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CASE REPORT

Progressive pseudorheumatoid dysplasia. A case report and literature review

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Abstract

Objectives: Progressive pseudo-rheumatoid dysplasia (PPRD) is a rare autosomal recessive disorder characterized by articular cartilage degeneration causing joint stiffness, abnormal gait and significant morbidity. Its prevalence is estimated as one per million but the disease remains underdiagnosed mainly due to the overlap features with juvenile idiopathic arthritis (JIA).
Material and Methods: Case report and literature review
Outcomes: We report the case of a 17-year-old short stature boy with a provisional diagnosis of rheumatoid factor negative polyarticular juvenile idiopathic arthritis (JIA) with unsatisfactory clinical evolution on immunosuppressive therapy. PPRD was suspected based on the clinical presentation, progression of the disease and the aspect of the X-rays of hands and spine, while whole exome sequencing confirmed the diagnosis. Our aim is to review the literature concerning clinical, laboratory and radiological features of PPRD in order to enable early diagnosis and spare the patients from unnecessary investigations and toxic medications.
Conclusions: Prompt recognition of this entity and subsequent confirmation of the diagnosis is of particular interest for paediatric rheumatologists due to the considerable impact it has on the patients' quality of life.
Keywords: pseudo-rheumatoid dysplasia, autosomal recessive, cartilage degeneration, paediatric rheumatology.

Introduction

Progressive pseudorheumatoid dysplasia (PPRD) is a rare autosomal recessive non-inflammatory musculoskeletal disorder characterized by articular cartilage degeneration leading to joint stiffness, abnormal gait and significant morbidity. Its prevalence is estimated as one per million but the disease remains underdiagnosed mainly due to the overlap features with juvenile idiopathic arthritis (JIA).

Methods

A literature search was performed on Pubmed database using key words such as progressive pseudo-rheumatoid dysplasia, spondyloepiphyseal dysplasia tarda with progressive arthropathy and misdiagnosed juvenile idiopathic arthritis. Based on the scarcely available literature, we discussed the clinical, paraclinical phenotypes and the management of the disease. The clinical case included in this paper is aimed to highlight the fact that PPRD can often mimic JIA and efforts to acknowledge this disorder are needed.

Case presentation

A 17-year-old boy diagnosed with rheumatoid factor negative polyarticular JIA at the age of ten was referred to rheumatology for a second opinion. His postnatal and early childhood periods were uneventful with normal developmental milestones.

His medical history started with progressive loss of the upward bending motion of the right ankle joint and shortly afterwards development of equinus foot (Figure 1). No ankle injury preceded the diagnosis. The boy was periodically assessed by an orthopedist doctor, attended physical therapy sessions and used orthotic devices. Three years later, joint pain in the affected ankle became more severe and the boy started experiencing mechanical pain also in the left knee and hip. Neurological exam and electromyography test were normal. He progressively associated pain and limited range of movement in the cervical spine. A slow-down in height gain was recorded at the age of thirteen. He soon acquired visible deformities in the

interphalangeal joints (Figure 2). He was diagnosed with rheumatoid factor negative polyarticular JIA and he started methotrexate 25 mg weekly and oral methylprednisolone in medium doses.

Knee aspiration with intra-articular corticosteroid injection had been repeatedly performed over the last year. His clinical evolution was nevertheless far from satisfactory. His main complaints upon presentation in our clinic were mechanical pain, tumefaction and restricted range of movement of the right knee.

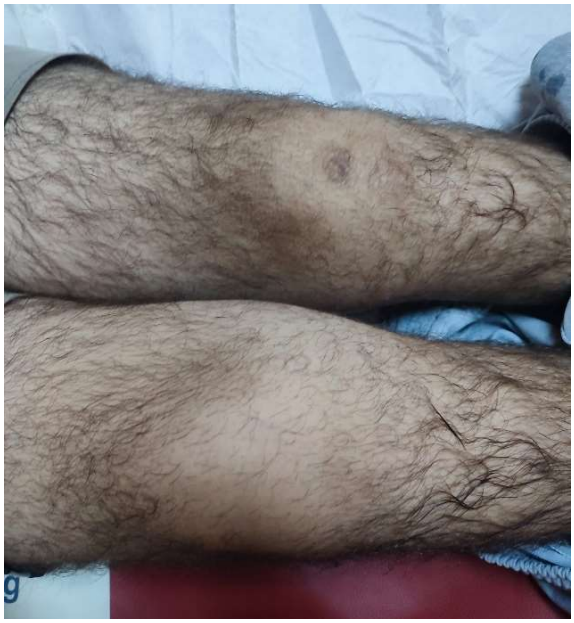

Figure 1. Swollen and painful knees during exertion.

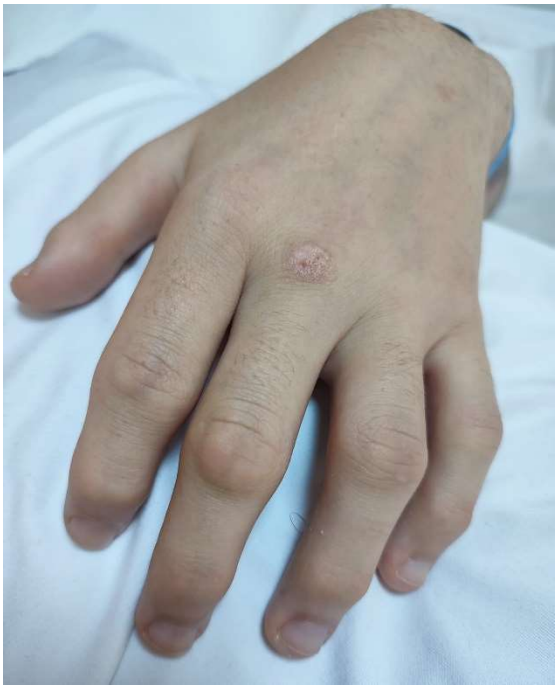

Figure 2. Swollen proximal and distal interphalangeal joints of the hand.

Clinical exam revealed short stature, thoracic kyphosis, right clubfoot, flexion deformity of the right knee, bilateral knee crepitus, ankylosis of hips and camptodactyly.

The right knee was swollen, with a positive patellar tap test, but non-tender on palpation (Figure 3). Limited range of motion of the spine was assessed with a Schober test of 3.5 cm.

Figure 3. Equinus deformity.

Laboratory workup resulted in normal inflammatory markers, negative anti-citrullinated protein antibodies and HLA-B27 test. Routine blood tests including calcium, alkaline phosphatase, thyroid and parathyroid function tests were within normal limits.

Musculoskeletal ultrasound pointed out minimal synovial proliferation of the left knee and moderate quantity of synovial effusion in the lateral parapatellar compartment. Important structural lesions of osteoarthritis were found in both knees and small joints of the hands. Pelvic X-ray identified normal aspect of the sacroiliac joints (Figure 4).

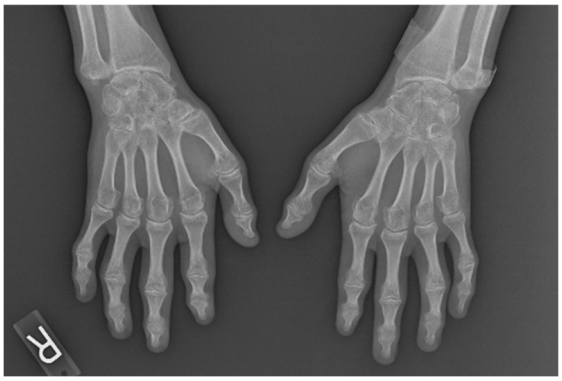

Figure 4. X-rays of the hands showed large epiphyseal and widened metaphyses of the metacarpals and phalanges without erosive lesion**s**.

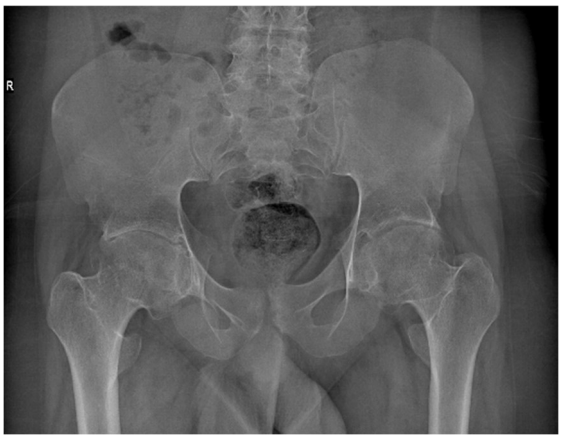

Figure 5. X-rays of the pelvis: normal aspect of the

sacroiliac joints.

In addition, X-rays showed epiphyseal enlargement of the proximal phalanges and platyspondyly with anterior beaking in the lumbar vertebrae, an aspect visible on MRI of the spine as well. (Figures 5 and 6). Bone age was consistent with the chronological age.

PPRD was suspected based on these images so a skeletal dysplasia panel was performed (whole exome sequencing), identifying a compound heterozygous pathogenic mutation of CCN6 gene (c.993G>A; c.49-13T>G).

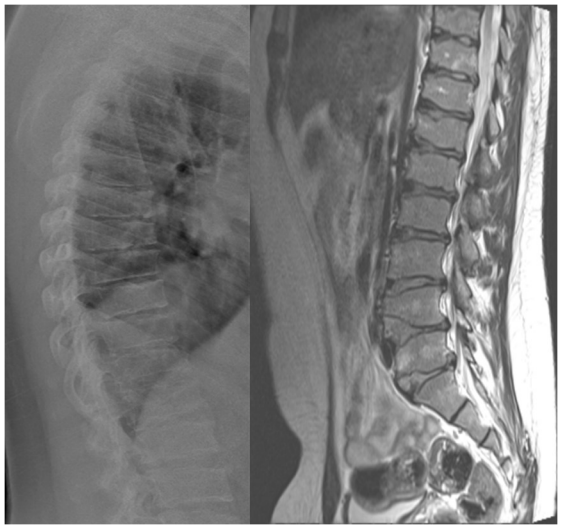

Figure 6. X-rays and MRI of the spine: beaking of the anterior vertebral bodies and platyspondyly with narrowing of intervertebral disc spaces.

Disease modifying drugs and corticosteroids were stopped. Supportive treatment and orthopaedic follow-up were indicated. Surgical intervention including knee joint replacement in the future is also taken into consideration.

Discussions

Progressive pseudorheumatoid dysplasia: epidemiology and pathogenesis

PPRD is caused by mutations in the WNT1-inducible signalling pathway protein 3 (WISP 3) gene, also named cellular communication network factor 6 (CCN6), which is essential for normal postnatal skeletal growth and cartilage homeostasis [1]. This gene is located on chromosome 6q22 [2]. In vitro studies showed that WISP-3 regulates collagen II and aggrecan expression, and may also promote superoxide dismutase expression and activity in chondrocytes [3].

The prevalence of PPRD is estimated to be around one per million. Although data is scarcely available, this condition seems to be more frequently encountered in Turkey and Middle East. Even so, this is thought to be underdiagnosed no matter the region, since many cases are misdiagnosed as juvenile idiopathic arthritis [4].

Clinical features

This condition usually starts in childhood, between 3 and 8 years. The onset is commonly represented by an abnormal walking pattern, motor weakness or fatigue and knobbly interphalangeal joints of the hands [5].

Over time, large joint and spine involvement would lead to significant joint contractures, abnormal posture and gait disturbance. Short stature is evident in adolescence since development in the early childhood is normal. Despite the significant morbidity, pain is not a major feature of these patients.

Diagnosis

Due to the insufficient clinical data available, no formal diagnostic criteria for PPRD are available. Nevertheless, as the number of cases reported is increasing, clinical, radiological features and laboratory features were summarized [2].

Diagnosis is suggested by onset of the disease in early childhood, stiffness and pain in multiple joints, enlarged interphalangeal joints, absence of inflammatory markers and absence of extra-skeletal manifestations. Characteristic radiographic features are illustrated by platyspondyly (abnormally shaped flattened bones in the spine), which determines kyphosis and a short torso, metaphyseal enlargement of the interphalangeal joints and reduced articular space with dysplastic epiphyses in the hip and knee. Also, compared to JIA, bone erosions are absent.

Identification of biallelic pathogenic variants in CCN6 on molecular genetic testing confirms the diagnosis. More than 70 WISP3 mutations have been reported so far. Genetic testing should start with the study of genomic DNA extracted from blood leucocytes, but in patients with typical PPRD findings and negative mutation screening of genomic DNA, skin biopsy can be useful [5].

Molecular genetic testing approaches can include gene-targeted testing and comprehensive genomic testing.

Targeted sequencing can be used when the clinical presentation is suggestive for PPRD. Nevertheless, whole exome sequencing (WES) enables identifying new pathogenic genes (apart from CCN6) or new mutation sites on the CCN6 when diagnosis is less evident. The frequency of the different mutations in the CCN6 vary geographically. A single-centre cohort of 61 Chinese patients genetically diagnosed with PPRD were analysed in terms of corelations between genotypic and phenotypic features. Five hotspots variants were described. Among them, c.634dupA was associated with later onset of the disease and more extensive joint involvement [6]. Data regarding the phenotypes in Romania are scarcely available and no specific phenotype has been characterized by the mutation identified in our patient.

Differential diagnosis

As already stated, the clinical presentation of PPRD may initially resemble JIA, but negative inflammatory markers, typical radiographic features and decrease in growth rate can help in making the

diagnosis.

Myopathies might also be considered, but normal muscle enzymes are distinctive features. To be noted that electromyography may show minimal non-specific myopathic changes in patients with PPRD [5].

PPRD has an early onset and progressive evolution, which differentiate it from other bone dysplasia conditions.

Other disorders presenting with platyspondyly, such as mucopolysaccharidosis, might need to be taken into account as well, but they usually associate extra-skeletal manifestations including intellectual disability.

Treatment and management

The current treatment for PPRD is only supportive consisting of pain killers, physical therapy and surgical interventions. No benefit was observed after using immunosuppressive therapies [7] and anti-inflammatory drugs lead to little clinical improvement.

Conclusion

PPRD is of particular interest for paediatric rheumatologists because its clinical manifestations closely intricate with JIA. Due to the considerable impact it has on the patients' quality of life, early recognition of this entity and subsequent confirmation of the diagnosis can spare the patients from unnecessary investigations and toxic medications and can offer the patient access to genetic counselling.

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