis of both femur with only small marrow space.

In our patient blood picture showed leukoerythroblastosis which was suggesting bone marrow infiltration. There was also hepatosplenomegaly. History was too long for a malignancy infiltrating bone marrow. Langerhans cell histiocytosis and storage dissease were also in the differential diagnosis. But mental functions were preserved and there was not histiocytic infiltration in the marrow biopsy. Roentgenograms confirmed osteopetrosis.

Defect in resorbtion of osteoclasts is suggested to be the result of abnormalities in lysosomal enzymes or an abnormality in the osteoclast membrane[8]. Decreased intracellular bacterial killing of peripheral blood monocytes which results in susceptibility to infection is also reported[9].

Transfusion, splenectomy, steroid, 1a hydroxyvitamin D_3 and IFNg are used in the treatment of osteopetrosis[10-12]. High dose active vitamin D is suggested to increase bone resorption and IFNg would improve superoxide formation of fagocytes. Though IFNg stimulates phagocytes, it reduces osteoclast formation[13]. All these trials in addition to high dose G-CSF failed to cure osteosclerosis and hematopoesis[12].

Studies showing hematopoetic origin of osteoclasts, Walker's demonstration of bone marrow and splenic cell transfusion in osteopetrotic rodents were mile stones in the treatment of osteopetrosis[8,14,15]. After Ballet's bone marrow transplantation of a three month-old baby from her sibling in 1977, transplantation procedure in malignant osteopetrosis increased[16]. In the last 100 years, about 15 transplantations were reported[17,18]. Mean age for transplantation was 4 months[17].

Before transplantation, neurologic evaluation of the patients is essential. In 75% of the patients blindness develop in the first year. Blindness is mainly the result of narrowing of the cranial nerve foramina and encroachment on marrow spaces but in some patients primary retina degeneration is also reported[19].

Sensorioneural deafness is the result of pressure on the eight nerve. Sclerosis of the middle ear bones, disfunction of the eustachian tube causes conductive type hearing loss[7].

Alkaline phosphatase is generally increased but it was within normal limits in our patient[20].

Hydrocephalus is a complication of osteopetrosis but to our knowledge tethered cord is not reported[20].

Only 30% of the patients with infantile malignant osteopetrosis survive beyond 6 years without bone marrow transplantation[20]. Irreversible neurologic deficits develops in infancy. In this report as other reports from our country, we want to emphasize that delay in diagnosis eliminates chance of cure[21]. Bone marrow transplantation is curative in infantile malignant osteopetrosis.

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Address for Correspondence:

Nazan SARPER, MD

Caferağa Mahallesi Dr. Şakir Paşa Sokak
No: 7/4 Huzur Apartmanı
81300, Kadıköy, İstanbul, TURKEY

e-mail: *nazan_sarper@hotmail*