

## Spondyloepiphyseal Dysplasia Tarda with Progressive Arthropathy with Delayed Diagnosis

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**Abstract:** Spondyloepiphyseal dysplasia tarda with progressive arthropathy (SED-T-PA) is a rare autosomal recessive hereditary skeletal disease, and mutations in WISP3 are responsible for its onset. WISP3 is essential for maintaining cartilage integrity mainly by regulating the expression of collagen II, and mutations of WISP3 linked to SED-T-PA can compromise this function and lead to cartilage loss, which is frequently misdiagnosed as juvenile idiopathic arthritis. It is characterized by arthralgia, joint contractures, bony swelling of metacarpophalangeal and interphalangeal joints and platyspondyly. Clinical and laboratory signs of joint inflammation such as synovitis, a high erythrocyte sedimentation rate and an elevated C-reactive protein level are usually absent. Although the disease begins early in life (usually between 3 and 8 years of age), the diagnosis may be delayed. In the present case report, we describe a female patient diagnosed with SED-T-PA at the age of 40 years, although she had been exhibiting the typical radiological and clinical features of the disease since the age of 8 years. Genetic disorders like SED-T-PA may also have rheumatological involvement, and thus should be kept in mind in the differential diagnosis of inflammatory joint diseases.

**Key Words:** Spondyloepiphyseal dysplasia, pseudorheumatoid arthropathy, progressive arthropathy, osteochondrodysplasias

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### Tanısı Gecikmiş Progresif Artropati ile Seyreden Spondiloepifizeal Displazi Tarda

**Özet:** Progresif artropati ile seyreden spondiloepifizeal displazi tarda ("Spondyloepiphyseal dysplasia tarda with progressive arthropathy" SED-T-PA) otozomal resesif kalıtmı nadir bir iskelet hastalığıdır ve WISP3 genindeki mutasyonlar SED-T-PA'nın başlangıcından sorumludur. WISP3, kartilaj bütünlüğünün sürdürülmesinde gerekli olan bir genidir. Kollajen II'nin ekspresyonunu regüle ederek, kartilaj bütünlüğünün korunmasından sorumludur. SED-T-PA ile ilgili olan WISP3 mutasyonları, bu fonksiyonu engelleyerek kartilaj kaybına sebep olmakla birlikte, genellikle hastalar bu sebeple juvenil idiyopatik artrit olarak yanlış tanı almaktadırlar. Hastalık artralji, eklem kontraktürü, metakarpofalangeal ve interfalangeal eklemlerde kemiksi şişlikler ve platispandili ile karakterizedir. Sinovit gibi, eklem inflamasyonunun klinik ve laboratuvar işaretleri olan, yüksek eritrosit sedimentasyon hızı ve yükselmiş C-reaktif protein seviyeleri genellikle bulunmamaktadır. Hastalık erken yaşlarda başlamakla birlikte (genellikle 3-8 yaş arası), tanısı gecikmiş olabilir. Mevcut vaka raporunda, hastamız 8 yaşından beri SED-T-PA'nın tipik radyolojik ve klinik özelliklerini göstermesine rağmen, 40 yaşında iken SED-T-PA olarak tarafımızdan tanımlanmıştır. SED-T-PA gibi genetik hastalıklar, romatolojik bulgulara da sahip olabildiğinden inflamatuvar eklem hastalıklarının ayırıcı tanısında akılda bulundurulmalıdır.

**Anahtar Sözcükler:** Spondiloepifizeal displazi, psödoromatoid artropati, progresif artropati, osteokondrodizplaziler

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### Introduction

Spondyloepiphyseal dysplasia tarda with progressive arthropathy (SED-T-PA) is a single gene disorder that is inherited in an autosomal recessive manner. Alternative names of the disease are "progressive pseudorheumatoid arthropathy of childhood (PPAC)" and "progressive pseudorheumatoid dysplasia (PPD)" (MIM 208230) (1,2). The first cases were described in 1980 and 1982 under the designation "progressive pseudorheumatoid arthritis of childhood" (3). In 1997, SED-T-PA was classified in the International Nomenclature and Classification of the Osteochondrodysplasias, and was listed as an autosomal recessive disorder in group 10: "other spondylo-(meta)-physeal dysplasias [SE(M)D]" (4).

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Mutations in WNT-1 inducible secreted protein 3 (WISP3) cause SEDT-PA (5). WISP3, a member of the connective tissue growth factor/cysteine-rich protein 61/nephroblastoma overexpressed growth factor family, maps to chromosome 6q21-22 and encodes a protein containing 354 amino acids. WISP3 is important in many biological pathways including the development of the skeleton, nerve fibers, and blood vessels through the regulation of cell proliferation and differentiation (6). WISP3 can function as a ligand and signal via autocrine and/or paracrine modes upon being secreted by chondrocytes (7). Recently, it was shown that WISP3 can regulate the sensitivity of mammary epithelial cells to insulin-like growth factor-I (IGF-I) and alter the activation of IGF-I receptor (IGF-IR) signaling pathways (6). In SEDT-PA, the mutant WISP3 triggers the phenotypic changes of the articular chondrocytes by losing the function of inhibiting IGF-I. IGF-I then stimulates the articular chondrocytes to undergo hypertrophic and terminal differentiation, as in endstage osteoarthritis (5).

The main clinical features are arthralgia, joint contractures, enlarged metacarpophalangeal and interphalangeal joints, platyspondyly and short stature (8). The disease generally begins between the ages of 3-8 years with abnormal gait and fatigability (9). The nature of the disease is progressive and clinically indiffernt from juvenile idiopathic arthritis (JIA) (10). Though rare, because of this resemblance, diagnosing this entity is important to prevent inappropriate treatment (1). In the present case report, we describe a female patient diagnosed with SEDT-PA as late as at the age of 40 years, although she had been displaying the typical clinical and radiological features of the disease since childhood.

**Case Report**

A 40-year-old female patient admitted to the outpatient clinic of the Chest Department with breathlessness complaints. Medical consultation was requested from our department for progressive deformity in her joints. Parents of the patient were first cousins. She had three sisters and one brother. The 42-year-old brother was reported as having the same clinical characteristics as our patient; he did not agree to be consulted due to his psychological status. Our patient is married and has two healthy children, a boy and a girl. The pedigree of our patient is shown in Figure 1.

After the complete description of the study to the subjects, including photographs, written informed consent was obtained and approval received by the local ethics committee.

Our patient’s first symptoms began as difficulty in walking and genu valgum deformity of both knees at the age of eight years. However, she suffered progressive stiffness and pain in all joints and a generalized muscle weakness in the following years. She was diagnosed as JIA and started on antirheumatic drug therapy but her condition deteriorated further.

The height of the patient was 133 cm and her weight was 61 kg. Her vital signs were stable. Her systemic examination was normal, including the eyes, chest, abdomen and cardiovascular and genitourinary system examinations. Her intelligence was normal. Several symptoms were diagnosed in the musculoskeletal system, and the spirometric tests were found abnormal, showing restrictive feature. She had a short stature with increased thoracic kyphosis and lumbar lordosis. Shoulders, elbows and wrists were minimally painful and the range of motion (ROM) was limited to 25% in the shoulders, elbows and wrists. Metacarpophalangeal joints and interphalangeal joints were painful. Bilateral mild flexion deformities were present in interphalangeal joints where spindle-shaped swelling was also prominent. She was unable to make a fist (Figure 2). Hips were painful and

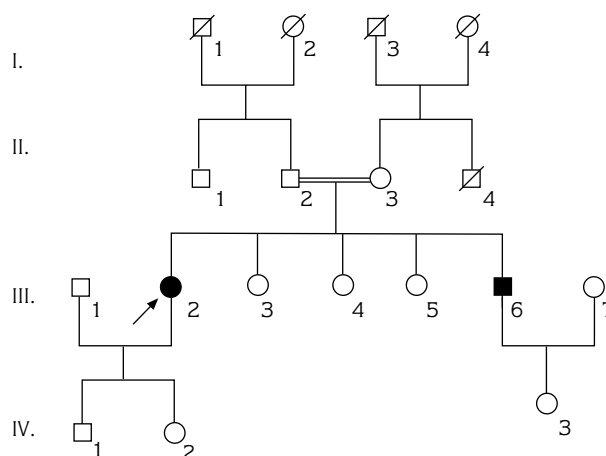


Figure 1. The pedigree of our proband.

Arrow indicates the proband. Roman numerals/figures show the generations. Arabic numerals show individuals.

□: Healthy male. ○: Healthy female.  
 ■: Affected male. ●: Affected female.

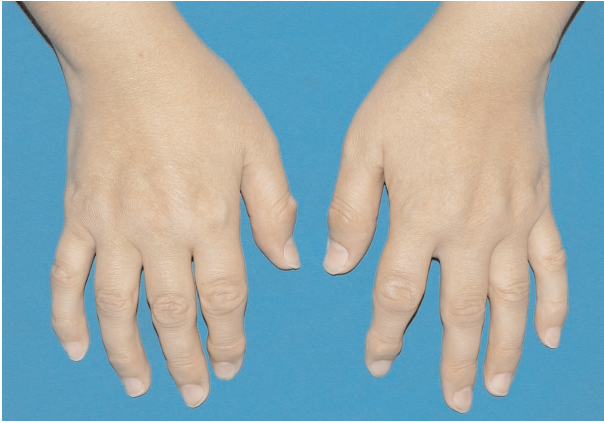


Figure 2. Flexion deformity and 'apparent' swelling of proximal interphalangeal joints.

ROM was severely limited. Knees were painful, ROM was limited and there were bilateral genu valgum deformities (Figure 3). Neurologic examination was normal other than a generalized muscular weakness, thought to be due to disuse.

Radiological evaluation was made by radiology consultants of our hospital. Lateral thoracic spine radiograph revealed increased kyphosis, generalized platyspondyly with increased anteroposterior (AP) diameters and loss of height in vertebral bodies. Hyperostotic bone deposited on the posterior two-thirds of the end plates was evident in the lumbar spine. On AP lumbar spine radiograph, scoliosis was detected (Figure 4). AP radiograph of the hip demonstrated bilateral narrow and irregular joint spaces and subchondral sclerosis, with widened and flattened femoral heads (Figure 5).

Radiographs of the knees revealed osseous enlargement of the tibiofemoral joints. Bilateral tibiofemoral and patellofemoral joint spaces were narrowed and joint contours were irregular (Figures 6 and 7). Radiographs of the hands showed general narrowing of the joint spaces and osseous enlargement of the basis of the metacarpal bones and metacarpophalangeal, proximal and distal interphalangeal joints (Figure 8). There was diminished density of the bony structures compatible with osteoporosis on all X-rays, which was confirmed by dual energy X-ray absorptiometry (DEXA).

The results of a urine analysis, complete blood count and routine blood chemistry (including serum creatinine, calcium, phosphorus, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase) were



Figure 3. Osseous enlargement of the tibiofemoral joints.

normal. The thyroid stimulating hormone, follicle-stimulating hormone, luteinizing hormone and testosterone levels were normal. Anti-streptolysin O (ASO) titer was 284 IU/ml (N: 0-200 IU/ml), C-reactive protein (CRP) 31.7 mg/L (N: 0-6 mg/L), erythrocyte sedimentation rate (ESR) 20 mm/hr, and rheumatoid factor, antinuclear antibody, and anti-dsDNA were negative. C3, C4, immunoglobulins and thyroid function tests, and parathyroid hormone level were normal. Hepatitis markers and group agglutination tests (Salmonella, Shigella) were negative. All cultures were negative, including throat, stool, urine and blood cultures.

She was diagnosed as SEDT-PA and was treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and advised about physical therapy, and her pain diminished to a significant degree. The family and the patient were informed about the disease, joint protection and exercise programs.



Figure 4. Lateral thoracic spine radiograph shows generalized osteopenia, increased kyphosis, generalized platyspondyly with increased AP diameters and loss of height in vertebral bodies. Note hyperostotic bone deposited on the posterior lumbar spine.

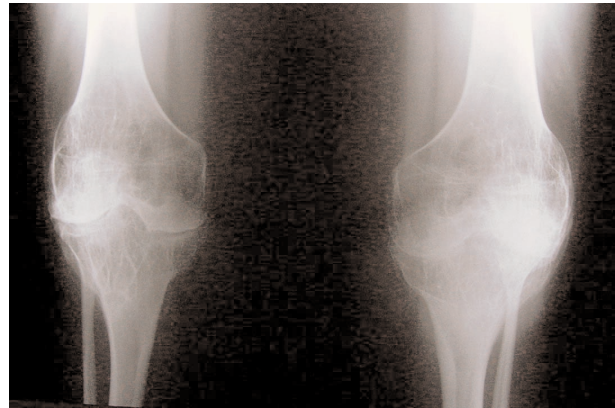


Figure 6. AP radiographs of the bilateral knees show generalized osteopenia and osseous enlargement of the tibiofemoral joints. Bilateral tibiofemoral joint spaces are extremely narrow and joint contours are irregular.



Figure 5. AP radiograph of the hip demonstrates generalized osteopenia, bilateral narrow and irregular joint spaces and subchondral sclerosis with widened and flattened femoral heads.



Figure 7. Lateral radiograph of the knee reveals that the patellofemoral joint space is narrow.

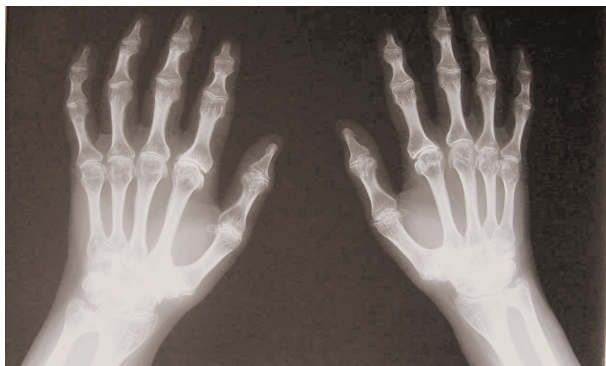


Figure 8. The hand radiographs reveal general narrowing of the joint spaces and osseous enlargement in the metacarpal bones and metacarpophalangeal and proximal-distal interphalangeal joints and subchondral sclerosis in the second metacarpophalangeal joint.

## Discussion

SEDT-PA is a rare hereditary disorder with autosomal recessive inheritance with symptoms consisting of stiffness, swelling of joints, motor weakness and joint contractures. (5,11). Although the prevalence of SEDT-PA in Turkey is not precisely known, it is apparently rare in western countries, with an incidence of one per million in the United Kingdom. It is probably more frequent in the Middle East and Gulf States, with more than two-thirds of the reported patients belonging to Arab and Mediterranean populations (3,12,13). To the best of our knowledge, this is the eighth case report of a patient with SEDT-PA from Turkey (8,4).

Spondyloepiphyseal dysplasia can be divided into two major groups: SED congenita and SED tarda. The autosomal dominant inherited SED congenita form manifests in the neonatal period and is associated with stigmas such as pectus carinatum, cleft palate and hypertelorism. Spondyloepiphyseal dysplasia tarda forms (SED tarda [SEDT] and SED tarda with progressive arthropathy [SEDT-PA]) have rheumatologic implications. SEDT is inherited as either X-linked, autosomal recessive or autosomal dominant (14). The parents of our patient were first-degree cousins, and a sibling of our patient has the same illness. Therefore, we suspect autosomal recessive inheritance pattern. Thus, the proband inherited the mutant allele of the WISP3 gene from each of the possibly heterozygote parents, with a risk of 1/4 each.

All case reports published from Turkey are similar in clinical features and inheritance form. All cases from Turkey have shown an autosomal recessive inheritance pattern and parental consanguinity. In all cases, onset of the symptoms was between the ages of 3 and 8 years. Also similar were the symptoms such as involvement of the spine and epiphyses of bones, leading subsequently to disproportionate short stature and thoracic kyphoscoliosis and pain, swelling and stiffness of multiple articulations, most frequently in the joints of hands, hips, elbows and feet (1,4,8,13-15). In the SEDT-PA cases presented from Europe and other countries, all three inheritance patterns could be seen. X-linked SEDT-PA (MIM 313400) is characterized by moderate short stature, barrel chest deformity and minor epiphyseal abnormalities (16).

Initial mapping studies assigned the WISP3 gene responsible for the disease to the long arm of chromosome 6 (17). WISP3 is a gene of the CCN (cyr61, ctgf, nov) family that encodes cysteine-rich proteins involved in cell growth and differentiation (8,3). WISP3, which is expressed in the proliferating chondrocytes of the fetal growth plates, may play a major role in bone growth and cartilage metabolism (3,5). WISP3-mediated regulation of collagen II and aggrecan corroborates the concept that WISP3 plays a major role in cartilage growth and maintenance (5). Using a positional candidate approach, Hurvitz et al. (12) first identified nine different WISP3 gene mutations in affected individuals in 13 SEDT-PA families (4,6). Yang et al. (5) identified a compound WISP3 heterozygous gene mutation in a SEDT-PA patient. They hypothesized that mutant WISP3 loses the function of IGF-1, which is mediated by the insulin-like growth factor binding proteins (IGFBPs) domain and promotes the sensitivity to IGF-1 in chondrocytes. IGF-1 triggers the stable articular chondrocyte to undergo hypertrophic and terminal differentiation, which reduces the expression of types II and IX collagen in SEDT-PA as in endstage osteoarthritis (5).

SEDT-PA is a rare childhood disease that must be differentiated from JIA to ensure optimal treatment and to avoid unnecessary exposure to immunosuppressants (3). Although this 40-year-old patient showed typical clinical symptoms of SEDT-PA, it was not possible to prevent cartilage loss due to misdiagnosis. The patient was diagnosed and treated for JIA for a long period.

SEDT-PA is frequently misdiagnosed as JIA, together with other inherited diseases such as Stickler syndrome,

a dominantly inherited disease characterized by ocular abnormalities; Kniest syndrome, an autosomal dominant condition with facial dysmorphia; and SEDT, which develops at an older age (3). There are at least five case reports describing its striking similarity to JIA (10,13). The main reasons for misdiagnosis appear to be onset in childhood with swelling and restriction of peripheral and axial joints. However, the absence of arthritic and other inflammatory findings, especially synovitis, and radiological absence of destructive joint changes should alert the clinician in excluding JIA and considering other diagnostic possibilities. Furthermore, a normal ESR and a normal level of CRP may be additional clues in excluding JIA, in addition to platyspondyly, which is highly unusual for JIA. Our patient had been misdiagnosed as JIA due to the swelling of her proximal interphalangeal and metacarpophalangeal joints and was given NSAIDs until 40 years of age. We diagnosed SEDT-PA due to the characteristic radiographic findings such as generalized osteoporosis, platyspondyly, typical enlargements of the ends of the short tubular bones of the hands and epiphyseal changes of the femoral head.

In our case, there were typical radiological findings of the disease, in addition to osteoporosis as determined on all X-rays and confirmed by DEXA. This is an interesting feature of the present case because the patient did not display any clinical or laboratory signs of other disorders associated with osteoporosis. We suggest that the decreased bone density may be a direct consequence of

SEDT-PA. However, the exact mechanism of this relation is unclear at present. The absence of systemic signs, history of parental consanguinity and a poor response to anti-rheumatoid treatment were among the other important features which guided us in diagnosis of SEDT-PA in our case.

Consequently, SEDT-PA is a rare disease of childhood. The primarily genetic origin of disorders should be remembered among childhood rheumatic diseases so that inappropriate therapy can be prevented and genetic counseling can be offered to the family for the next generations. The family was also enlightened about the risk of consanguineous marriage, and marriage with persons carrying the mutations. Our patient has two siblings with healthy phenotype, but it is expected that they have inherited the mutant gene in heterozygote form from their homozygote mother. For the next step of our study, we plan to diagnose the mutant homozygote alleles of the mother and the heterozygote allele from the siblings by molecular analysis. We believe that it is necessary to perform molecular analysis of the cases. With this knowledge, we think that more detailed genetic counseling may be given to the family.

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