PACHYDERMOPIEROSTOSIS MIMICKING ACROMEGALY: A RARE CASE REPORT IN SARDJITO GENERAL HOSPITAL YOGYAKARTA INDONESIA

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ABSTRACT
Pachydermoperiostosis is a genetic disorder characterized by pachydermia and periostosis. The clinical and radiological features of pachydermoperiostosis are similar to acromegaly. The Prevalence of pachydermoperiostosis is estimated 0.16%. The ratio of male-to-female incidence is 7 to 1. We report a man 26 years old with complaints of pain and swelling in the wrist joints, fingers, knee joints and ankle joints bilaterally; seborrheic dermatitis, eyelid ptosis, and thickening of facial skin, which has been progressive since he was 17 years old. Manus, genu and pedis x-ray results showed a features of mixed connective tissue disease. Magnetic resonance imaging result of the pituitary gland with contrast was normal. Laboratory results for growth hormone (GH) and insulin growth factor-1 (IGF-1) were normal. Histopathology results of the facial skin biopsy showed grade 1 pachydermia in pachydermoperiostosis. In conclusion, the appearance of pachydermia on skin biopsy, with normal growth hormone and insulin growth factor-1 results can differentiate pachydermoperiostosis from acromegaly.

Keywords: Pachydermoperiostosis, Mimicking, Acromegaly.

INTRODUCTION
Touraine, Solente, and Gole defined pachydermoperiostosis as a variant of primary hypertrophic osteoarthropathy resulting from acromegaly and malignancy. The first case of pachydermoperiostosis was reported by Friedreich in 1868. The clinical features, signs and symptoms of pachydermoperiostosis are similar to acromegaly and these may cause diagnostic confusion. In the evaluation of patients with acromegaloid features, pachydermoperiostosis should be considered as a differential diagnosis (Baykan & Türkyılmaz, 2022). Manifestations of pachydermoperiostosis generally occur in childhood to adolescence and may often occur at 5-20 years old. The prevalence of pachydermoperiostosis is estimated at 0.16% (Alessandrella et al., 2018). The ratio of male-to-female incidence is 7 to 1 (Baykan & Türkyılmaz, 2022).

Until now there is no specific modality for treatment of pachydermoperiostosis due to mutations encoding the enzyme 15-hydroxyprostaglandin dehydrogenase (15-HPGD) and transporter defects (SLCO2A1 mutations). Current therapy is mostly aimed at reducing the effects of increased prostaglandins and correcting joint deformities and for cosmetic purposes (Nakanishi et al., 2021); (Zhang & Yang, 2017).

Typical symptoms of pachydermoperiostosis include thickening and hardening of the scalp (pachydermia), clubbing fingers, edema of the lower limbs, arthritis either with or without joint effusion, and periostosis (swelling of the periarticular tissue and new bone subperiosteal formation).
Other typical features of pachydermoperiostosis include seborrheic dermatitis, long eyelashes, blepharoptosis, periarticular edema, synovial effusion, and diarrhea. Hypertrophy of the dermal and sebaceous glands will result in skin manifestations such as thickening of the forehead skin and excessive sweating (Marques et al., 2020). This case report aims to increase clinical knowledge about pachydermoperiostosis and differentiate it from acromegaly, which has very similar clinical features.

**CASE ILLUSTRATION**

We report a man, 26 years old, with complaints of pain and swelling in the wrist joints, fingers, knee joints, ankle joints, and toes; seborrheic dermatitis and thickening of facial skin, which has been progressive since he was 17 years old. There was fluid in the knee joint bilaterally. At the General Hospital previously, this patient was diagnosed with a suspected autoimmune disease and was treated with methylprednisolone 16 mg twice a day po and ciclosporin 50 mg once a day po.

Complaints became aggravated; on January 25, 2023, this patient was referred to the Rheumatology, RSUP Dr. Sardjito Yogyakarta, and was consulted to Endocrinology for establishing the diagnosis. On physical examination, the scalp appears rough, thick and stiff hairs. Facial skin appears hypertrophic, rough, and thick. There are prominent skin folds on the forehead, naso-facial, and both eyelids with ptosis. Examination of the extremities revealed swelling of both wrists, clubbing fingers, and swelling of both knees, ankles, and toes. Hand and foot joint pain when moved.

![Figure 1. Photo of the patient's extremity abnormalities](image)

There are clubbing fingers and wrist joints swelling bilaterally (A). Swelling in both knee joints (B). Swelling in both ankle joints and toes bilaterally (C).

![Figure 2. Radiological image of wrist joint, phalanges manus, and knee joint patient bilaterally.](image)
Manus x-ray shows features of osteopenia, especially the metacarpophalangeal (MCP) joints with irregularity of intermedia phalanges and narrowing of joint space to distal interphalangeal (DIP) of left wrist joint suggestive of mixed connective tissue disease (MCTD) (A). In the bilateral knee joints x-ray, the impression of soft tissue swelling with irregularity of the left tibia and patella bone leads to an MCTD image (B).

Laboratory results showed anti-ds-DNA 12.9 mU/L, C-reactive protein (CRP) 17.5 mg/dL, complement C3 141 mg/dL, complement C4 32.1 mg/dL, growth hormone (GH) 0.46 ng/mL, and insulin growth factor-1 (IGF-1) 1.16 ng/mL, which all of these are within normal limits, and rheumatoid factor positive. Cytology results of knee joint fluid showed protozoa (amoeba) with a size of 10-12 µm cyst and trophozoite, with unclear cell nuclei. Histopathological results of forehead skin biopsy were suggestive of grade 1 pachydermia in pachydermoperiostosis.

The epidermis shows basketweave-type orthokeratosis and focal acanthosis. Dermis with the normal structure of sebaceous glands that have increased in number and size; the appearance of sebaceous lobules grouped around ducts that are dilated and filled with keratin debris (A). The partial dermis is edematous, with focal mucin deposition (B).
This patient was diagnosed with grade 1 pachydermia in pachydermoperiostosis, seropositive rheumatoid arthritis, amoebic joint effusion genu, ODS anterior uveitis, and ODS ptosis. This patient was treated with methylprednisolone 8 mg once a day po, methotrexate 10 mg once a week po, folic acid 1 mg once a day po, ascorbic acid 20 mg twice a day po, metronidazole 500 mg three times a day po, sodium hyaluronate (eye drop 1 mg/ml) 1 gtt ODS four times a day.

RESULTS AND DISCUSSION

The most common clinical features of pachydermoperiostosis are associated with joint pain, polyarthritis, verticis gyrata cutis, seborrheic dermatitis, and hyperhidrosis. Pachydermoperiostosis, otherwise known as primary hypertrophic osteoarthropathy, is characterized by clubbing fingers, pachydermia, and new bone subperiosteal formation (Alessandrella et al., 2018). The prominent radiological feature of pachydermoperiostosis is osteoarthrodermopathic disorder with clinical and radiographic features that may resemble acromegaly (Baykan & Türkyılmaz, 2022). Radiological findings of pachydermoperiostosis include new bone subperiosteal formation, cortical thickening, and joint space narrowing. Resorption of the distal phalanx bones and ossification of the membranes and ligaments between the bones can also be seen (Mangupli et al., 2017). In 1935, French physicians Touraine, Solente, and Gole classified pachydermoperiostosis into three forms:

1. Complete or classic form (pachydermia and periostosis)
   There is thickening of the skin, changes in the skeleton, and clubbing fingers.
2. Incomplete form (skeletal changes without skin involvement)
   There are changes in the skeleton without the involvement of skin disorders (pachydermia).
3. Frusta form (minimal skeletal changes and pachydermia)
   There is minimal skin thickening and no changes in the skeleton (Baykan & Türkyılmaz, 2022).

The diagnosis of pachydermoperiostosis is made if there are two of the following characteristics, namely a positive family history, hypertrophic skin changes, bone pain or radiographic changes, or clubbing fingers (Baykan & Türkyılmaz, 2022). Specific symptoms of pachydermoperiostosis that are not present in acromegaly are long eyelashes, blepharoptosis, myelofibrosis, hypoalbuminemia, gastric ulcers, stomach cancer or diarrhea in response to certain triggers, such as cold drinks, oily foods, or sexual activity (Marques et al., 2020).

To confirm the diagnosis of pachydermoperiostosis from acromegaly, the first step that must be carried out is a biochemical examination and imaging examination to determine the cause of excessive growth hormone (GH) secretion (Oh et al., 2012). Acromegaly is a disease characterized by hypersecretion of GH, often as a result of a pituitary adenoma (Grasso et al., 2013). However, other conditions can mimic the clinical manifestations seen in acromegaly without GH or IGF-1 abnormalities, which is referred to as pseudoacromegaly (Marques et al., 2020). Excess GH and IGF-1 in acromegaly causes periosteal bone formation, growth of synovial tissue, and cartilage and causes arthropathy hypertrophic associated with pain and deformity, which is also seen in pachydermoperiostosis (Chanson & Salenave, 2008).

Knowing serum levels of IGF-1 is the best diagnostic test for acromegaly. Increased GH and IGF-1 concentrations occur in almost all acromegaly patients. In pachydermoperiostosis patients, IGF-1 and GH are normal, and there are no adenomas in the pituitary gland (Alessandrella et al., 2018). During an oral glucose tolerance test (OGTT), a serum GH level <1 µg/L means the diagnosis of acromegaly is excluded (Alessandrella et al., 2018).
The characteristics that appear in patients with acromegaly are caused by the effects of excess GH, especially from pituitary tumors (Pandey et al., 2005). Clinical manifestations in childhood and adolescence vary depending on the opening of the epiphyseal growth plate. If it occurs before epiphyseal fusion, there is a significant acceleration in growth rate, a condition also known as gigantism. However, suppose it occurs after epiphyseal fusion is complete, the clinical symptoms resemble acromegaly in adults, including rough facial features, a widened nose, hands, and feet, organomegaly, and hyperhidrosis (Laws et al., 1985).

Skin changes in acromegaly are caused by excess action of GH and IGF-1 on skin cells and adnexa. The skin is swollen due to the accumulation of dermal glycosaminoglycans, and edema is most prominent on the face, hands, and feet. Oily skin with large pores, hypertrichosis, and excessive sweating are common features of acromegaly. Pigmented skin tags and acanthosis nigricans are also found (Laws et al., 1985).

The presence of clubbing fingers and periostosis is often seen in pachydermoperiostosis but not in acromegaly. Acral abnormalities associated with pachydermoperiostosis may overlap with symptoms of acromegaly, including limb enlargement, thickened and shortened fingers, and thickened soft tissues. Vertical gyrate cutis, facial roughness, hyperhidrosis, seborrheoa, and acne often occur in pachydermoperiostosis and also in acromegaly. Tall stature is not a classic feature of pachydermoperiostosis. However, some cases have been found to be up to 200 cm tall, so it would add a diagnostic challenge to differentiating it from acromegaly (Marques et al., 2020). Confirmation of the diagnosis by imaging can be done with an magnetic resonance imaging (MRI) of the head to confirm the presence of a pituitary adenoma. However, normal head MRI results do not rule out a diagnosis of microadenoma (Oh et al., 2012).

Molecular analysis can be performed to confirm the diagnosis of pachydermoperiostosis, which shows a new homozygous gene mutation in SLCO2A1 as the gene coding for the prostaglandin transporter (Alessandrella et al., 2018). Autosomal recessive homozygous mutations of 15-hydroxyprostaglandin dehydrogenase (15-HPGD) enzyme, which codes for catabolism prostaglandin E2 (PGE2), and transporter defect (SLCO2A1 mutation), which codes for prostaglandin transporter (PGT) responsible for absorption of PGE2. Both mutations play a role in occurring pachydermoperiostosis (Uppal et al., 2008); (Zhang et al., 2012); (Tanese et al., 2015); (Mangupli et al., 2017).

Prostaglandins are important lipid mediators that maintain physiological and homeostatic functions. However, they can also induce pathological responses such as inflammatory and nociceptive responses. Prostaglandins are synthesized from arachidonic acid (AA), which is released from cell membranes by phospholipase A2 (PLA2). The cyclooxygenase isoform-1 (COX-1) and cyclooxygenase isoform-2 (COX-2) enzymes metabolize arachidonic acid into prostaglandin G2 (PGG2) and then into prostaglandin H2 (PGH2) through bis-oxygenation and peroxidation reactions, respectively. Prostaglandin H2 (PGH2) is a common precursor of the four major bioactive prostaglandins (PGDs), such as PGI2, PGE2, PGF2α and prostanoid thromboxane A2 (TXA2), which is synthesized by cell-and-tissue-specific isomerases synthase (Jiang et al., 2021).

There is no specific modality for the treatment of pachydermoperiostosis. Current therapy is mostly aimed at reducing the effects of increased prostaglandins and correcting joint deformities for cosmetic purposes (Nakanishi et al., 2021); (Zhang & Yang, 2017). Controlling excessive secretion of
GH and IGF-1 will relieve most cutaneous manifestations of acromegaly; however, regression may be incomplete (Laws et al., 1985).

COX inhibitors (nonsteroidal anti-inflammatory drugs, acetylsalicylic acid, and corticosteroids) can inhibit COX enzymes and suppress PGE2 biosynthesis. These drugs are promising agents in the treatment of pachydermoperiostosis. This is in accordance with the pathogenesis of pachydermoperiostosis due to mutations in 15-hydroxyprostaglandin dehydrogenase (15-HPGD) and mutations in the SLCO2A1 gene, which results in increased prostaglandin (PGE) synthesis (Nakanishi et al., 2021).

Previous studies observed marked improvement in skin findings and joint pain with hydroxychloroquine therapy in pachydermoperiostosis patients with homozygous SLCO2A1 gene mutations. Intra-articular steroid injections may also be considered in the treatment of severe arthritis (Alessandrella et al., 2018).

Bisphosphonates such as pamidronate are used in the therapy of pachydermoperiostosis because of their antiresorptive and osteoclast-inhibitory properties (Guyot-Drouot et al., 2000). Other therapeutic agents used in the medical therapy of pachydermoperiostosis include aescin, bisphosphonates, colchicine, retinoids, tricyclic antidepressants, and tamoxifen citrate. Botulinum toxin A has also been used for cosmetic reasons. Surgery is used to correct bone deformities, and plastic surgery (blepharoplasty) can be used to correct the thickening of the forehead skin (Zhang & Yang, 2017).

CONCLUSION

Pachydermoperiostosis is a rare genetic disorder with clinical manifestations similar to acromegaly. A proper diagnosis must be made using various diagnostic methods such as laboratory analysis, x-ray of joint disorders, magnetic resonance imaging of pituitary gland and biopsy of skin abnormalities. The presence of pachydermia on skin biopsy, with normal growth hormone (GH) and insulin growth factor-1 (IGF-1) and normal magnetic resonance imaging results of pituitary gland, can differentiate pachydermoperiostosis from acromegaly.

REFERENCES


Saiful Anam, Hemi Sinorita
Pachydermoperiostosis Mimicking Acromegaly: a Rare Case Report in Sardjito General Hospital Yogyakarta Indonesia


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