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Case Report

Pachydermoperiostosis Mimicking Inflammatory Arthritis: Case Description and Narrative Review

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Abstract: Pachydermoperiostosis (PDP), also called primary hypertrophic osteoarthropathy (HOA), is a rare genetic disease with typical thickening of the skin (pachydermia) and rheumatic manifestations, with clubbing of the fingers and toes and periostosis of the long bones visible on X-rays, as well as arthritis in large joints sometimes. *Case*: We describe a 23-year-old man with a complete form of PDP who presented with polyarthritis of the ankles and knees, with clubbing of the fingers and toes. He was treated with a non-steroidal anti-inflammatory drug (NSAID), etoricoxib, and with bisphosphonates (initially pamidronic acid i.v. and later oral risedronate 35 mg weekly). His joint pains and swelling disappeared, so that he could resume his daily activities. After eight years, the periostosis on the X-rays had disappeared. *Discussion*: The case is discussed, the literature regarding PDP is summarized and the differential diagnosis and treatment options are reviewed. *Conclusions:* PDP may present as polyarthritis. Clinicians should be aware of this diagnosis, as treatment is available and may improve the outcome of the patient. It is important to rule out secondary HOA due to pulmonary or cardiac disease, gastrointestinal malignancies and liver cirrhosis, especially when the dermatological findings are not typical. Further, acromegaly, thyroid acropachy and rheumatologic diseases should be excluded.

Keywords: pachydermoperiostosis; arthritis; primary hypertrophic osteoarthropathy; touraine–solente–golé syndrome; hypertrophic osteoarthropathy

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1. Introduction

Pachydermoperiostosis (PDP) is a rare clinical syndrome that was described for the first time in 1868 by Friedreich in two brothers and named 'hyperostosis of the entire skeleton' [1]. In 1935, Touraine et al. recognized PDP as an entity distinct from acromegaly and also different from hypertrophic pulmonary osteoarthropathy, as seen in patients with pulmonary or cardiac disease [2]. PDP is the primary idiopathic form of hypertrophic osteoarthropathy (HOA) and characteristic features are: pachydermia combined with enlarged hands and feet, with clubbing of the fingers and toes, with peri-osseous bony proliferation on X-rays. PDP is a genetic disease with autosomal dominant transmission in half of the families that have been studied, and in the remaining families, the transmission is probably autosomal recessive. PDP varies in prevalence and severity of features, also within families [3]. PDP occurs mainly in men and has been described in populations all over the world. The pathogenesis of the disease remains unclear, with many different findings published. We describe a patient with PDP who visited the rheumatology department of the BSMMU, Dhaka, Bangladesh, and provide a narrative review of the literature.

2. Case Report

A 23-year-old man came to our clinic in 2014 complaining of painful and swollen joints. He lived about 250 km from the clinic in Dhaka.

History: His complaints started when he was 19 years of age, with occasional pain in multiple joints after playing football as a hobby; since 2013, symptoms had increased and, gradually, his knees, ankles, hands and feet became continuously swollen, warm and painful. He also complained of sweating on the palms of both hands and the soles of his feet.

He had noticed that his hands and feet had become larger over the years, and the skin on his forehead became thicker. He had no pain in his lower back, no painful red eye, no gastrointestinal complaints, diarrhea or urethral discharge and he mentioned no abuse of laxatives. In his family, nobody had a history of joint pain in combination with skin lesions like he had; there was no consanguinity between his parents. He had two healthy sisters, and his mother has had 'rheumatism' (no data available).

On physical examination we found a forehead with thickened skin and with folds (Figure 1). His knees and ankles were swollen and painful as were his hands and feet, with clubbing of all fingers and toes with palmar and plantar hyperhidrosis (Figures 2 and 3). On examination of thorax and abdomen, no abnormalities were found. He had almost no pubic and facial hair growth.

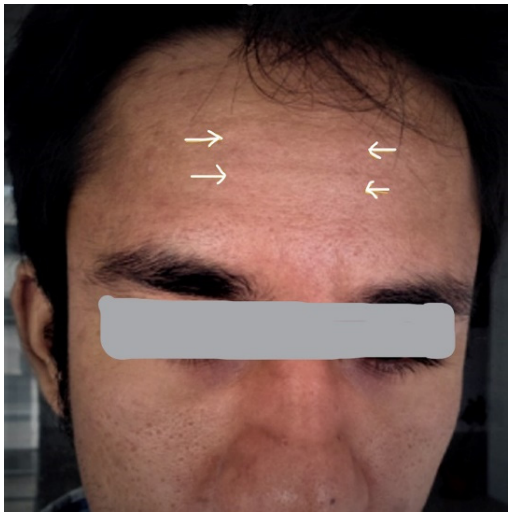

Figure 1. Pachydermia in early phase with thickening of the forehead skin with folds, marked with arrows.

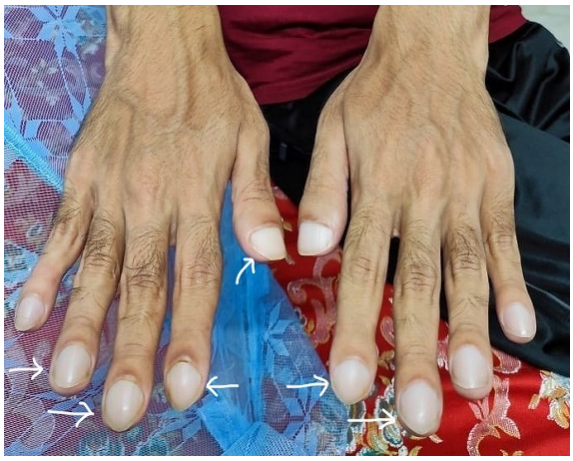

Figure 2. Clubbing of the fingers, marked with arrows.

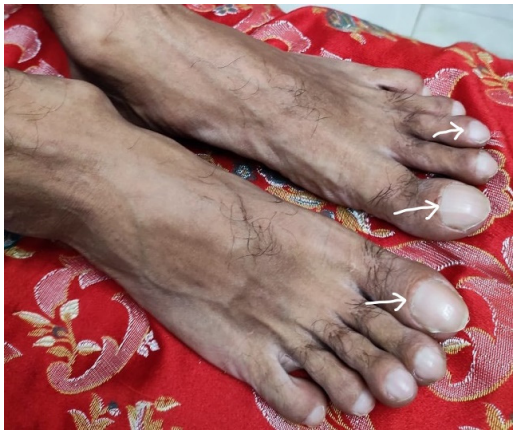

Figure 3. Clubbing of the toes, marked with arrows.

Laboratory analyses showed a normal hemoglobin level of 13.7 (Hb, normal range 15 ± 2 mg/dL), normal erythrocyte sedimentation rate (ESR, normal range 0–10) and C-reactive protein (CRP, normal range < 5 mg/L). Synovial fluid was not investigated. The liver and kidney function tests were normal, as was urinalysis. Rheumatoid factor test, anti-nuclear antibody (ANA) test and HLA-B27 were negative.

Upon X-rays of the hands and feet, irregular periosteal hypertrophy was found, with hyperostosis of phalanges and metacarpal and metatarsal bones bilaterally, as well as soft tissue swelling (Figures 4 and 5). Radiographs of the chest and SI joints showed no abnormalities. Ultrasound examination of the abdomen was normal, as was electrocardiography (ECG).

Diagnosis and treatment. PDP in the early phase was diagnosed with characteristic features: pachydermia, clubbing of fingers and toes and periostosis of the long bones of hands and feet on X-rays being present [3]. He had polyarthritis as the presenting complaint. His laboratory tests were normal and he had no diseases of the heart, lungs, liver or intestines. Secondary HOA, acromegaly and rheumatologic diseases were excluded. He was put on an NSAID, etoricoxib 90 mg daily, combined with bisphosphonate pamidronic acid (90 mg i.v), and his pains and joint swelling improved considerably within three days. The patient came for follow-up after six weeks without any pain and with no swelling of the knees and ankles.

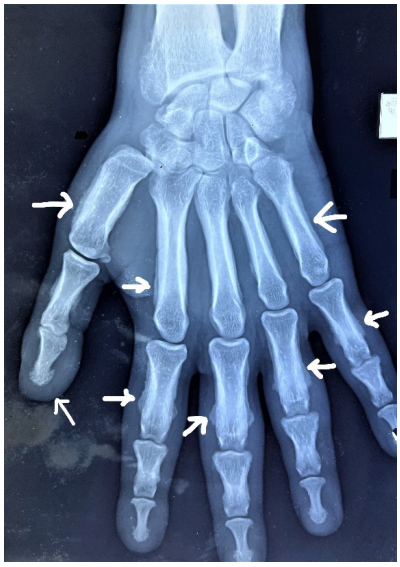

Figure 4. X-ray of hand (2014) showing irregular periosteal hypertrophy with soft tissue swelling and new bone formations affecting metacarpal bones and phalanges. New bone formation and soft tissue swelling are marked with arrows.

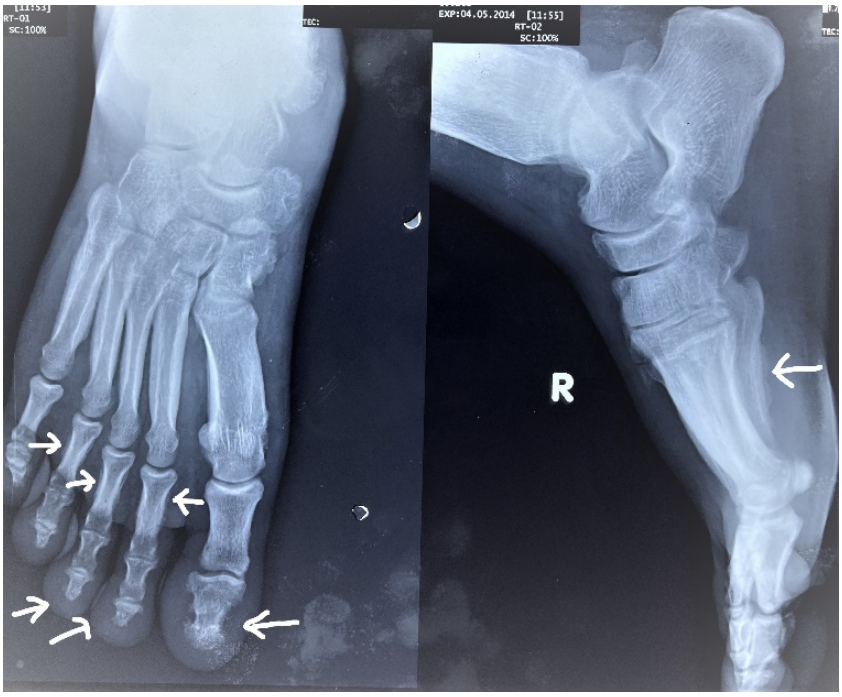

Figure 5. X-rays of right foot (2014) showing irregular periosteal hypertrophy with soft tissue swelling. The new bone formations affecting metatarsal bones and phalanges and the soft tissue swelling are marked with arrows.

Follow-up: Over the following years, we had occasional contact over the phone and he remained well with etoricoxib 90 mg per day on demand. In November 2021, he had increased pain and swelling of his joints, and he was then put on oral risedronate 35 mg weekly, after which the pain and swelling improved considerably so that he could resume his daily activities. In May 2022, he was seen again in our clinic and was doing well on this regimen. On physical examination, the clubbing of the fingers and toes had not changed. On the X-rays of his hands and feet, no periosteal hypertrophy was visible anymore (Figures 6 and 7).

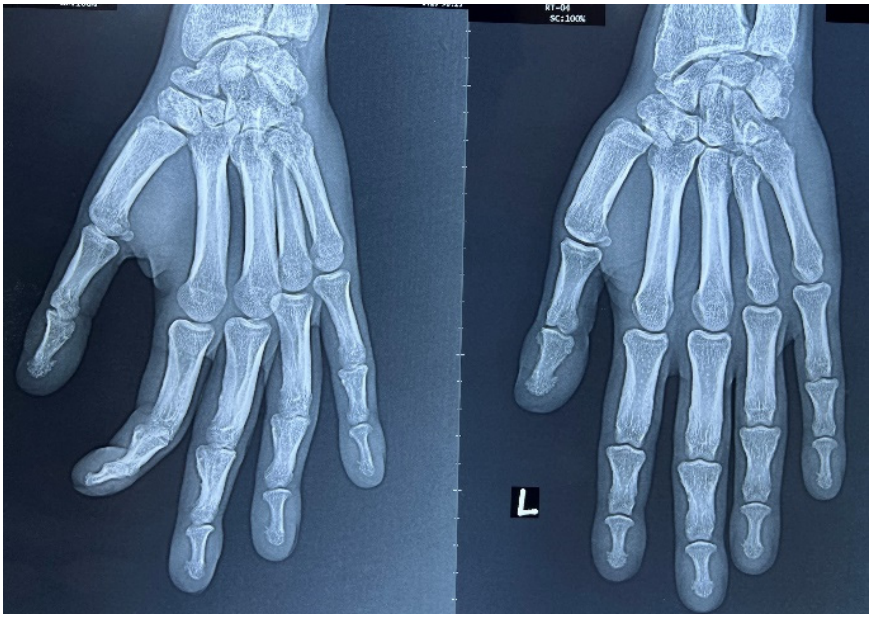

Figure 6. X-rays of the left hand (2022) showing that periosteal hypertrophy and calcifications had disappeared but that the soft tissue around distal phalanges was still swollen.

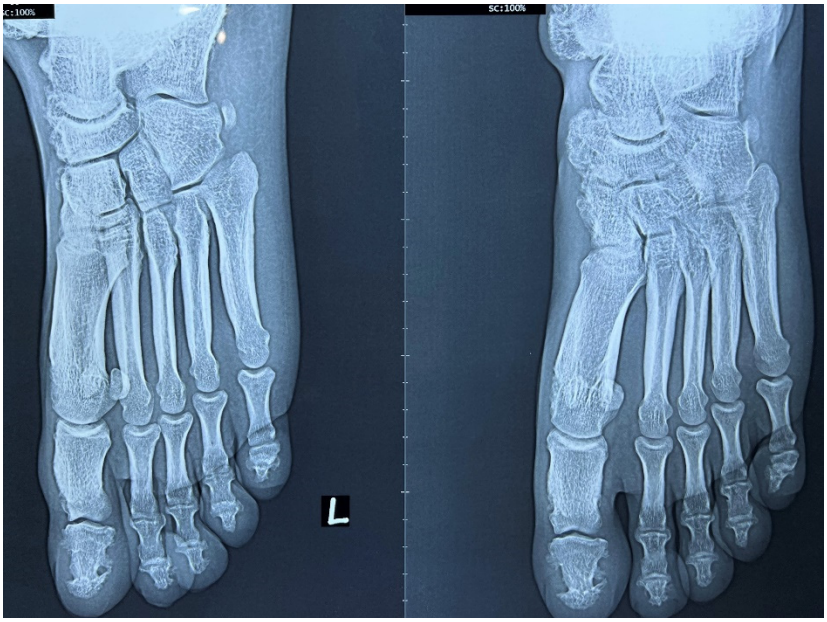

Figure 7. X ray of the feet (2022) showing that the periostal hypertrophy and calcifications had disappeared, but that the soft tissue around the distal phalanges was still swollen.

3. Discussion

As far as we know, this is the second patient with pachydermoperiostosis (PDP) described in Bangladesh, with almost 170 million inhabitants. The first case regarded a 25-year-old male, published in 2017 [4]. PDP is also called Touraine–Solente–Golé syndrome or primary, or idiopathic, hypertrophic osteoarthropathy (HOA). Secondary HOA, as seen in patients with pulmonary or cardiac disease, is much more common, and the primary form accounts for only 3–5% of all HOA cases [5]. The clinical manifestations of PDP may vary. In some cases, the skin abnormalities may be prominent, while in others, the clubbing and joint complaints prevail.

Most PDP patients develop normally until adolescence, when thickening of the skin, joint swelling and pain may start, as in our case. In the following years, these changes may progress and generally stabilize in the late twenties [6]. PDP is more frequently seen in men than in women, with a sex ratio of nine to one. A family history of PDP is seen in 25–38% of the cases [7]. Our patient reported no other cases in his family.

3.1. Pathophysiology

PDP can be inherited in an autosomal-dominant way, with variable expression, clinically manifested in an incomplete form. In some families, inheritance can be in an autosomal-recessive way, associated with the complete presentation of PDP and with more severe abnormalities in skin, bones and joints. This X-linked inheritance cannot explain the skewed male–female ratio in PDP [3].

Hereditary, primary and secondary HOA show identical histological changes, suggesting an overlap of pathogenetic mechanisms. In PDP families, genetic studies show that degradation of prostaglandin E2 (PGE2) is slowed, resulting in increased levels. The acro-osteolysis and periosteal bone formation may be explained by the fact that PGE2 can influence osteoblast activity. Apart from that, digital clubbing may be explained by continued local vasodilatory effects of PGE2 [8–10].

On histopathology, the skin in PDP shows oedema, deposition of mucin, fibrosis, loss of elastic fibers and hyperplasia of sebaceous glands. These findings correlate with the severity of pachydermia [11]. It is not clear what role the infiltration of mast cells plays in the skin and also in other organs of PDP patients [12].

3.2. Differential Diagnoses

PDP can be diagnosed when pachydermia, finger clubbing and periostosis of the long bones on X-rays of hands and feet are present and other diseases are excluded. In the first place, secondary HOA should be excluded, as can be seen with pulmonary or gastrointestinal malignancies, liver cirrhosis, cardiac disease and with sepsis lenta due to bacterial endocarditis. To differentiate carefully between primary and secondary HOA is especially important when the dermatological findings are mild or not typical [3,13,14]. PDP can also mimic acromegaly [15–18].

Thyroid acropachy [19] should be excluded as well as arthritis due to inflammatory rheumatologic diseases, as was the case in our patient. Less frequent diagnoses should be thought of like the pustulosis hyperostosis and osteitis syndrome [20], the Camurati–Engelman disease and periostosis due to chronic syphilis.

3.3. Clinical Symptoms and Signs

Cutaneous findings: PDP is characterized by clubbing of the fingers and toes, seen in 89% of cases, pachydermia with thickened and wrinkled skin, especially of the forehead, and nasolabial folds [21]. In 30–40%, hypertrophy of the eyelids is seen and eyelid dropping may be prominent, as described in a case from Iran [22].

Thickening of the arms and legs can be very prominent, due to thickened skin combined with bony enlargement; thus, PDP is sometimes called the elephant skin disease [13]. In some patients, the skin deformities cause major cosmetic problems [23].

In more than 90% of cases, seborrhea is seen, sometimes with acne or folliculitis [20]. Hyperhidrosis, especially on the palms of the hands and foot soles, is common (44%) and may also be seen in the major folds. Growth of hair in the pubic region and on the face is almost always rare [20].

Gastrointestinal: Matucci-Cerenic et al. found gastric ulcers in 6 of 20 patients [24]. In rare cases, gastrointestinal complaints may be seen. A Chinese PDP patient complained of flatulence, heartburn and intermittent diarrhea; upon gastroscopy, a thickened stomach wall was seen, with wrinkled gastric-mucosa-like brain sulcus and gyri [25].

Heart: Heart failure has been described in one case of PDP, with severely decreased left ventricular systolic function om echocardiography. After treatment, cardiac function and symptoms improved [26].

Bony changes: Symmetric irregular periosteal new bone formation is most severe in the extremities, but any bone can be involved, though, rarely, the skull and vertebrae are affected [6]. In 80–97% of patients, a diffuse and irregular shaggy periostosis may be seen on radiographs along the bones, including the epiphyses. This is more prominent with longer disease duration [24,27]. Acro-osteolysis may be observed in 78% of cases [20].

Articular findings: Arthralgia and muscle discomfort are common complaints, and effusion of the large joints is seen in 41% of patients, often in the knees [20]. Polyarthritis is found in 20–40% of patients, which is often symmetric [20]. Even bilateral hip arthritis has been described [5]. Arthritis can be misleading, and some patients were initially diagnosed with rheumatoid arthritis. Intermittent joint swelling is quite common and can be painful but can also be asymptomatic. The articular surfaces of the joints are not affected [6]. Our patient complained of severe pain in both small and large joints.

3.4. Treatment

Generally, symptomatic treatment is sufficient, relieving pain with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids or colchicine [4,7,24,28]. We chose etoricoxib as a symptomatic treatment, with a reasonable effect also described in other cases [29–31]. In a severe case, a TNF-α (tumor necrosis factor-alpha) blocking agent, infliximab, has been successfully applied [32], but use of TNF-α blockers is generally not indicated. The use of methotrexate (MTX) has been described in two PDP cases with severe arthritis, with a corticosteroid and NSAID sparing effect [33].

Pain in the bones and joints can also be treated successfully with bisphosphonates, such as pamidronic acid, risedronate or zelodronic acid [7,28,32,34,35]. The effect of bisphosphonates is ascribed to inhibition of osteoclastic bone resorption, reducing bone remodeling and, thus, decreasing inflammation. In our case, after treatment, the periosteal calcifications disappeared and the complaints improved. Arthroscopic synovectomy has been successfully applied for treating persisting arthritis [29].

Many PDP patients complain about their appearance [6,23]. In a patient from Sri Lanka, severe acne improved with retinoids; this patient also had major cosmetic concerns about his cutis verticis gyrate, for which he received botulinum toxin injections [23]. In some cases, plastic surgery may be indicated to improve the appearance of the face [36].

4. Conclusions

PDP may present as polyarthritis and clinicians should be aware of this diagnosis, as treatment is available and may improve the outcome of the patient.

It is important to rule out secondary HOA due to pulmonary or cardiac disease, gastrointestinal malignancies, liver cirrhosis, et cetera, especially when the dermatological findings are not typical. Further, acromegaly, thyroid acropachy and rheumatologic diseases should be excluded.

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Data Availability Statement: Data can be requested from the first author.

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