

A Complete Form of Pachydermoperiostosis Accompanied by a Pituitary Microadenoma

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Abstract: Pachydermoperiostosis is a rare genetic disease that is associated with HPGD (15-hydroxyprostaglandin dehydrogenase) and SLCO2A1 (solute carrier organic anion transporter family member 2A1) gene mutations. It is characterized by three major phenotypes, namely, pachydermia, periostosis, and digital clubbing. Clinically, misdiagnoses such as acromegaly and thyroid acropachy are commonly confused with pachydermoperiostosis. Integral medical history, physical examination, endocrinological tests, and multiple disciplinary cooperation are extremely significant in the accurate diagnosis of pachydermoperiostosis. The co-existence of pachydermoperiostosis and pituitary adenoma is rarely recorded and discussed. In this case, we present a young male patient with a complete form of pachydermoperiostosis and a nonfunctional pituitary microadenoma, which has rarely been reported.

Keywords: pachydermoperiostosis, pituitary microadenoma, acromegaly, thyroid acropachy

Introduction

Pachydermoperiostosis (PDP), also known as primary hypertrophic osteoarthropathy, is an autosomal recessive or perhaps an X-linked inherited disorder that is associated with HPGD (15-hydroxyprostaglandin dehydrogenase) and SLCO2A1 (solute carrier organic anion transporter family member 2A1) gene mutations.¹ The proteins encoded by the genes are responsible for the metabolism of prostaglandins. Increased levels of prostaglandin E2 resulting from gene mutations contribute to bone and soft tissue changes in PDP by simulating the activity of osteoblasts and osteoclasts as well as prolonging local vasodilatory effects.² PDP is characterized by pachydermia, periostosis, digital clubbing, oily skin, hyperhidrosis and arthropathy.¹ It occurs predominantly in adolescent males.² Three clinical variants of PDP were defined in 1935: the complete form, with both pachydermia, periostosis and digital clubbing (as shown in this case); the incomplete form, with periostosis but lacking cutis verticis gyrata (CVG); and the forme fruste, with classical skin changes but with minimal periostosis.³

Pituitary adenomas are one of the most common brain tumours and display an array of hormonal and proliferative activities.^{4,5} They are classified into microadenomas (size < 10 mm) and macroadenomas (size ≥ 10 mm). According to a previous literature report, the prevalence of pituitary adenomas was estimated at 16.7% (14.4% in autopsy studies and 22.5% in radiologic studies).⁵ Nonfunctional pituitary adenomas account for 14–54% of pituitary adenomas, lack clinical or biochemical evidence of hormone excess and can be referred to as clinically silent adenomas.⁶ Most pituitary tumours occur sporadically without known genetic predisposition, but in a significant minority of cases, somatic mutations and germline mutations can be identified in patients with pituitary adenomas.⁷

Pituitary adenomas are fairly common in the general population. However, the incidence of pituitary adenoma is scarcer in PDP patients. To the best of our knowledge, only a 58-year-old male with a pituitary microadenoma and a 34-year-old male with a pituitary macroadenoma have been previously reported.^{8,9} The present case reports a young male patient with a complete form of PDP and a nonfunctional pituitary microadenoma that has not been previously described.

Case Report

A 26-year-old male presented to our outpatient department with a 6-year history of digital clubbing of the fingers and a 5-year facial appearance of CVG. He had excessive excretion of facial sebum. Hyperhidrosis and arthralgia were denied. Visual symptoms were absent. He denied any similar symptoms in his family. His parents were in a nonconsanguineous marriage. On physical examination, thickening and furrowing of the facial skin, bilateral eyelid ptosis (Figure 1A), digital clubbing (Figure 1B) and enlargement of the wrist, elbow, knee, and ankle joints were observed. Laboratory tests revealed normal levels of thyroid stimulating hormone (2.910 mU/L, reference range (RR) 0.27–4.2 mU/L), free triiodothyronine (5.10 pmol/L, RR 3.60–7.50 pmol/L), free thyroxine (16.90 pmol/L, RR 12.0–22.0 pmol/L), growth hormone (GH) (0.09 ng/mL, RR 0.030–2.47 ng/mL), adrenocorticotrophic hormone (48.72 ng/L, RR 5.00–78.00 ng/L), and plasma total cortisol at 8.00 h (507.00 nmol/L, RR 133.0–537.0 nmol/L) and a decreased level of insulin-like growth factor-1 (IGF-1) (64.83 ng/mL, RR 137–278 ng/mL). Computed tomography of his chest and echocardiography were unremarkable. Radiographic examination of the long bones showed cortical thickening (Figure 1C). Contrast-enhanced magnetic resonance imaging (MRI) of the pituitary revealed a hypointense signal with a size of 3 mm×5 mm on coronal T2-weighted images (Figure 1D). The patient received diagnoses of a complete form of PDP and a nonfunctional pituitary microadenoma. He was referred to receive further gene analysis and a treatment modality with oral etoricoxib, but he refused.

Discussion

PDP is rare and is characterized by pachydermia, periostosis, and digital clubbing, as noted. Pachydermia, which usually presents as an appearance of CVG on the scalp, forehead, cheek, or chin, is the most frequent skin symptom. Periostosis of PDP might manifest as swelling of periarticular tissue and arthritis and radiographically display as periosteal thickening or reaction, commonly involving the tibia, fibula, radius and ulna.^{10,11} Digital clubbing, which often results in a drumstick appearance on the distal fingers or toes, can be determined by measuring the hyponychial angle, Lovibond angle, phalangeal depth ratio or Schamroth sign.¹⁰ Notably, diarrhoea, gastric ulcer, anaemia, hypoalbuminemia and even visual field disturbances, and blindness were also reported in PDP patients along with skin and arthrological symptoms.^{12,13} Therefore, regular follow-up monitoring is recommended for the possible association with gastrointestinal and ophthalmological involvement.

Before the final diagnosis of PDP is made, other possible diseases should be ruled out, such as acromegaly and thyroid acropachy (TA) (Table 1). Acromegaly is a rare and underdiagnosed disease that results from the overproduction of GH and IGF-1. The most common signs and symptoms are acral growth, deformity of facial features, soft tissue swelling and increased sweating.¹⁴ The systemic comorbidities related to acromegaly are variable. Digital clubbing and periostosis are not seen in acromegaly.^{11,15} Endocrine testing and pituitary MRI examination are important to confirm the diagnosis of acromegaly. Measurement of serum IGF-1 to rule out acromegaly has been recommended in any patients harbouring a pituitary adenoma, and a normal serum IGF-1 concentration is strong evidence that the patient does not have acromegaly.^{11,16} Both serum GH concentrations and IGF-1 concentrations are increased in virtually all patients with acromegaly.¹⁵ TA is a rare extrathyroid manifestation of autoimmune thyroid disease (AITD), which manifests as soft

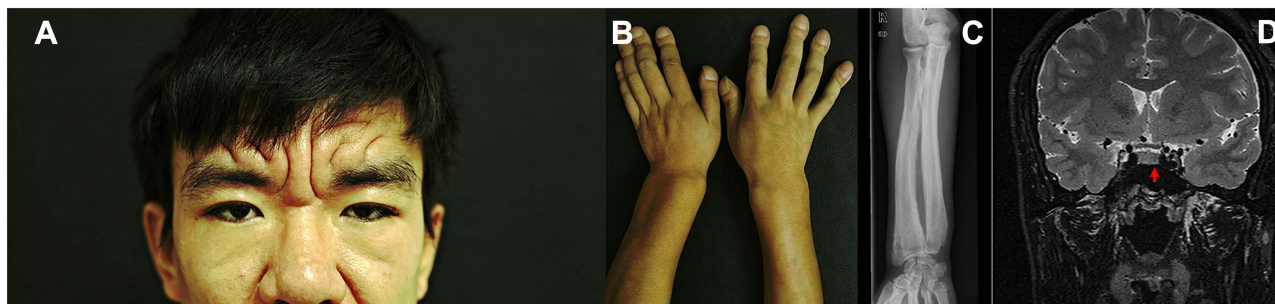


Figure 1 Skin furrowing and thickening, bilateral eyelids ptosis (A), digital clubbing of the fingers (B), radiographic examination showed cortical thickening in the long bones (C), contrast-enhanced magnetic resonance imaging of the pituitary revealed a hypointense signal on T2-weighted images (3×5mm) (D).

Table I The Main Differential Diagnoses Compared with Pachydermoperiostosis

	Sex predominance	Onset age (years)	Skin involvements
Pachydermoperiostosis ^{11,15}	Males	Childhood or adolescence	Skin thickening and furrowing (face and scalp) Digital clubbing
Acromegaly ¹⁴	Equal	40–50	Over secretion of sebum and hyperhidrosis Diffuse skin thickening and roughness Prone to sweating Excessive sebum secretion Hypertrophy of eyelids, ears, nose, lips Deep skin wrinkles and nasolabial folds Acral growth Pigmentation Coarse hair
Thyroid acropachy ^{18,19}	Females	50	Digital clubbing Swelling of the soft tissues Hyperpigmentation and hyperkeratotic Pretibial myxedema
	Extra-skin involvements	Tests to confirm the diagnosis	
Pachydermoperiostosis ^{11,15}	Arthritis of knees and ankles Gastrointestinal symptoms: flatulence, heartburn, abdominal pain, intermittent diarrhea, frothy and greasy stools and malnourished Ophthalmological symptoms: floppy eyelid, mechanical ptosis, visual field disturbances and blindness Multisystems involving: Musculoskeletal features: joint swelling, hypermobility, and cartilaginous thickening; Respiratory symptoms: snoring and obstructive sleep apnea; Cardiovascular symptoms: hypertension, left ventricular hypertrophy, cardiomyopathy, arrhythmias; Gastrointestinal system: colonic polyps, colon cancer; Endocrine disorders: insulin resistance; impaired glucose tolerance; diabetes mellitus; dyslipidemia; Neuropsychiatric symptoms: Impaired self-esteem; body image distortion; disruption in interpersonal relations; Ophthalmological symptoms: loss of vision	Gene analysis: HPGD or SLCO2A1 gene mutation X ray of the long bones show cortical thickening and periosteal reaction	
Acromegaly ¹⁴	Exophthalmos Cardiovascular symptoms: tachyarrhythmia, congestive heart failure, angina Extremity pain and arthralgia	GH and IGF-I hypersecretion MRI of pituitary shows microadenomas or macroadenomas	
Thyroid acropachy ^{18,19}		Thyroid function tests; Radiological study shows periosteal and cortical hyperplasia of the radial side of the first, second, and fifth metacarpals, the proximal and middle phalanges of the fingers, rarely involving tibia and fibula, radius, and ulna	

Abbreviations: HPGD, 15-hydroxyprostaglandin dehydrogenase; SLCO2A1, solute carrier organic anion transporter family member 2A1; GH, growth hormone; IGF, insulin-like growth factor; MRI, magnetic resonance imaging.

tissue swelling with digital clubbing and always associated with thyroid ophthalmopathy and dermatopathy. For the chronological sequence of extrathyroidal manifestations of AITD, thyroid dysfunction develops first, followed by ophthalmopathy, dermatopathy, and finally, acropachy.^{17,18} TA can occur in hyperthyroid, euthyroid or hypothyroid patients.^{17,18} Radiological study reveals periosteal reactions predominantly in metacarpals and phalanges of the fingers, and rarely in long bones.^{10,19} In this case, the patient was diagnosed with PDP due to facial disfigurement, digital clubbing and the periostosis of the long bones, although a pituitary microadenoma was found.

Table 2 Comparison Among PDP Patients with Pituitary Adenomas

	Case 1 ⁸	Case 2 ⁹	Case 3 (This Case)
Age	58y	34y	26y
Sex	M	M	M
Onset age	Unknown	9y	20y
Skin symptoms	Face/scalp furrows Clubbed fingers/toes Greasiness Perspiration	Furrows on forehead/scalp Digital clubbing Floppy hypertrophic eyelids Lower extremity myxedema Diffuse joint pain	Facial furrows Digital clubbing of the fingers Ptosis Greasy skin
Arthropathy	–	–	–
Family history	–	–	–
Endocrinological tests			
Thyroid hormones	N	N	N
ACTH	N	Unknown	N
Cortisol	N	Unknown	N
GH	7.5 I ng/mL (RR 0.03–0.42 ng/mL)	N	N
IGF-I	Unknown	Unknown	Decreased
LH	N	Unknown	Unknown
FSH	N	Unknown	Unknown
PRL	N	Unknown	Unknown
Radiographic findings	Periostosis in proximal phalanges and distal end of radius	Periostosis of the long bones	Periostosis of the long bones
Pituitary MRI	5mm pituitary adenoma	11mm pituitary adenoma	3*5mm pituitary adenoma
Diagnosis	Acromegaly+PDP	Nonsecreting pituitary macroadenoma+PDP	Nonfunctional pituitary microadenoma+PDP
Treatment	Surgery (pituitary tumor resection)	Alendronate+calcium+vitamin D; Eyelid tightening procedure	–

Abbreviations: y, years old; M, male; N, normal; PDP, pachydermoperiostosis; ACTH, adrenocorticotropic hormone; GH, growth hormone; RR, reference range; IGF-I, insulin-like growth factor-I; LH, luteinizing hormone; FSH, follicle stimulating hormone; PRL, prolactin; MRI, magnetic resonance imaging.

According to the previous literature, only one case reported a nonsecreting pituitary macroadenoma in a male PDP patient, and another reported a functional pituitary microadenoma in an aged Japanese male (Table 2).^{8,9} A nonfunctional pituitary microadenoma in a young male patient with PDP has never been described before. All the reported patients were male with characteristic features of PDP, but no family history was noted. Endocrinological examinations found an increased GH level in a patient with a pituitary microadenoma, but the diagnosis was acromegaly associated with PDP. Generally, microadenomas are more likely to be asymptomatic or lack hormone excess than macroadenomas, corresponding with the condition in our patient. It is intriguing that the level of IGF-1 was low in our patient; conditions that can reduce IGF-1 levels, such as malnutrition, sepsis, liver disease, uncontrolled diabetes, hypothyroidism, and obesity, were not present.²⁰ We suggest that the possible causes may be related to GH deficiency, which could be confirmed by further determination of GH secretion provocative tests or GH insensitivity, which may be associated with internal medical conditions, as mentioned above, and characterized by low serum IGF-1, GH binding protein and increased serum GH.²¹ In our case, the cause was not ultimately identified.

In the absence of studies on this disease, treatment options are limited and largely based on case reports. Administration of oral nonsteroidal anti-inflammatory drugs could relieve joint pain and swelling. Etoricoxib (60 mg per day) and hydroxychloroquine (400 mg per day) were proven to be effective in the control of both skin and joint conditions.^{22,23} Plastic surgery and injection of botulinum toxin (BTX) may improve skin syndrome.²⁴ However, BTX is an off-label use, and both procedures may cause a severe financial burden on patients. None of the treatment strategies were attempted in this patient, as he refused to take the risks of medication complications or any surgery-related adverse effects. Microadenoma growth occurs in only 10.6% of patients. Imaging follow-up of the pituitary MRI is recommended

every 1, 2, and 5 years, and repeat scanning should be performed less frequently in these patients. Surgical resection is generally not indicated.²⁵

In general, this case report presents a young male patient with complete PDP and a nonfunctional pituitary microadenoma. Age and sexuality predilection, clinical features, radiographic changes and endocrinological tests should be addressed in the diagnosis of PDP. Genetic study is of significance. Regrettably, it was unable to be performed in this case. Multidisciplinary cooperation should be recommended for periodic follow-ups in PDP patients. Despite the absence of clinical symptoms, the association between PDP and pituitary microadenoma or macroadenoma needs to be mentioned.

Ethics Statement

Ethical committee approval was not required for this case report.

Patient Consent

Informed consent for this case and associated images were obtained from the patient for publication.

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Disclosure

The authors report no conflicts of interest in this work.

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