

Review Article**Pachydermoperiostosis (Touraine–Solente–Gole syndrome) imitating Acromegaly****Richmond Ronald Gomes**

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Abstract.

Pachydermoperiostosis (PDP), also known as Touraine-Solente-Golé syndrome/Rosenfeld-Kloepfer syndrome/primary or idiopathic Hypertrophic osteoarthropathy, is an autosomal-dominant/autosomal recessive inherited disorder with variable expression. In its complete form, it is characterized by pachyderma (thickening of the facial skin), skeletal changes (periostosis), excessive sweating (hyperhidrosis), and acropachia (digital clubbing) and presents usually at puberty. At least two gene mutations have been implicated, namely 15-hydroxyprostaglandin dehydrogenase (15HPGD) and SLCO2A1. Clinical manifestations of PDP are thought to relate to excessive collagen formation and dysregulation of matrix proteins because of fibroblastic hyperactivation. Disease progresses for 5–20 years before stabilizing. We describe a case of 25 year old male who presented with thickened skin on the face and scalp (resembling cutis verticis gyrata), palmoplantar hyperhidrosis and clubbing. The patient required a close follow-up because of complications that might develop on the long-term.

Key Words: Pachydermoperiostosis, Hypertrophic, osteoarthropathy, pachyderma, hyperhidrosis, acropachia

Introduction

PDP is the primary form of hypertrophic osteoarthropathy (HOA) which should be distinguished from the secondary form of HOA, which is much more frequent and mostly associated with severe pulmonary disease, bronchogenic carcinoma, lung empyema, bronchiectasis, congenital heart disease, and thyroid or GI malignancy 1. It was first described by Friedreich² in 1868, who called it 'Hyperostosis of the entire skeleton'. In 1907, Unna named the term 'cutis verticis gyrate' for thick, transversely folded skin of scalp and forehead.³ In 1935, three dermatologists, Touraine, et al,⁴ recognized this condition as a familial disorder with three forms: complete (periostosis and pachyderma), incomplete (without pachyderma) and the forme fruste (pachydermia with minimal skeletal changes). In 1965, Rimoin⁵ observed affected persons in successive generations.

Jajic estimated the prevalence of the disease is 0.16%.^{6,7} Symptoms usually appear around puberty, with a male to female ratio of 7:1, and males are severely affected.⁸ In a review of 68 published families with PDP, including 204 patients, Castori et al⁷ found that 37 families

showed autosomal dominant inheritance and autosomal recessive inheritance was suggested in the remaining families. The main features are digital clubbing, skin changes (flushing, blanching, hyperhidrosis and hypertrophy) causing coarse facial features with thickening, furrowing and excessive oiliness of the skin of the face and forehead. Bone and joint involvement includes arthritis, arthralgia, periosteal new bone formation, subperiosteal ossification, acro-osteolysis and osteoporosis. Gastric hypertrophy, gastric ulcer and other endocrine abnormalities have been described. This condition progresses slowly for a few years and is self-limiting thereafter.⁹

The pathogenesis of PDP is not fully known. The 15-hydroxyprostaglandin dehydrogenase gene and the solute carrier organic anion transporter family member 2A1 have been found to be associated with PDP^{10,11,12,13}. It is thought that increased levels of prostaglandin E₂ (PGE₂) as a result of defective selective uptake across the plasma membrane by solute carrier organic anion transporter family member 2A1 and/or intracellular degradation by 15-hydroxyprostaglandin dehydrogenase is central to the pathogenesis of PDP^{14,15,16}. Elevated PGE₂ levels are hypothesized to induce cytokine-mediated tissue remodeling and vascular stimulation, leading to hyperhidrosis, acro-osteolysis, periostosis, arthritis, and pachyderma as seen in PDP patients¹⁷.

Case report

A 22 years old student from rural Bangladesh, presented to our outpatient department with the complaints of pain small joints of both hands and feet for 2 years. The pain was insidious in onset, throbbing in nature and not relieved by over-the-counter medications. There was neither morning stiffness nor back pain or sole pain. The patient also complained of profuse sweating, progressive enlargement of hands and feet and gradual coarsening of facial features. His family history was significant for consanguinity – his grandparents have a consanguineous relationship. There was otherwise no history of a similar illness in the family members, and this was the first time the patient sought medical attention for this issue. There was no history of scalp dandruff or rashes, and the patient denied having symptoms such as fatigue, eye redness, eye or mouth dryness, chest pain, or exertional dyspnea. There was no history of fever, palpitations, heat intolerance, tremors, trauma or fracture.

On examination, he had leonine facies with pronounced folds in the

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area of forehead, between the eyes, in the nasolabial grooves and on the chin, furrowing on his forehead skin (Figure 1). His nose was excessively enlarged with thickened skin folds. The development of the patient's skin folds was insidious and progressive. Clubbing of his fingers and toes (Figure 2 and 3) was noticed. Patient has profuse sweating and seborrhea in his axillae, hands, and feet. Cardiovascular, respiratory, neurological, and thyroid examination performed for the patient was otherwise unremarkable. There was no scalp dandruff, rashes, joint swelling, psoriatic nail changes, subcutaneous nodules, or eye redness noted on examination.

Laboratory analyses showed normal erythrocyte sedimentation rate, C-reactive protein, random blood sugar, serum calcium, liver function tests, renal function tests and thyroid function tests. Negative results were obtained for rheumatoid factor, anticyclic citrullinated protein (anti-CCP) antibodies, ANA and HLA-B27. As there was a suspicion of acromegaly, performed an oral glucose tolerance test; the results of both of these tests were normal. Radiography of the skull showed mild cortical and subperiosteal thickening (Figure 4). X ray of tibia and fibula demonstrated irregular subperiosteal newbone formation and cortical thickening of tibia and fibula (Figure 5). The x-rays of



Figure 1, 2 and 3: Furrowing of forehead, clubbing of fingers and toes with swollen both ankle joints

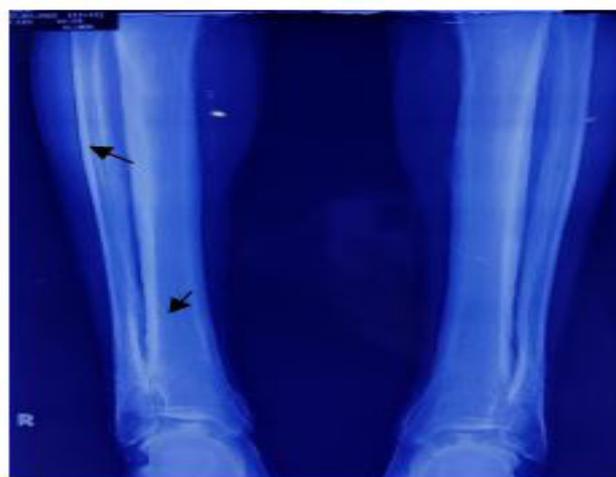


Figure 4, 5 and 6: X-ray skull showed mild cortical and subperiosteal thickening (black arrow), X ray of tibia and fibula demonstrated irregular subperiosteal newbone formation and cortical thickening of tibia and fibula (black arrow), x-rays of bilateral hands showed soft tissue tumefaction, particularly in the distal phalanges and periostitis and hyperostosis of metacarpal and proximal phalanges.

bilateral hands showed soft tissue tumefaction, particularly in the distal phalanges and periostitis and hyperostosis of metacarpal and proximal phalanges (Figure 6). Patient refused for skin biopsy and Urinary PGE-2 level was not available in our country. Based on pachydermia, digital clubbing, and typical radiologic findings of diffuse periostosis, a diagnosis of the complete form of pachydermoperiostosis was established.

The patient stayed in our center for 7 days and was managed with steroids (Prednisolone 7.5 mg PO, OD), oral bisphosphonate (risedronate 35 mg once weekly), oral propanthelene (15 mg twice daily) and isotretinoin ointment. The joint pain and swelling improved markedly with treatment. He was subsequently discharged with outpatient follow-up scheduled 1 month later. On follow-up, it was found that his joint pain and swelling was minimal and the pachyderma had reduced gradually since discharge. The patient experienced no relapses or complications from the condition or the medications. He refused for plastic surgical referral due to financial constraints.

Discussion

PDP or Touraine-Solente-Gole syndrome is the primary form of HOA. Although an autosomal dominant inheritance with incomplete penetrance and variable expression has been confirmed, both autosomal recessive and X-linked inheritance has been suggested.⁷ PDP is related to mutations of the gene encoding for 15-hydroxyprostaglandin dehydrogenase (15HPGD)¹⁰. PDP patients have high levels of PGE₂ and decreased levels of PGE-M (the metabolite of PGE₂). PGE₂ can mimic the activity of osteoblasts and osteoclasts, which may be responsible for the acro-osteolysis and periosteal bone formation.¹¹ PGE₂ also has vasodilatory effects, which may be responsible for prolonged local vasodilation resulting in digital clubbing.¹¹ A familial history is found in 25 to 38 percent of patients. Our patient did not have family history.

PDP makes 3%-5% of cases of hypertrophic osteoarthropathy and should be distinguished from the secondary form before a diagnosis of PDP is established.¹⁸ The secondary form usually results from cardiopulmonary diseases (eg, bronchiectasis, cystic fibrosis, congenital heart diseases, and tuberculosis), hepatic diseases (eg, portal and biliary cirrhosis), gastrointestinal diseases (eg, inflammatory bowel disease and polyposis), and certain malignancies (eg, Hodgkin's disease, nasopharyngeal carcinoma, and chronic myeloid leukemia). Clinically, in secondary form, the cutaneous findings (pachydermia, seborrhea, oiliness) are less frequent than primary PDP; the osteoarthropathy is more severe and painful, especially with congenital cyanotic heart disease.¹⁹ In secondary form due to neoplasia, only treatment of the underlying illness causes improvement of the associated symptoms.²⁰

Other differential diagnoses include acromegaly, thyroid acropathy, van Buchem's disease (in which there is absence of clubbing and skin changes), psoriasis, and rheumatoid arthritis. Patients with forme frusta have to be differentiated from the rare hyperelasticity disorders such as Ehler-Danlos syndrome, cutis laxa, Meretoga's syndrome, Marfan's syndrome, and pseudoxanthoma elasticum, which may cause forehead furrows.²¹

In up to 30% of the patients, PDP presents as a hereditary disease with autosomal dominance of variable penetrance. Although pathogenesis

is currently unknown, an increased level of prostaglandin E₂ which motivates the overexpression of the vascular endothelial growth factor has been proposed as a main factor. Due to high M:Fratio, X-linked transmission and role of testosterone hormone have been suggested as other factors.²² Recently, hydroxyprostaglandin dehydrogenase (HPGD) and solute carrier organic anion transporter family member 2A1 (SLCO2A1) were described as pathogenic genes responsible for PDP. When germline SLCO2A1 mutations are detected, myelofibrosis, a life-threatening complication, should be suspected and individual followed up periodically. Alcoholic consumption might be a contributing factor by alteration of prostaglandin metabolism.²³ Unfortunately, genetic testing for our reported case was not available at our center.

The diagnostic criteria for pachydermoperiostosis^{9,24} are:

• **Major criteria:** pachyderma, periostosis, finger clubbing.

• **Minor criteria:** hyperhidrosis, arthralgia, gastric ulcer, cutis verticis gyrate, blepharoptosis, joint effusion, column-like legs, edema, seborrhea, acne, flushing. Our patient had all three major criteria i.e., hyperostosis, finger clubbing, and pachyderma. Martinez-Lavin¹³ proposed the pathology for pachydermoperiostosis is due to increased amount of proliferation of collagen fibers from actively proliferating fibroblasts.

Pachydermia²⁵—which affects the face and limbs—is the most frequent skin symptom.

The grading of pachyderma is as follows – grade 0:- absence, grade 1:- mild to moderate involvement (cutaneous thickening without puckering), grade 2:- severe (cutaneous thickening and puckering). Patients may also present with seborrhea (90% of cases), acne, folliculitis, dilated pores, hyperhidrosis of the palms and soles (44–67% of cases) may be associated with flushing, thickened eyelids (30–40% of cases), cutis verticis gyrate (24% of cases), and reduced facial and pubic hair. Digital clubbing is seen in 89% of cases and nail bed capillary microscopy shows slight capillary enlargement and increased tortuosity. Arthritis is seen in 20–40% of cases²⁶ and a joint effusion is seen in 41%. Irregular periosteal ossification affects predominantly the distal ends of long bones seen in 80–97% of patients.

A range of processes (some malignant) has been reported in association with pachydermoperiostosis. These include facial epidermoid carcinoma,²⁰ hypertrophic gastritis, peptic ulcer, gastric adenocarcinoma,²⁷ Crohn's disease, and myelofibrosis.²⁸ As a consequence of increased soft tissue bulk and hyperostosis, complications may arise such as ptosis, compression of the nerve endings, hearing problems, kyphosis, arthrosis, osteonecrosis of the femoral head, and carpal tunnel syndrome.

Variants of pachydermoperiostosis include Rosenfeld-Kloepfer syndrome (characterized by enlargement of the jaws, especially mandible, and of the hands and feet, nose, lips, tongue, and forehead, along with cutis verticis gyrate and corneal leukoma); Currarino idiopathic osteoarthropathy (an incomplete form of PDP seen in children and adolescents and characterized by the presence of eczema and sutural diastases); and a localized form with only the radiographic features of PDP in the lower extremities.

The diagnosis was confirmed by histopathological study. Histopathological examination of skin samples taken from patients with PDP shows epidermal acanthosis and hyperkeratosis, different degrees of

fibrosis and capillary ectasia of the dermis as well as sebaceous gland hypertrophy. Bone biopsy showed cortical hyperostosis and thickening of the periosteum with bands of partially hyalinized connective tissue in addition to vascular hyperplasia, with a reduction in trabecular bone. In cases with arthritis, the synovial membranes showed vascular congestion and stromal edema, lymphocytic and monocytic infiltration, and formation of solitary lymphatic follicles.^{29,30} Radiographs of the hands and feet show joint space narrowing, swelling in the soft tissues, and acro-osteolysis of the distal phalanges. There is also symmetrical periostosis that is more prominent in the distal lower limbs.³¹

This syndrome can be distinguished from acromegaly on the basis of clinical features and laboratory findings. In contrast to PDP, acromegaly presents clinically with larger bones in the face, skull and limbs, jaw prognathism, along with elevated insulin-like growth factor-1 levels and positive oral glucose tolerance test.^{32,33,34} Acromegaly is often caused by a pituitary tumor, and the potential manifestations of the tumor's local compression and hormonal disruption additionally help to distinguish it from PDP. In our patient, closer scrutiny in the clinical examination coupled with the negative biochemical markers for acromegaly effectively allowed us to rule out this differential.

The case presented here is a complete form of the syndrome, with the presence of most of the clinical characteristic and radiological findings. The patient had significant joint involvement and severe digital clubbing, and the presence of bony excrescences was detected in the X-rays of his hands and feet. In this case, cutis verticis gyrata affected only his forehead and small area of the scalp. Furthermore, although this syndrome has a strong association with heredity, in this case, there was no report of relatives with similar characteristics.

No specific treatment exists; however, in most cases, PDP tends to stabilize over time. Conventional PDP drug treatments to decrease inflammation and pain include aspirin, NSAIDs and corticosteroids.³⁵ Rheumatologic symptoms can be improved by treatment with bisphosphonates, such as pamidronate or risedronate.³⁵ In isolated cases, tamoxifen was effective in PDP treatment, especially for bone and joint pain.³⁵ Retinoids are used to improve skin manifestations. Isotretinoin improves cosmetic features by inducing apoptosis within human sebaceous glands. As a result, the increase of connective tissue and hyperplasia of sebaceous glands is inhibited. Retinoids also decrease procollagen mRNA in fibroblasts, improving pachyderma and cutis verticis gyrata.^{36,37} Colchicine can also improve articular symptoms and skin manifestations such as folliculitis, and pachyderma.³⁵ The use of Botulinum toxin type A (BTX-A) may improve the leonine facies. Da Costa et al reported the use of infliximab in a patient with refractory arthritis.³⁸ Surgical methods, including facelifts and facial rhytidectomy, have also been used to improve facial appearance.³⁹

Conclusion

The diagnosis of PDP is based on the combination of digital clubbing, periostitis and pachyderma with the absence of any cardiovascular, pulmonary, liver, intestinal and mediastinal diseases. Since PDP is a disease associated with stigmatization and a consequent reduction in the patient's quality of life, diagnosis of its various clinical forms and regular follow-up by a team that includes a plastic surgeon, rheumatologist, and orthopedic are factors of ultimate importance. Clinical

presentations of PDP can be confused with secondary hypertrophic osteoarthropathy, psoriatic arthritis, rheumatoid arthritis, thyroid acropachy, and acromegaly. Awareness of the significance of clubbing under these circumstances is likely to prevent misdiagnosis.

Conflict of interest: None declared

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