Transient Generalized Osteosclerosis in a Newborn Mimicking Congenital Osteopetrosis with Negative Comprehensive Genetic Workup: A Case Report

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We present a newborn with transient generalized osteosclerosis and negative genetic workup. The etiology of this condition is unknown. Given overlapping radiologic signs with severe forms of osteopetrosis, familiarity with this condition is crucial for correct diagnosis and management. *(J Pediatr 2024;11:200100).*

Osteosclerosis is a descriptive term for increased bone mineral density, usually detected by radiographic imaging. The prevalence of this finding overall is unclear. Multiple conditions are associated with this finding, which may be generalized and involve both axial and appendicular skeleton (eg, osteopetrosis, carbonic anhydrase II deficiency, or pyknodysostosis) or localized (eg, osteopoikilosis or osteopathia striata). Many of these conditions have been associated with genetic etiology.

The osteopetroses refer to a rare group of heritable bone disorders that are primarily characterized by a generalized increase in bone density. The incidence of these disorders has been reported as 1 in 250 000 births for the autosomal-recessive form and 1 in 20 000 for the autosomal-dominant form.[1] There is also an x-linked form of the disease. The autosomal-dominant form is generally milder and is associated with bone fractures in adulthood.[2] The autosomal-recessive form has a severe presentation, usually at early infancy, characterized by bone marrow failure with anemia, thrombocytopenia and extramedullary hematopoiesis, cranial nerves compression leading to vision and hearing impairment, proneness to fractures, and in many cases, a fatal progression.[2] Osteopetrosis is a heterogenous condition. Pathogenic variants in 7 genes (*TCIRG1*, *CLCN7*, *TNFRSF11A*, *TNFSF11*, *OSTM1*, *SNX10*, and *PLEKHM1*) are found in 80% of children with malignant osteopetrosis of infancy.[3] Poor osteoclastic bone absorption is thought to be the mechanism for all forms of osteopetrosis.[4] Management of the malignant form of osteopetrosis is primarily symptomatic and involves transfusions of erythrocytes, calcium supplementation, antibiotics to treat infections, and surgical decompression of cranial nerves.

The only curative treatment for osteopetrosis is allogeneic hematopoietic stem cell transplantation (HSCT). This treatment is indicated only for cases of osteopetrosis that are derived by intrinsic osteoclast malfunction with hematologic failure requiring transfusions, clear risk for blindness, and/or other clinical complications that significantly decrease life expectancy or quality of life. In these cases, early HSCT is crucial, and a 5-year disease-free survival can be as high as 88% in human leukocyte antigen (HLA)–identical HSCT.[3] Although osteopetrosis is a life-long condition with known genetic etiology, there have been reports of transient generalized osteosclerosis of infancy that may be mistakenly diagnosed as osteopetrosis in the newborn period.[2,5] This case report follows a neonate who presented with generalized osteosclerosis and mild hematologic abnormalities concerning for congenital osteopetrosis. Stable clinical condition and resolution of radiographic findings at 9 months of age confirmed the diagnosis of transient osteosclerosis of infancy. Negative whole-genome sequencing is suggestive of environmental etiology, although a yet unknown genetic etiology cannot be ruled out.

HSCT	Hematopoietic stem cell transplantation

Case Report

A Hispanic male infant weighing 8 lbs, 4.3 oz (3.75 kg) was born via induced vaginal delivery at 38 weeks to a 24-year-old G1P1001 woman. Parents are non-consanguinous. The neonate was of appropriate height (52 cm, 88th percentile) and head circumference (36 cm, 91st percentile). The pregnancy was complicated by maternal obesity, intrahepatic cholestasis of pregnancy, positive depression screen, and chorioamnionitis at the time of delivery. Imaging studies during pregnancy were unremarkable. At birth, the infant arrived limp and needed positive pressure ventilation for less than 1 minute and continuous positive airway pressure for 20 minutes. At 30 minutes, the infant was weaned onto room air and did not have further breathing difficulties. Mother and baby had a fever, which resolved with antibiotics. Group B *Streptococcus* status for the mother was negative, and aerobic blood cultures isolated no organism. The family history was

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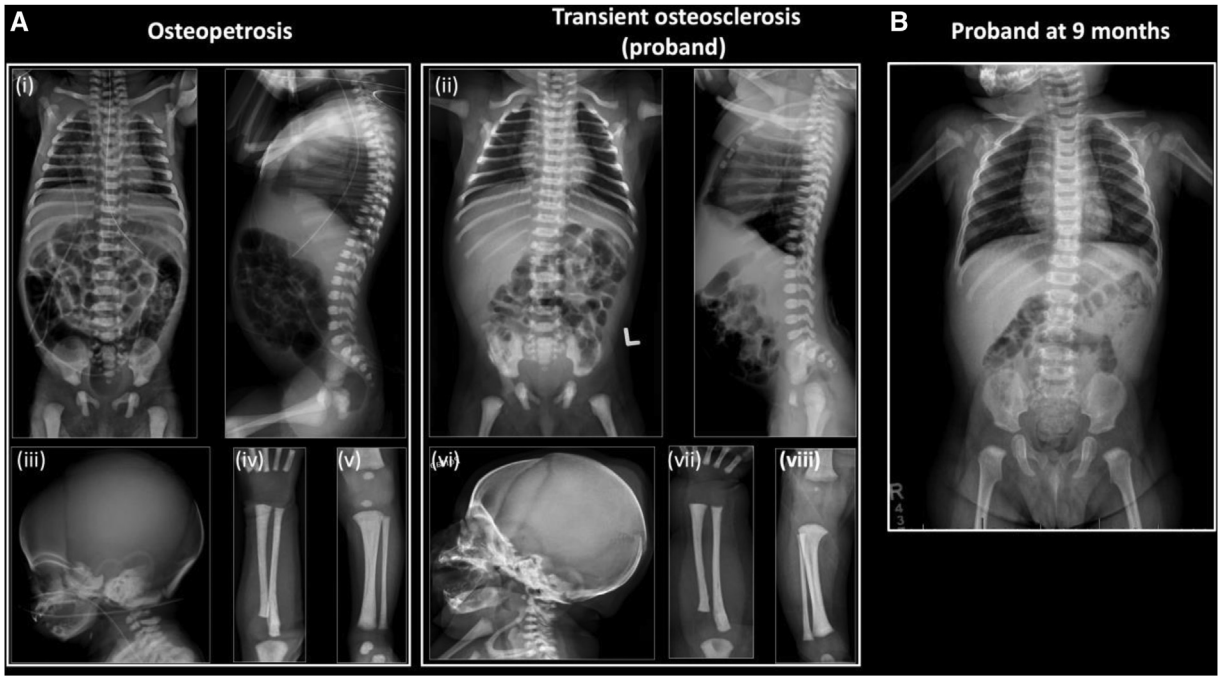

Figure. **A,** Comparison of radiographs from 8-day-old child with infantile osteopetrosis (*left panel*) and the proband with transient osteosclerosis at 1 day of life (*right panel*). (i) and (ii) show coronal view (*left*) and sagittal view (*right*) of chest, abdomen, and pelvis; (iii) and (vi) skull sagittal view; (iv) and (vii) left forearm; and (v) and (viii) lower limb. **B,** Chest, abdomen, and pelvis radiographs of proband with transient osteosclerosis at 9 months showing complete resolution of radiologic findings.

negative for osteopetrosis or other bone-related illnesses. There were no reported documented infections or exposures to environmental toxins or illicit substances during the pregnancy.

Findings of the physical examination were unremarkable besides asymmetric Moro reflex and minimal left arm movement, as well as bruising as the result of trauma during delivery. Clinical concern for Erb palsy vs fracture was raised. Radiographs were taken at 3 times at different occasions over days of life 2 and 3 and included radiographs of the left clavicle, shoulder, humerus, forearm, and a skeletal survey. No fractures were noted, and Erb palsy was diagnosed. Severe osteosclerosis, concerning for osteopetrosis, was reported in all bones, attributable to increased radiodensity in visualized bony structures (**Figure, A**). A complete blood count and ionized calcium were obtained and showed no abnormalities, and the child was started on vitamin D supplementation. He passed his newborn hearing screen. Three days after delivery, the Erb palsy resolved with restored motor function in the left arm, and family was discharged. The patient was lost to follow-up resulting from insurance constraints. He was seen again at 3 months of age with no new health concerns. Complete blood count at this time showed low reticulocyte count ($0.034 \times 10^6/\mu L$) as well as a decreased immature reticulocyte fraction (8.3%) and neutropenia with an absolute neutrophil count of $0.81 \times 10^3/\mu L$ with no history of fever or other signs of infection. Calcium was mildly elevated (10.9 mg/dL, normal range 8.0-10.7 mg/dL). He was evaluated by hematology for additional bone marrow abnormalities. All additional workup at this time, including sedimentation rate, C-reactive protein, alkaline phosphatase, osteocalcin, lactate dehydrogenase, liver panel, and urinalysis, were within normal limits (**Table**). Cytomegalovirus screen at 5 months of age was reactive, suggestive of past or current infection with no clinical manifestations.

Table. Laboratory values of proband's blood work at 3 and 9 months of age

Laboratory tests	3 mo	9 mo	Normal range
Hemoglobin, g/dL	10.7	12.5	10.5-14
Platelets, $\times 10^3/mm^3$	363	322	150-450
WBCs, $\times 10^3/mm^3$	6.97	10.05	6-17
Lymphocyte, %	72.5	78.6	34-88
Eosinophils, %	5.8↑	3.5	0-3
Neutrophil, %	14.0	12.1	4-12
Absolute neutrophil, $\times 10^3/\mu L$	0.81↓	1.22	1.0-8.5
Immature reticulocyte fraction, %	8.3↓	4.4↓	11.4-25.8
Reticulocyte absolute, $\times 10^6/\mu L$	0.034↓	0.043↓	0.048-0.088
Alkaline phosphatase, units/L	256	288	150-420
LDH, units/L	315	296	170-580
Calcium, total, mg/dL	10.9↑	NA	8.8-10.8
Sodium, mEq/L	133	NA	130-147
Potassium, mEq/L	4.3	NA	3.4-5.6
Chloride, mEq/L	104	NA	95-108

LDH, lactate dehydrogenase; *NA*, not available; *WBC*, white blood cells.
"↓" indicates value is lower than normal range. "↑" indicates value is higher than normal range.

The infant continued to grow well and gained weight appropriately. He achieved all milestones, including eye tracking and social smile at 2 months, and had no feeding difficulties. Audiology and ophthalmology evaluations were normal. Abdominal ultrasound scan was normal with no signs of hepatosplenomegaly. Extensive genetic workup including trio whole-genome sequencing did not identify a genetic cause for the infant's generalized osteosclerosis.

At 9 months, follow-up radiographs showed normal bone mineral density with no evidence of sclerosis (**Figure, B**). This was accompanied by a partial and gradual improvement in the neutropenia and in reticulocytes count, with absolute neutrophil count of $1.22 \times 10^3/\mu L$ and absolute reticulocyte count of $0.043 \times 10^6/\mu L$ with immature reticulocyte fraction of 4.4% (**Table**). The child's height, weight, and head circumference were in the 99th, 81st, and 98th percentiles, respectively.

Discussion

Other cases of transient generalized osteosclerosis of the newborn have been reported in the literature.[2,5] These case reports include a total of 3 male patients, but none have been reported since the 1990s, to the best of our knowledge. Similarities between the cases include incidental finding of the condition through radiographs and normal electrolyte and complete blood count, as well as child's normal growth and development. Because of the infrequency of ordering radiographs for neonates, the true prevalence of transient osteosclerosis of the newborn is unknown, and this condition is most probably underdiagnosed. The mild hematologic changes in the presented case, including neutropenia and decrease in absolute reticulocytes number, may indicate of a prolonged subclinical infection or mild and transient bone marrow disfunction that may or may not be related to the bone findings. Nondiagnostic genetic workup increases the likelihood of an environmental cause but does not entirely rule out a genetic etiology that affects osteoclasts activity in utero. Spontaneous microphthalmia blanc rat models have shown a congenital transient osteopetrosis that resolves within 8 months.[6] Microphthalmia blanc rats were found to be homozygous for a large deletion in the 3' half of the microphthalmia transcription factor gene (*mi*) and showed decrease in bone reabsorption with low absolute osteoclast numbers, lack of ruffled border formation by osteoclasts, and decreased levels of mRNA for carbonic anhydrase II and tartrate-resistant ATPase. Both the osteoclast function and number normalized by 4 weeks of life.[6] This model is suggestive a genetic cause yet to be revealed. Careful review of our patient's trio whole-genome sequencing for deleterious variants in *MITF* gene did not yield potential candidate variants.

Environmentally driven etiology is supported by some evidence suggesting that viral infections may lead to osteoclast dysfunction. Bovine transient osteosclerosis had been reported in a calf with persistent bovine viral diarrhea virus infection.[7] Full resolution of symptoms was reported at 13 months of age. A case of osteopetrosis had been reported in a 10-day-old boy with interleukin-2 receptor–related severe combined immunodeficiency.[8] Reportedly, bone and marrow biopsy samples showed findings consistent with osteopetrosis. Genetic workup, including osteopetrosis gene panel and whole-exome sequencing, did not identify a genetic etiology for the osteopetrosis. The child was found to have persistent chronic viremia with chromosomally integrated human herpesvirus-6 inherited from his parent. This viremia significantly improved after allogeneic hematopoietic stem cell transplantation with the recovery of the hematopoietic and immune function. Complete resolution of the radiologic findings was achieved a year after the transplantation. The authors suggested that chromosomally integrated human herpesvirus-6 is the cause for the osteosclerosis seen on radiographs in an in utero virus-mediated osteoclasts dysfunction.[8] Another form of transient osteosclerosis is seen in Caffey disease. This condition is characterized by significant hyperostosis of the bones presenting with fever, joint swelling, and pain in the first 5 months of life. The bone changes slowly resolve within 2 years.[9] Caffey disease is associated with a pathogenic variant in *COL1A1* (c.3040C>T) leading to abnormalities in type I collagen.[9] This condition is suggestive of a concomitant inflammatory event and a genetic predisposition effect on bone homeostasis that result in transient osteosclerosis.

Because malignant osteopetrosis of infancy is a rare and clinically variable condition, early confirmation of the diagnosis with broad next-generation sequencing genetic testing can help to avoid multiple invasive diagnostic procedures and may allow early treatment with life-saving hematopoietic stem cell transplant.[10] Yet, in cases of classical radiographs findings and negative genetic test results, familiarity with the entity of transient osteosclerosis of infancy and careful clinical follow-up and evaluation with periodic skeletal imaging can save clinicians and families valuable time and money when ordering additional tests for potential diagnoses. ■

CRediT authorship contribution statement

Jeffrey Hauck: Writing – original draft. **Amanda Gerard:** Writing – review & editing, Supervision, Investigation. **James E. Crowe:** Writing – review & editing, Investigation, Conceptualization. **Caridad A. Martinez:** Writing – review & editing, Supervision, Investigation. **Keren Machol:** Writing – review & editing, Supervision, Investigation, Conceptualization.

Declaration of Competing Interest

The authors have nothing to disclose.

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