Optic Nerve Compression in Infantile Malignant Autosomal Recessive Osteopetrosis

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Abstract. A 6-month-old infant was diagnosed with infantile malignant autosomal recessive osteopetrosis. An ophthalmologic examination revealed optic nerve pallor and computed tomography of the brain showed narrowing of the orbital fissure. Unrelated umbilical cord blood transplantation was performed. Four months later, the infant died of respiratory complications. *J Pediatr Ophthalmol Strabismus* 2004;41:241-244.

INTRODUCTION

Osteopetrosis is a rare hereditary disease characterized by increased bone radiodensity. There are three forms of osteopetrosis displaying a spectrum of clinical behavior. We report the case of a 6-month-old infant diagnosed as having the infantile malignant autosomal recessive form of osteopetrosis and optic nerve compression.

CASE REPORT

A 6-month-old, full-term male infant was evaluated for repeated respiratory infections and breathing problems. There were no other developmental abnormalities. A general physical examination revealed a high-arched palate, but no other dysmorphic features. An ophthalmologic examination revealed equal, round, and sluggishly pupils, full visual fields, conjugate gaze, and mild optic nerve pallor. A neurologic examination revealed normal strength and tone and a slight head lag when the infant was sitting up. A conventional radiograph of the chest showed a "bone-within-bone" appearance of the posterior ribs and generalized osteosclerosis, consistent with osteopetrosis. There was no history of osteopetrosis in the mother's family. A skeletal survey revealed increased radiodensity of bones throughout the skeleton. A computed tomography scan of the brain showed narrowing at the level of the orbital fissure to 1 mm (Fig. 1).

Given the clinical appearance and the radiographic findings, a diagnosis of infantile malignant autosomal recessive osteopetrosis was considered. The infant was administered alpha-interferon as an intervention to preserve bone marrow pending bone marrow transplantation. Unrelated umbilical cord blood transplantation was performed. Four months later, at the age of 10 months, the infant died of res-
piratory complications. A postmortem examination was performed.

**AUTOPSY FINDINGS**

Sections through the sphenoid bone showed severe narrowing of the optic canals. Luxol fast blue stain (Sigma Chemical Co., St. Louis, MO) was used for the optic nerves and chiasm and showed areas of normal myelination (Fig. 2A), foci of a mild decrease in myelin content (Fig. 2B), and foci of complete loss of myelin (Fig. 2C). There was reactive gliosis in the regions of demyelination.

Zones of normal and abnormal bone were present in the sphenoid bone indicating that osteoclast function had been normal at some periods of the infant's life. The abnormal bony trabeculae were typical of osteopetrosis. They contained basophilic and unremodeled cartilage intermixed with eosinophilic immature bone and showed sparse hematopoiesis (Fig. 3A) compared with adjacent areas that were more normal in appearance with intact trilineage hematopoiesis (Fig. 3B). Osteoclasts were more frequent on the surface of abnormal trabeculae than on the surface of normal tra-
beculae. Large expanses of calcified cartilage persisted within the sphenoid bone. The zones of normal bone had trabeculae with immature areas and large, irregularly spaced osteocytes within large lacunae.

Continous with the immature bone was mature bone having more regularly distributed, compact osteocytes within small lacunae. The lamellar appearance of the mature bone was confirmed by polarization microscopy. Much of the marrow between the morphologically normal trabeculae had normal-appearing trilineage hematopoiesis, although there were areas of loose fibrous tissue with sparse hematopoietic cells. The bone did not appear to compress the vascular supply into the nerve.

Other major findings at autopsy included bilateral, severe, exudative diffuse alveolar damage, mild graft-versus-host disease of the liver, moderate veno-occlusive disease of the liver, markedly hypocellular vertebral bone marrow with evidence of early reconstitution, hydrocephalus, and hippocampal sclerosis.

**DISCUSSION**

Osteopetrosis is a rare hereditary disease characterized by increased bone radiodensity.\(^1\,^2\) Three forms of osteopetrosis are distinguished by their clinical manifestations: infantile malignant autosomal recessive, intermediate autosomal recessive, and benign autosomal dominant. Infantile malignant autosomal recessive osteopetrosis, also referred to as osteopetrosis congenita, is manifest in infancy by either increased bone fragility with pathological fractures or failure to thrive with frequent upper respiratory infections. Bone marrow failure results from a lack of sufficient marrow-forming regions of the bone due to plugging by calcified cartilage and woven bone that persists due to failure of resorption. Extramedullary hematopoiesis often results in hepatosplenomegaly. This form of osteopetrosis is fatal within the first few years of life, although infants receiving marrow from a human leukocyte antigen complex-identical sibling or an unrelated donor have a 5-year rate of survival with a functioning graft of 50\% to 70\%.\(^3\) Infantile malignant autosomal recessive osteopetrosis is rare, with an estimated incidence in most countries of approximately 1 case per 300,000 newborns.\(^3\)

Intermediate autosomal recessive osteopetrosis, also known as marble bone disease, is usually diagnosed toward the end of the first decade of life when the child develops a fracture and an x-ray reveals abnormally dense bone. Children with intermediate recessive osteopetrosis have short stature due to short limbs, macrocephaly, recurrent fractures, and dental abnormalities. Only a few patients with this form of osteopetrosis have been described, and they have survived into adulthood.\(^2\) Benign autosomal dominant osteopetrosis, also called osteopetrosis tarda, is asymptomatic in approximately half of those who have it and a full life expectancy is the norm.

Radiographic studies are of prime importance in diagnosing osteopetrosis, with all forms having increased radiodensity throughout the skeleton.\(^2\) Advanced cases have absence of the normal corticomedullary demarcation, and the metaphyses are wider than normal due to failure of metaphyseal remodeling. The bone-within-bone or endobone phenomenon is most frequently noted in the tarsal bones, vertebral bodies, phalanges of the hands and feet, and pelvis.\(^2\) Computed tomography scans of the optic and auditory canals are important for observing patients over time, especially after treatment.

Neurologic and ophthalmologic manifestations of osteopetrosis are frequent in the infantile malignant autosomal recessive form, but are absent in the other forms, with the exception of sensorineural hearing loss in the intermediate autosomal recessive form.\(^2\,^4\,^5\) Ophthalmologic complications include optic atrophy, papilledema, exophthalmos, strabismus, paralysis of extraocular muscles, ptosis, anisocoria, tortuosity of retinal vessels, chemosis, hypertelorism, and primary retinal degeneration.\(^2\,^4\,^6\,^7\) Optic atrophy usually results from optic nerve compression in the optic canal, although rare cases may result from primary retinal degeneration.\(^5\,^7\) In the current case, there was mild loss of myelin involving both nerves and the chiasm, and there were small foci of more severe demyelination. There was mild optic atrophy, but no evidence of ischemic neuropathy. Although the autopsy excluded examination of the eyes, no retinal or choroidal abnormalities were noted clinically. The postmortem findings indicate that optic atrophy was due to compression of the nerve within a markedly stenotic canal. Optic nerve decompression in early childhood may improve or at least stabilize visual function.\(^2\)
The presence of large islands of unresorbed calcified cartilage and unremodeled cartilage remaining in newly formed osseous trabeculae is typical of the bone abnormalities in the infantile malignant autosomal recessive form of osteopetrosis. Osteoclasts are more frequent around the abnormal cartilage–bone trabeculae and typically have a normal location relative to the bone and cartilage. Experimental findings in animal models suggest defects in osteoclast function or the bone microenvironment regulating osteoclast function. In animals with a primary defect in osteoclast function, bone marrow transplantation is curative, although it fails to cure those animals whose osteopetrosis results from a defect in the bone microenvironment. Similar heterogeneity exists in humans with the infantile malignant autosomal recessive form of osteopetrosis, as evidenced by only some infants being cured with bone marrow transplantation. For children without a suitable marrow donor, treatment with recombinant human alpha-interferon leads to an increase in bone marrow space and hemoglobin concentration, but the long-term efficacy of this therapy is not established.

REFERENCES