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Case Report

Pachydermoperiostosis Due to a Novel *HPGD* Splicing Site Mutation Masquerading as Acromegaly

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Abstract

Hypertrophic osteoarthropathy (HOA: MIM 167100)) is classified into primary and secondary types. Primary HOA, also known as pachydermoperiostosis (PDP), is a rare genetic condition with distinct clinical features including digital clubbing, skin thickening, and periostosis. Secondary HOA often occurs as a paraneoplastic syndrome or is associated with systemic diseases. In this report, we present a 17-year-old male patient who initially presented with significant digital clubbing, enlarged hands and feet, and excessive sweating. Although the initial suspected diagnosis was acromegaly, the patient's plasma level of insulin-like growth factor 1 was normal and growth hormone levels suppressed to <1 ng/dL following oral glucose tolerance test. Whole exome sequencing followed by Sanger sequencing of leukocyte deoxyribonucleic acid revealed a novel splicing variant in the 15-hydroxyprostaglandin dehydrogenase (*HPGD*) gene (NM_000860.6: c.662 + 5_662 + 8del). Reverse transcription polymerase chain reaction confirmed that this variant led to defective splicing with skipping of exon 6, a frameshift, and truncation at codon 13 of exon 7 downstream. His symptoms did not respond well to nonsteroidal anti-inflammatory drugs but showed excellent response to a trial of lanreotide autogel that has been used for about 1 year.

Key Words: pachydermoperiostosis, acromegaly, pseudoacromegaly, HPGD, somatostatin analogues

Abbreviations: GH, growth hormone; HOA, hypertrophic osteoarthropathy; HPGD, 15-hydroxyprostaglandin dehydrogenase; IGF-1, insulin-like growth factor 1; NSAID, nonsteroidal anti-inflammatory drug; OGTT, oral glucose tolerance test; PCR, polymerase chain reaction; PGE2, prostaglandin E2; PDP, pachydermoperiostosis; VEGF, vascular endothelial growth factor.

Introduction

Hypertrophic osteoarthropathy (HOA) is a rare medical condition affecting bones, joints and skin. It is characterized by clubbing of the fingers and toes and periostosis (new bone formation) of the distal parts of the long bones of the forearms and legs [1]. It also causes skin thickening and enlargement of the hands and feet [1]. HOA is classified into primary and secondary forms. Primary HOA, commonly called pachydermoperiostosis (PDP), is a rare genetic disorder with autosomal dominant and recessive patterns [2, 3]. PDP is distinguished by a combination of digital clubbing, pachyderma (thickening of the skin), excessive sweating, periostosis, and enlargement of the hands and feet [4]. Due to its overlap with acromegaly, PDP is frequently misdiagnosed as acromegaly based on the clinical features [5–9]. It most commonly affects adolescent males and is associated with mutations in the 15-hydroxyprostaglandin dehydrogenase (*HPGD*) or the solute carrier organic anion transporter family member 2A1 (*SLCO2A1*) genes [3]. These genetic mutations lead to elevated prostaglandin E2 (PGE2) levels and impaired PGE2 uptake, which in turn activates fibroblasts and various growth factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) [4]. Secondary HOA, on the other hand, is often associated with underlying medical conditions such as malignancies, cardiovascular disorders, and gastrointestinal diseases, with more pronounced bone changes and fewer dermatological manifestations [3, 10, 11]. Due to the rarity of these conditions, especially PDP, it is not uncommon to be missed or misdiagnosed. In this report, we present a young man who was initially suspected to have acromegaly. However, his plasma level of insulin-like growth factor 1 (IGF-1) was normal and growth hormone (GH) levels were well suppressed after oral glucose tolerance test (OGTT). This prompted further investigation, including genetic testing, which confirmed the diagnosis of PDP due to a novel splice-site deletion variant in the *HPGD* gene.

Case Presentation

A 17-year-old male presented with excessive sweating, progressive enlargement of the hands and feet, and thickening of the skin of the face and scalp. These symptoms were first

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noted at age 12 years but worsened during puberty, particularly the excessive sweating of the hands and feet. The patient was a product of normal pregnancy with normal vaginal delivery. He achieved developmental milestones on time, with no significant past medical history. His parents are first-degree cousins, and he also has 2 half-siblings from another mother (who is also a first-degree cousin to the father) with similar symptoms (Fig. 1). Physical examination showed that his blood pressure was 107/71 mm Hg, heart rate 82 beats/minute, weight 61 kg, height 161 cm, and body mass index 23.5 kg/m^2. He had thick skin folds on the forehead and scalp, a large nose with pronounced nasolabial folds, and coarse moist skin on the face and extremities. During clinic visits, he had very excessive sweating, especially on the hands and feet, which needed repeated washing and drying. There was a symmetrical enlargement of the hands and feet, and digital clubbing (Fig. 2), although no prognathism or spread of the teeth was observed. Ophthalmic, cardiovascular, respiratory, neurological, and thyroid examinations were normal. He had normal pubertal development with normal facial, axillary, chest, and genital hair distribution and normal male external genitalia and testes. He was evaluated initially at a community hospital. Based on the clinical features only without further laboratory evaluation, he was suspected to have acromegaly and referred to our hospital for further management.

Diagnostic Assessment

Laboratory tests, including complete blood count, liver and renal function tests, blood glucose levels, and erythrocyte sedimentation rate, were within normal limits. Hormonal evaluations, including GH, IGF-1, thyroid function tests, and fasting and postmeal glucose levels, were also normal (Table 1).

Radiological assessment of the hands, feet, and long bones showed acro-osteolysis, with more pronounced severity detected in the feet, and mild dextroconvex thoracic scoliosis (Fig. 2). There was no evidence of periosteal reaction or bone enlargement. The cranial radiograph revealed no abnormalities (Fig. 2). The results of an echocardiography and magnetic resonance imaging of the pituitary gland were normal. Acromegaly was excluded, as values of IGF-1 and GH were within the normal range and the GH levels following OGTT were normal (GH suppressed to < 1 ng/dL). The diagnosis of PDP was verified through the examination of clinical characteristics and genetic testing.

Following an approval from the institutional review board and ethics committee at King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia (ORA# 2130015), an informed consent was obtained from the patient's guardian (Mother). Genetic testing was performed by isolating DNA from peripheral leucocytes using the QIAamp DNA Blood Mini Kit (QIAGEN GmbH, Germany) as per the kit instructions. Whole exome sequencing and bioinformatics analysis were performed as previously described [12]. The mutation identified was confirmed by polymerase chain reaction (PCR) and Sanger sequencing. The primers used were sense 5′-AAGCTTGTGTTCATTTCTCAACTG-3′ and anti-sense 5′-GATGCTTTAATGATCAGTTTGTCC-3′ and the PCR conditions were as follows: initial denaturation for 4 minutes (94 °C) then 35 cycles of denaturation at 94 °C for 30 seconds, annealing at 62 °C for 45 seconds, extension at 72 °C for 45 seconds. The reaction was completed with a final extension for 5 minutes at 72 °C and stored at 4 °C. Whole exome sequencing and Sanger sequencing showed a novel homozygous 4-nucleotide deletion variant (NM_000860.6; c.662 + 5_662 + 8del) in the *HPGD* gene, located 5 nucleotides downstream of the last nucleotide of exon 6 (Fig. 3A). This deletion variant was suspected to cause a splicing failure of intron 6 and skipping of exon 6, resulting in alternative splicing and joining of exon 5 to exon 7 directly with frameshift and truncation at codon 13 of exon 7. To confirm the expected effect of this deletion on splicing, we isolated total RNA from a blood sample, synthesized cDNA, and performed PCR and Sanger sequencing (Fig. 3A) on the synthesized cDNA as previously described [13]. The RT-PCR confirmed that this variant affected splicing, resulting in the skipping of exon 6 and joining of exon 5 with exon 7 (Fig. 3B). This frameshift resulted in the creation of a stop codon and truncation at codon 13 of exon 7 (Fig. 3B).

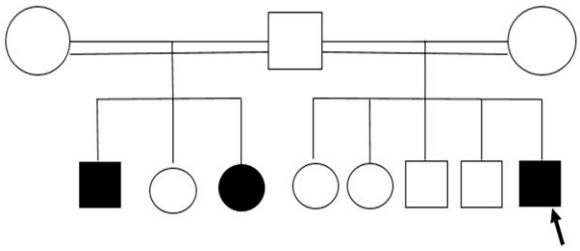

Figure 1. Family pedigree showing the index case with 4 unaffected full siblings and 2 affected and 1 unaffected half sibling from another mother. Parents are first-degree cousins.

Treatment

The patient was treated with nonsteroidal anti-inflammatory drugs (NSAIDs) for symptomatic relief; however, he had no significant benefit. Given the lack of response to NSAIDs and the severe symptoms that interfered with the patient's quality of life and based on some reported cases from the literature, we counseled the patient and his parents about a trial of somatostatin analogue. They agreed and we initiated lanreotide autogel, a long-acting somatostatin analogue, at a dose of 60 mg intramuscularly monthly. He has been on this therapy for 12 months.

Outcome and Follow-Up

Lanreotide autogel therapy resulted in significant improvement in the patient's symptoms, especially sweating and arthralgia, and we continue to monitor him closely, and now, 12 months after treatment initiation, he reported satisfaction with the results without significant adverse effects. He is actively engaged in daily activities and his social interactions have notably improved, particularly due to a reduction in sweating, which had previously affected his quality of life and led to social isolation.

Discussion

PDP accounts for 3% to 5% of cases of primary HOA and is characterized by atypical proliferation of bones and skin [5]. First described by Friedreich in 1868 [14], HOA was classified into complete, incomplete, and fruste forms by Touraine et al in 1935 [15]. Complete-type HOA involves the bone and skin

Figure 2. Radiological assessment (left upper panel) showed acro-osteolysis, with more pronounced severity detected in the feet. The patient had mild dextroconvex thoracic scoliosis. There is no evidence of periosteal reaction or bone enlargement. The cranial radiograph revealed no abnormalities. The other pictures are of the feet and hands (dorsal and plantar aspects) showing a bulky appearance with pseudo clubbing.

Table 1. Serum hormonal levels in a 17-year-old man with pachydermoperiostosis

Hormonal markers	Values	Normal range
Luteinizing hormone (LH)	2.3 IU/L 2.3 mIU/mL	0.6-12.1 IU/L 0.6-1.2 mIU/mL
Follicle-stimulating hormone (FSH)	4.15 IU/L 4.15 mIU/mL	0.95-12 IU/L 1-12 mIU/mL
Testosterone	21.5 nmol/L 620.1 ng/dL	4.94-32 nmol/L 142.4-922.9 ng/dL
Prolactin	12 µg/L 255.3.4 mIU/L	4.04-15.2 µg/L 86-324 mIU/L
Thyroid-stimulating hormone (TSH)	0.92 mIU/L 0.92 uIU/mL	0.5-5 mIU/L 0.5-5 uIU/mL
Free thyroxin 4 (FT4)	12.5 pmol/L 0.97 ng/dL	9-19 pmol/L 0.7-1.48 ng/dL
Adrenocorticotropic hormone (ACTH)	7.18 pmol/L 32.6 pg/mL	1.32-10.12 pmol/L 6-46 pg/mL
Cortisol	399 nmol/L 14.46 µg/dL	184.9-623.8 nmol/L 6.7-22.6 µg/dL
Growth hormone (baseline)	0.48 mIU/L 0.15 ng/mL	5.4-10.3 mIU/L 1.79-3.42 ng/mL
Insulin-like growth factor 1 (IGF-1)	39.88 nmol/L 305.04 ng/mL	29-67.4 nmol/L 221.8-515.5 ng/mL

and is characterized by a full triad of symptoms, including thickened skin (pachydermia), inflammation of the bone's outer layer (periostitis), and digital clubbing [16]. Incomplete type HOA presents with some features of the complete type but not all. For instance, it may include skin thickening and bone inflammation without digital clubbing [17]. Fruste-type features are relatively mild and involve mainly the skin with minimal or no periostitis [4, 17]. In this type, symptoms are often less noticeable and may be detected later in life.

HOA typically manifests during puberty and progresses unpredictably over 5 to 20 years before stabilization. It predominantly affects males, with a 7:1 male-to-female ratio [4, 9, 18]. It is crucial to differentiate primary HOA from secondary forms, which are associated with underlying diseases such as malignancy and cardiothoracic disorders. Secondary forms present with fewer cutaneous signs and more severe osteoarthropathy [3, 19]. Primary HOA is caused by genetic mutations in *HPGD* and *SLCO2A1* [20–22]. These mutations result in higher levels of PGE2, which in turn cause aberrant tissue remodeling and growth of bones [4].

HPGD (OMIM 601688) is a 7-exon, 801-nucleotide gene located on chromosome 4q34.1. It encodes prostaglandin E2, a 267–amino acid protein. All previous splice-site mutations were in the canonical splicing sites (donor site GA or acceptor site GT). However, the 4-nucleotide deletion in our patient has not been previously reported.

PDP presents a challenge in management due to its rarity and the variability in symptoms. Treatment options primarily focus on alleviating symptoms and improving quality of life. Studies have demonstrated that NSAIDs can relieve symptoms of arthralgia and periostitis [23]. Nevertheless, the effect on additional symptoms such as changes in skin, sweating, and digital clubbing is limited. In some cases, aspirin and corticosteroids have been used to effectively control severe symptoms. Corticosteroids have also been used, but they are less commonly prescribed due

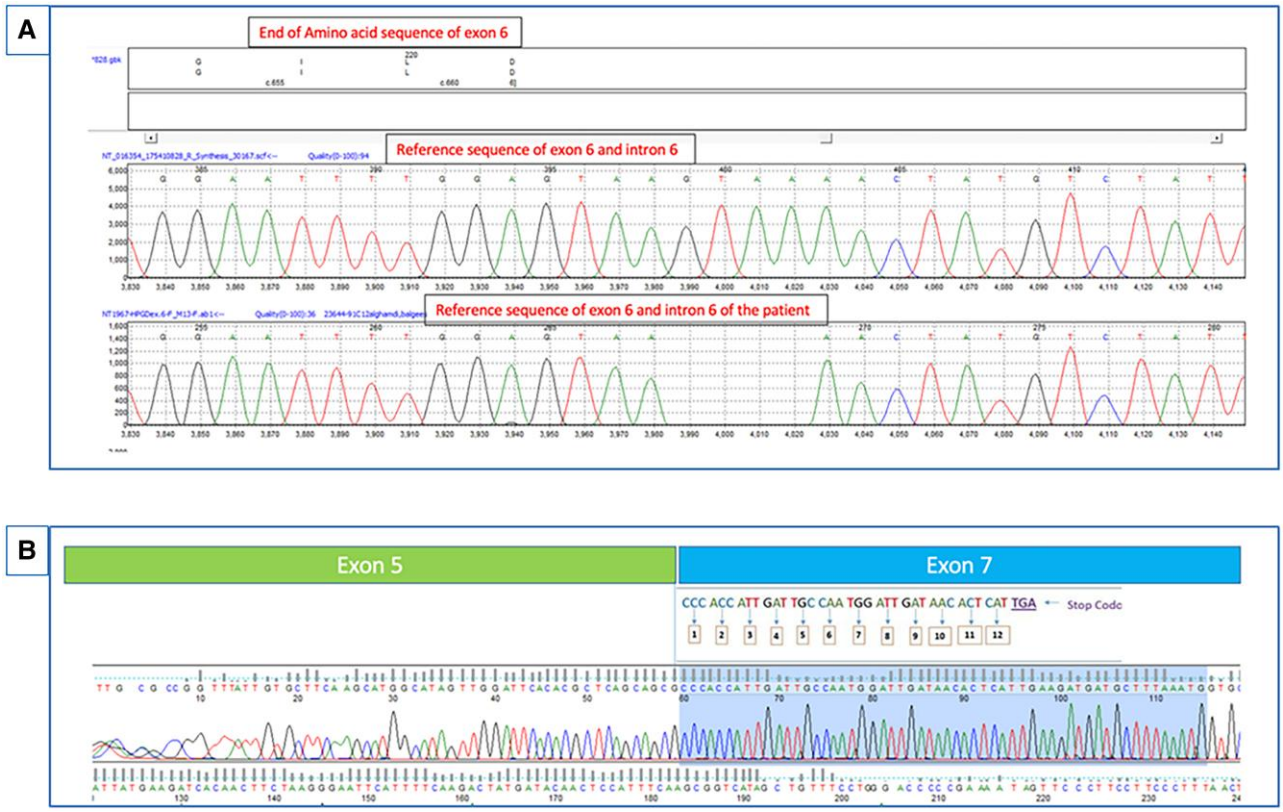

Figure 3. A chromatogram of 3′ end of exon 6 and part of intron 6 showing a novel homozygous 4-nucleotide deletion variant (NM_000860.6; c.662 + 5_662 + 8del) in the *HPGD* gene, located 5 nucleotides downstream of the last nucleotide of exon 6 (A). This deletion led to the failure of splicing at this position with an alternative splicing between exons 5 and 7 and skipping of exon 6. The frameshift that resulted from this alternative splicing led to the creation of a stop codon and truncation at 13 codons downstream in exon 7 (B).

to potential side effects and variable response [24]. Additionally, hydroxychloroquine has been studied for its possible benefits in managing primary HOA. Bisphosphonates have also been studied in primary and secondary HOA and a recent meta-analysis suggested that they are safe and effective although no randomized clinical trials [25]. Surgical intervention may be considered for severe cases of HOA that do not respond to medical therapy; however, it is rarely needed.

Somatostatin analogues have also been rarely used to treat symptoms, especially for excessive sweating and pain. Octreotide has shown efficacy in lowering sweating and arthralgia in 2 patients with secondary HOA [26, 27]. Birch et al described a patient with painful HOA secondary to lung cancer who responded well to octreotide therapy [26]. Maroto et al reported another patient with painful HOA who had a dramatic response to treatment with octreotide and suggested that this response might be due to lowering effects of octreotide on PGE2 and VEGF levels [27]. In both cases, the patients had secondary forms of HOA. Our patient is the first case in which a somatostatin analogue was used to treat PDP. Studies in rat glial cells showed that somatostatin analogues in physiological doses decrease PGE2 synthesis and suggested that it could play a therapeutic role in brain inflammatory conditions [28].

In summary, PDP, although rare, can be misdiagnosed as acromegaly. The identification of a novel genetic variant in this case highlights the importance of genetic testing in confirming the diagnosis. Although the pathogenesis of this condition is completely different from acromegaly, somatostatin analogues might be beneficial in symptom management, although treatment responses may vary.

Learning Points

- HOA is a rare condition classified to primary (usually due to *HPGD* or *SLCO2A1* genetic mutations) and secondary types (usually due to malignancy or cyanotic lung or heart disease).
- HOA is characterized by thickening of the skin, clubbing, and active periosteal reaction (periostitis).
- HOA could be misdiagnosed as acromegaly (pseudoacromegaly). However, biochemical and genetic testing are of greatest values for its diagnosis.
- Somatostatin analogues might be of therapeutic value for patients with excessive sweating and severe joint pains.

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Contributors

All authors made individual contributions to authorship. M.A.: clinical evaluation and case description. B.A.: Laboratory work and preparation of figures. A.B.: Laboratory work. A.A.: Whole exome sequencing and

bioinformatics analysis. A.S.A.: Conceptualization, Overall supervision, manuscript writing, and submission. All authors reviewed and approved the final draft.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's guardian (mother).

Data Availability Statement

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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