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CASE REPORT

Severe tracheobronchial stenosis and cervical vertebral subluxation in X-linked recessive chondrodysplasia punctata

Gerhard S. Mundinger · Clifford Weiss · Elliot K. Fishman

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Abstract Radiologic manifestations of X-linked chondrodysplasia punctata (CDPX1) typically include chondrodysplasia, epiphyseal stippling, punctate calcification of cartilage, distal phalangeal hypoplasia, and nasal/midface hypoplasia. We present an infant with CDPX1 demonstrating calcification and stenosis of the entire trachea and mainstem bronchi, as well as possible anterior C1 subluxation due to progression of congenital vertebral dysplasia.

Keywords X-linked chondrodysplasia punctata · CDPX1 · Tracheal stenosis · Vertebral dysplasia

Introduction

Chondrodysplasia punctata (CDP) is a generic term for a group of skeletal dysplasias of varying genotypic and environmental etiology characterized by stippled epiphyses during infancy [1]. The X-linked recessive form of chondrodysplasia punctata (CDPX1) is caused by a defect in the vitamin K-dependent enzyme arylsulfatase E [2]. Manifestations typically include chondrodysplasia, epiphyseal stippling, punctate calcification of cartilage, distal phalangeal hypoplasia, nasal/midface hypoplasia, and mixed hearing loss [2, 3]. In this report we present a male infant with CDPX1 demonstrating typical radiologic manifestations of the disease. Additionally, this patient exhibited severe calcification and stenosis of the entire trachea and mainstem bronchi, and developed probable anterior subluxation of C1 relative to C2 due to progression of congenital vertebral dysplasia.

G. S. Mundinger (✉)
Division of Plastic, Reconstructive, and Maxillofacial Surgery,
Johns Hopkins Hospital,
601 N. Caroline St., JHOC 8-152,
Baltimore, MD 21287-0006, USA
e-mail: gsm@jhmi.edu

C. Weiss · E. K. Fishman
The Russell H. Morgan Department of Radiology and
Radiological Science, Johns Hopkins Hospital,
600 North Wolfe Street,
Baltimore, MD, USA

Case report

A male infant was delivered at 34 weeks' gestation via cesarean section. His mother had no exposure to warfarin or hydantoin during pregnancy. At the time of birth, the infant was noted to have nasomaxillary hypoplasia, short fingers, noisy breathing and occasional oxygen desaturations not requiring intubation. The infant failed his newborn hearing screen. His family history was notable for mixed hearing loss and nasomaxillary hypoplasia in a brother, as well as short stature in his mother. A conventional radiograph shortly after birth revealed diffuse calcification of the trachea and bronchi (image not available).

At 5 months of age, the child presented to the emergency department with acute worsening of fixed biphasic stridor. Admission films demonstrated diffuse calcification of the epiglottis, larynx, hyoid bone, cricoid, and thyroid cartilages (Fig. 1). Extensive tracheal calcifications extended through the bronchial tree. CT revealed a severely and diffusely stenotic trachea with a minimum diameter of 1.3 mm and a maximum diameter of 3.5 mm immediately superior to the carina. His mainstem bronchi were also significantly narrowed due to extensive calcification, with diameters of 2.0–2.5 mm. Skeletal survey revealed stippled calcifications of the fingers, feet, and posterior spinal processes of the lumbosacral spine (Fig. 2). The third and fourth metacarpals were somewhat shortened bilaterally,

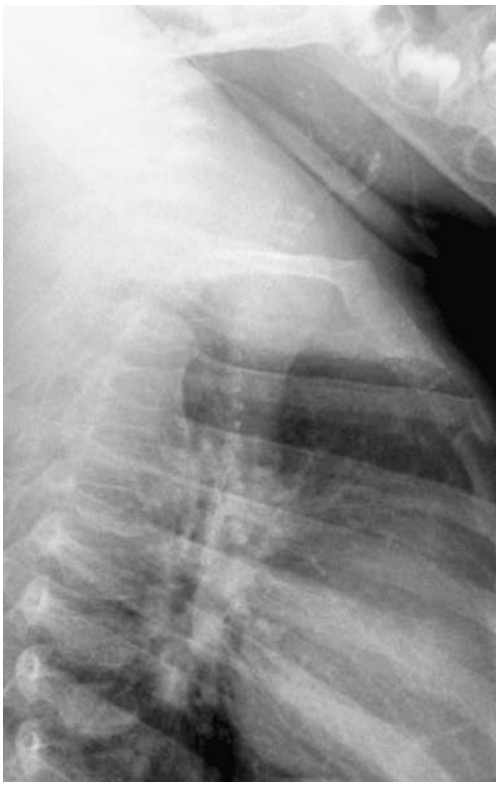

Fig. 1 Lateral radiograph of the chest at 17 months demonstrates diffuse calcification of the tracheal cartilage, hyoid bone and larynx

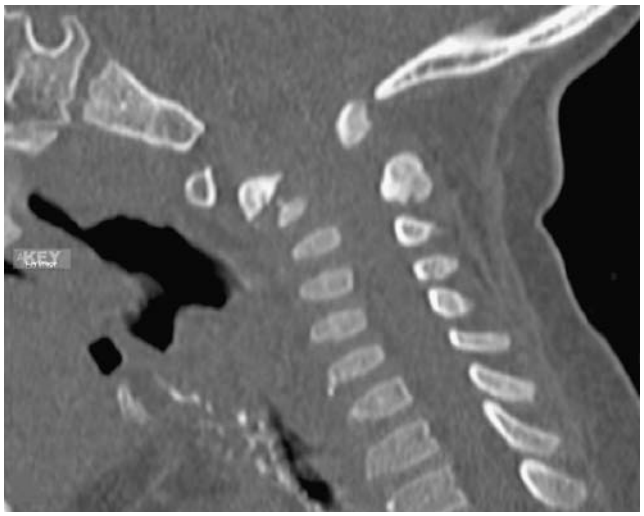

Fig. 3 CT of the cervical spine at 2 years of age. Sagittal multiplanar reconstruction demonstrates hypoplasia of the C2 vertebral body, a dysplastic dens, and possible anterior subluxation of C1 relative to C2. Dysplastic vertebral bodies are also evident

and an unusual configuration of the proximal right middle metacarpal was evident. Hypoplasia of the cervical vertebral bodies was also present. No vertebral subluxation was evident at this time. Cardiac and renal US was unremarkable. During admission, the patient improved with intravenous steroids, racemic epinephrine, and supplemental oxygen. The child's mother decided against surgical intervention for tracheal stenosis.

A repeat thoracic CT scan was performed during admission at 2 years of age. While the extent of tracheal calcification appeared stable, areas of atelectasis were now noted in the right middle lobe, and the tracheal diameter was nearly identical to measurements taken at 5 months of age. Cervical spine films revealed marked increase in prevertebral soft tissue, and suggested os odontoidum with possible anterior subluxation of the anterior arch of C1 over the body of C2. A CT scan of the cervical spine during admission 1 month later demonstrated C2 vertebral body hypoplasia, a dysplastic dens with hypoplasia of the mid and apical portions, and probable anterior subluxation of C1 relative to C2 (Fig. 3). No neurologic symptoms were evident on physical examination.

A the time of this report at 3 years of age, the child continues to be admitted periodically for stridor exacerbations due to the extent of his airway disease (Fig. 4). He does not display any neurologic symptoms. Surgical

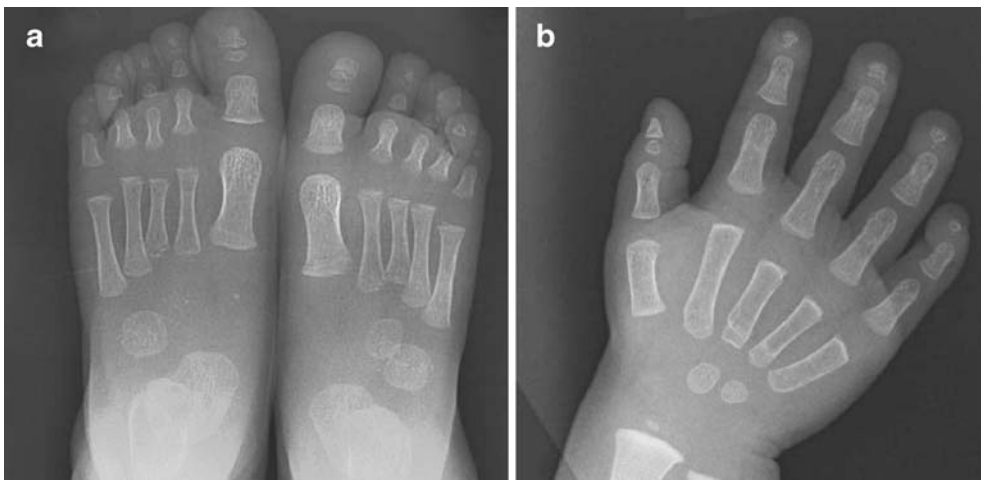

Fig. 2 Skeletal survey radiographs at 20 months demonstrate stippled calcifications in the soft tissues surrounding the (**a**) tarsal bones and distal phalanges of the feet as well as (**b**) shortening of the second and third metacarpals and distal phalanges. Epiphyses are generally normal in appearance in this patient with none of the blotchy stippling noted in some chondrodysplasia punctata subtypes

intervention to correct tracheal stenosis or stabilize the cervical spine has been avoided given the low likelihood of successful intubation due to extensive airway calcification.

Discussion

CDPX1 (also known as brachytelephalangic chondrodysplasia punctata) is a rare congenital disorder caused by a defect in the vitamin K-dependant enzyme arylsulfatase E, localized to the Xq22.3 locus [2]. CDPX1 is grouped with other rare genetic and acquired disorders that similarly display punctate calcific depositions ("stippling") in areas of enchondral bone formation. CDP is the umbrella term used to refer to these osteochondrodysplasias collectively. Specific genetic entities composing CDP include CDPX1, rhizomelic or autosomal recessive CDP (RCDP), X-linked dominant CDP (CDPX2, also known as Conradi-Hünermann syndrome), Smith-Lemli Opitz syndrome (SLOS), and congenital hemidysplasia, ichthyosis form erythroderma, limb defects syndrome (CHILD syndrome) [2, 3]. Additionally, Keutal syndrome, a rare disorder of glutamic acid protein modification, can cause prominent, diffuse calcification of the epiglottis, nose, larynx, tracheobronchial tree, and cerebrum [3]. Fetal exposure to warfarin and hydantoin, congenital vitamin K deficiency, and maternal systemic lupus erythematosus are recognized acquired causes of CDP [3]. As no biochemical or molecular testing is currently available to detect arylsulfatase E deficiency, CDPX1 remains a clinical diagnosis. Our patient's physical and radiographic findings, sex, family history, and prenatal history were all consistent with a diagnosis of CDPX1 [3].

While our patient displayed the radiographic findings of diffuse cartilaginous stippling and distal phalangeal hypoplasia

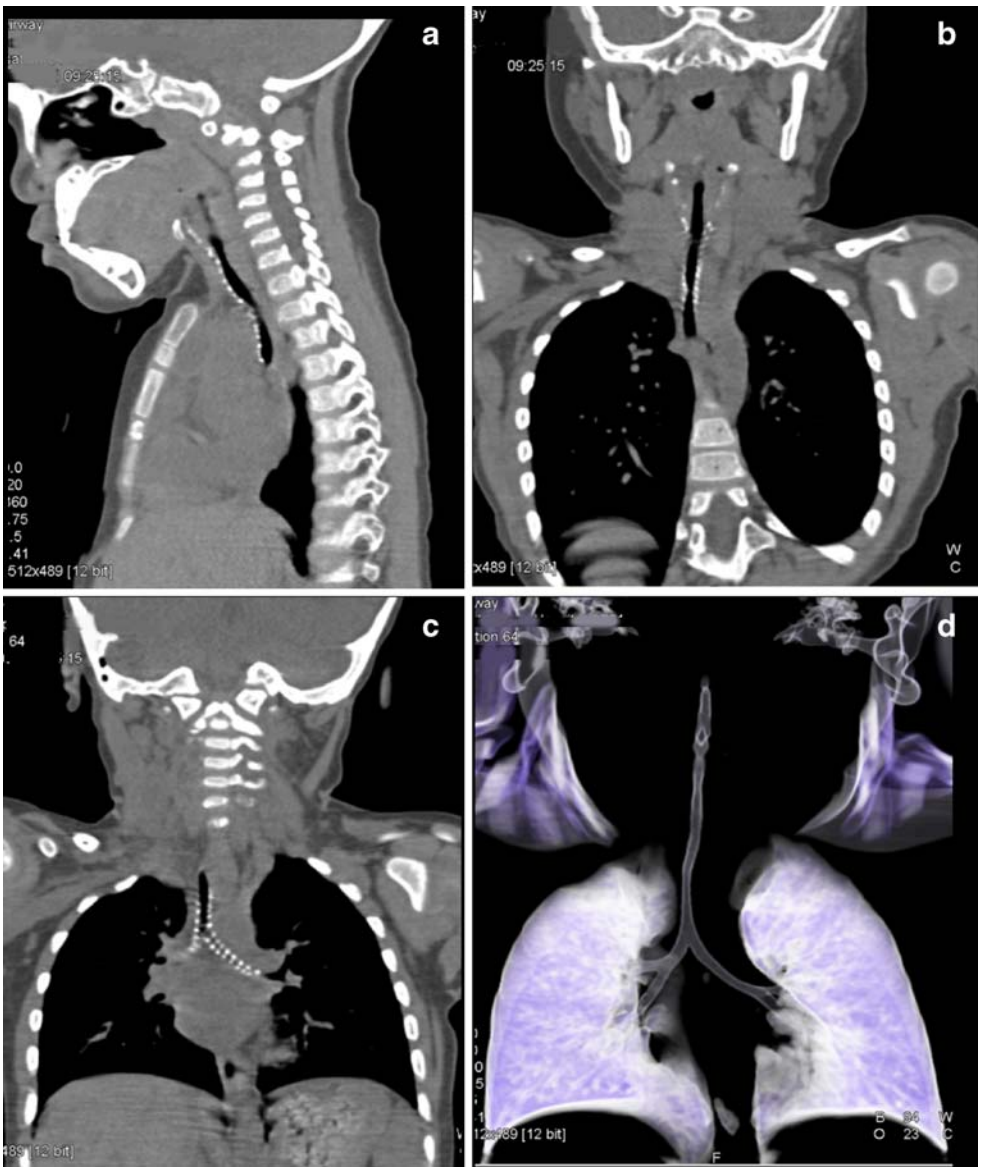

Fig. 4 CT of the chest at 3 years of age. Sagittal (**a**), coronal multiplanar (**b**, **c**) and volume-rendered (**d**) reconstructions reveal a severely stenotic and diffusely calcified airway

typical of CDPX1, the associated findings of extensive tracheobronchial calcification and cervical vertebral dysplasia are unusual.

The severity and anatomic extent of tracheal and mainstem bronchial calcification present in this patient is atypical for CDPX1. Three children with CDP of unknown etiology and tracheal stenosis due to extensive calcific deposition have been previously described [4]. Airway calcification progressed over time in all three children, requiring tracheostomy in one child, and only one child appeared to have normal tracheal growth. A variety of surgical options for correction of tracheal stenosis exist, but would likely not be successful in our patient due to the severity and extent of airway calcification precluding successful intubation [3].

Attempts to categorize spinal abnormalities in CDP have been complicated by lack of resolution in associating specific etiologies of CDP with observed spinal anomalies. A retrospective study of 20 patients with CDP identified three types of spinal deformity: C2 basal dens disruption, slowly progressive scoliosis, and rapidly progressive dysplastic kyphoscoliosis [1]. This study was unable to correlate these three types of spinal deformity with specific genetic or environmental causes of CDP, as the etiology of CDP in each patient was unknown. Our patient had a cervical anomaly similar to the C2 basal dens disruption described in one patient in this series. This child was successfully treated at 1.6 years of age with occiput to C2 posterior arthrodesis with Minerva casting. Unfortunately, it is not possible to discern whether atlantoaxial anomalies should be considered a more common feature of CDPX1 than previously thought, as the specific etiology of CDP for each patient in this series was unknown.

Four articles have reported congenital cervical spinal stenosis in patients with CDXP1 [5–8]. Cord compression appears to fall into two groups, with compression occurring either at the atlantoaxial level or lower in the cervical column. Cervical spinal cord compression at the C1 level was generally diagnosed via prenatal or perinatal imaging [5, 6]. One patient presented at 3 months of age [8]. In all patients cervical stenosis at the atlantoaxial level was due to bone dysplasia and heterogeneous bone formation, except in one patient in whom atlantoaxial dislocation was diagnosed 3 days after birth and was fatal at 3 months [6]. The worsening of cervical spine alignment in our patient is consistent with the findings of Mason et al. [1], who concluded that spinal anomalies in CDP patients tend to progress, requiring repeated surgical correction.

In summary, we describe the unusual findings of severe tracheobronchial calcification and accompanying airway stenosis, as well as progressive C1-C2 anomalies resulting from congenital cervical vertebral dysplasia in a patient with CDPX1. Further investigation addressing anatomic anomalies in patients with CDP, their progression, and successful means of treatment is needed to determine whether these manifestations of CDPX1 are more common than our report suggests. Specifically, CDP patients need to be evaluated by etiologic subgroup. This determination will be aided by advances in the molecular characterization of patients with CDP [2]. Radiographic recognition of CDPX1 and cognizance of its complications can facilitate prompt, appropriate treatment of CDPX1 patients.

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