A Case of Cytomegalovirus Infection in a Neonate with Osteopetrosis

Sang Hyun Lee, Jeong Hee Shin, Byung Min Choi, Yun-Kyung Kim
Department of Pediatrics, Korea University College of Medicine, Seoul, Korea

Infantile osteopetrosis is a rare congenital disorder caused by abnormal bone resorption. Patients with osteopetrosis can have severe anemia, thrombocytopenia, hepatosplenomegaly, rickets, visual impairment, and deafness. Cytomegalovirus also can cause a congenital infection with anemia, thrombocytopenia, hepatosplenomegaly, and calcifications in the brain. We report a 38-day-old infant with severe hepatosplenomegaly, hypocalcemia, and growth failure. Real time polymerase chain reaction detected cytomegalovirus in the plasma. Skeletal radiography revealed generalized bone sclerosis. He was diagnosed with osteopetrosis along with cytomegalovirus infection. Only the test for mutation of the CLCN7 gene, representing the most common and heterogeneous form of osteopetrosis, was available, and the result was negative. With supportive care and antiviral treatment, severe thrombocytopenia due to the cytomegalovirus infection almost normalized despite the possible immunosuppression caused by osteopetrosis. We present the first report of an infant who suffered from osteopetrosis and CMV infection which was successfully treated by long term antiviral agent therapy.

Key Words: Osteopetrosis, Cytomegalovirus infection, Infant

Introduction

Osteopetrosis is a genetic disorder characterized by sclerosis of the skeleton caused by osteoclast failure and presents with variable severity and symptoms. Autosomal recessive osteopetrosis may have the most severe course, with an incidence of 1:250,000 in the general population. Infants with the recessive type rarely survive >2 years, and have severe bone marrow failure and splenomegaly that can mimic hematologic malignancy. In contrast, autosomal dominant osteopetrosis is defined as a benign adult form and it has two types. Autosomal dominant type I is generally very mild, with diffuse sclerosis and no changes in bone turnover biochemical markers or blood cell counts. Autosomal dominant type II has an extremely heterogeneous course, ranging from an asymptomatic to a severe phenotype. Different genetic mutations described include those observed in TCIRG1 (encoding the a3 subunit of ruffled membrane), CLCN7, OSTM1, and PLEKHM1.3,4

Congenital cytomegalovirus (CMV) infection presents with anemia, thrombocytopenia, hepatosplenomegaly,
and calcifications in the brain. It can cause neurologic sequelae, including sensorineural hearing loss, cerebral palsy, microcephaly, cognitive impairments, and mental retardation.

We encountered CMV infection in a neonate with osteopetrosis presenting with hepatosplenomegaly and thrombocytopenia.

Case Report

A 38-day-old male infant, born full-term by vaginal delivery, presented with irritability and petechiae on the forehead. The baby had been very irritable and had eaten poorly for 2 weeks before presentation. Petechiae developed on the forehead and spread to the trunk 1 week prior to presentation. The weight was below the third percentile and height was 5 percentile; at birth, his weight was 30 percentile. The abdomen was distended, and hepatomegaly (4.0 cm) and splenomegaly (5.5 cm) were noted.

Biochemical analysis showed the following measurements: white blood cell (WBC) count, 32,000/μL (neutrophil 27.8%, lymphocyte 58.2%, monocyte 11.6%, eosinophil 2.4%); Hb level, 8.2 g/dL; platelet count, 20,000/μL; aspartate aminotransferase (AST)/alanine aminotransferase (ALT), 152/41 U/L (normal: 8–60/7–55 U/L). The serum calcium level was 8.3 mg/dL (normal: 8.8–10.8 mg/dL), phosphorous level was 3.4 mg/dL (normal: 3.8–6.5 mg/dL), and alkaline phosphatase level was 578 U/L (normal: 54–369 U/L). The infant was anicteric, but was positive for serum CMV IgM, and CMV culture and polymerase chain reaction (PCR) were positive in blood and urine (363,117 copies/mL and 16,600 copies/mL). Laboratory tests for the evaluation of hypocalcemia showed elevated parathyroid hormone levels at 223.2 pg/mL (normal: 15–65 pg/mL) and normal levels of calcidiol and calcitriol. No evidence of rickets was seen on radiography. Other congenital infections, including toxoplasmosis, rubella, and syphilis, were ruled out by serologic testing.

An ophthalmic examination revealed moderate to severe CMV retinitis with optic nerve atrophy with peripheral retinal hemorrhage. Brain computed tomography (CT) showed markedly increased skull density (Fig. 1). Extremity radiography and temporal bone CT of our patient was specific for radiologic findings of osteopetrosis (Fig. 2 and 3).

For treatment of CMV infection, 6 mg/kg/day of intravenous ganciclovir was administered. Anemia and severe thrombocytopenia persisted for 5 weeks despite

![Fig. 1. Osteopetrosis on brain computed tomography. No evidence of intracranial calcification is observed. Sclerotic change of the skull could represent osteopetrosis.](image)

![Fig. 2. Osteopetrosis on extremity radiography. Metaphyseal flaring and increased bone density of long bones is consistent with osteopetrosis.](image)
antiviral treatment. However, over the next 2 months of antiviral therapy, the real time PCR value of CMV viral load kept decreasing, CMV retinitis healed, and platelet counts and hemoglobin levels increased (Fig. 4). Vitamin D was administered to try to stimulate osteoclastic function.

Genetic analysis can be used to differentiate osteopetrosis subtypes, providing information about the response to treatment and the recurrence rate. Only the test for mutation of the \textit{CLCN7} gene, representing the most common and heterogeneous form of osteopetrosis, was available, and the result was negative.

Discussion

Osteopetrosis, also known as Albers-Schönberg or Marble bone disease, is a rare genetic bone disorder with abnormal bone remodeling due to defective osteoclasts, resulting in decreased bone resorption \cite{7}. Osteopetrosis is clinically a highly heterogeneous group of conditions that share the hallmark of increased bone density on radiographs \cite{2}. There are two main forms of osteopetrosis: a mild, autosomal dominant form, which is usually diagnosed by chance, and presents with mild symptoms with good long-term survival; and the severe autosomal recessive form, which is a fatal disorder with poor prognosis \cite{8}.

Meanwhile, CMV infection is the most frequent con-
genital infection in humans, with a wide range of clinical manifestations. These include jaundice, petechiae, and hepatosplenomegaly, with oligohydramnios, polyhydramnios, prematurity, intrauterine growth retardation, hypotonia, poor feeding, cerebral ventriculomegaly, microcephaly, intracranial periventricular calcifications, “blueberry muffin” spots, sensorineural hearing loss, and mental retardation. An infant with hepatosplenomegaly, anemia, thrombocytopenia, and elevated liver function test measurements is usually evaluated for congenital infections including CMV. Congenital CMV infection is diagnosed by isolation of the virus in urine, blood, or saliva within the first 3 weeks of life. Methods of detection include routine virus culture combined with immunofluorescence and PCR. Although this patient was not tested for CMV in the first 3 weeks of life, he had similar clinical manifestations of congenital infection, with severe hematologic abnormalities, hepatitis with hepatosplenomegaly, and bilateral retinitis. There was no evidence of intracranial calcification on brain CT, but sclerotic change of the skull was noted, which could coincide with osteopetrosis. Further skeletal radiologic studies confirmed osteopetrosis.

Hematological abnormalities can present in both CMV infection and osteopetrosis. At the early stage of antiviral treatment, the cause of anemia, thrombocytopenia, and elevated liver function test measurements remained uncertain because the anemia and severe thrombocytopenia persisted during 5 weeks of antiviral treatment. Four possible causes of persistent thrombocytopenia were considered: bone marrow suppression caused by osteopetrosis, severe splenomegaly, refractory CMV infection, and adverse effects of ganciclovir. However, with prolonged antiviral therapy, a gradual decrease of real time PCR values of CMV viral load and increased platelet counts were noted. The patient had recovery of almost normal platelet counts and hemoglobin, even after cessation of ganciclovir.

Mutation in the TCIRG1 or CLCN7 gene is found in nearly 70% of all patients with autosomal recessive osteopetrosis. The patient was considered to be an autosomal recessive osteopetrosis because of his clinical manifestations such as growth retardation, hypocalcemia, haematologic impairment, visual impairment and central nervous system symptoms. Although he had no family history of osteopetrosis, genetic analysis is important for treatment planning because immediate bone marrow transplantation can be very beneficial in patients with osteopetrosis with the CLCN7 gene mutation. However, mutation in CLCN7 was not detected in this case, and hematopoietic stem cell transplantation was not performed owing to parental refusal. Therefore, treatment was largely supportive for osteopetrosis. The patient was fed via a gastric tube owing to feeding difficulty and severe growth failure, and weighed 3.7 kg at 15 months of age. He died of pneumonia and sepsis complicated with gastrostomy insertion at 16 months of age.

We present the first report of an infant with both osteopetrosis and CMV infection. Although osteopetrosis can suppress immune function, CMV was successfully treated by long-term antiviral therapy.

References

요약

골화석증은 골격의 경화증이 특징적으로 나타나는 드문 유전 질환으로 뼈 흡수 기전에 손상이 오며 조기 사망하는 질환이다. 반면 거대세포바이러스 감염은 가장 흔한 선천성 감염 중 하나로 빈혈, 혈소판 감소증과 간비장증, 뇌 석회화 등이 나타날 수 있다. 심한 간비비대, 혈소판 감소증 및 저칼슘혈증과 발달지연으로 내원한 환자에서 두 가지 질환이 함께 있어 항바이러스제 치료 및 대증치료를 시행하였고, 치료 반응이 빠르게 나타나지 않으면 지속적인 치료 결과 대부분의 수치가 정상화 되는 것을 확인하였다. 본 증례는 골화석증 신생아에 동반된 거대세포바이러스 감염의 첫 증례 보고로, 거대세포바이러스 감염에 대한 항바이러스제의 장기 치료로 호전된 사례이다.