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Axial spondylometaphyseal dysplasia with retinitis pigmentosa —a clinical report and diagnostic clues

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Introduction

The spondylometaphyseal dysplasias (SMDs) is a large heterogeneous group of skeletal dysplasias characterized radiologically by vertebral abnormalities and metaphyseal changes in the tubular bones (Maroteaux and Spranger 1991; Taybi and Lachman 2007; Warman et al. 2011; Rimoin et al. 2007; Marik et al. 2012). There are five well-described distinct entities; these include SMD-Kozlowski (SMD-K), SMD-corner fracture type (SMD-CF), SMD-Sedaghatian, and a recently delineated SMD associated with cone-rod dystrophy (SMD-CRD; Kitoh et al. 2011). The International Skeletal Dysplasia Society Nosology Group recently included a type of SMD termed SMD with retinal degeneration, axial type. A few other forms of SMD consist mostly of single case reports. A classification of the

SMDs was attempted in the early 1990s (primarily based on severity and sites of metaphyseal changes), but it has seemed to have added little to the specific delineation of these disorders. Unless there are other clinical clues, even the concept of separating the SMDs into common, uncommon, and rare is not that helpful. Clinically, most types present in early childhood with short stature and gait problems, leading to clinical and radiological evaluation.

Here, we present the clinical and radiographic features of a patient with SMD axial type with retinal degeneration and discuss the key recognizable characteristics of this condition that should aid the clinician with a diagnosis.

Case report

This male patient was initially referred to the genetics clinic at 10 years of age for short stature, first noticed at the age of 2 years, and a rib cage deformity. He was born to a 31-year-old mother and a 45-year-old father. The parents denied consanguinity and there was no family history of skeletal dysplasia on either side. The patient had normal weight and length at birth; he met all developmental milestones appropriately and psychomotor development was normal. At the age of 10 years, the pertinent findings noted on physical examination included a height of 117.6 cm ($-3.5SD$) and an upper to lower segment ratio of 1.12 ($+2SD$). The chest examination was significant for a marked symmetrical deformity of the anterior thorax with normal sternum, “hollowing” of the ribs in the mid-parasternal region, and flaring of the lower costal margins. He was not dysmorphic and neurologic examination was normal. Color blindness and nystagmus with amblyopia were noted on ophthalmologic examination at the age of 10 years and endocrinology investigation was normal. A brain magnetic resonance imaging (MRI) scan, performed for headaches, was normal. The patient was seen again in the skeletal dysplasia clinic at the age of 14 years. At this visit, his height was 144 cm ($-3SD$), psychomotor and sexual development were normal, and no dysmorphic facial features were noted. On physical examination, scoliosis of the thoracic spine and rhizomesomelic shortening of the extremities were noted, with full range of motion in all joints. The chest deformity was unchanged. A follow up examination at the age of 16 years revealed that his height remained the same since the age of 14 years and no new physical findings were noted (Fig. 1). He continues to perform well in regular classes and reported gastrointestinal bleeding and microcytic anemia, leading to a diagnosis of ulcerative colitis.

Methods and results

Genetic evaluation

Because of the mild vertebral involvement and unusual femoral neck sclerosis, some consideration was given to the metaphyseal chondrodysplasia Shwachman–Diamond syndrome (MCD-SDS). However, sequencing analysis of the *SDS* gene did not reveal disease-causing mutations. In addition, because of the unusual thorax configuration, chromosome 14 uniparental disomy was excluded. A tentative diagnosis of unclassified spondylometaphyseal dysplasia was made.

Radiological evaluation

A complete genetic skeletal survey was obtained at 10 years of age and two views of the thorax were performed at 15 years of age. The bone survey at 10 years of age demonstrated the following findings (Fig. 2). In the thorax, the ribs were moderately short with marked anterior widening/-flaring. The spine showed mild posterior wedging of thoracolumbar vertebral bodies with mild osteopenia, but no significant platyspondyly. The hands showed marked delay (~3 years) of epiphyseal and carpal maturation. Carpal and metacarpal bones were normal. In the pelvis, the sacrosciatic notches were mildly narrowed and the acetabular roofs were poorly formed. There were unusual, irregular sclerotic lesions involving the entire neck of both femurs, including the proximal femoral metaphyses, and extending from the growth plate down to the intertrochanteric groove. The iliac wings were slightly small without a lacy pelvis, but the ischium and pubis were normal. The skull was also noted to be normal. No other long- or short-bone metaphyses or epiphyses were affected, including the proximal humeri. Repeat radiographs AP and lateral of the thorax at 15 years of age contributed no other significant findings. Due to the radiological similarities to the recently delineated axial SMD, he was further referred for a follow up ophthalmologic examination, which demonstrated secondary pigmentary degeneration of the peripheral retina in both eyes with tortuous retinal veins, consistent with retinitis pigmentosa.

Discussion

The SMDs are a heterogeneous group of disorders characterized radiographically by metaphyseal abnormalities of tubular bones and dysplasia of the spine. The progressive abnormalities lead to changes in the size and shape of the limbs and trunk, often resulting in disproportionate short stature, which is a major clinical feature of SMDs. The classification of the SMDs is still limited to the characteristics of the clinical and radiographic features. An exception is SMD-Kozlowski type, an autosomal dominant condition, for which the molecular defect in TRPV4 has been discovered. SMD can occasionally be associated with extra-skeletal abnormalities. The patient reported here presented with early-onset postnatal short stature with a peculiar chest deformity and progressive retinal dystrophy that was only identified at the age of 16 years, supporting a diagnosis of SMD axial type with retinal degeneration (Krakow et al. 2009; Isidor et al. 2010). Suzuki et al. (2011) have recently delineated the phenotype of axial SMD in seven individuals. The radiological hallmarks include short ribs with flared, cupped anterior ends, mild vertebral changes, infrequent lacy iliac crests, and metaphyseal irregularities essentially confined to the proximal femurs. Clinically, these patients have postnatal growth failure, rhizomelic short stature in early childhood evolving into short trunk short stature in late childhood, and thoracic hypoplasia/dysplasia that could potentially cause mild to moderate respiratory problems in the neonatal period and later susceptibility to airway infection. Axial SMD shares some similar radiographic features with Shwachman–Diamond syndrome (SDS). Patients with SDS can exhibit mild vertebral abnormality (usually square vertebral bodies; Nishimura et al. 2007). This was noted in our case and in at least one of the patients described by Suzuki et al. (2011); this patient received initially a tentative diagnosis of SDS. However, clinically, patients with SDS should have evidence of pancreatic insufficiency or hematological

abnormalities (cytopenia of at least one lineage) that are required for establishment of the clinical diagnosis.

In axial SMD, impaired visual acuity comes to medical attention in early life and function rapidly deteriorates. Retinal changes are diagnosed as retinitis pigmentosa or pigmentary retinal degeneration on fundoscopic examination. It is unclear as to whether SMD with cone-rod dystrophy is a separate or allelic entity (the radiographic changes are much more severe). Suzuki et al.'s report includes an equally affected sibling pair of opposite gender and parental consanguinity, suggestive that axial SMD is recessively inherited (Suzuki et al. 2011). Notably, although the patient reported here was closely followed for color blindness, nystagmus, and amblyopia since the age of 2 years, clinically apparent retinal changes were identified only at 16 years of age, leading to the clinical diagnosis. In previous reports, retinitis pigmentosa was diagnosed as early as in the neonatal period (age 3 weeks; Suzuki et al. 2011) and up to 9 years of age; a few of the reported patients ultimately became blind (Krakow et al. 2009; Isidor et al. 2010).

Retinitis pigmentosa is a heterogeneous group of inherited—syndromic and non-syndromic—disorders in which abnormalities of the photoreceptors (rods and cones) of the retina lead to progressive visual loss. A common initial symptom of retinitis pigmentosa often observed during childhood or adolescence is “night blindness” and a correlation between the age of night blindness onset to the severity of retinitis pigmentosa has been suggested. The genetics of retinitis pigmentosa is very complex, with more than 40 genes and loci involved and all modes of inheritance. Further complicating the genetics of retinitis pigmentosa is the observation that up to 50 % of patients are single cases in their family, with an unknown mode of inheritance (Pagon et al. 2005). Recently developed technologies have facilitated the ability to identify genes for recessively inherited skeletal dysplasia using identity-by-descent mapping and next-generation sequence analysis using small numbers of consanguineous families, and even in a single patient. However, in most cases, performing exome sequencing on multiple family members may increase the likelihood of finding disease-causing mutations. Unfortunately, in this case, DNA is not available for additional investigation. Further gene analysis studies in larger cohorts of axial SMD patients are most likely underway. Gene identification will promote our understanding of this condition and allow the development of diagnostic guidelines for axial SMD that are based also on molecular testing. In conclusion, we present the clinical and radiographic features of a recently delineated skeletal dysplasia termed axial SMD with retinal dystrophy. Recognition of the key clinical (short stature and impaired visual acuity) and radiographic (short ribs, mild spondylodysplasia, and femoral neck sclerosis) features will facilitate early diagnosis and appropriate intervention in the pediatric patient. Any patient with this constellation of findings should have repeated in-depth ophthalmologic examination.

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Fig. 1. Clinical features of the patient with axial spondylometaphyseal dysplasias (SMDs) and retinal dystrophy at the age of 16 years: **a** lateral; **b** front; **c** back views. Note short stature and trunk, and symmetrical deformity with mild narrowing of the anterior thorax

Fig. 2.

Radiological features of the patient with axial SMD and retinal dystrophy at the age of 10 years. **a** AP view of the pelvis and hips: marked sclerosis of the entire femoral neck extending from the growth plate to the intratrochanteric groove. Mild acetabular roof hypoplasia and sacrospinous notch narrowing. **b** Lateral view of the thoracolumbar spine: mild osteopenia with posterior notching/wedging of multiple vertebral bodies. **c** Lateral view of the thorax: markedly splayed anterior rib ends and abnormal posterior course of ribs extending from their articulations with vertebrae. **d** AP view of the upper T-spine: marked angulations of posterior rib articulations, which are also separated from the vertebrae