

# Juvenile Idiopathic Arthritis associated with incomplete primary hypertrophic osteoarthropathy (Pachydermoperiostosis)

Vasilia Cristina Iorgoveanu<sup>1</sup>, Raluca Ionescu<sup>1</sup>, Laura Groseanu<sup>1,2</sup>, Ruxandra Ionescu<sup>1,2</sup>

<sup>1</sup>Department of Internal Medicine and Rheumatology, Sf. Maria Clinical Hospital, Bucharest, RCRD

<sup>2</sup>Carol Davila University of Medicine and Pharmacy, Bucharest

Mention: Vasilia Cristina Iorgoveanu and Raluca Ionescu had an equal contribution in editing the present paper.

## ABSTRACT

**Introduction.** Hypertrophic osteoarthropathy (HOA) is a rare, hereditary disease characterized by clubbing and new bone formation in the periosteal region that may be associated with joint pain, cutaneous abnormalities, seb-orrhea or hyperhydrosis. Juvenile idiopathic arthritis (JIA) is one of the most frequent chronic diseases with childhood onset, patients develop inflammatory joint pain and extra-articular manifestations with immunologic substrate. The association of the two diseases is very rare.

24 years old patient related disease onset at the age of 14 with arthritis of proximal interphalangeal joints (PIP), knees and right ankle. He is diagnosed with oligoarticular form of juvenile idiopathic arthritis. He receives Methotrexate, Sulphasalazine and association of the two, but after 5 years biological therapy with Etanercept is started. Later on, repeated physical examination revealed digital clubbing, non-painful enlargement of hands and feet with sweaty teguments. Radiological examination with subperiosteal new bone formation of the distal tibia, the fibula, the radius, the ulna, the metacarpals and the phalanges confirms the suspicion of HOA – pachydermoperiostosis (PDP).

**Conclusion.** Final diagnosis considers both entities. The incomplete form of PDP included hands and feet enlargement with extensive periostitis, palmoplantar hyperhydrosis, but no significant facial changes. The specific treatment for JIA did not influence the evolution of PDP.

**Keywords:** pachydermoperiostosis, hypertrophic osteoarthropathy, juvenile idiopathic arthritis, rheumatoid arthritis, biological therapy

## INTRODUCTION

Pachydermoperiostosis (PDP), primary hypertrophic osteoarthropathy (HOA) or Touraine-Solente-Golé syndrome is a rare genetic disease with both autosomal dominant and recessive inheritance, with various levels of penetration. The autosomal dominant inheritance is associated with the incomplete form, while the recessive form is associated with the complete form with poorer prognosis. PDP represents only 5% of HOA, the majority being secondary forms related to cardiovascular or malignant pathologies. The primary form favors the Afro-American race, and the male: female ratio is 7:1 (1). The typical age of onset is late childhood or adolescence with a gradual progression and auto limitation after approximately 5 years of evolution.

## CASE PRESENTATION

24 years old patient related insidious disease onset at the age of 14 (august 2005) with arthritis in 2<sup>nd</sup>-5<sup>th</sup> bilateral proximal interphalangeal (PIP) joints, knees and right ankle joint. Lab examinations at that time revealed mild inflammatory syndrome (ESR=40 mm/h, CRP=28 mg/l), negative rheumatoid factor, negative antinuclear antibodies and negative for HLAB27. After a couple of months, he is finally diagnosed with juvenile idiopathic arthritis, therefore the patient is recommended treatment with Sulphasalazine (SSZ) up to 2,5 g per day in association with NSAIDS. This treatment plan is followed for 2 years, during which he presents with multiple episodes of arthritis. Consecutively, Methotrexate

(MTX) is added, but with scarce results. Therefore, in 2008, when he is transferred to an adult rheumatology clinic, biological therapy is started with Etanercept (ETN) 25 mg twice a week in association with Methotrexate. He soon reached clinical and biological remission, sustained since 2010.

Since the age of 16, at the physical examination, clubbing of the fingers, diffuse hand and feet swelling and enlargement (Figure 1, Figure 2) were noticed. The skin of the face was a little greasy and thickened but without major facial changes. He also reported excessive perspiration, erectile dysfunction. The father and the grandfather of the patient were very tall and had similar swelling of the fingers and toes, but never been investigated.



**FIGURE 1.** Clinical examination of hands



**FIGURE 2.** Clinical examination of feet

Radiological investigation of both arms and legs reveal bilateral extensive irregular periosteal reaction of the radius and ulna with diffuse soft tissue swelling; same changes were noticed in the metacarpophalanges, and the first and second phalanges of the second to the fifth hand fingers (Figure 3) and diffuse demineralization with periosteal reaction and secondary arthrosis of the tarso-metatarsal bones (Figure 4). Moreover, hand ultrasound examination of feet (August 2014) (Figure 5, Figure 6) shows

cortical neregularities in the perimalleolar region bilaterally and synovial effusion in the knees, tarsal and metatarsal joints.

Clinical and radiological changes were considered to be features of primary hypertrophic osteoarthropathy (also known as pachydermoperiostitis). For differential diagnosis acromegalia and gigantism were taken into consideration, and excluded after full endocrinological evaluation (normal head CT, normal serum levels of cortisol, TSH, testosterone, IGF-1 and GH). The patient had no abnormal respiratory, cardiovascular or gastrointestinal symptoms. Still, several other tests were performed to exclude secondary form of hypertrophic osteoarthropathy: heart echocardiography, lung computerized tomography, blood smear.

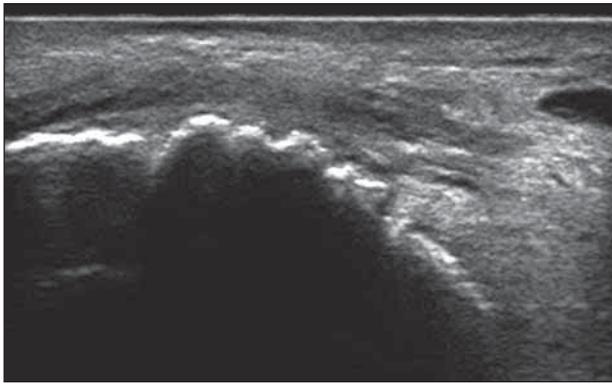
Although PPD has limited evolution, in our case hand and feet enlargement continues with physical and psychological impact on the patient's daily living. As we would have expected, none on the JIA treatments (DMARDs or biological therapy) influence the PPD's evolution.



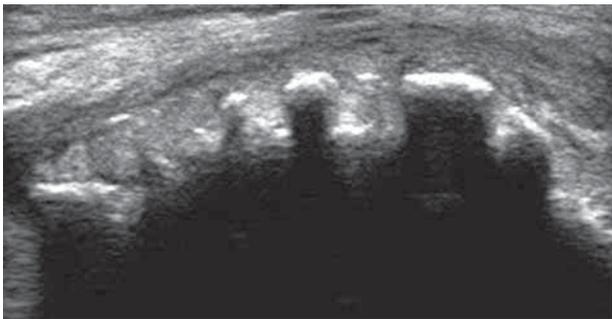
**FIGURE 3.** Hand x-Ray



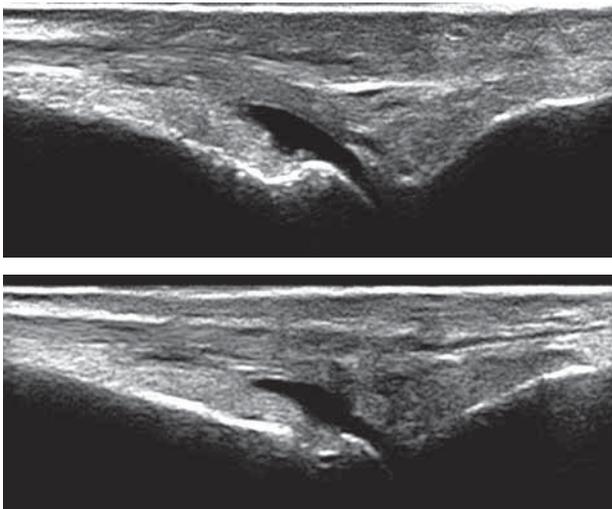
**FIGURE 4.** Foot x-Ray



**FIGURE 5.** *Ultrasound of the ankle – malleolar irregularities*



**FIGURE 6.** *Ultrasound of the ankle – malleolar irregularities*



**FIGURE 7.** *Ultrasound of the foot – joint effusion*

## DISCUSSION

Pachydermoperiostosis is a rare genetic disorder characterized by skin (thickening, seborrheic dermatitis, cutis gyrata), bone (thickening, clubbing of the fingers) and nail (curved nails) involvement. The male/female ratio favors the male sex, with childhood/adolescence onset and a self-limited evolution. This disorder can be associated with JIA and other rheumatic and non-rheumatic diseases. Our case presents a young male with JIA, currently under treatment with Etanercept that also presents with

pachydermoperiostosis, with the illustration of the clinical, radiologic and ultrasound features.

PDP was classified by Touraine et al (2) in 3 subtypes: the complete associated to pachyderma and periostosis, the incomplete form with bone abnormalities and absence of pachyderma, and a fruste form characterized by thickened dermis and minimal to absent bone involvement.

## Pathophysiology

PDP is associated with 15-hydroxyprostaglandin dehydrogenase (HPGD) gene mutations which encodes 15 HPGD, resulting in a persistent elevation of circulating PGE<sub>2</sub> levels (3). Also a deficiency of SLCO2A1, a prostaglandin transporter, is described as the primary cause of pathology (4). Some data focus on the increased levels of IL6 and receptor activator of nuclear factor-kappaB ligand (RANKL) during diseases activity (5).

## Clinical presentation

At the clinical overview skin, hair and finger nail involvement is observed including: scleroderma-like thickening of facial skin, leonine facies with hair over the cheek bones and forehead, cutis verrucosus gyrata, seborrheic dermatitis involving the face and scalp, hand and foot hyperkeratosis, bilateral blepharoptosis, facial acne, clubbing, findings also observed in our patients.

Given the physical abnormalities PDP produces, it is important to exclude diseases as acromegaly, thyroid acropachy or syphilitic periostosis.

Numerous case reports of PDP described as clinical manifestations of other diseases: gastrointestinal involvement (6) (gastric carcinoma, Crohn disease, peptic ulcer, chronic gastritis), ginecomastia (7), compressive neuropathy, psoriatic nail involvement (8), congenital heart disease (9), atherotrombotic cerebral infarction (10), osteoporosis (11), rheumatoid arthritis (12), ankylosing spondylitis (13). In some cases, pathologies known to be associated with PDP became clinically active years after PDP onset, recorded cases included Crohn disease, myelofibrosis and congenital heart disease (14). During follow-up, our patient has not developed any symptomatology or signs of cardio-pulmonary disease or neoplastic pathology.

## Imaging

Presence of subperiosteal bone formation, especially along the distal tibia, fibula, radius and ulna,

metacarpophalangs and phalanges is a characteristic of PDP. There have been cases reported with thickening but not narrowing of the spinal canal and enlargement of the paranasal sinuses (16).

## CONCLUSION

Persistence of arthritis and inflammatory syndrome, symmetrical polyarticular involvement and a good response to biological therapy arguments the

diagnosis of JIA. Hyperhydrosis, periostitis and finger clubbing with the radiological abnormalities raises the suspicion of PDP. As far as we know, few cases have been reported in which both entities PDP and JIA are associated (15), but further research is needed in both diagnosis and monitoring of rheumatological conditions associated to PDP and response to treatment, especially to biological treatment.

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