

Original Article

Primary hypertrophic osteoarthropathy (pachydermoperiostosis). Report of 2 familial cases and literature review

Norberto Gómez Rodríguez, * Jesús Ibáñez Ruán, and Marisol González Pérez

Servicio de Reumatología, Hospital POVISA, Vigo, Pontevedra, Spain

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ABSTRACT

The primary hypertrophic osteoarthropathy (pachydermoperiostosis) is a hereditary disease characterized by skin thickening (pachydermia), finger clubbing, and proliferation of periosteum (periostitis) with subperiosteal new bone formation. We describe the cases of 2 brothers of 30 and 24 years, who consulted due to bone pain, arthralgia, and oligoarthritis. Pachydermia, hyperhidrosis, seborrhea, digital clubbing, periostosis, and non-inflammatory effusions of the knees. The first had been diagnosed with juvenile idiopathic arthritis at age 15, while the youngest also presented with a thoracic scoliosis, hypertrophic gastritis, iron deficiency anemia, and glucose intolerance by pancreatic endocrine dysfunction. In both patients, symptoms were controlled satisfactorily with etoricoxib (90 mg/day) and risedronate (35 mg/week).

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Osteoartropatía hipertrófica primaria (paquidermoperiostosis). Aportación de 2 casos familiares y revisión de la literatura

RESUMEN

La osteoartropatía hipertrófica primaria (paquidermoperiostosis) es una enfermedad hereditaria caracterizada por engrosamiento cutáneo (paquidermia), dedos en palillo de tambor y proliferación perióstica (periostosis) con neoformación ósea subcortical. Describimos los casos de 2 hermanos de 30 y 24 años, que consultaron por dolores óseos, artralgias y oligoartritis. En ambos casos se objetivó paquidermia, hiperhidrosis, seborrea, hipocratismo digital, periostosis y derrame articular en las rodillas de características no inflamatorias. El primero había sido diagnosticado de artritis idiopática juvenil a los 15 años, mientras que el más joven también presentaba una escoliosis dorsal, gastritis hipertrófica, anemia ferropénica crónica e intolerancia a la glucosa por disfunción endocrina pancreática. Los síntomas se controlaron satisfactoriamente en ambos enfermos con etoricoxib (90 mg/día) y risedronato (35 mg/ semana).

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Introduction

Pachydermoperiostosis or primary hypertrophic osteoarthropathy (PHO) is a hereditary disease characterized by finger clubbing, periostosis, and skin thickening (pachydermia), coexisting with a variety of clinical manifestations including, among others, hyperhidrosis, joint pain, arthritis, cutis verticis gyrata, ptosis, and

hypertrophic gastritis.¹⁻⁶ It was initially described by Friedreich⁷ in 1868 and then by Touraine, Solente and Golé⁸ in 1935, who recognized its familial nature and described 3 forms of presentation: complete (digital clubbing, pachydermia, and periostosis), incomplete (no pachydermia), and frustre (prominent pachydermia with few skeletal manifestations).

Pachydermoperiostosis represents approximately 5% of the total of hypertrophic osteoarthropathy, but its prevalence is unknown for the general population. Jajic et al⁹ have communicated 5 cases of PHO among patients seen during a month, which represents 0.16%. It has a marked predominance in males (7–9:1) and has familial aggregation in 25% to 38% of cases, being mainly autosomic dominant in nature. The main motives for consulting the physician are the skin and joint manifestations, as well as bone and joint pain, being the

* Corresponding author.

E-mail address: ngomez@povisa.es (N. Gómez Rodríguez).

latter 2 the ones capable of inducing confusion when diagnosing the disease.^{10,11} Because of this we have considered interesting the following description of 2 young male patients with PHO, members of the same family, who came to the office due to musculoskeletal manifestations.

Clinical cases

Case 1

The first case is a 30-year-old male who came to the clinic due to mechanical joint pain of the knees and ankles, which started during his adolescence and were of an incapacitating nature. He had been seen by orthopedic surgeons, trauma and rheumatology specialists in his health jurisdiction, where he was diagnosed with juvenile idiopathic arthritis. He was treated using non-steroidal anti-inflammatory drugs and low-dose prednisone, as well as intramuscular gold salts, with little response.

Physical examination showed facial seborrhea and prominent skin folds on the face (Figure 1A), short fingers, and toes and distal clubbing, rounded fingernails (Figure 1B) with a Lovibond angle of 206°, a widening of the legs that gave them a tubular appearance as well as dorsal dextroconvex scoliosis. The knees had an increase in local temperature with moderate effusion and mild but painful restriction when flexing over 110° on the right side and 105° on the left.

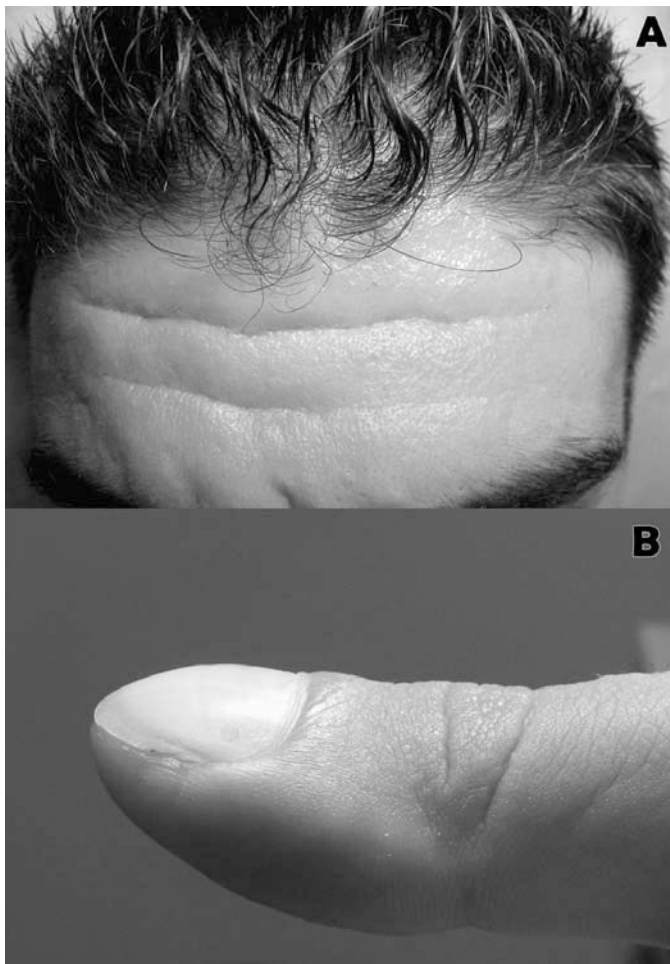


Figure 1. A) Thickening of the facial skin folds. B) Digital clubbing and round nails.

Laboratory analysis showed a mild increase in ESR (24 mm/firsth; normal <15) and C-reactive protein (5.7 mg/L; normal <5). The following parameters were normal or negative: hemogram, glucose, urea, creatinine, GOT-ASAT, GPT-ALAT, GGT, alkaline phosphatases, billirrubin, cholesterol, triglycerides, lactic dehydrogenase (LDH), creatininkinase(CK),calcium,phosphorus,sodium,potassium,chloride, proteins, serum iron, ferritin, TSH, T4 (free), GH, immunoglobulins (IgM, IgG, IgA), complement (C3, C4), rheumatoid factor (latex), antinuclear antibodies (ANA), and tests for syphilis (treponemic and reagents). An arthrocentesis obtained 21 mL of synovial fluid of the right knee and 32 mL of the left knee, of mechanical characteristics in both cases showing 320 cel/mm³ predominantly lymphocytes (90%) and normal glucose concentrations. No crystals were seen using polarized light microscopy.

Chest, spine, pelvis, hands, knees (Figure 2), ankles, and feet x rays were performed, showing cortical widening, long bone dyaphysis, and metaphysis periostosis (tibia, fibula, femur). No signs of acroosteolysis were seen in the distal phalanges. Abdominal and cardiac ecography were normal.

Clinical and radiological data led to the diagnosis of PHO and the patient was successfully treated with etoricoxib (90 mg/day) and risedronic acid (35 mg/week), with gradual clinical improvement. During 3 years of follow-up, there has not been any recurrence of arthritis and joint pain has been reduced by half, allowing him to lead a normal life.

Case 2

This case was a 24-year-old male who came to the clinic due to mechanical joint pain and swelling of the knees and ankles. These symptoms started when the patient was 16 years of age and motivated his study at another center where analysis found iron deficiency hypochromic microcytic anemia and hyperglycemia in diabetic range associated to low serum insulin concentrations. An upper digestive tract endoscopy showed a thickening of gastric folds (hypertrophic gastritis). Colonoscopy was normal.

His phenotype was similar to his older brother (case 1), in addition to presenting inflammatory acne (facial and interscapular regions), pitting edema of the distal half of the legs and perimaleolar region, finger clubbing (Lovibond angle of 202°) and a telesystolic ejection murmur, audible on the aortic area.

ESR and C-reactive protein were somewhat elevated, with values of 23 mm/firsth and 5.9 mg/L, respectively. Except hyperglycemia (121 mg/dL), low serum iron (23 µg/dL; normal, 50-160 µg/dL) and hypoferritin (11 ng/mL; normal, 15-200 ng/mL), the following laboratory parameters were normal: urea, creatinine, transaminases, GGT, alkaline phosphatases, billirrubin, cholesterol, triglycerides, LDH, CK, calcium, phosphorus, sodium, potassium, chloride, proteins, TSH, T4 (free), GH, immunoglobulins and serum complement (C3, C4). No rheumatoid factor, ANA, ANCA, or antibodies for *Borrelia burgdorferi* or syphilis (treponemic and reagents) were found. Guayac test was repeatedly negative. A right knee arthrocentesis obtained 16 mL of mechanical synovial fluid that had 240 cel/mm³ with a predominance of lymphocytes (95%), normal protein and glucose concentrations and no crystals (polarized light microscopy).

The chest x-ray was normal. The bone series showed shortening and widening of the hand and feet phalanges, giving it a tubular aspect, as well as speculated periostosis in the inferior third of the tibial dyaphysis. An echocardiogram was normal (functional systolic murmur).

The patient was treated with etoricoxib (90 mg/day) and risedronate (35 mg/week), with important symptom improvement in the 2 years of follow up.

None of the first and second degree relatives had any phenotypical characteristics of PHO.



Figure 1. A) Lateral x-ray of the right knee in which cortical hyperostosis of the tibia and fibula can be seen (arrows). B) Detail of the speculated periostosis on the right tibia (arrows).

Discussion

In total, familial aggregation can be seen in more than a third of patients with PHO^{12,13} but, apart from the described brothers, we found no other first or second degree family members with a typical phenotype. Autosomal dominant with variable expression inheritance and incomplete penetration constitutes the main method of transmission of pachydermoperiostosis; however, in some patients, heredity has been autosomal recessive or even X-linked.^{1,14,15}

The etiopathogenesis of PHO is unknown. Jajic et al¹⁶ communicated a larger prevalence of HLA-B12, but this has not been confirmed in other studies. A pathogenic role for vascular endothelial growth factor has also been suggested¹⁷ due to good responses to octeotide and the frequent finding of capillary endothelial hypertrophy in skin biopsies. Mutations in the gene coding for 15-hydroxyprostaglandin-dehydrogenase (HPGD) located on chromosome 4q33–4q34 and which would lead to high maintained concentrations of prostaglandin E2, a mediator in some processes involved in digital clubbing, skin thickening and periostosis, has recently been described.¹⁸ In addition, Rendina et al¹⁹ found an increase in the concentrations of interleukin 6 and a deregulation of the osteoprotegerin/RANKL system.

Histological studies manifested epidermal acanthosis and hyperkeratosis, different degrees of fibrosis and capillary ectasia of the dermis as well as sebaceous gland hypertrophy.¹⁵ These findings were more pronounced in the periungueal region. Bone tissue showed cortical hyperostosis and a thickening of the periosteum with bands of partially hyalinized connective tissue in addition to vascular hyperplasia, with a reduction in trabecular bone. In those cases with arthritis, the synovial membrane presented vascular congestion and stromal edema, lymphocytic and monocytic infiltration and even formation of solitary lymphatic follicles.¹⁵

Symptoms of PHO usually appear during puberty and are more frequent and intense in males.^{5,6} Among the skin manifestations, as seen in our 2 cases, sebaceous hypersecretion associated to acne, hyperhidrosis, skin fold thickening or pachydermia, originating deep facial skin folds around the nose, mouth and on the forehead, as well as lower limb edema.^{1,2,5,6,13} Ptosis of the eyelids is less frequent,^{1,20,21}

as is the development of cerebroid folds on the scalp and forehead (*cutis verticis gyrata*), and the rarefaction of facial and pubic hair. Musculoskeletal manifestations are typically finger clubbing, joint (50%–70%) and bone pain, worsened by alcohol consumption, as well as joint effusion, especially on the knees and ankles, generally of a non-inflammatory nature. However, as occurred in our cases, a third of the patients had swelling, pain and functional impairment of a sufficient intensity to interfere with activities of daily living,^{5,12} which obliges a differential diagnosis with inflammatory arthropathies. In addition, co-morbidity is possible and the association of pachydermoperiostosis with ankylosing spondylitis,²² rheumatoid arthritis,¹¹ and palindromic rheumatism,²³ has been reported. The co-existence of psoriatic nail disease and PHO, with the resulting confusion with psoriatic arthritis, especially its onicopachydermoperiostosis variant, has been described.^{24,25} In pachydermoperiostosis, in contrast to secondary hypertrophic hyperostosis, it is rare to see symmetric arthritis with an intense inflammatory component or villonodular synovial proliferation.¹⁴ Pachydermia with minimal bone disease can be seen as can prominent bone and joint manifestations without pachydermia.^{5,26,27} Other manifestations are gynecomastia, dental abnormalities²⁸ and a delay in cranial suture formation when the disease is present during the earliest stages of growth.²⁹

During the progression of PHO, compressive neuropathy can develop, mainly peripheral as in carpal (or tarsal) tunnel syndrome and, rarely, femoral head osteonecrosis.³⁰ Bone marrow insufficiency can also be seen rarely associated with massive endosteal hyperostosis.¹

Simple x-rays permit the evaluation of hyperostosis of the ribs, cranium, and pelvis, but it is especially useful for long bones analysis of the diaphysis, metaphysis and epiphysis. Another frequent finding is acro-osteolysis of the distal phalanges.³¹ Bone scans with Tc⁹⁹ methylendiphosphonate show increased uptake in more than a third of patients, particularly in the areas of active periosteal deposit as well as in swollen joints.¹ Although seldom performed, thermography has shown hypothermia, occasionally intense, in the acral parts of the extremities. Capillaroscopy usually shows dilated and tortuous vessels.²

More than 20% of patients with PHO present hypertrophic gastritis or gastric ulcer, as well as elevated concentrations of pepsinogen^{2,32,33}; however, other gastric processes can be considered as casual associations, such as gastric polyps, gastric adenocarcinoma,³⁴ Crohn's disease,³⁵ or protein-losing enteropathy. There are also anecdotal cases of skin co-morbidities such as facial squamous carcinomas,³⁷ popular mucinosis,³⁸ palmoplantar keratoderma,³⁹ or pyoderma gangrenosum.⁴⁰

The diagnosis is established from clinical and radiological data. It is necessary to exclude secondary forms of hypertrophic osteoarthropathy, which are much more frequent (95% cases), especially those associated to lung neoplasia⁴¹ and, to a lesser degree, to hepatic cirrhosis, cardiopathy, chronic obstructive pulmonary disease, bronchiectasia, and some forms of cancer.^{42,43}

Non-steroidal anti-inflammatory drugs are employed as symptomatic treatment of joint and bone pain, and when refractory oligoarthritis is present, joint infiltration with steroids can be employed.¹⁵ There is no consensus about on background medication, but good results have been shown in isolated cases or series of patients with the following drugs: octreotide,¹⁷ colchicine,⁴⁴ retinoids,⁴⁵ tamoxifen citrate,^{46,47} and bisphosphonates.^{48,49} Colchicine and retinoids improved skin manifestations, while tamoxifen and bisphosphonates significantly alleviated musculoskeletal symptoms, especially joint and bone pain. The use of tamoxifen was based on a prior finding of overexpression of nuclear receptors for steroids, associated to reduced levels of cytosol receptors for androgens and progesterone,⁵⁰ making the reduction of estrogen activity a therapeutic strategy in PHO. The administration of bisphosphonates has the objective of reducing the degree of bone remodeling, which is increased in the active stages of the disease.^{48,49,51} Plastic surgery is reserved for those patients with significant eyelid ptosis⁵² or those with severe aesthetic problems.^{52,1} In our patients, as a symptomatic treatment and to reduce the possibility of gastropathy due to non-steroidal anti-inflammatory drugs, etoricoxib was employed. On the other hand, oral risedronate was used for the control of rheumatic manifestations with good clinical results.

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