



Complete pachydermoperiostosis with diffuse keratoderma mimicking thyroid Acropachy: A case report and review of literature

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Abstract

Pachydermoperiostosis (PDP) is a rare genodermatosis with prominent cutaneous, soft tissue and skeletal manifestations. It can mimic secondary causes of hypertrophic osteoarthropathy such as thyroid acropachy. Cutaneous manifestations can be debilitating and constitute critical clues to formulating an accurate diagnosis. Palmoplantar keratoderma is a seldom reported manifestation of the disease hence, its significance as a phenotypic variant of pachydermoperiostosis is unknown.

We describe a rare case of complete pachydermoperiostosis with diffuse palmoplantar keratoderma in a young African man presenting with hyperhidrosis, hyper-defecation and weight loss who had been previously misdiagnosed with thyroid acropachy. The aim is to provide a detailed clinical description of both common and unconventional features of this rare disease.

Pachydermoperiostosis manifests with diverse genotypic and phenotypic characteristics that can mimic treatable, secondary causes of hypertrophic osteoarthropathy. Keratoderma and hyper-defecation are seldom reported manifestations that may represent unique variants of PDP. Awareness of characteristic dermatological manifestations of the disease can enhance early and accurate clinical diagnosis and prevent needless investigations.

Keywords: *Pachydermoperiostosis, primary hypertrophic osteoarthropathy, Touraine-Solente-Gole syndrome, pachydermia, thyroid acropachy, keratoderma*

Introduction

Pachydermoperiostosis (PDP) also known as

Touraine-Solente-Gole syndrome is a rare genetic disease with prominent and distinctive cutaneous, soft tissue and skeletal manifestations. It can be easily confused with various musculoskeletal and endocrine disorders including juvenile rheumatoid arthritis, acromegaly and thyroid disease. Various genotypic and phenotypic variants of the disease may contribute to the diagnostic dilemma. Here we illustrate a case of complete PDP misdiagnosed as

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thyroid acropachy who presented with rare symptoms of hyper-defecation and keratoderma in addition to other classical symptoms of PDP.

Case report

A 21-year-old African man of Yoruba lineage was referred to our dermatology clinic from the endocrinology department where he was being investigated for suspected thyroid disease. His symptoms began 10 years earlier around the onset of puberty when he developed debilitating hyperhidrosis on his palms and soles. The hyperhidrosis had progressively gotten worse and was aggravated by anxiety and emotional distress. It significantly interfered with activities such as writing, the use of devices requiring fingerprint recognition, and social interaction with friends. There was no history of anterior neck swelling, heat intolerance, or palpitations but he had been experiencing excessive bowel movements with an increase in the frequency of stooling from once a day to 3-5 motions per day. Stools passed were of normal consistency and color and were devoid of visible blood. He did not have abdominal cramps, bloating, or a change in appetite. He however had significant unintentional weight loss which had become worrisome.

He developed furrowing of his facial skin, thickening of his eyelids, and recession of his eyes with progressive deterioration in his vision 8 years before. He required wearing glasses with an extremely thick lens to visualize fine print. He could not ascertain the diagnosis of his visual impairment and temporarily declined referral for further assessment by the ophthalmologist due to dwindling finances. He had noticed disproportionate enlargement of his hands and feet, thickening of his palms and soles, bulbous enlargement of his fingertips and progressive swelling of his knees and ankle joints a few years earlier. He did not have joint pains, recurrent headaches or a rapid increase in height. There was no history of seizures, hearing impairment, or learning difficulties.

The patient was born to non-consanguineous parents who were symptom-free. Neither his siblings nor parents had visual impairment. No other close relative had similar symptoms. His past medical history was significant for umbilical herniorrhaphy performed when he was an infant and a history of recurrent bullous skin eruptions that

healed with hyperpigmentation (**figure 1**) following exposure to drugs that contained sulpha (fixed drug eruption). He had no history of seizures, cardiovascular disease, diabetes, or renal impairment. He did not consume alcohol, smoke cigarette, or use any form of recreational drugs.

Physical examination revealed a young man with distinctive facies characterized by deep and thick cerebriiform forehead wrinkles, marked seborrhea and moderately severe acne (**figure 2**). He had sweaty spade-like hands, large feet, column-like legs, grade IV digital clubbing involving all 20 digits and diffuse palmoplantar hyperkeratosis (**figure 3**). The base of the fingers showed firm bulbous swellings around the proximal nail folds of most of the fingers (**figure 4**). Multiple irregularly shaped well demarcated non-scaly hyperpigmented patches measuring 3-5 cm in diameter (**figure 1**) were noticed scattered in various locations on the trunk and proximal aspects of the upper limbs. Findings on abdominal, cardiovascular, neurological and respiratory examinations were normal.

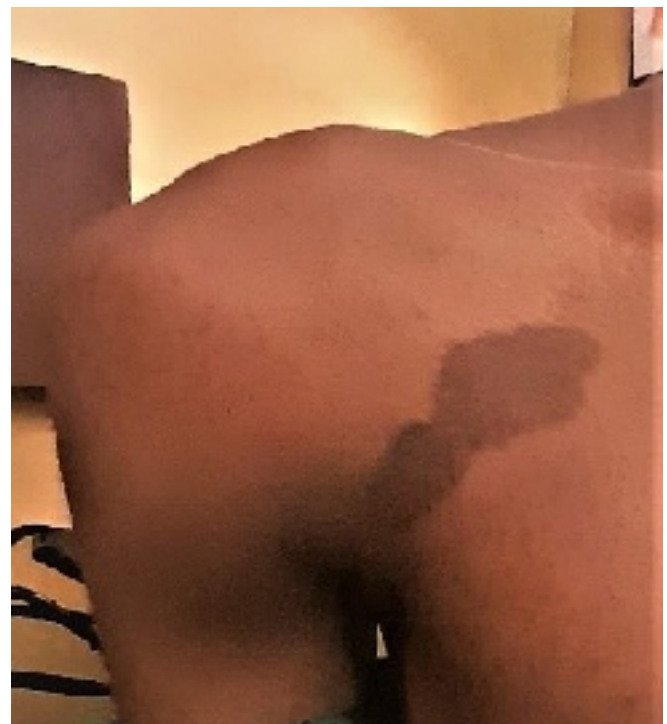


Figure 1: Prominence of the shoulder joints with loss of the natural rounding of the shoulder. Hyperpigmented patches represent post-inflammatory erpigmentation following fixed drug eruption.



Figure 2: Cerebriform wrinkling of the forehead, blepharoptosis, seborrhea, acne, and prominent thickening of the lips.



Figure 3: Spade-like hands with diffuse palmar keratoderma in the patient (right upper photograph). A closer view (image below) highlights bulbous swelling around the proximal nail fold (white arrows)



Figure 4: Clubbed toes, column-like legs with swelling around the knees and ankles bilaterally

Laboratory tests for HIV, thyroid function, screening for diabetes mellitus, hematocrit and white cell count, liver and renal function as well as cardiovascular work-up including echocardiography and electrocardiography were carried out and were all normal. X-rays of the hands, knees, and feet (**figure 5**) showed shaggy subperiosteal bone formation with preserved joint spaces.

A diagnosis of pachydermoperiostosis (PDP) was made with the patient fulfilling all three components of the major diagnostic criteria (pachydermia, periostosis and finger clubbing) and additional components of the minor criteria (seborrhea, acne, hyperhidrosis, and column-like legs) for the diagnosis of PDP.¹ Co-morbid palmoplantar keratoderma (based on diffuse thickening of the palms and soles) and cutaneous adverse drug reaction to sulphonamides were also noted. Secondary hypertrophic osteoarthropathy was excluded by normal findings on systemic examination and relevant laboratory tests.

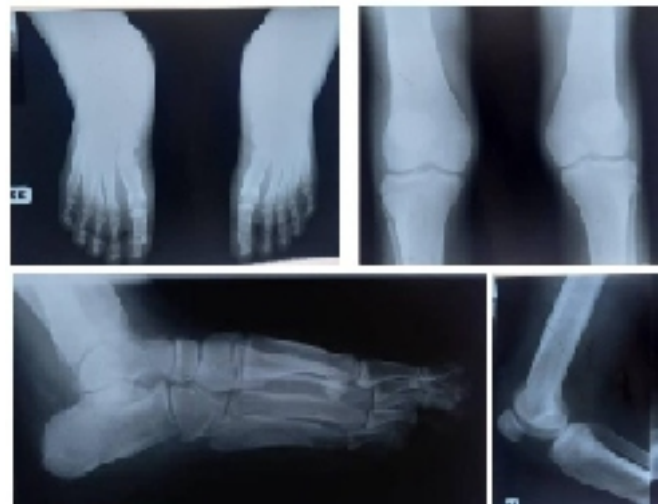


Figure 5: Radiographs of the patient’s feet and legs showing symmetric shaggy subperiosteal sclerosis in the diaphysis of the distal femur and metatarsal bones bilaterally

The patient was counseled and placed on topical retinoids for the seborrhea/acne and aluminum chloride powder for the hyperhidrosis with

significant clinical improvement (**figure 6**). Genetic testing could not be performed due to a lack of laboratory support; however, he was referred to the gastroenterologist and ophthalmologists for further evaluation and multidisciplinary care.



Figure 6: Visible improvement in acne and seborrhea following retinoid therapy (left photo – before retinoid therapy right photo- after topical retinoid therapy)

Discussion and literature review

This case illustrates both typical and atypical presentations of pachydermoperiostosis and its tendency to mimic other causes of hypertrophic osteoarthropathy particularly thyroid disease. PDP can be easily confused with thyroid acropachy due to shared symptoms of hyperhidrosis and hypertrophic osteoarthropathy. In the index case, the presence of hyper-defecation and weight loss further contributed to the diagnostic confusion. In addition, the rarity of PDP makes it less likely to be the first diagnosis considered by non-specialists who may be unaware of the diagnostic implication of other prominent cutaneous manifestations. As such the subject was first referred to the endocrinologist as a case of thyroid acropachy based on a history of hyperhidrosis, hyper-defecation, weight loss, and prominent finger clubbing. However, his thyroid function tests were normal, and the presence of striking cutaneous features particularly the prominent forehead furrows raised suspicion of the possibility of an alternative diagnosis hence the referral to the

dermatologist.

The true global prevalence of PDP is unknown. One report estimates a prevalence of 0.16%, with a striking male preponderance of ratio 9:1.^{2,3} Family history is present in only about 25 – 38 % of cases. The mode of inheritance is variable, with various reports documenting autosomal dominant, autosomal recessive, and x-linked patterns.⁴⁻⁶ According to Castori et al,⁴ the onset of symptoms appears to coincide with puberty as observed in the index case. This suggests that hormones may play a significant role in the pathogenesis of the disease. This hypothesis though yet to be proven is probably true. Gender differences have been shown to exist not only in epidemiology but also in the clinical features of the disease.^{3,7,8} Biologic males tend to have the more severe musculoskeletal disease and more prominent cutaneous involvement than females.⁷

Mutations in either one of two genes: (a) Hydroxyprostaglandin dehydrogenase (HPGD) and (b) Solute Carrier Organic Anion Transporter 2A1 (SLCO2A1) have been implicated in the pathogenesis of the diseases.^{4,5,9,10} These genes are involved in the degradation and metabolism of prostaglandin E2(PGE2).^{4,5,9} HPGD gene encodes the 15-hydroxyprostaglandin dehydrogenase enzyme involved in the degradation of PGE2 while SLCO2A1 encodes the prostaglandin transporter responsible for cellular uptake of PGE2.^{5,11} Mutations in either gene can cause elevated circulating and urinary levels of PGE2. Subjects with SLCO2A1 mutation additionally have increased urinary PGE-M (a metabolite of PGE2).¹¹ Although elevated PGE2 does not explain all the clinical features of PDP, it plays a central role in the pathogenesis and clinical manifestations of PDP by stimulating osteolysis and periosteal bone formation leading to increased bone turnover. It is also responsible for the prominent digital clubbing associated with PDP, through its vasodilatory effects and may be implicated in the increased prevalence of patent ductus arteriosus and myelofibrosis in subjects with PDP.¹¹⁻¹⁴

Three main distinctive variants of PDP were described by Touraine et al in 1935 based on the predominant clinical manifestations.¹⁵ These include Complete PDP- characterized by a triad of characterized by pachydermia, digital clubbing, and

periostosis, Fruste PDP; in which the patient presents with prominent pachydermia with minimal skeletal changes, and Incomplete PDP: skeletal changes without pachydermia. Various cutaneous and extra-cutaneous disorders have also been described in association with PDP. These include folliculitis, palmoplantar keratoderma, gynecomastia, congenital heart disease, and hematological and gastrointestinal disease.^{5,8,11,16,17}

Diffuse palmoplantar keratoderma (hyperkeratosis) is not a common finding in complete forms of PDP.^{6,18-20} A few cases of a triad of keratoderma, digital clubbing, and hyperhidrosis have however been previously documented.^{10,21,22} Stephan et al¹⁰ established HPGD mutation in one patient with this triad. However, other cutaneous findings including pachydermia were absent from their description of the case.¹⁰ As such, a triad of keratoderma, digital clubbing, and hyperhidrosis may represent minimally expressed phenotypes of fruste variants of the disease suggesting there may be more than three variants of the disease as originally described by Touraine et al. Ocular manifestations characterized by troublesome ptosis and blepharitis are common clinical manifestations.⁴ The case presented had both blepharoptosis (**figure 2**) and severe visual impairment. Other ocular symptoms that have been previously reported include floppy eyelid syndrome, corneal leukoma, presenile cataract, and macular dystrophy.^{23,24} All though the underlying cause of the visual impairment could not be ascertained in the index case, severe visual impairment with severely diminished visual acuity has been previously documented in patients with pachydermoperiostosis²⁵ and as such may be an extracutaneous manifestation of the disease.

Although genetic analysis was not performed, we postulate that the presence of severe palmoplantar keratoderma, severely diminished visual acuity and hyper-defecation may be manifestations of a unique variant of PDP with a distinct genotypic blueprint. It is also plausible that beyond HPGD and SLCO2A1 mutations, other factors including gender and hormones may play a role in the etiopathogenesis and clinical expression of the syndrome.^{3,7,8,11} Subjects with SLCO2A1 mutation have an increased frequency of anemia which may be severe probably due to associated occult hematochezia and/or myelofibrosis.¹¹ They also have more

prominent gastrointestinal manifestations.¹⁸ A syndrome of chronic persistent gastrointestinal bleeding, multiple intestinal ulcers, edema and abdominal pain associated with SLCO2A1 mutation has been described and termed “chronic enteropathy associated with SLCO2A1(CEAS)”.¹⁶ This disorder is frequently associated with PDP, particularly in males. In a study by Umeno et al,¹⁶ at least one or more features of PDP were present in 30% of subjects with CEAS with 11% of them having complete PDP. In the same study, more than half of male subjects with CEAS had associated clinical features of PDP. The case highlighted had a history of hyper-defecation, however recurrent abdominal pain, bloating and gastrointestinal bleeding were absent.

Given the diversity of clinical manifestations of PDP, making a clinical diagnosis can be quite challenging. Borochowitz¹ proposed diagnostic criteria for PDP consisting of 4 major criteria: family history of PDP, Pachydermia, digital clubbing, and presence of clinical or radiological evidence of bone involvement) and the following minor criteria: hyperhidrosis, arthralgia, gastric ulcer, cutis vertices gyrata, blepharoptosis, joint effusion, column-like leg edema, seborrhea, acne and flushing.¹⁹ A diagnosis of PDP can be made in the presence of two or more major criteria.^{1,19}

Although the diagnosis of PDP can be made clinically, it is imperative to obtain laboratory or radiological evidence of the disease. Plain radiographs of the hands and feet and other joints can help establish a diagnosis of periosteal proliferation, soft tissue swelling and joint effusion. In addition, pulmonary causes of secondary hypertrophic osteoarthropathy can also be detected using a plain radiograph. Screening for urinary PGE2 and PGE-M can also be useful, particularly in resource-limited settings where genetic testing may be unavailable. Endoscopic evaluation of the gastrointestinal tract may be required particularly in those with prominent gastrointestinal symptoms and anemia. Other investigations should be tailored and guided by the clinical presentation.

Differential diagnoses particularly potentially treatable causes of secondary hypertrophic osteoarthropathy such as thyroid acropachy, bronchogenic carcinoma, gastrointestinal and hepatobiliary diseases must be considered and

excluded particularly in older patients presenting with incomplete forms of PDP. In those with the fruste form, differential diagnoses include other causes of cutis verticis gyrata including familial nonsyndromic forms, Ehlers Danlos syndrome, Marfan syndrome, amyloidosis, myxedema and syphilis.

The treatment of PDP is non-specific and is largely symptomatic aimed to relieve symptoms, improve aesthetic appearance and address complications such as anemia when present. Non-steroidal anti-inflammatory drugs (NSAIDs) are effective in controlling painful joint symptoms while seborrhea, acne and pachydermia improve mildly with oral isotretinoin.¹⁹ For patients with disfiguring forehead furrows and debilitating hyperhidrosis, temporary improvement in facial appearance and relief of hyperhidrosis can be achieved with the use of botulinum toxin injections.²⁶ Surgical intervention including rhytidectomy and simple skin excision may be performed to achieve sustained improvement in cosmetic appearance in patients with more profound manifestations.²⁷ Genetic testing and counseling should be offered to both patients and family members even when asymptomatic as autosomal recessive forms have been reported.

Conclusion

Pachydermoperiostosis is a rare genodermatosis with varied phenotypic manifestations that are influenced by both gene and gender. The clinical expression of the disease can be confused with thyroid acropachy from which it can be distinguished based on peculiar cutaneous findings. Awareness of distinct dermatological manifestations of the disease can enhance early and accurate clinical diagnosis and prevent needless investigations.

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