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

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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. 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 (periostitis) con neoformación ósea subcortical. Describimos los casos de 2 hermanos de 30 y 24 años, que consultaron por dolores óseos, artralgias y derrames articulares 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 risedronate (35 mg/semana).

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Introduction

Pachydermoperiostosis or primary hypertrophic osteoarthropathy (PHO) is a hereditary disease characterized by finger clubbing, periostitis, 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.1-4 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...
latter 2 the ones capable of inducing confusion when diagnosing the disease. 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 focal 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 intramuscular gold salts, with little response.

Figure 1. A) Thickening of the facial skin folds. B) Digital clubbing and round nails.
Heredity has been autosomal recessive or even X-linked. In some patients, 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.14,15

The epidemiology 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 octeotride and the frequent finding of capillary endothelial hypertrophy in skin biopsies. Mutations in the gene coding for 15-hydroxiprostaglandin-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 (IL)-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 perungual region. Bone tissue showed cortical hyperostosis and a thickening of the periostium 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 hyperplasia, with a reduction in trabecular bone. In those cases with arthritis, the synovial membrane presented vascular congestion and hyperplasia, with a reduction in trabecular bone. In those cases with arthritis, the synovial membrane presented vascular congestion and hyperplasia, with a reduction in trabecular bone.

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, hyperhydrosis, skin fold thickening or pachydermia, originating deep facial skin folds around the nose, mouth and on the forehead, as well as lower limb edema.12,13,15 Ptosis of the eyelids is less frequent1,16,19 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.3,12 This obliges a differential diagnosis with inflammatory arthropathies. In addition, co-morbidity is possible and the association of pachydermoperiostosis with ankylosing spondylitis,22 rheumatoid arthritis,23 and polyarthritis nodosa has been described.24 In pachydermoperiostosis, in contrast to secondary hypertrophic hyperostosis, it is rare to see symmetric arthritis with an intense inflammatory component or villonodular synovial proliferation.24 Pachydermia with minimal bone disease can be seen as can prominent bone and joint manifestations without pachydermia.5,12,13,25 Other manifestations are gynecomastia, dental abnormalities26 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.10 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 distal phalanges.31 Bone scans with TC99 methylendiphosphonate show increased uptake in more than a third of patients, particularly in the areas of active periostic 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

**Discussion**

In total, familial aggregation can be seen in more than a third of patients with PHO5,6,13 but, apart from the described brothers, we found no other first or second degree family members with a typical phenotype. Autosomic 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.14,15

The ethiopathogenesis 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 octeotride and the frequent finding of capillary endothelial hypertrophy in skin biopsies. Mutations in the gene coding for 15-hydroxiprostaglandin-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 (IL)-6 and a deregulation of the osteoprotegerin/RANKL system.

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**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).
More than 20% of patients with PHO present hypertrophic gastritis or gastric ulcer, as well as elevated concentrations of pepsinogen. However, other gastric processes can be considered as casual associations, such as gastric polyps, gastric adenocarcinoma, and Crohn’s disease, or protein-losing enteropathy. There are also anecdotal cases of skin co-morbidities such as facial squamous carcinomas, popular mucinosis, palmpomural keratoderma, or pyoderma gangrenosum.

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 neoplasia and to a lesser degree, to hepatic cirrhosis, cardiopathy, chronic obstructive pulmonary disease, bronchiectasis, and some forms of cancer.

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. 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, colchicine, retinoids, tamoxifen citrate, and biphosphonates. Colchicine and retinoids improved skin manifestations, while tamoxifen and biphosphonates 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 making the reduction of estrogen activity a therapeutic strategy in PHO. The administration of biphosphonates has the objective of reducing the degree of bone remodeling, which is increased in the active stages of the disease. Plastic surgery is reserved for those patients with significant eyelid ptosis or those with severe aesthetic problems. 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 risperedone was used for the control of rheumatic manifestations with good clinical results.

References

