Pachydermoperiostosis complicated by recurrent hypokalemia: A rare case report

By Sarmini Varatharajan

WORD COUNT 2176
TIME SUBMITTED 06-JAN-2025 06:53PM
PAPER ID 113892832

Pachydermoperiostosis complicated by recurrent hypokalemia: A rare case report

Sarmini Varatharajan[1], Abinaya Srinivasa Rangan[1], Saranya Chinnadurai[2]

[1]Department of General Medicine, Saveetha Medical College and Hospital, SIMATS Deemed University, Chennai, Tamil Nadu, India

[2]Department of Rheumatology, Saveetha Medical College and Hospital, SIMATS Deemed University, Chennai, Tamil Nadu, India

Sarmini Varatharajan **ORCID ID:** 0009-0006-4647-7105

Abinaya Srinivasa Rangan **ORCID ID:** 0009-0001-0918-2993

Saranya Chinnadurai **ORCID ID:** 0000-0001-9979-4493

Corresponding author:

Sarmini Varatharajan

E-mail: sarminiv@hotmail.com

Abstract:

Pachydermoperiostosis (PDP) is a rare genetic condition involving cutaneous and osseous tissues, characterized by pachydermia, digital clubbing, and periostosis. Though primarily associated with dermatological and osteoarticular symptoms, PDP has occasionally been linked to metabolic disturbances such as hypokalemia.

We present a case of a 22-year-old male with complete PDP who experienced recurrent hypokalemia, requiring frequent potassium supplementation. Laboratory findings suggested renal potassium loss, with elevated urinary potassium and chloride levels, although the precise mechanism remains unclear. This case highlights the multisystemic nature of PDP and the therapeutic challenge of managing recurrent hypokalemia. Elevated PGE2 (prostaglandin E2) levels may contribute to the metabolic disturbance, emphasizing the need for further research into the renal effects of PGE2 dysregulation and more targeted treatment strategies for PDP-associated hypokalemia.

Keywords: digital clubbing, hyperhidrosis, prostaglandin E2, potassium-losing nephropathy

INTRODUCTION

Pachydermoperiostosis (PDP), also known as Touraine-Solente-Golé syndrome or primary hypertrophic osteoarthropathy, is a rare genetic disorder typically inherited in an autosomal dominant manner. The pathophysiology of PDP centers around mutations in the SLCO2A1 (Solute Carrier Organic Anion Transporter Family Member 2A1) and HPGD (Hydroxyprostaglandin 2 Dehydrogenase) genes. These mutations impair the degradation of prostaglandin E2 (PGE2), resulting in elevated PGE2 levels, which promotes the hallmark features of the condition periostosis (new bone formation), digital clubbing, and pachydermia (thickening of the skin).

PDP is classified into three clinical subtypes: (1) complete, where both pachydermia and periostosis are present; (2) incomplete, where periostosis occurs without pachydermia; and (3) forme fruste, which is characterized by pachydermia with minimal skeletal involvement. The condition predominantly affects males and usually manifests during adolescence or early adulthood, although the severity and clinical course can vary considerably among individuals.

In addition to its dermatological and skeletal manifestations, PDP can lead to systemic complications, including metabolic disturbances. One such complication is recurrent hypokalemia, a rare but significant issue linked to PGE2-mediated renal potassium loss. Elevated PGE2 levels can affect renal function, particularly by influencing renal tubular transport, leading to excessive potassium excretion and subsequent hypokalemia.

We report the case of a young male with complete PDP who developed recurrent hypokalemia, illustrating the complex multisystemic nature of the disorder. The patient's hypokalemia proved to be a challenge in terms of management, necessitating frequent potassium supplementation. This case highlights the need for ongoing research into the renal effects of PGE2 dysregulation and the potential therapeutic strategies to address both the systemic and metabolic aspects of PDP. Despite treatment, the recurrent nature of the hypokalemia underscores the complexity of managing PDP in patients with overlapping metabolic disturbances.

CASE DESCRIPTION

A 22-year-old male presented to the rheumatology clinic with a 5-year history of progressive bulbous swelling of the tips of fingers and toes, and thickened skin over his forehead and

scalp. He also reported increased sweating and oily skin. Patient presented with generalized weakness, pain and swelling of DIP (distal interphalangeal) joints of both hands for 3 months, which worsened over the recent weeks.

In 2019, the patient presented with multiple joint pain and swelling involving both small joints of hands, knees and ankles. On physical examination, the patient had marked, cutis verticis gyrata, a distinctive scalp appearance characterized by deep, undulating folds, (Figure 1) and seborrheic dermatitis involving scalp. There was significant grade 4 clubbing of all fingers and toes, with drumstick-like deformities, (Figure 2&3) with arthritis of the distal interphalangeal joints. The skin over his forehead and face exhibited thickened, furrowed ridges, giving the characteristic leonine facies seen in advanced PDP. He had left knee synovitis with effusion and bilateral ankle arthritis. On evaluation, his inflammatory markers were elevated with negative rheumatoid factor and positive anti-cyclic citrullinated peptide (anti-CCP) antibodies. He was diagnosed to have complete pachydermoperiositis with a possible variant of psoriatic arthritis. He was treated with anti-inflammatory medications and disease-modifying antirheumatic drug (DMARD) therapy (oral methotrexate 10 mg once a week).

In 2021, the patient's clinical course took an unexpected turn with recurrent episodes of hypokalemia, complicating his management and prompting further investigation. He was evaluated and maintained with oral potassium and DMARD therapy since then. For the past 6 months, he discontinued oral methotrexate and landed up with present symptoms.

Laboratory investigations revealed persistent hypokalemia, with serum potassium level of 2.2 mmol/L (reference range: 3.5-5.0 mmol/L) and inflammatory markers were within normal limits. 24-hour urinary potassium excretion was significantly elevated at 646.8 mmol/day (normal range: 25-125 mmol/day), suggesting renal potassium loss. However, the patient's serum creatinine, blood urea nitrogen, and glomerular filtration rate were within normal limits, ruling out significant renal impairment. Arterial blood gas analysis were normal, ruling out metabolic acidosis or alkalosis. Additionally, urine chloride levels were also elevated, with a urine chloride concentration of 94 mmol/L (normal range: 10-20 mmol/L), consistent with potassium-losing nephropathy.

Thyroid function tests, serum aldosterone, and renin levels were within normal limits, making primary hyperaldosteronism an unlikely cause of hypokalemia. The differential diagnoses of pachydermatoperiostosis include hypovitaminosis A, thyroid acropachy, lung cancer,

acromegaly and carcinomatous polyarthritis which were ruled out.

Radiographic imaging of the hands (Figure 4) and long bones demonstrated a periosteal reaction with diaphyseal widening, consistent with the periostosis observed in PDP. There was thickening of the cortical bone with subperiosteal new bone formation, particularly affecting the tibia, radius, and ulna (Figure 5). The bone changes were predominantly symmetric. No evidence of erosive arthropathy was noted on the hand X-rays, despite the clinical findings of DIP joint arthritis.

12
Based on these clinical features and radiological findings, a diagnosis of complete pachydermoperiostosis with a possible variant of psoriatic arthritis and recurrent hypokalemia was made. The recurrent hypokalemia was attributed to potassium-losing nephropathy, possibly related to prostaglandin E2 dysregulation in the kidneys, though the precise mechanism remains unclear.

The patient was started on a cyclooxygenase-2 (COX-2) inhibitor for joint pain relief, given the role of prostaglandins in both joint and periosteal symptoms in PDP. His hypokalemia was managed with intravenous potassium, followed by oral supplementation. Upon regular follow5 up, his joint symptoms improved, and his serum potassium levels stabilized with ongoing oral potassium supplementation and DMARD therapy (maintenance methotrexate 10 mg/week) was continued.

DISCUSSION

6
Pachydermoperiostosis (PDP), also referred to as Touraine-Solente-Golé syndrome or primary hypertrophic osteoarthropathy, is a rare hereditary disorder characterized by skin thickening (pachydermia), digital clubbing, and periostosis. First described by Friedrich in 1868 [1], and later elaborated by Touraine, Solente, and Golé in 1935 [2], PDP has since been recognized as a condition with a strong male predilection and an autosomal dominant or X- linked inheritance pattern.

The hallmark features of PDP—pachydermia, digital clubbing, and periostosis are primarily driven by elevated levels of prostaglandin E2, often due to mutations in the HPGD and SLCO2A1 genes. PGE2 plays a central role in osteoblast and osteoclast activity, leading to periosteal proliferation and new bone formation. In addition, PGE2 exerts stimulatory effects

on the dermis and sebaceous glands, explaining the cutaneous manifestations, including cutis verticis gyrata and seborrhea, seen in advanced cases of PDP.

In this case, the patient presented with recurrent hypokalemia, a rare but important complication in PDP. Although the precise mechanism of potassium loss in PDP remains unclear, the elevated urinary potassium excretion in our patient suggests a potassium-losing nephropathy. Previous case reports have highlighted similar findings.

A retrospective case study conducted by Z. Q. Tao et al. at Sun Yat-sen Memorial Hospital, Sun Yat-sen University, from 2017 to 2023, analyzed four cases of PDP, offering insights into this rare genetic disorder. The study included 4 male patients with a mean age of 22 years, aligning with the age of our patient. Among the cases, one presented with recurrent hypokalemia and was diagnosed with potassium-losing nephropathy, a rare but significant metabolic complication. The findings are particularly relevant to our case, highlighting the need to recognize and address the systemic and metabolic dimensions of PDP to optimize patient outcomes [3].

Further supporting this connection, Jiang Ruimei et al. reported a familial case of primary hypertrophic osteoarthropathy (PHO) involving two brothers, one of whom exhibited recurrent hypokalemia. Genetic analysis revealed mutations in the *SLCO2A1* gene in both siblings. Over a 10-year period, the affected brother experienced persistent hypokalemia, with potassium levels fluctuating between 1.6 and 2.5 mmol/L, requiring intermittent intravenous or oral potassium supplementation. The study speculated that elevated PGE2 levels might trigger secondary hyperreninemia and hyperaldosteronemia, leading to renal potassium loss [4]. However, in our patient, renin and aldosterone levels were within normal limits, ruling out this mechanism and pointing to a different or unexplored pathway for potassium loss in PDP. This highlights the complexity of metabolic disturbances in PDP and the renal effects of PGE2 dysregulation in PDP.

Another intriguing case study was described by Jiang Y et al. in a Chinese family with primary hypertrophic osteoarthropathy (PHO) and Bartter-like hypokalemia, where a 33- year-old male proband experienced severe hypokalemia attributed to renal potassium loss. Genetic analysis identified a novel compound heterozygous mutation in the SLCO2A1 gene, p.I284V and p.C459R, in two affected family members. The patient's hypokalemia was treated with the COX-2 inhibitor etoricoxib, resulting in a rapid normalization of serum potassium levels. This

improvement was accompanied by a significant reduction in serum PGE2 and its metabolites, supporting the hypothesis that elevated PGE2 levels play a central role in both the bone and renal manifestations of PHO. These findings suggest that Bartter-like hypokalemia is a new complication of PHO caused by PGE2 dysregulation [5].

An additional significant observation in this case was the presence of seborrheic dermatitis, positive anti-cyclic citrullinated peptide antibodies, and involvement of distal interphalangeal joints, which suggested the possibility of a psoriatic arthritis (PsA) variant alongside PDP. This underscores the need to consider concurrent conditions, such as PsA, when assessing complex cases with features of both PDP and autoimmune markers, which can guide the treatment approach and prognosis.

The management of PDP remains largely symptomatic. For patients with recurrent hypokalemia, potassium supplementation is the cornerstone of treatment. Nonsteroidal anti-inflammatory drugs, which inhibit prostaglandin synthesis, may help alleviate bone pain and reduce periosteal activity, though their long-term efficacy in managing metabolic complications like hypokalemia remains unclear. In severe cases, surgical interventions may be necessary for correcting joint deformities or improving the cosmetic appearance of cutis verticis gyrata.

In this case, the patient was treated with methotrexate for his arthropathy and potassium supplementation was employed to manage his hypokalemia. Despite these interventions, the recurrent nature of his hypokalemia underscores the complexities involved in managing PDP with overlapping metabolic disturbances. The role of PGE2 in this process, particularly its renal effects, warrants further exploration to improve patient outcomes in future cases.

CONCLUSION

This case highlights the complexity of pachydermoperiostosis, particularly when complicated by recurrent hypokalemia. PDP, a rare genetic disorder, is known for its distinct dermatological and skeletal manifestations, but this case underscores the potential for broader systemic involvement, including metabolic disturbances such as potassium loss.
The exact pathophysiology underlying hypokalemia in PDP remains poorly understood, though elevated urinary potassium excretion and abnormal renal function suggest a potassium-losing nephropathy possibly linked to prostaglandin E2 dysregulation.

The patient's normal renin and aldosterone levels differentiate this case from previously reported examples where hyperreninemia and hyperaldosteronism were implicated, pointing to the need for further investigation into the renal effects of PGE2 in PDP. Management of PDP continues to be symptomatic, with potassium supplementation and nonsteroidal anti-inflammatory drugs (NSAIDs) to alleviate bone pain and inhibit prostaglandin synthesis. Despite these treatments, the persistence of hypokalemia in this case suggests that more effective therapeutic strategies are needed to address metabolic complications.

This case emphasizes the importance of recognizing and managing the multisystemic nature of PDP, and further research into its underlying mechanisms may provide insights into improving treatment and outcomes for patients with similar presentations.

3

Conflict of interest: The authors stated that they do not have any financial or personal relationships that might bias the content of this work.

References:

1. Friedreich N. Hyperostose des gesammten skelettes. Virchows Arch Pathol Anat. 1868;43:83.
2. Touraine A, Solente G, Golé L. Un syndrome osteodermopathique: la pachydermie plicaturee avec pachyperiostose des extremites. Presse Med. 1935;43:1820-4.
3. Tao ZQ, Li QH, Dai L. Clinical analysis of four cases of pachydermoperiostosis. Ann Rheum Dis. 2024;83(Suppl 1):2065.2. doi:10.1136/annrheumdis-2024-eular.5481.
4. Jiang R, Li J, Wang Z, Shen J, Niu M. A case of familial primary hypertrophic osteoarthropathy combined with renal potassium loss. Chin J Intern Med. 2020;59(9):721-724. doi:10.3760/cma.j.cn112138-20190918-00637.
5. Jiang Y, Du J, Song YW, Wang WB, Pang QQ, Li M et al. Novel SLCO2A1 compound heterozygous mutation causing primary hypertrophic osteoarthropathy with Bartter-like hypokalemia in a Chinese family. J Endocrinol Invest. 2019;42(10):1245-52.
6. Rastogi R, Suma GN, Prakash R, Rastogi UC, Bhargava S, Rastogi V. Pachydermoperiostosis or primary hypertrophic osteoarthropathy: a rare clinicoradiologic case. Indian J Radiol Imaging. 2009;19:123-6