

DIFFERENTIAL DIAGNOSIS OF ACROMEGALY: PACHYDERMOPERIOSTOSIS TWO NEW CASES, TURKEY

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What is already known on this topic?

Pachydermoperiostosis is a rare condition characterised by digital clubbing, joint problems and pachydermia, but other skin manifestations due to dermal and sebaceous gland hypertrophy can be found.

What this study adds?

Pachydermoperiostosis cases mimicking acromegaly have been reported to bring them to the attention of practitioners. Although both acromegaly and pachydermoperiostosis are infrequently encountered, avoidance of diagnostic confusion is important because of the prognostic and therapeutic implications. Awareness of the significance of clubbing under these circumstances is likely to prevent misdiagnosis.

ABSTRACT

Pachydermoperiostosis (PDP), also known as primary hypertrophic osteoarthropathy is a rare genetic disorder characterized by pachyderma and periostosis. Acromegaly is a condition caused by excessive secretion of growth hormone leading to elevated insulin growth factor-1 levels, which is characterised by somatic overgrowth and physical disfigurement notably affecting hands and feet. We presented two cases referred with an initial diagnosis of acromegaly and were ultimately diagnosed as PDP. Case 1: A 17-years old boy presented with enlargement in both feet and hands, finger clubbing, swelling in knee joints, knee pain, coarsening at facial lines and forehead skin, and excessive sweating which increased gradually over five years. There were prominent skin folds on the forehead, face, and eyelids. Also, there was an enlargement in both hands and clubbing at the fingers. There was marked swelling at knee joints and ankles. Genetic analysis revealed a novel homozygous variant NM_005630: c.31C>T (p.Q11*) in *SLCO2A1* gene. Case 2: A 16-years old boy presented with coarsening at forehead skin and scalp, excessive sweating, and pain at elbow and knee over three years. Skin folds were prominent at forehead skin and scalp. Genetic analysis revealed a homozygous variant NM_005630.2:c.86delG(p.G29Afs*48) in *SLCO2A1* gene. Such clinical presentation in corroboration with normal growth hormone level and prominent radiological abnormalities prompted us to make a diagnosis of pachydermoperiostosis. Consequently, pachydermoperiostosis is a very rare osteoarthrodermopathic disorder whose clinical and radiographic presentations may mimic those of acromegaly. In the evaluation of patients with acromegaloïd appearances, pachydermoperiostosis should be considered as a differential diagnosis.

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09.12.2020

29.04.2021

Introduction

Pachydermoperiostosis (PDP), also known as primary hypertrophic osteoarthropathy is a rare genetic disorder characterized by pachyderma and periostosis. In 1935, the disorder was classified into three forms by three French dermatologists, Touraine, Solente, and Gole: complete (pachyderma and periostosis), incomplete (without pachyderma), and rough (pachyderma and minimal skeletal changes) forms(1). Diagnosis should be made when two of the following features: positive family history, hypertrophic skin changes, osseous pain/radiographic changes, or clubbing(2). Although the exact incidence is unknown in PDP, its prevalence is estimated at 0.16% (3). It generally manifests at puberty and male: female ratio is 7: 1(4). The clinical features, signs and symptoms have stark similarities with acromegaly and can cause diagnostic confusion(5). We presented two cases referred with an initial diagnosis of acromegaly and were ultimately diagnosed as PDP.

CASE 1

A 17-years old boy initially presented to the family doctor with enlargement in both feet and hands and excessive sweating over five years, and he was referred to an endocrine outpatient clinic with an initial diagnosis of acromegaly. The patient's parents are cousins. The patient has a brother and a sister. In family history, there was no finding of similar complaints. In the anamnesis, it was found that his complaints have been worsened gradually over five years and that there was an enlargement in both feet and hands, clubbing in fingers, swelling in knee joints, knee pain, coarsening at facial lines, particularly at forehead skin, and excessive sweating. In physical examination, anthropometric measurements were as follows: height, 183 cm; body weight, 79 kg; and fathom distance, 183 cm. There were prominent skin folds at the forehead, face, and eyelids (Figure 1). Also, there was an enlargement in both hands and clubbing at the fingers (Figure 1). There was marked swelling at knee joints and ankles (Figure 1). Secondary sex characteristics were normal and the Tanner stage was five. Systemic examination including cardiovascular and respiratory systems, neurological examination, and thyroid was normal. There was no scaling in the scalp, rash, psoriatic nail changes, subcutaneous nodules, or red-eye in the physical examination. Complete blood count, hepatic and renal functions were within the normal range. Thyroid functions, Follicle-Stimulating Hormone (FSH), Luteinizing hormone (LH), total testosterone, prolactin, rheumatoid factor, and anti-cyclic citrullinated peptide were normal. In blood gas analysis, the following results were recorded: pH, 7.36; HCO₃, 24.7; sO₂, 98%. C-reactive protein was found to be increased (39.8mg/L, reference: 0-5). Serological tests were performed to evaluate connective tissue disorder and vasculitis, which were found as normal. As acromegaly was suspected, insulin-like growth factor-1 (IGF-1) and growth hormone (GH) measurements were performed. IGF1:235 ng/mL (111–509), fasting GH:0.35 mcg/L(0.07–5). The oral glucose tolerance test (OGTT) demonstrated normal, suppression of GH less than 1 µg/L. On bilateral hand radiographs, periostitis and hyperostosis were detected at metacarpal and proximal phalanges (Figure 2). De novo bone formation and cortical thickening were detected on bilateral knee radiographs (Figure 2). Irregular subperiosteal de novo bone formation and cortical thickening were observed at tibia, fibula, calcaneum, and talus on bilateral ankle radiographs (Figure 3). No pituitary adenoma was detected on pituitary magnetic resonance imaging (MRG). Chest radiograph and echocardiography were considered as normal. No abnormal finding was detected in abdominal and thoracic computed tomography (CT) scans. The patient was diagnosed as a classical PDP based on clinical, biochemical, and radiological findings. Genetic analysis revealed a novel homozygous nonsense variant NM_005630:c.31C>T (p.Q11*) in exon 1 of the *SLCO2A1* (solute carrier organic anion transporter family member 2A1) gene. Thus, selective Cox-2 inhibitor (meloxicam, 15 mg twice daily, PO) and steroid (methylprednisolone, 5 mg/day, PO) were prescribed. Marked improvement was detected in joint pain, swelling, and sweating on month one. In the control visit on month 6, regression was detected in the thickening at the forehead.

CASE 2

An 16-years old boy with coarsening at forehead skin and scalp, excessive sweating, and pain at elbow and knee over three years was referred to an endocrine outpatient clinic with an initial diagnosis of acromegaly. In family history, there was no finding of a similar disorder or consanguinity between parents. The patient has a sister. In physical examination, anthropometric measurements were as follows: height, 176 cm; body weight, 69 kg; and fathom distance, 176 cm. Skin folds were prominent at forehead skin and scalp (Figure 4). No abnormal finding was detected in the examination of the elbow and knee joint. Secondary sex characteristics were normal and the Tanner stage was five. Systemic examination including cardiovascular and respiratory systems, neurological examination, and thyroid was normal. Complete blood count, hepatic and renal functions were within the normal range. In blood gas analysis, the following results were recorded: pH, 7.38; HCO₃, 23.8; sO₂, 99%. C-reactive protein was found to be increased (11.4 mg/L; reference: 0-5). Thyroid functions, FSH, LH, total testosterone, prolactin, rheumatoid factor, and anti-cyclic citrullinated peptide were normal. Serological tests were performed to evaluate connective tissue disorder and vasculitis, which were found as normal. As acromegaly was suspected, IGF-1 and GH measurements were performed. IGF1: 311 ng/mL (111–509), fasting GH: 0.45 mcg/L (0.07–5). The OGTT demonstrated normal, suppression of GH less than 1 µg/L. Bilateral knee and hand radiographs were considered as normal (Figure 5). No pituitary adenoma was detected on pituitary MRG imaging. Chest radiograph and echocardiography were considered as normal. No abnormal finding was detected in abdominal and thoracic CT scans. The patient was diagnosed with an as rough form of PDP based on clinical, biochemical, and radiological findings. Genetic analysis revealed a homozygous frameshift variant NM_005630.2:c.86delG (p.G29Afs*48) in exon 1 of the *SLCO2A1* gene. This variant was previously reported in ClinVar database as pathogenic. Thus, selective Cox-2 inhibitor (meloxicam, 15 mg twice daily, PO) and steroid (methylprednisolone, 5 mg/day, PO) were prescribed. On day 6, melena was developed in the patient; thus, the patient underwent esophagogastroduodenoscopy which revealed a duodenal ulcer (2 cm in diameter). The meloxicam and prednisolone therapy were withdrawn and hydroxychloroquine was prescribed (200 mg twice daily, PO). On month one, regression was detected in joint pain and sweating. Marked regression was detected in skin thickening on month 6.

DISCUSSION

Pachydermoperiostosis is a rare hereditary disorder which inheritance pattern has not been fully elucidated yet (6). The first case with PDP was reported by Friedreich in 1868. Touraine, Solente, and Gole defined PDP as a variant of hypertrophic osteoarthropathy secondary to acromegaly and malignancy (1). PDP predominantly affected with male-to-female ratio of approximately 7:1 (4). PDP begins during childhood or adolescence and progresses gradually over the next 5–20 years before stabilizing (5). The typical presentations include thickening and coarsening of skin and/or scalp (pachydermia), clubbing of digits, oedema in the lower legs, arthritis both with and without joint effusion and periostosis (swelling of periarticular tissue and subperiosteal new bone formation). The most common findings are associated with polyarthritis, cutis verticis gyrata, seborrhea and hyperhidrosis. PDP can manifest in three forms: classical or complete form (skin thickening, skeletal changes, and clubbing at fingers), incomplete form (skeletal changes without skin involvement), and rough form (minimal skeletal change and skin thickening) (1).

Pachydermoperiostosis is very rare, and its clinical and radiological presentations can be confused with those of acromegaly, pseudoacromegaly with severe insulin resistance, secondary hypertrophic osteoarthropathy, Marfan's syndrome, McCune Albright syndrome, syphilitic periostitis, psoriatic onycho-pachydermo-periostitis (POPP) and Paget's disease (5-11).

Acromegaly is caused by very rarely encountered sporadic or familial GH-secreting adenomas arising during childhood or puberty. These features that are present in patients with acromegaly are due to the effect of excess growth hormones, mainly from pituitary tumours (12). The clinical picture in children and adolescents varies depending on whether the epiphyseal growth plate is open. Before epiphyseal fusion, there is a significant acceleration in growth rate, a condition also known as 'gigantism'; once the epiphyseal fusion is complete, clinical symptoms become more similar to those in acromegalic adults (coarse facial features, broadened nose, large hands and feet, organomegaly, sweating) (13). In acromegaly, excessive GH / IGF-1 production leads to periosteal bone formation, growth of synovial tissue, cartilage and precursor hypertrophic arthropathy associated with pain, and deformity as seen in pachydermoperiostosis. Acral abnormalities associated with PDP may overlap with those seen in acromegaly, including enlarged limbs, enlarged, thickened and short fingers, and thickened

soft tissue. While digital clubbing and periostosis are seen in PDP, these findings are not seen in acromegaly (14). Facial coarsening, cutis verticis gyrata, seborrhea, acne and hyperhidrosis, are common in pachydermoperiostosis and in acromegaly.

Symptoms specific to pachydermoperiostosis but not seen in acromegaly, are long eyelashes, blepharoptosis, myelofibrosis, hypoalbuminemia, peptic ulcer, gastric cancer or watery diarrhoea in response to certain triggers, such as cold drinks, greasy food or sexual activity (15).

The pathogenesis of PDP is not yet clearly understood; however, the previous evidence suggest that vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) could play a central role (6). Recent studies demonstrated prostaglandin mediated pathway as the key player in the pathogenesis of PDP. The 15-hydroxyprostaglandin dehydrogenase (HPGD) enzyme plays an important role in prostaglandin degradation and increased prostaglandin levels (particularly prostaglandin E₂ (PGE₂)) (16). The two major genetic lesions both lead to an increase in prostaglandin E₂, either by decreased degradation due to enzymatic loss (HPGD mutations) or a transporter defect (with *SLCO2A1* mutations). The genetic assay was performed in both cases in our report, revealing a novel homozygous *SLCO2A1* NM_005630.2: c.31 C>T (p.Q11*) mutation in the first case and a previously reported homozygous *SLCO2A1*/NM_005630.2:c.86delG (p.G29Afs*48) mutation in the second case. Radiological findings in pachydermoperiostosis subperiosteal newbone formation, cortical thickening, and narrowing of the joint spaces. Resorption of bone of the distal phalanges and ossification of inter-osseous membranes and ligaments can also be seen (17). In our first case, bilateral hand radiographs revealed periostitis and hyperostosis in the metacarpal and proximal phalanges. In our second case, radiographic examinations were found to be normal.

There is no specific treatment modality for PDP disease. Both *15 HPGD* and *SLCO2A1* genes are involved in PGE₂ synthesis (18,19). COX inhibitors (nonsteroidal anti-inflammatory drugs, acetylsalicylic acid and corticosteroid) that inhibit COX enzyme and suppress PGE₂ biosynthesis are promising agents in PDP treatment. We achieved a good response in the first case, but treatment was discontinued in the second case, treatment was withdrawn due to upper gastrointestinal bleeding from duodenal ulcer. In the first case, after six months of meloxicam and prednisolone treatment, the patient's complaints regressed significantly, so prednisolone treatment was discontinued by titration and followed up with meloxicam treatment. Alessandrella A et al. observed a marked improvement in skin findings and joint pain with hydroxychloroquine in a PDP patient with homozygous *SLCO2A1* gene mutation (20). In the second case in our report, hydroxychloroquine therapy was initiated as a homozygous *SLCO2A1* gene mutation was detected in genetic testing, and marked regression was achieved in skin findings. PDP includes other agents used in medical therapy, aescin, bisphosphonate, colchicine, retinoids, tricyclic antidepressants, and tamoxifen citrate. (21,22). Botulinum toxin A was attempted for cosmetic reasons. Surgery is used to correct bone deformity if present and plastic surgery can be used to restore thickening in the forehead skin.

When a patient is suspected of having acromegaly, the first step is biochemical testing to confirm the clinical diagnosis, followed by imaging to determine the cause of excessive growth hormone (GH) secretion. Pituitary adenoma is present in more than 95 percent of cases (23). The best single test for the diagnosis of acromegaly is measurement of serum insulin-like growth factor-1 (IGF-1). Both serum GH concentrations and IGF-1 concentrations are increased in virtually all patients with acromegaly. During OGTT, serum GH level <1 µg / L diagnosis of acromegaly is excluded. PDP patient, IGF-1 and growth hormone are normal and there is no adenoma in the pituitary (20). In both of our patients, GH and IGF-1 were found to be normal and GH after OGTT were <1 ng / ml, pituitary MRI no adenoma detected. Although transsphenoidal surgery is recommended as the first step in treatment, treatment with a long-acting somatostatin analogue is also used in cases that do not respond to surgery (24).

In conclusion, clinical presentations of pachydermoperiostosis can be confused with multiple other diagnoses, especially acromegaly. This great mimicker should be considered in the differential diagnosis of individuals presenting with acromegaloid feature.

Compliance with ethical standards

Conflict of Interest All authors declare that they have no conflict of interest.

Ethical Approval All procedures performed during this retrospective study were following the ethical standards of the institutional and/ or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The ethical committee approval is not required for case reports.

Informed consent forms were obtained from the patients and their families.

Funding sources: None.

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Figure 1.



Figure 2.



Figure 3.



Figure 4.

Uncorrected proof



Figure 5.

