Mucolipidosis II

A term male infant, born to a 20-year-old primigravida, was admitted for respiratory distress. A prenatal ultrasound examination showed shortened long bones. The parents were orthodox Jews and there was history of second-degree consanguinity. A deceased paternal cousin was diagnosed with mucolipidosis. Birthweight (2175 g), length, and head circumference were below the third percentile. On physical examination, the infant had a prominent forehead with a large fontanelle, low set ears, prominent eyes, telecanthus, maxillary hypoplasia, gingival hyperplasia, a narrow chest, distended abdomen, short limbs, bowing of the lower extremities, and generalized hypotonia. Radiographs revealed a bell-shaped chest, small thoracic cavity, small lung volumes with bilateral rib fractures (**Figure**, C), diffuse osteopenia and, subperiosteal bone destruction and new formation, and decreased size of the vertebral bodies (**Figure**, A-G). Lysosomal enzyme hydrolase levels in plasma were high, with normal activity in leukocytes. Urinary glycosaminoglycans and oligosaccharides were negative and the diagnosis of mucolipidosis II was confirmed on genetic testing.

Mucolipidosis II alpha/beta or inclusion cell disease is an autosomal-recessive lysosomal storage disorder caused by a mutation of the gene GNPTAB (alpha and beta subunits of *N*-acetylglucosamine-1-phosphotransferase), which is located on chromosome 12q23.2. This alteration leads to a deficiency of the enzyme *N*-acetylglucosamine-1-phosphotransferase that normally transfers phosphate to mannose residues. This deficiency disrupts the normal post-translational modification of lysosomal acid hydrolases and leads to increased extracellular secretion and a profound intracellular deficiency of acid hydrolases, thereby leading to accumulation of substrates, which is the usual pathology in lysosomal storage diseases. Because it is characterized by the presence of vacuole-like inclusions in lymphocytes it is also called inclusion cell disease. In early infancy, radiographic features may resemble rickets or hyperparathyroidism with decreased bone mineralization, periosteal "cloaking," ossification delay, epiphyseal dysplasia, platyspondyly (butterfly or anterior beaking) of the vertebral bodies, wide oar-shaped ribs, hypoplasia of ilea with shallow acetabular fossae, and pelvic dysplasia. Because this disorder is progressive, later signs may include sclerosis, stippling, and joint restriction and other multisystem effects such as severe neuropsychomotor developmental disorder.

Potential management of several lysosomal storage disorders, including mucopolysaccharidosis, includes enzyme replacement therapy, enzyme enhancement therapeutics, substrate reduction therapy, small molecule therapy, hematopoietic stem cell transplantation, gene therapy, and clustered regularly interspaced short palindromic repeats based genome editing. In mucolipidosis II alpha/beta, treatment such as hematopoietic stem cell transplantation, even when instituted in the first few months of life, have not proven to be beneficial. Some of the difficulties encountered are related to the inability of genome edited cells or genome editing machinery to cross the blood brain barrier and early diagnosis and treatment. Other reasons for limited improvement after the delivery of active phosphotransferase enzyme after hematopoietic stem cell transplantation could be due to the number of pathways affected. Studies on ultrasound-mediated blood-brain barrier disruption, cell penetrating peptides, and nanoparticle delivery systems are ongoing. At present, treatment is supportive. ■

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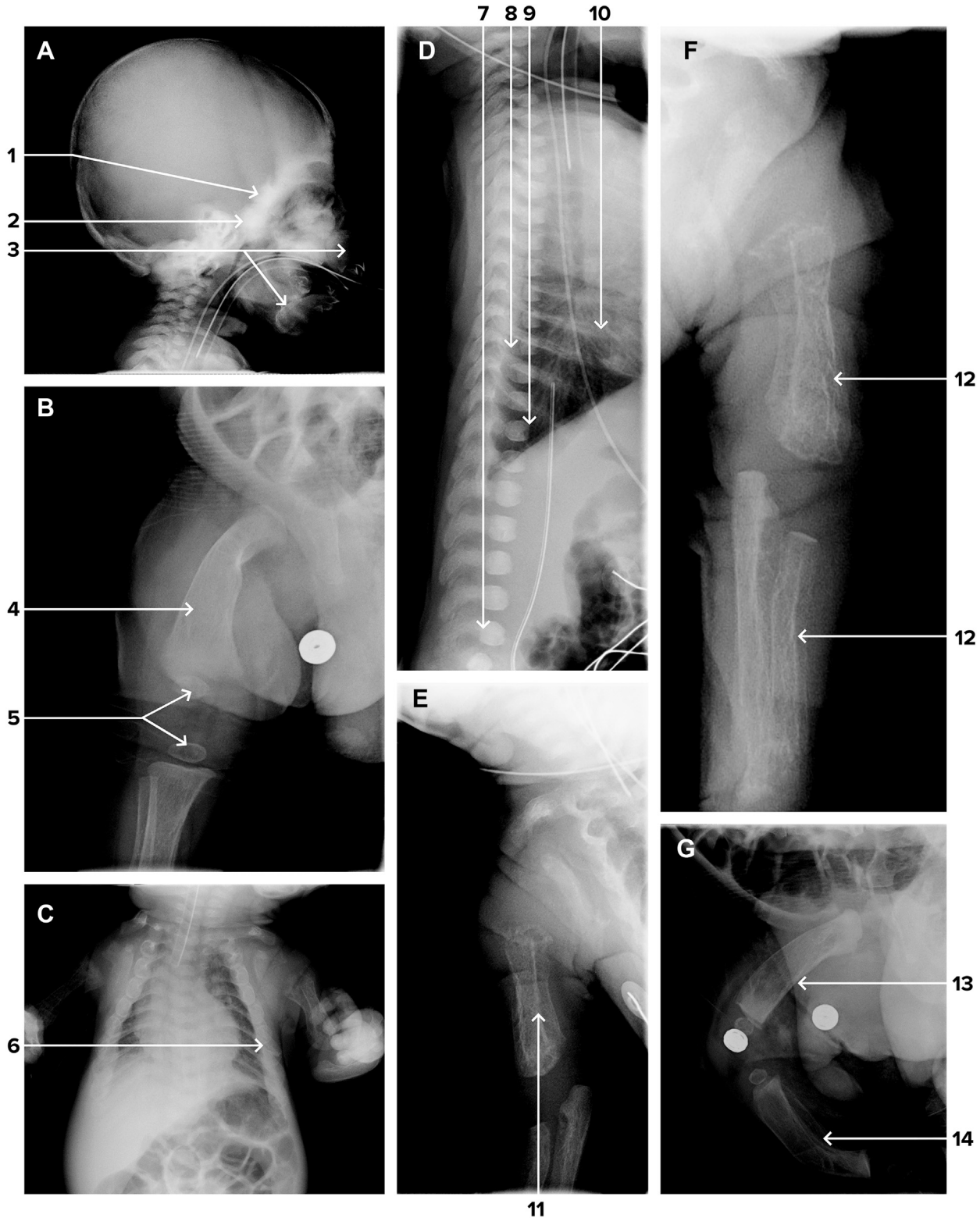

Figure. Characteristic radiologic features of mucolipidosis II alpha/beta in early infancy. **A,** Skull. 1. Abnormal sella tursica. 2. Sphenoid bones show subperiosteal bone destruction and new bone formation. 3. Osseous malformation of facial bones due to new bone formation of the mandible and maxilla with multiple un-erupted teeth. **B,** Lower limb. 4. Osteopenia/hypomineralization of the long bones femur, tibia, and fibula with metaphyseal fraying, under tubulation of the diaphyseal shafts and diaphyseal expansion. 5. Punctate calcifications (early stippled epiphyses). **C,** Chest. 6. Bell-shaped chest and pulmonary hypoplasia. **D,** Spine. 7. Early anterior beaking of the vertebral bodies (early hook shape). 8. Short anteroposterior diameter of the vertebral

bodies. 9. Biconvex upper and lower endplates, and platyspondyly (spinal bone between the chest and the abdomen). 10. Enlarged "oar-shaped" ribs with periosteal reaction. **E,** Upper limb. 11. Metaphyseal fraying and periosteal cloaking. **F,** Lower limb. 12. Hypomineralization, classic metaphyseal fraying subperiosteal bony destruction and periosteal reaction and new bone formation (periosteal cloaking), most prominent at the metaphyses of the femur. **G,** Lower limb. 13. Hypomineralization, classic metaphyseal fraying subperiosteal bony destruction and periosteal reaction, and new bone formation (periosteal cloaking), most prominent at the metaphyses of the femur. 14. Anterior convex bowing deformity of the distal tibia.

Cyst-Like: An Incongruent Chest Radiograph

A 10-month-old boy was admitted with cough and fever despite a course of oral antibiotics. Oxygen saturation was normal in air. There were reduced breath sounds posteriorly on the left side of the chest, with normal percussion. Bowel sounds were not heard in the chest.

Chest radiography (**Figure 1**) showed an unusual multilocular cystic lesion, suggestive of bowel loops, on the left side of the chest, with lung tissue seen inferiorly and minimal mediastinal deviation to the right. This suggested a left-sided diaphragmatic hernia. Chest computed tomography (**Figure 2**) revealed a left sided cystic parenchymal lung lesion.

Congenital diaphragmatic hernia is being increasingly diagnosed antenatally. Postnatally, it can present with respiratory distress, a scaphoid abdomen, bowel sounds in the chest and abnormal chest radiograph. It occasionally presents in childhood with respiratory or abdominal symptoms.[1] The differential diagnosis includes congenital cystic adenomatoid malformation, bronchogenic cyst, pulmonary sequestration, or necrotizing staphylococcal pneumonia. Congenital thoracic malformations are usually smaller with later presentation or, if extensive, evident from birth or antenatally. Children with staphylococcal pneumonia would be very ill.

Open lobectomy and histology (**Figures 3** and **4**) revealed the rare primary neoplasm pleuropulmonary blastoma (PPB), type II. The 3 histological subtypes of PPB correlate with age of presentation and long-term outcome.[2] Type I has multiloculated cysts with thin septa. Types II and III are very aggressive, with cystic and solid components in type II and only solid components in type III, in which survival is the lowest.[3] In 25% of cases PPB is associated with a germline loss-of-function (non-sense) mutation in the *DICER1* gene on chromosome 14q32, for which this patient tested positive. A second tumor-specific missense mutation in the RNase IIIb domain may also be present, for which this patient was not tested. Patients with the *DICER1* mutation and their families should have surveillance for PPB, thyroid nodules and tumors, germ cell tumors in females, Wilms tumor, and retinoblastoma.[4,5]

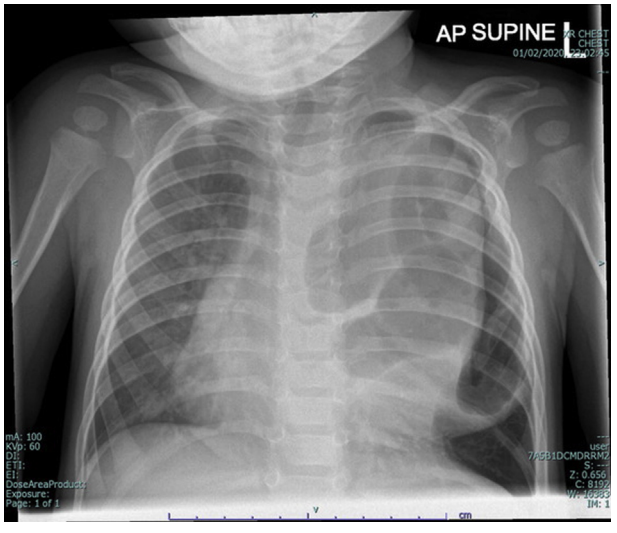

Figure 1. Chest radiograph showing the unusual cystic lesion.

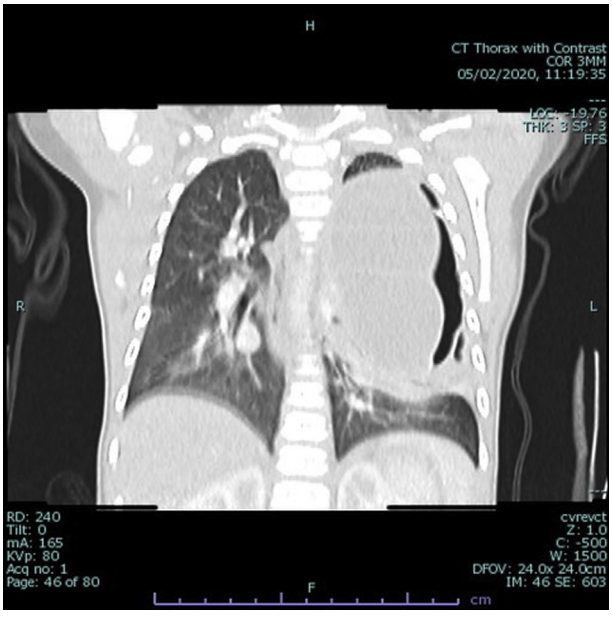

Figure 2. Computed tomography scan of the chest showing a large multiloculated fluid-filled mass within the left hemithorax causing mediastinal deviation to the right.

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