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Case Report

Schmid metaphyseal chondrodysplasia: an example of radiology guidance to molecular diagnosis ☆☆☆

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ABSTRACT

Schmid metaphyseal chondrodysplasia is a rare genetic cause of skeletal dysplasia. Patients usually present skeletal abnormalities but no major visceral malformations or intellectual disability. We report a case of a 2-year-old male patient with short stature, progressive *genu varum*, and waddling gait. Radiographic findings were essential to guide investigation and molecular confirmation, allowing proper treatment and genetic counseling.

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Introduction

Schmid metaphyseal chondrodysplasia (SMC) is a rare cause of skeletal dysplasia [1]. It is a genetic disease and radiological findings are essential to guide the investigation and diagnosis. The disorder is characterized by short stature, *genu varum*, and waddling gait that develop along the first years of life. Bone abnormalities are progressive and joint pain is common. Skeletal manifestation can cause motor developmental delay and limit physical activity. Intellectual disability, dysmorphic features,

macrocephaly, and extraskeletal anomalies are absent. We report a case of SMC caused by a novel pathogenic variant in gene *COL10A1*. Appropriate diagnosis of skeletal dysplasias is essential for genetic counseling and treatment [2].

Case report

A 2-year-old male patient was evaluated at the Medical Genetics Center after referred by orthopedist due to bilateral *genu*

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Fig. 1 – Pelvis and lower limbs radiograph shows bowing femurs and tibiae, large capital epiphyses and short femoral necks. All growth plates of tubular bones are wide. Metaphysis present beak aspect mainly in the medial portions of the extremities. Metaphyseal ossification appears markedly disrupted.

varum. He was the only child of a nonconsanguineous couple. The familial and gestational history were unremarkable, except for maternal hypothyroidism, properly treated during pregnancy. The findings of an obstetric ultrasound captured at the 38th week gestational age displayed a short femur. He was delivered by vaginal birth, at the 39th week gestational age, with 9 and 10 Apgar score at 1' and 5', respectively. His neonatal measurements were normal – weight 3150 g (25th–50th percentile), length 48 cm (10th–25th percentile), and head circumference 34 cm (percentile 25th–50th percentile). Patient was diagnosed with distal hypospadias at birth and no limb deformities were evident. After 10 months parents noticed bowing legs, that progressed during the following years. At 20 months of age patient underwent surgical correction for hypospadias.

On first physical exam patient presented 13 kg weight (25th–50th percentile), 81cm height (<3rd percentile) and 49 cm head circumference (25th percentile). He also had mild rectus abdominal diastasis and signs of corrected hypospadias, without any dysmorphic features. The disproportionate short stature was also evident due to rhizomelic shortening. Global development was normal for his age.

Patient initiated investigation with blood tests (complete blood count, electrolytes, thyroid function, parathyroid function, 25-OH vitamin D, IGF-1, and IGFBP-3 serum levels), hand and wrists radiographs in order to calculate bone age, karyotype, echocardiogram, abdominal ultrasound, and retinal



Fig. 2 – Upper limbs radiograph presents distal and proximal humeral metaphyseal ossification markedly disrupted. Tubular bones are short and enlarged. There are mild metaphyseal irregularities of the radius and ulna.

mapping. All of them showed normal results. A full skeletal radiography was also performed. Skull and thorax radiographs showed no significant abnormalities. Spine and pelvis radiographies presented mild accentuation of lumbar lordosis, horizontalization of the sacrum, and coxa vara (Fig. 1). Limbs images demonstrated short limbs with rhizomelia, bilateral femoral, and tibial bowing, generalized enlarged metaphyses, enlarged humerus, short and broad middle falanges, and generalized reduced bone density (Fig. 2).

Based on clinical and radiological presentation, the main hypothesis was SMC. To elucidate the diagnosis patient Sanger sequencing of gene *COL10A1* was performed. This molecular test identified a novel heterozygous frameshift variant: NM_00493.4(*COL10A1*):c.1900del;p.(Asp634Ilefs*43). According to the American College of Medical Genetics and Genomics guidelines, this variant is classified as pathogenic and establishes molecular confirmation of SMC.

During follow-up, patient underwent bilateral tibial osteotomy at 4 years of age. Hormone growth therapy was contraindicated. Currently, patient maintains normal global development and short stature. Diagnosis allowed appropriate genetic counseling and surveillance, according to guidelines and scientific literature information.

Discussion

SMC was first described by Stephens in 1943 [3]. Although the author reported a large family with radiological features of SMC, he wrongly attributed the diagnosis of achondroplasia at that time. In 1967, Silverman and Brunner published an ar-

ticle pointing mistakes in skeletal dysplasias diagnosis and Stephens initial publication was highlighted as a case of SMC. The original case outlining a novel condition was written in 1949 by Schmid. Later in 1993, Warman identified that mutations in collagen X were the molecular basis for SMC [4–6].

During some years, spondylometaphyseal dysplasia Japanese type (SDJT) was considered an entity apart from SMC. Although both shared limb anomalies, spinal affection was considered a particularity of SDJT. In 2000, Savarirayan et al suggested that SDJT and SMC were the same condition. Spinal alterations were less frequent and probably underestimated, but could be found also in SMC [7]. Currently, both are considered the same pathology and spine changes are considered part of SMC phenotype.

SMC is a type of skeletal dysplasia caused by heterozygous pathogenic variant on *COL10A1* gene. It is a genetic disease inherited in an autosomal dominant manner. The prevalence is estimated as 3-6:1.000.000. Penetrance is considered complete and expressivity is variable [8].

According to Lachman et al, the most important imaging findings are mild hypoplasia and/or acetabular roof irregularity, coxa vara, femoral bowing, enlarged capital femoral epiphyses, and abnormal proximal and distal femoral metaphyses [9]. Less common are proximal tibial metaphyseal abnormalities and wrist metaphyseal changes. Tibial and fibular bowing can also be observed. Currently, it is also known that mild platyspondyly and endplate irregularity can occur. Signs of osteoarthritis are absent. Hand abnormalities such as metaphyseal cupping and short middle phalanges are less frequent [8,9].

During skeleton formation, endochondral ossification is an essential process, in which bone substitutes calcified cartilage. During normal circumstances, chondrocytes undergo a proliferative, a hypertrophic and a degenerative phase, sequentially. At second stage, type X collagen (XC) is highly express.

COL10A1 is the gene which encodes XC. It is located on chromosome 6 (cytogenetic location: 6q22.1) and contains 3 exons. Each XC molecule has 2 terminal domains (NC1 and NC2), the main triple helical domain and a signal peptide. XC molecules are organized in triplets and secreted by hypertrophic chondrocytes of growth plate cartilage into extracellular matrix [10].

Warman et al identified that pathogenic variants in type X collagen (XC) were responsible for the development of SMC in patients [6]. More recently, Bateman reported that XC haploinsufficiency is probably the main mechanism of pathogenicity. The author suggests that specific-tissue nonsense-mediated mRNA decay occurs. It causes complete mutant XC mRNA degradation in cartilage and leads to loss of regular endochondral ossification [11].

Follow-up of patients diagnosed with SMC must include a multiprofessional healthcare team. At the moment, curative treatment is not available. Surgical intervention (osteotomy) might be considered with progressive and/or symptomatic deformity, in order to preserve function and avoid pain. Physiotherapy and occupational therapy are also indicated to rec-

ommend joint-friendly exercises and adapted environment for short stature. Patients also may benefit from psychological support [2].

Genetic counseling is essential for family planning. Each affected patient has 50% chance of having an affected child. It is important to highlight that members of the same family could have more subtle or exuberant phenotype, because of variable expressivity. Due to this, patient's parents must always be carefully evaluated [2].

Skeletal dysplasia is a large group of diseases and radiological findings are essential to guide proper investigation. Our case highlights that clinical findings associated with a rapid and low cost exam, such as full body radiography, guides confirmation of the molecular diagnosis and avoid unnecessary exams and prolonged investigation.

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