

Three Cases of Spondyloepiphyseal Dysplasia Tarda in One Korean Family

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Spondyloepiphyseal dysplasia (SED) tarda is an inherited skeletal arthropathy. Because SED tarda involves the joints and resemble the clinical findings of chronic arthropathies, this disease is frequently misdiagnosed as juvenile idiopathic arthritis (JIA). We report here on three patients (father and his two daughters) in one family with SED tarda. All patients had back pain and polyarthralgia. Their radiographs revealed typical changes for SED tarda including platyspondyly and dysplastic bone changes. This rare disease has major clinical importance in that it is similar with JIA or rheumatoid arthritis.

Key Words: Spondyloepiphyseal dysplasia tarda, platyspondyly, progressive arthropathy

INTRODUCTION

The spondyloepiphyseal dysplasia (SED) tarda is a hereditary skeletal dysplasia caused by genes involved in bone growth and cartilage maintenance. This disease is characterized by platyspondyly and enlarged long bones due to the abnormal enchondral ossification in the vertebral bodies and proximal epiphyses of long bones. Progressive degeneration of articular cartilage and premature osteoarthritis is observed in multiple joints including shoulders, hips, and knees. Various enchondral growth centers of peripheral joints are affected to a similar deformity seen in rheumatoid arthritis (RA).¹ Thus, SED tarda is often mistaken as juvenile idiopathic arthritis (JIA). However, it differs from inflammatory arthritis by the absence of synovitis or other inflammatory changes. Furthermore, the disorder does not respond to anti-rheumatoid treatment.²

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A few cases of SED tarda have been described. We describe clinical and radiological findings of a family whose members are a 49-year-old father misdiagnosed as having RA, and his two daughters who had musculoskeletal features similar to those of their father.

CASE REPORT

A 49-year-old man visited the orthopedics clinic in our hospital for paraesthesia and radiating pain in all four extremities. He was scheduled to undergo decompression surgery for radiculopathies attributed to cervical spinal stenosis. Because he had been taking disease modifying antirheumatic drugs (DMARDs) for RA for the past 6 years, he was referred to the rheumatology clinic for preoperative evaluation.

He had pain and swelling in knees since teenager, and was diagnosed as having JIA. At the age 19, total hip replacement arthroplasty was performed on both hips. He started on DMARDs including methotrexate at the age of 43. At admission, his stature was 164 cm and walked on clutches due to radiculopathic pain and knee stiffness. On physical examination, bony swelling was observed on bilateral metacarpophalangeal joints and proximal and distal interphalangeal joints. Range of motion was limited in cervical spine, shoulders, elbows, and wrists. Laboratory examinations including complete blood count,

erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (anti-CCP), and antinuclear antibody (ANA) showed normal results. Lumbar spine X-ray showed flattened vertebral bodies (platyspondyly) with biconcave deformities (Fig. 1A). Osteoarthritic changes such as joint space narrowing, extensive osteophytes, and/or loose bodies were observed in all involved joints including shoulders, wrists, and knees (Fig. 2). Hand X-ray showed widened epiphyses of phalanges and periarticular osteoporosis (Fig. 2C).

Posterior decompression at multiple levels of cervical spine was performed. During surgery, hypertrophic bony spur at C1-2 was observed. Histologic examination of removed bone

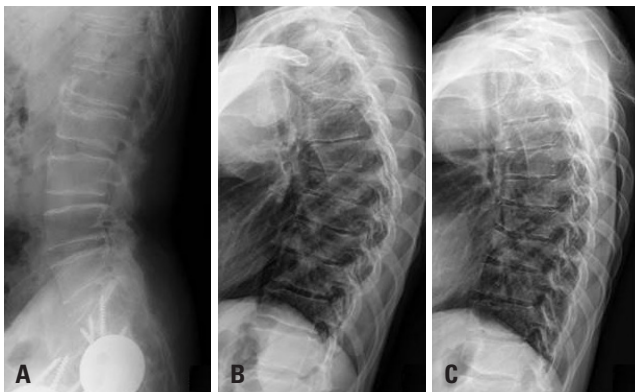


Fig. 1. Lateral view of the thoracic and lumbar spine. (A) Case 1, (B) case 2, (C) case 3. All radiographs revealed to characteristic platyspondyly.

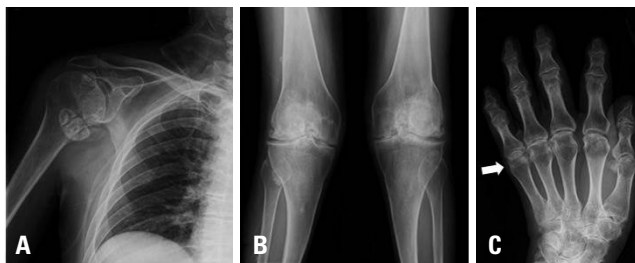


Fig. 2. Osteoarthritis of involved joints including shoulder (A), knee (B) with extensive osteophytes and loose bodies. Widening of the epiphyses of the phalanges and periarticular osteoporosis (white arrow, C).

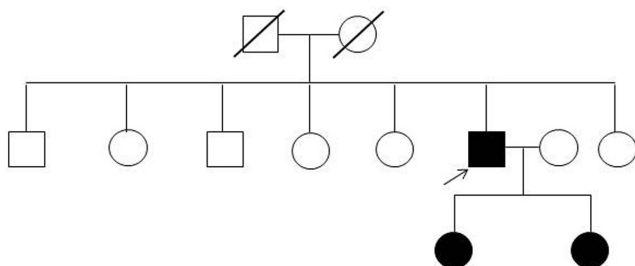


Fig. 3. The pedigree of the family. Black symbols denote affected subjects. The arrow indicates the current case (49-year-old man). All open boxes represent healthy males and open circles represent healthy females. Boxes or circles with a diagonal line indicate that the person has already died.

showed woven bone formation with granulation tissue. Based on the radiographic and clinical findings, the patient was diagnosed as having SED tarda rather than JIA. Nonsteroidal anti-inflammatory drugs and a physiotherapy program were planned. He has been followed up at our outpatient clinic and his symptoms has waxed and waned.

His parents had no medical history of arthropathy, and died at seventh decades. He had two brothers and four sisters, none of whom had arthropathy. However, his two daughters had the similar phenotype: clinical and radiological evaluations of his daughters revealed that they had SED tarda, too. The pedigree of our patient is shown in Fig. 3.

A 20-year-old woman, the older daughter of the first case, visited our hospital with pain in hips, knees, and lower back. On physical examination, limited range of motion was noted in the hips. Laboratory examinations showed normal findings. X-ray images revealed platyspondyly (Fig. 1B), and deformed hips and knees with degenerative changes.

A 18-year-old girl, the younger daughter of the first case, had suffered from both knee pain for the last 10 years. Physical examination showed limited range of motion in hips and knees. Laboratory findings were within normal limits. Radiographic findings showed platyspondyly (Fig. 1C), and degenerative change of all involved joints. Two daughters were diagnosed as having SED tarda.

DISCUSSION

SED is a rare genetic disorder with an incidence of 1 to 4 per million population. In general, SED is divided into two major types; SED congenita and SED tarda, according to the onset age and clinical severity.³ SED congenita shows autosomal dominant inheritance, neonatal onset, and more obvious short-trunk dwarfism compared with SED tarda. In contrast, SED tarda is inherited as either X-linked, autosomal dominant or autosomal recessive.^{4,5} In SED tarda, symptoms are noted in childhood and progressive arthropathy is a common presentation. There is only mild shortening of the trunk.

Autosomal dominant SED tarda is caused by mutations in the gene encoding the type II procollagen α -1 chain (COL2A1). These mutations may produce an abnormally short pro-alpha 1 (II) chain or an incorrect amino acid substitution in the pro-alpha 1 (II) chain. These changes affect the immature formation of triple-stranded type II collagen molecules, which results in autosomal dominant SED.⁶

X-linked SED tarda is caused by mutations of the TRAPPC2 gene.⁷ TRAPPC2 gene is localized in Xp22 and encodes putative 140 amino acid protein (Sedlin).⁸ TANGO1 assists procollagen packing by recruiting Sedlin. This joint action of TANGO1 and Sedlin sustains the ER export of procollagen, and its derangement may explain the defective chondrogenesis underlying SED tarda.^{9,10}

Table 1. Case Reports of Spondyloepiphyseal Dysplasia Tarda in Korea

Authors	Age (yrs)	Gender	Onset time	Symptoms	Radiographic findings	Genetic test	Pedigree analysis
Oh, et al. ¹³	29	M	12-yrs-old	Back pain, both ankle pain	Platyspondyly, severe OA in both hip joints	No	No
Ryu, et al. ¹⁴	14	M	Late childhood	Disproportionately short stature	Platyspondyly, flattend femoral head	TRAPPC2	Five males on maternal side were affected
Kim, et al. ¹⁵	15	M		Disproportionately short stature, barrel shaped chest	Platyspondyly, flattened femoral head	TRAPPC2	Mother was a heterozygous carrier
Current case	49	M	Teenager	Radiating pain in four extremities, knee stiffness	Platyspondyly, severe OA in shoulders, wrists, hands, knees, ankles	No	Two daughters were affected
	20	F	Teenager	Lower back pain, hip and knee pain	Platyspondyly, OA in hips and knees	No	
	18	F	Teenager	Both knee pain	Platyspondyly, OA in hips, knees, and shoulders	No	

OA, osteoarthritis.

Autosomal recessive SED tarda is attributed to loss-of-function mutations of Wnt1-inducible signaling pathway protein 3 (WISP3) gene located on chromosome 6q22.¹¹ WISP3 up-regulates the expression of the cartilage specific gene encoding type II collagen (COL2A1) and aggrecan in chondrocytes, and is an important molecule in the regulation of cartilage homeostasis.¹²

In the family reported herein, none of the parents or siblings of the case showed any sign of SED tarda. The pedigree seen in Fig. 3 makes us suspect three types of inheritance; autosomal recessive, X-linked or sporadic autosomal dominant mutation of the current case. However, we could not perform the genetic test for this family.

The exact prevalence of SED tarda in Korea is unknown. Only three SED tarda cases were reported in Korea prior to this current case. One case was misdiagnosed as having ankylosing spondylitis, after radiographic evaluations, SED tarda was diagnosed clinically, but without genetic testing.¹³ Genetic test was performed in the other cases, and they were reported as X-linked inheritance by the identification of a TRAPPC2 mutation.^{14,15} The authors reviewed the SED tarda cases reported in Korea (Table 1).

This rare disease has major clinical importance in that progressive joint deformity as well as bony swelling mimics inflammatory rheumatic diseases such as JIA or RA. Especially, SED tarda can be misdiagnosed as seronegative RA, as in our patient. Although SED tarda may be similar with RA clinically, there are significant differences on radiographic findings. Characteristic radiographic findings of SED tarda are platyspondyly and widened epiphyses of phalanges of the hands.¹ Clinically, the absence of laboratory changes, indicating systemic or synovial inflammation, helps differential diagnosis.² Lack of response to antirheumatic drugs is another important clue to differentiate SED tarda from RA.¹⁶

Our present case led us to conclude that SED tarda should be considered in differential diagnosis of RA, thus avoiding unnecessary immunosuppressive treatment. Careful assessment of radiographic finding, non-inflammatory clinical findings of the patient, and negative acute phase reactant may facilitate the diagnosis of SED tarda.

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