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Concurrent Malignant Infantile Osteopetrosis and Hypophosphatasia in a Six-year-old Boy: A Case Report

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Abstract: Malignant infantile osteopetrosis is a rare inherited disease of bone metabolism, in which osteoclast dysfunction and diminished bone turnover lead to diffuse sclerosis with obliteration of the medullary cavities and narrowing of the skull base neural foramina. We report a case of malignant infantile osteopetrosis with bone marrow failure and optic atrophy that co-occurred with hypophosphatasia, another rare inherited bone disease, in a 6-year-old boy. Key imaging signs of these rare diseases are discussed.

Keywords: *osteopetrosis, malignant infantile osteopetrosis, hypophosphatasia*

Case Presentation

A 6-year-old boy presented to our institution for the treatment of malignant infantile osteopetrosis (MIOP). Skeletal radiographic survey showed MIOP-specific features, including diffusely increased osseous mineralization, Erlenmeyer flask bone deformity, and sandwich vertebrae (Figure 1). The patient's left fibula had a fracture line from an injury sustained over a year ago, suggestive of delayed healing, although with bony bridging already being developed (Figure 1C). Dual-energy x-ray absorptiometry (DEXA) showed a Z-score of 21.7. Given a history of numerous transfusions, magnetic resonance imaging (MRI) of the abdomen was performed to assess iron overload. The examination showed diffuse low signal intensity of the liver on T2-weighted images, consistent with hemosiderosis (Figure 2A). On the same MRI examination, T1-weighted and T2-weighted images showed diffuse low signal intensity of the bone marrow, consistent with osteopetrosis (Figure 2B). Computed tomography (CT) of the head revealed marked

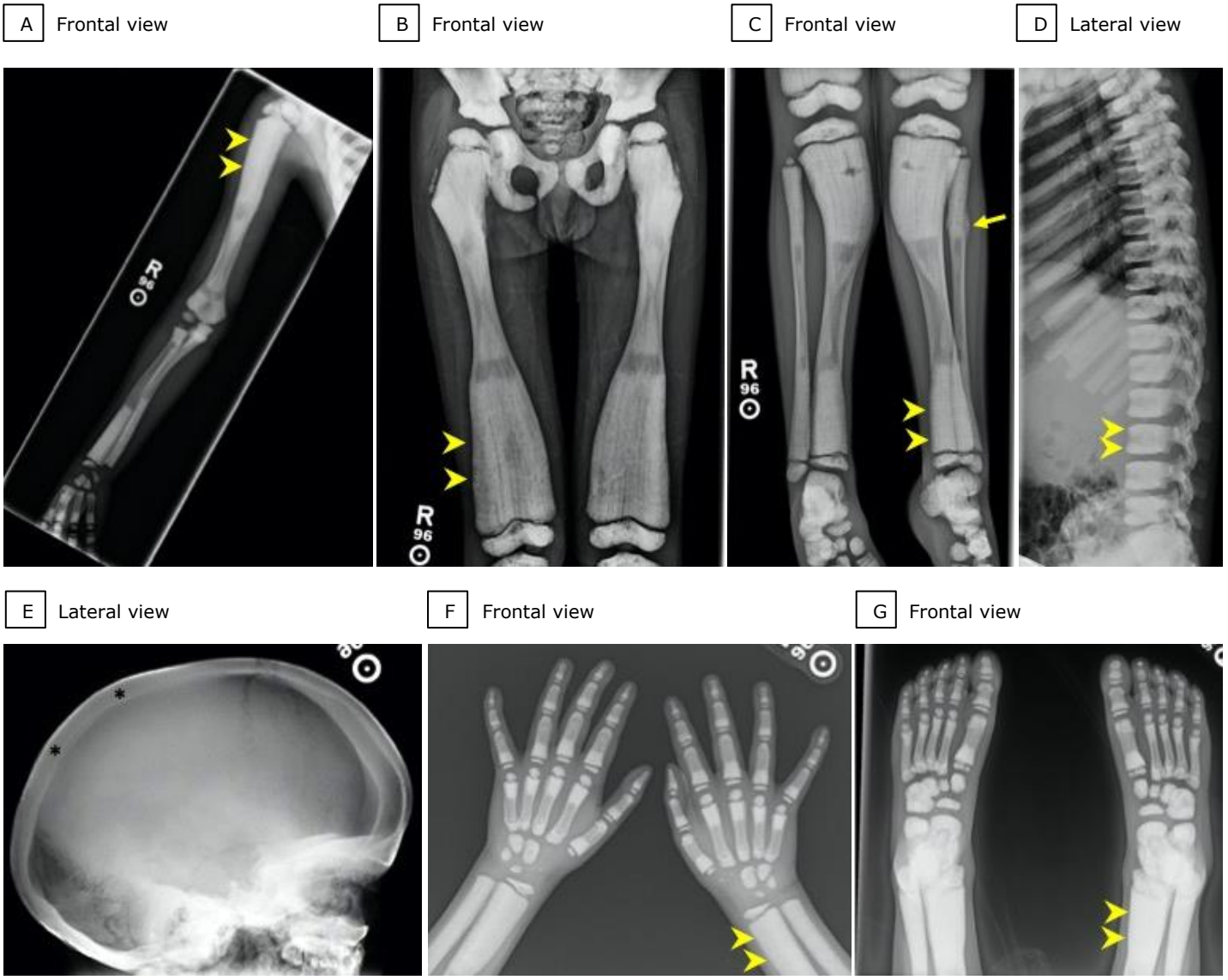
Key Points

- Malignant infantile osteopetrosis (MIOP) is a rare inherited metabolic bone disease that is caused by osteoclast dysfunction and manifests itself radiographically as diffuse bony sclerosis, sclerotic vertebral endplates ("sandwich vertebrae"), and flared metadiaphyses of the long bones (Erlenmeyer flask bone deformity).
- Hypophosphatasia is a rare inherited metabolic bone disease that is caused by deficient activity of tissue-nonspecific alkaline phosphatase and results in diffuse skeletal demineralization, rachitic changes, and premature exfoliation of deciduous teeth.
- Radiology plays a key role in the diagnosis of MIOP and hypophosphatasia, facilitating early genetic counseling and management.

Abbreviations

MIOP: malignant infantile osteopetrosis
MRI: magnetic resonance imaging
CT: computed tomography
TNSALP: tissue-nonspecific alkaline phosphatase

Figure 1. Skeletal Survey of a 6-year-old Boy with Malignant Infantile Osteopetrosis.



(A-G) Radiographs show diffuse osteosclerosis, lost corticomedullary differentiation, and obliterated medullary cavities (B and C, asterisks). (A, B, C, F, G) Frontal views of the right arm, the lower extremities, and the hands show the Erlenmeyer flask deformity of the long bones (A-C, F, and G, arrowheads). (C) Image shows the left fibula with delayed fracture healing (C, arrow). (D) Lateral view of the thoracic and upper lumbar spine shows "sandwich vertebrae" with sclerotic endplates (D, arrowheads). (E) Lateral view of the skull shows calvarial thickening (E, asterisks).

calvarial thickening and severe stenosis of the skull base foramina (Figure 3).

During infancy, the patient was hospitalized for splenomegaly, anemia (hemoglobin 8.9 g/dL; reference range: 9.0-15.0 g/dL), mild thrombocytopenia (platelet count 184 x $10^3/\mu L$; reference range: 140-440 x $10^3/\mu L$), and leukocytosis (white blood cell count 23.0 x $10^3/\mu L$; reference range: 5.0-19.5 x $10^3/\mu L$) (BMH Laboratory Services). The result of the patient's bone marrow biopsy was negative for hematopoietic neoplasm. Repeated platelet count and white blood cell count during the patient's follow-up visit showed normal results. Radiography of the femur revealed osseous demineralization, diffuse smooth periosteal thickening, and frayed and radiolucent metaphyseal margins. At the time, a differential diagnosis included congenital infection, metabolic bone disease, and bone marrow infiltrative

processes. Additional work-up revealed vitamin D deficiency, and the patient was subsequently diagnosed with rickets.

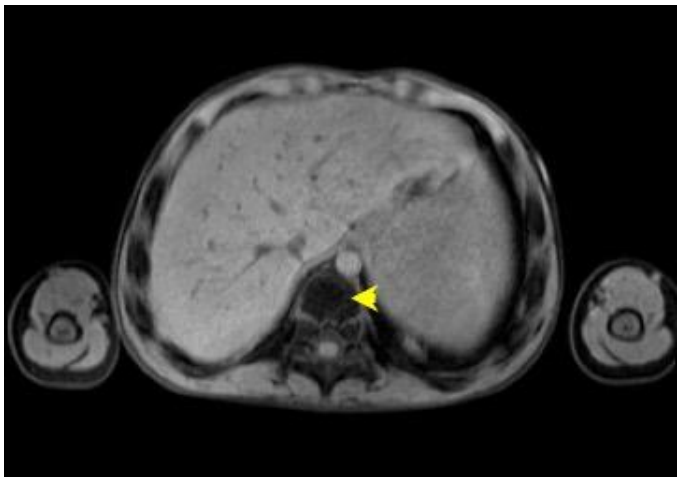
At approximately one year of age, the patient was evaluated by a geneticist. The patient's maternal family history included an unspecified bone disease that caused frequent fractures and dental abnormalities. The patient's younger brother had a mutation in the *ALPL* gene that encodes the enzyme tissue-nonspecific alkaline phosphatase (TNSALP), a deficiency of which is known to cause hypophosphatasia. The results of the patient's genetic testing also showed a mutation in the *ALPL* gene. In addition, laboratory test results showed low serum alkaline phosphatase level, 65 U/L (reference range: 117-390 U/L; BMH Laboratory Services), which supported a diagnosis of hypophosphatasia. To replace the deficient enzyme and to improve bone mineralization, the patient was prescribed asfotase alfa, a recombinant TNSALP.

During this period, the patient began experiencing premature tooth eruption, dental caries, chronic upper respiratory symptoms, and recurrent otitis media. The patient underwent adenoidectomy, bilateral tympanostomy, and tooth extraction for odontogenic infection. Computed tomography of the head, at two years of age, did not show signs of craniosynostosis but was notable for diffuse calvarial thickening. Skeletal survey showed increased mineralization of the axial and the appendicular skeleton and characteristic flaring and loss of concavity of the metadiaphyseal regions of the long bones. The result of electroencephalography that was administered to investigate the reasons for the patient's nighttime jerking movements was unremarkable.

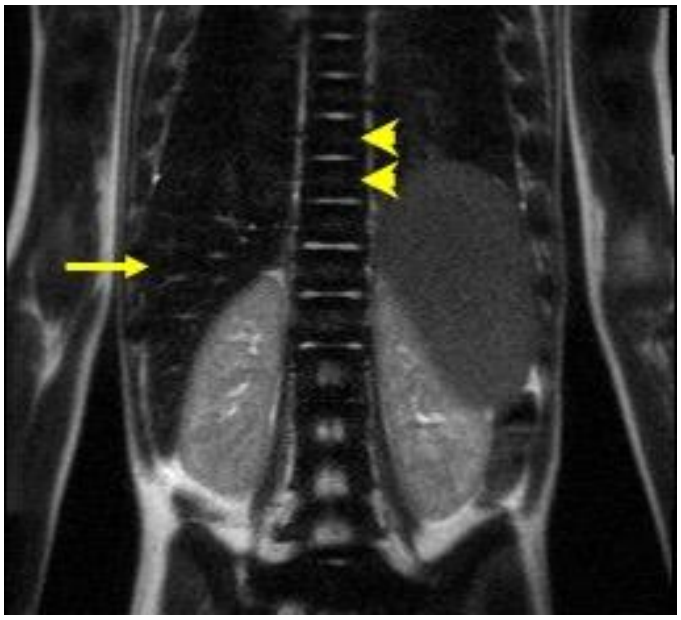
Skeletal radiographs, at approximately four years of age, revealed characteristic features of osteopetrosis involving the calvaria (marked calvarial marrow expansion and sclerosis), the long bones (dense epiphyses, dense and expanded metaphyses, and relative diaphyseal radiolucency of the long bones), the vertebrae (sandwich appearance with sclerotic endplates), and the axial skeleton (expanded and sclerotic ribs and sternum). During this period, the patient's vision declined. Repeated CT as well as MRI of the head and the neck revealed new sequelae of osteopetrosis, namely bilateral optic nerve compression, diffuse canalicular and foraminal narrowing of the carotid and the jugular canals, the foramina ovale, and the internal auditory canals, and underdeveloped middle ear cavities, paranasal sinuses, and mastoid air cells.

Figure 2. Abdominal MRI of a 6-year-old boy with Malignant Infantile Osteopetrosis.

A T1-weighted MRI, axial view



B T2-weighted MRI, coronal view



(A) T1-weighted image, axial view, shows the bone marrow (A, arrowhead) with diffusely low signal intensity. (B) T2-weighted image, coronal view, shows generalized sclerosis (B, arrowheads) of the spine. Low T2 signal intensity of the liver (B, arrow) is suggestive of hemosiderosis.

Within the next two years, the patient developed multiple complications, including bone marrow failure that required increasingly frequent transfusions, fibular fractures with delayed healing, and dental abscesses with mandibular osteomyelitis that necessitated repeated debridement. Further genetic testing showed a pathogenic mutation in the *TCIRG1* gene, confirming the presence of malignant infantile osteopetrosis.

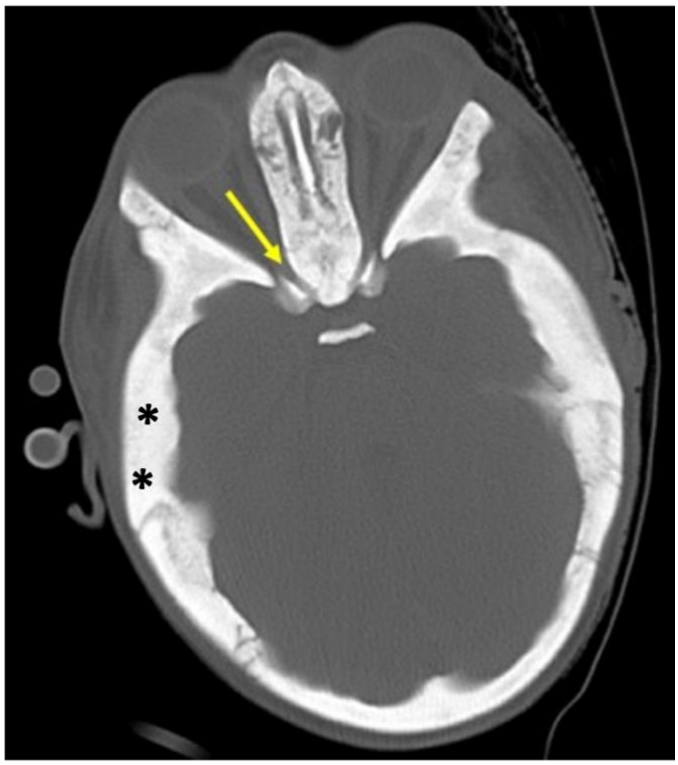
Discussion

Malignant infantile osteopetrosis (MIOP) (OMIM #259700) is a rare congenital metabolic bone disease that is caused by failure of osteoclasts and has an incidence of 1 in every 250 000 births.[1] Impairment of bone turnover and accumulation of calcified cartilage matrix are manifested in characteristic radiologic features, including osteosclerosis, loss of corticomedullary differentiation, and obliteration of medullary cavities.[2,3,4] Alternation between formation of abnormally dense bone and normal bone results in the "bone-in-bone" appearance.[3] Lost concavity and flared metadiaphyses of the long bones produce the characteristic appearance of Erlenmeyer flask bone deformity.[5,6] The development of dense bands of sclerosis along vertebral endplates creates the appearance of "sandwich" vertebrae.[2,6] Widened and irregular metaphyses and prominence of costochondral junctions can mimic rachitic changes.[4,5] Radiologic findings in the skull include thickening of the calvaria, obliteration of the cranial nerve foramina, macrocephaly with frontal bossing,[6] and sclerosis of the orbital bones.[5] The essential radiologic features of MIOP described here are in line with those found in our patient.

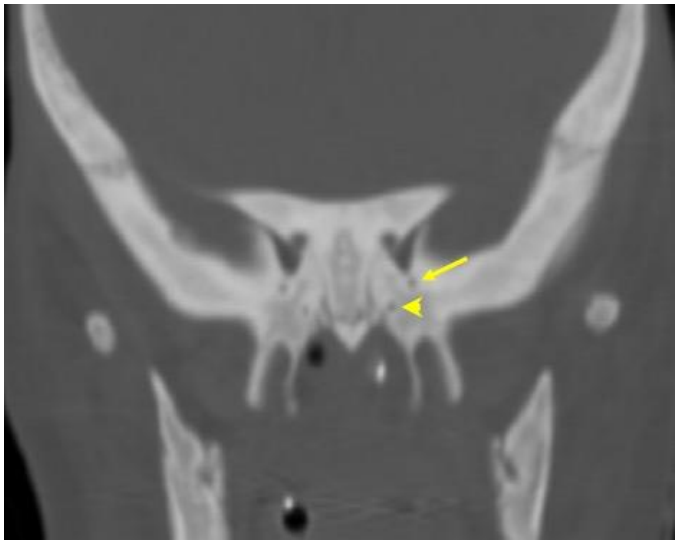
The autosomal recessive (malignant infantile) form of osteopetrosis is more severe than the autosomal dominant form of osteopetrosis that affects adults.[1,2,6] Infantile autosomal recessive osteopetrosis is usually lethal without treatment, but allogeneic hematopoietic stem cell transplant (HSCT) may improve the outcome of the disease.[1,4,5] Because the disease leads to failure of the bone marrow, distortion of nasal architecture,

Figure 3. Cranial CT of a 6-year-old Boy with Malignant Infantile Osteopetrosis.

A CT, axial view



B CT, coronal view



(A) Axial view at the level of the orbits shows the diffusely thickened calvaria (A, asterisks) with expansion of the diploic space and stenosis of the optic canals (A, arrow). (B) Coronal image of the central skull base at the level of the pterygoid processes shows stenotic foramina rotunda (B, arrow) and vidian/pterygoid canals (B, arrowhead).

and narrowing of the cranial foramina, patients present soon after birth or in the late infancy with anemia, frequent infections, hepatosplenomegaly, macrocephaly, electrolyte imbalance, visual or auditory impairment, and upper airway obstruction.[1,6,7] Other complications of unopposed osteoblast activity include pathologic fractures, osteomyelitis,[1,2] and secondary rickets.[8]

Genetic testing is necessary to confirm the diagnosis of osteopetrosis, to provide prognostic value, and to facilitate family counseling.[1] Malignant infantile osteopetrosis can be caused by mutations in one of multiple genes, including *TCIRG1* (T cell immune regulator 1), *CLCN7* (chloride voltage-gated channel 7), and *OSTM1* (osteoclastogenesis-associated transmembrane protein 1).[1] Hematopoietic stem cell transplant, particularly when following early diagnosis, can improve bone remodeling and increase long-term survival.[1,4,5] Radiologic imaging plays a key role in diagnosis and management of cases of MIOP.[1,4,5] For example, head and neck imaging can reveal neurologic complications at the cranial nerve foramina.[6,7]

As noted in this case presentation, our patient had another rare inherited metabolic bone disease—hypophosphatasia. This disease is caused by a mutation in the *ALPL* gene that encodes tissue-nonspecific alkaline phosphatase, the enzyme that hydrolyzes pyrophosphate to provide inorganic phosphate for bone mineralization.[9] Radiologic features of hypophosphatasia include diffuse skeletal demineralization, pathologic fractures, rachitic changes, and premature exfoliation of deciduous teeth.[10] Our patient had a mutation in the *ALPL* gene and low serum alkaline phosphatase level and received specific hypophosphatasia-related treatment. Although the subtype of hypophosphatasia that has affected our patient remains unclear, to our knowledge this is the first case of hypophosphatasia co-occurring with malignant infantile (autosomal recessive) osteopetrosis.

The clinical and radiologic findings in this case are characteristic of two concurrent rare congenital metabolic bone diseases with some overlapping features. Both MIOP and hypophosphatasia result in abnormal bone mineralization, pathologic fractures, and defective tooth development.[1,10,11] Our patient exhibited low bone mineral density during infancy, one of the sequelae of hypophosphatasia, and high bone mineral density in later childhood, evidently the result of osteopetrosis. Knowledge of the key imaging characteristics of these diseases is essential for radiologists to establish the diagnosis, facilitate genetic evaluation, and provide family and patient counseling.

Author Contributions

Conceptualization, T.Y.K. and S.G.K.; Writing – original draft preparation, T.Y.K.; Review and editing, S.G.K; Supervision, S.G.K. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

None to report.

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