CASE REPORT

A Case of Elephant Extremities in a Filipino Male: Primary Familial Pachydermoperiostosis

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ABSTRACT

This is a rare case of primary pachydermoperiostosis (PDP). A 28-year-old Filipino male presented with a lifelong history of enlarged hands and feet. He eventually developed symmetrical swelling of the ankles and knees associated with leg heaviness and knee pain with difficulty with ambulation, hence consult. His eldest brother also had the same "elephant-like" extremities. He had cutis vertices gyrata with a thickened corrugated hair pattern, deep lines on the forehead, deepened nasolabial folds, enlarged extremities especially distally, with coarse, thick skin, and prominent clubbing. The nails were convex "watch crystal-like." The wrists, knees, and ankles were tender and enlarged, with massive effusion of the knees. All joints were devoid of warmth and erythema.

Skeletal survey favored hypertrophic osteoarthropathy over acromegaly, with periosteal thickening of the metaphysis and digital clubbing. The filarial smear was negative for blood parasites. Skin biopsy showed keratoderma. Synovial fluid was non-inflammatory while arthroscopic synovial biopsy showed chronic inflammation eosinophilic amorphous tissue. Electrocardiogram, echocardiogram, thyroid function tests, complete blood count, peripheral blood smear, serum chemistries, coagulation tests, urinalysis, urine electrolytes, fecalysis, and chest CT scan were unremarkable. Whole abdomen ultrasound revealed the liver parenchymal disease. Hepatitis profile revealed chronic infection with hepatitis B, with low infectivity. The three major criteria for PDP (pachydermia, periostitis, and digital clubbing) were fulfilled. Possible secondary causes were either excluded or were non-contributory.

He was started on analgesics and anti-inflammatory medicines. Repeated arthrocenteses drained liters of synovial fluid per knee, and along with intra-articular steroid injections and compressive bandages, temporarily relieved his bilateral knee pain. He was referred to rehabilitation to maximize his range of motion and to address body image issues. The patient remains on regular follow-up for periodic arthrocentesis. The option of anti-VEGF treatment and arthrotomy was explored as possibilities but were not deemed practical.

PDP is a rare genodermatosis. Life span is not affected but the quality of life is dismal without supportive management, as there is no known cure. A multidisciplinary team composed of a rheumatologist, dermatologist, orthopedic surgeon, plastic surgeon, rehabilitation physician, and a psychiatrist should be available to assist in the needs of these patients.

Key Words: pachydermoperiostosis, hypertrophic osteoarthropathy, cutis verticis gyrata, pachydermia, clubbing

INTRODUCTION

Hypertrophic osteoarthropathy (HOA) is a syndrome characterized by digital clubbing, periostosis, and arthritis. The secondary form is associated with several diseases and sometimes occurs as a paraneoplastic syndrome.[1] HOA is divided into primary and secondary forms. Pachydermoperiostosis (PDP), the primary familial form of HOA, accounts for only 5% of all cases of HOA. Sporadic forms have also been described. Secondary HOA, sometimes called pulmonary HOA, is associated with underlying cardiopulmonary diseases and malignancies.[2]

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PDP is a rare hereditary disorder that is characterized by pachydermia, digital clubbing, and subperiosteal new bone formation. It was originally described by Friedreich in 1868 in two affected brothers as "hyperostosis of the entire skeleton." In 1935, Touraine individualized PDP as the primary form of HOA, distinct from the more common secondary HOA, which always associates with an underlying cause.[1] The precise incidence is unknown; less than 300 cases were found on a MEDLINE search.[3] PDP is often familial and occurs predominantly in men. It is believed to be inherited in an autosomal dominant pattern with variable penetrance; autosomal recessive forms have also been described.[1] Though diagnosis can be made based on clinical and radiologic features, it is often missed due to variable presentations. This rare condition often mimics some other well-known conditions like acromegaly and the leonine facies in leprosy.

We present a rare case of primary familial PDP that presented with diagnostic and thera-peutic difficulties. A multidisciplinary team facilitated the diagnosis and treatment of our patient.

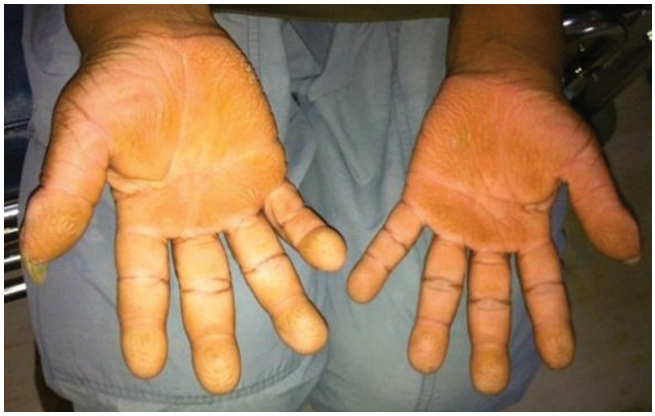

Figure 1. Coarsened, thickened skin on the palms.

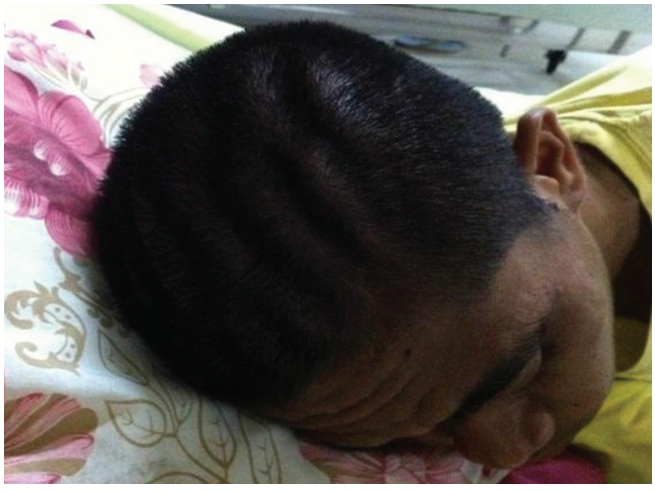

Figure 2. Cutis verticis gyrata.

CASE

RP, a single, 28-year-old male from Surigao del Norte consulted at the Philippine General Hospital for the chief complaint of enlargement of both hands and feet associated with mechanical joint pains.

His joints, hands, and feet were large since childhood, with a marked increase in the rapidity of enlargement at the time of puberty. The enlarged joints were symmetric involving both hands up to the wrists, and both feet, ankles, and knees. The consult was done only after the patient started having joint effusions and pain on recumbence and ambulation described as heaviness. On examination he was ambulatory, fairly-nourished, measuring 160 cm in height and 48 kg in weight. His skin is thick and coarse, most prominent on the forehead, the scalp, the palms, and the soles. (Figure 1) The thickened scalp was also remarkable for folds making a corrugated hair pattern (cutis verticis gyrata). (Figure 2)

There were prominent lines on the forehead and deepened nasolabial folds. There was no macroglossia, pragnathism, frontal bossing, or heightened cheekbones. (Figure 3) The wrists were bilaterally enlarged with effusions. All digits were clubbed with periungual erythema and softened nailbeds (Figure 4).

The knees were bilaterally enlarged, measuring 61 cm on the left and 62 cm on the right, and tense with effusions. (Figure 5) The ankles were likewise enlarged and effused (34 cm on the left, 34.5 cm on the right). The enlarged feet had digital clubbing as well (Figure 6). All joints were devoid of warmth and erythema. There was some limitation on passive and active movement because of the girth of the joints. Abdominal, chest, and heart findings were normal.

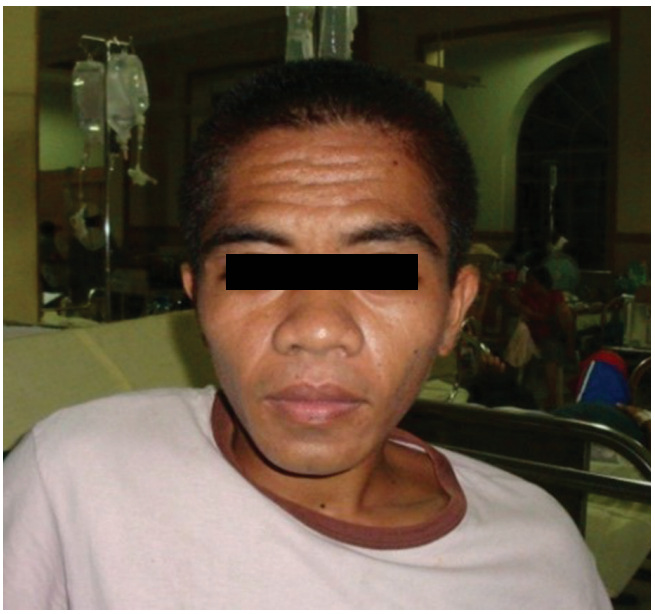

Figure 3. Facial features with prominent forehead lines, nasolabial folds.

Workup

Our patient was first seen at the out-patient clinics where dermatologists, endocrinologists, and rheumatologists initially assessed the patient to have HOA versus acromegaly. Before he was admitted for workup for secondary causes of HOA, a peripheral blood smear to rule out filariasis showed absence of blood parasites, and skin biopsy showed changes consistent with keratoderma. (Figure 7)

A skeletal survey showed a normal skull x-ray, normal vertebrae, marked and symmetric periosteal thickening at the radius, ulna, femur, tibia, and fibula, more prominent on the distal segments and, a bone island on the left acetabular rim. There was non-prominence of the phalangeal tufts and normal articular space; descriptions more consistent with hyperthrophic osteroarthropathy than acromegaly. (Figure 8) Acromegaly, the nearest differential, was therefore ruled out because the characteristic facial features of mandibular overgrowth, frontal bossing, heightened cheekbones, and jaw malocclusion were absent.

Arthrocentesis was done on both knees obtaining more than two liters of yellow, clear, non-bloody, viscous synovial fluid per knee. The analysis showed a non-inflammatory transudate with WBC of only 47 cells on the left, and 40 on the right. There was lymphocyte predominance of 76-88%. Glucose levels were normal. No crystals were observed in both samples. Cultures of both synovial fluid samples showed no growth.

Secondary causes of HOA were ruled out: high-resolution chest CT scan showed the normal result, 12-lead electrocardiogram and 2d-echocardiography were non-contributory,

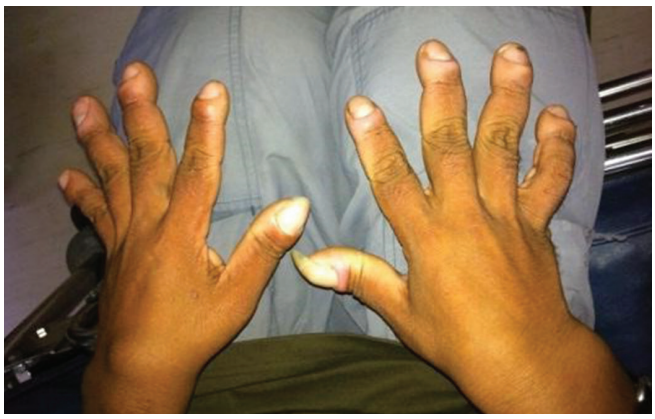

Figure 4. Bilateral digital clubbing.

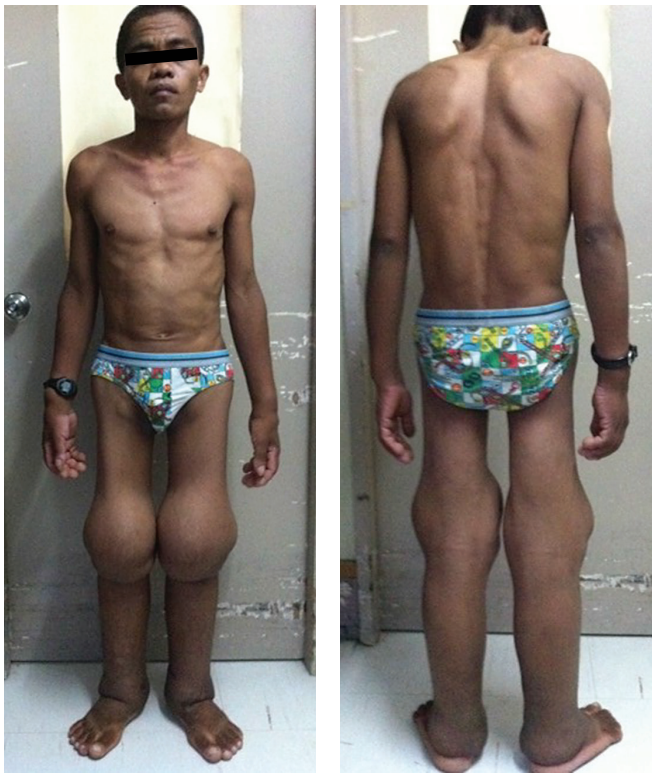

Figure 5. Enlarged hands, wrists, knees, ankles and feet.

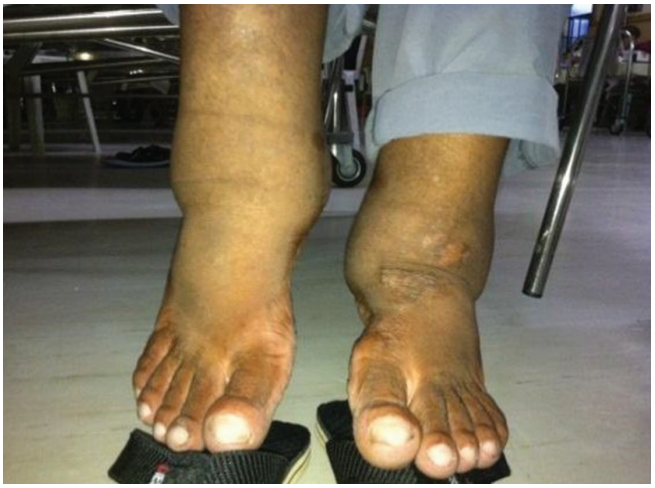

Figure 6. Enlarged ankles, clubbing of toes.

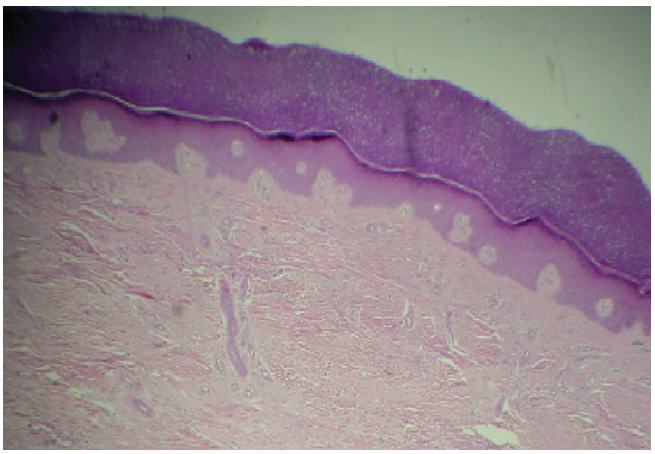

Figure 7. Skin biopsy showing non-specific keratoderma (haematoxylin-eosin stain; magnification 100x).

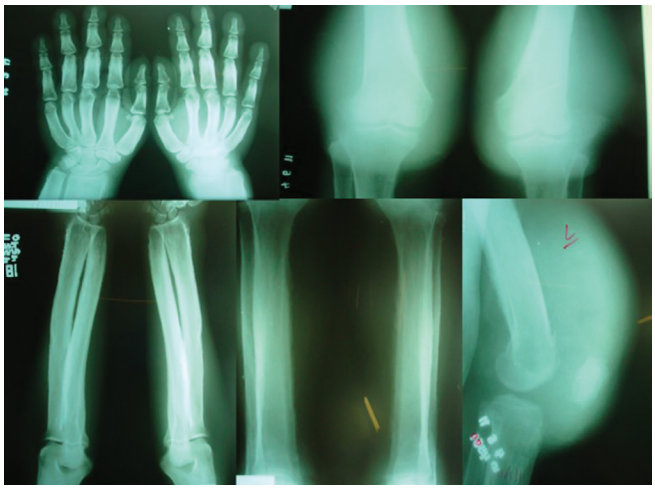

Figure 8. Skeletal survey showing phalangeal tufts, symmetric periosteal thickening of the radius, ulna, femur, tibia, and fibula.

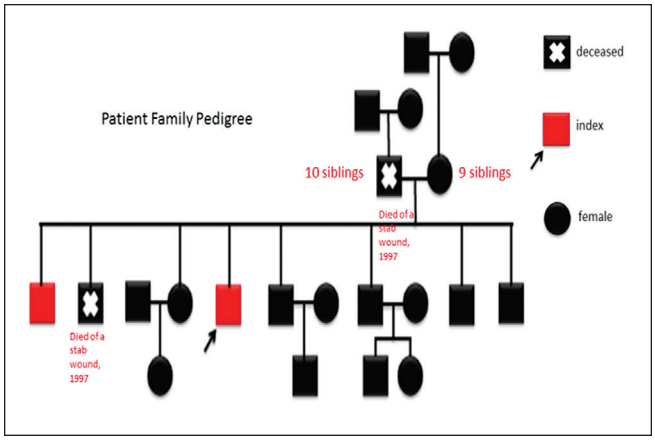

Figure 9. Pedigree showing a similar case in eldest sibling. The presence of chronic hepatitis B infection, a condition that could bring about pachydermoperiostosis, was deemed coincidental and not causative.

and thyroid-stimulating hormone was normal ruling out thyroid acropachy. Ultrasound of the entire abdomen showed liver parenchymal disease. Further workup showed the patient to have chronic hepatitis B with low infectivity. Other tests included an elevated ESR (49), normal prothrombin and partial thromboplastin times, normal electrolytes, normal arterial blood gases, normal transaminases, and urinalysis. Filariasis was also ruled out.

A team-approach involving dermatologists, endocrinologists, and rheumatologists was made to ascertain whether this patient had primary or secondary PDP. It was also presented during the conference that the patient's older brother (Figure 9) had the same condition (enlarged feet and hands, clubbing of digits). With the paucity of significant laboratory findings and the condition similarly presenting in the patient's older brother, a consensus was made on the diagnosis of primary familial PDP.

Treatment and Outcome

The patient underwent another arthrocentesis before discharge, evacuating more than a liter of clear synovial fluid from each knee, followed by intra-articular steroid injection and compressive bandages. He was started on an analgesic and a non-steroidal anti-inflammatory drug. Bedside rehabilitation was started for joint preservation techniques. The option of anti-VEGF treatment and arthrotomy with total synovectomy were explored as possibilities but were not deemed to be practical in the patient's case as this would entail very wide excision of the knee and debilitate the patient.

He was discharged improved with a final knee circumference of 44 cm on the left and 45 cm on the right. His pain improved drastically, initially scoring 8/10 on the visual analog scale to 2/10 on discharge. He was referred to Psychiatry for liaison and psychological support.

He initially consulted every month then dwindled to once every few months. He was last seen in 2019 for re-arthrocentesis of both knees. Effusions had been of lesser magnitude. Occasional pain is controlled by low-dose NSAIDs.

DISCUSSION

PDP is a rare genodermatosis affecting both skin and bones. The major diagnostic criteria include digital clubbing, periostosis, and pachydermia. Minor criteria include hyperhidrosis, arthralgia, gastric ulcer, cutis verticis gyrata, blepharoptosis, joint effusion, column-like legs, edema, seborrhea, acne, hyperhidrosis, and flushing. The clinical suspicion of PDP is confirmed by radiography of the long bones.[1]

Although the disease is not present with high frequency in the general population, the precise incidence and prevalence are still unknown.[2] It has an estimated prevalence of 0.16%.[4] PDP occurs predominantly in men with a ratio of 9:1 and has been reported in many races. Typically, men are affected more severely than women.[1]

Disease onset is often at puberty, with progressive thickening and furrowing of the scalp (pachydermia), enlargement of the fingertips (digital clubbing), swelling of periarticular tissue, and shaggy periosteal new bone formation of the long bones (periostosis). These changes usually progress for 5-20 years and remain stable afterward. The major complication is joint involvement, consisting of arthralgia, arthritis, and effusion.[5] All these were manifested in our patient.

Patients with PDP demonstrate increased plasma levels of several substances, including osteocalcin, endothelin-1, beta-thromboglobulin, platelet-derived growth factor, von Willebrand factor, and vascular endothelial growth factor, which lead to increased fibroblast proliferation in the bone marrow and skin biopsies, associated with diffuse dermal

endothelial hyperplasia, partial occlusion of the vascular lumen, pericapillary lymphohistiocytic infiltrate and thickening and packaging of collagen fibers.[3,6]

PDP has recently been mapped to band 4q33-q34. Two susceptibility genes have been identified underlying PDP: HPGD encoding 15-hydroxyprostaglandin dehydrogenase, the main enzyme of prostaglandin degradation, and SLCO2A1, involved in the transportation of prostaglandin.[7,8] A systematic review of published PDP families noted significant genetic heterogeneity. Both autosomal dominant and autosomal recessive modes of inheritance were demonstrated. In the latter mode, it was proposed that it may represent reduced penetrance or germinal mosaicism of an autosomal dominant mutation. Sporadic patients were also noted which could represent new mutations or segregation of a dominant mutation with incomplete penetrance and mild expression in the parents.[3]

Primary familial PDP may be expressed in 3 general ways: (a) the *complete form* which presents with the full-blown phenotype; (b) the *incomplete form* which has no pachydermia; and the (c) *"forme fruste"* which has prominent pachydermia and minimal skeletal changes.[1,3] In the latter form, thickening of the skin, coarsening of facial features akin to leonine facies of leprosy, and cutis verticis gyrata of the scalp are all present, giving the patient an acromegaloid appearance, while periosteal changes are either absent or minimal at the time of examination.[9]

This "*forme fruste*" form is the one which presents with the most problems in diagnosis. It can be mistaken for the leonine facies of leprosy, but associated signs and symptoms differentiate this from PDP.[10] The nearest differential is secondary HOA. The prevalence of HOA in primary lung cancer has been reported to be 4 to 32%. Other common associations are with adult congenital heart disease in which prevalence is 31% and chronic liver disease in which the prevalence is 28%.[11] Some extra-thoracic malignancies associated with periostitis and HOA include nasopharyngeal cancer,[12] mesothelioma,[13] pancreatic cancer,[14] and breast cancer.[15] Rheumatoid arthritis,[16] ankylosing spondylitis,[17] lupus,[18] and Takayasu arteritis[19] are just some the rheumatologic diseases wherein HOA has been reported in.

Chronic infections associated with cystic fibrosis, tuberculosis, subacute bacterial endocarditis, syphilis, acquired immunodeficiency syndrome, and vascular graft infections are also associated with HOA.[20] The presence of chronic hepatitis infection and liver parenchymal disease in our patient initially presented as a dilemma, but with the brother devoid of hepatitis, clearly, our patient has primary familial PDP.

Life span is not decreased in these kinds of patients but a curious palindrome occurs in some cases of primary HOA that should probably warrant long-term screening and follow-up. This palindrome has been reported in HOA associated with patent ductus arteriosus, Crohn's disease, and myelofibrosis.[20] There are also anecdotal associations with squamous cell carcinoma and multiple basal cell carcinoma, some that develop these malignancies 10-15 years after being diagnosed with PDP.[1]

Treatment is mainly supportive, using non-steroidal anti-inflammatory agents, colchicine, or intra-articular corticosteroids for relief of pain.[21] Trials of bisphosphonates for arthritis along with arthroscopic synovectomy are recent advances.[22,23] For cutaneous manifestations, isotretinoin, which reduces procollagen production, and botulinum toxin, which relaxes facial muscles, can also be of use.[24,25] Plastic surgery, such as direct rhytidectomy, also known as a "face-lift," is the simplest and most common strategy to decrease redundant flaps of skin.[26] Finger clubbing surgical reduction has also been tried with success.[1]

Genetic counseling is relatively easy in the presence of a pedigree illustrating a mendelian inheritance pattern. Difficulties can arise among apparently sporadic patients, where a careful clinical and radiological evaluation of at least, all the available first-degree relatives seems mandatory.[1,3]

CONCLUSION

A 28-year-old Filipino male was diagnosed with primary familial PDP after work-up for giant hands and feet. PDP is a rare genodermatosis, presenting most commonly as secondary PDB. Since PDB stems from abnormal proliferation of fibroblasts, treatment is mainly supportive. Life span is not affected but the quality of life is dismal without supportive management hence long-term follow-up and monitoring are necessary.

Recommendations

Since PDP is a familial disease and could skip generations, genetic counseling should be offered to patients with PDB and their families. Since a chromosomal abnormality has already been identified, a genetic screen and radiologic survey of relatives may be completed.

Statement of Authorship

All authors participated in managing the patient, writing the paper, and approval of the final submitted version.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

This paper was not funded.

REFERENCES

1. Auger DM, Stavrianeas PN. Pachydermoperiostosis. Orphanet Encyclopedia, April 2004.[Internet] cited August 21, 2021]. Available from: https://www.orpha.net/data/patho/GB/uk-pachydermoperiostosis.pdf
2. Lowenthal MN, Tombak A, Lowenthal A. Secondary hypertrophic osteoarthropathy mimicking primary HOA (pachydermoperiostosis or Touraine-Solente-Gole) syndrome. Isr Med Assoc J. 2004;6(1):64.

3. Honório MLP, Bezerra GH, Costa VLDC. Complete form of pachydermoperiostosis. An Bras Dermatol. 2020 Jan-Feb;95(1):98-101. doi: 10.1016/j.abd.2019.04.009. Epub 2019 Dec 18. PMID: 31889594; PMCID: PMC7058884.
4. Rastogi, R., Suma, G. N., Prakash, R., Rastogi, U. C., Bhargava, S., & Rastogi, V. Pachydermoperiostosis or primary hypertrophic osteoarthropathy: a rare clinicoradiologic case. Indian J Radiol Imaging. 2009; 19(2):123-6.
5. Bhaskaranand K, Shetty RR, Bhat AK. Pachydermoperiostosis: three case reports. Journal of Orthopaedic Surgery. 2001; 9(1):61-66.
6. Oikarinen A, Palatsi R, Kylmäniemi M, Keski-Oja J, Risteli J, Kallioinen M. Pachydermoperiostosis: analysis of connective tissue abnormality in one family. J Am Acad Dermatol. 1994; 31:947-53.
7. Uppal S, Diggle CP, Carr IM, Fishwick CWG, Ahmed M, Ibrahim GH, et al. Mutations in 15-hydroxyprostaglandin dehydrogenase cause primary hypertrophic osteoarthropathy. Nat Genet. 2008; 40(6): 789-93.
8. Du R, Fan L, Huang H, Xiang R. [Progress in genetic research on pachydermoperiostosis]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2016 Feb;33(1):105-7. Chinese. doi: 10.3760/cma.j.issn.1003-9406.2016.01.025. PMID: 26829746.
9. Harbison JB, Nice CM. Familial pachydermoperiostosis presenting as an acromegaly-like syndrome. Journal. 1971;112:3.
10. Ghosn S, Uthman I, Dahdah M, Kibbi AG, Rubeiz N. Treatment of pachydermoperiostosis pachydermia with botulinum toxin type A. J Am Acad Dermatol. 2010 Dec;63(6):1036-41. doi: 10.1016/j.jaad.2009.08.067. Epub 2010 Oct 8. PMID: 20933299.
11. Yao Q, Altman RD, Brahn E. Periostitis and hypertrophic pulmonary osteoarthropathy: report of 2 cases and review of the literature. Seminars in Arthritis and Rheumatism. 2009; 38(6):458-66.
12. Staalman CR, Umans U. Hypertrophic osteoarthropathy in childhood malignancy. Med Pediatr Oncol, 21 9 (1993), pp. 676–9.
13. McGavin C, Hughes P. Finger clubbing in malignant mesothelioma and benign asbestos pleural disease. Respir Med, 92 4 (1998), pp. 691–2.
14. Heylen W, Baert AL. Hypertrophic osteoarthropathy secondary to malignant islet-cell tumor of the pancreas. Inter Des, 62 1 (1979), pp. 79–82.
15. Collinson FJ, Bilous AM, Kefford RM. Hypertrophic osteoarthropathy from pulmonary metastatic phyllodes tumour of the breast. Med J Aust, 181 5 (2004), p. 279.
16. Diamond S, Momeni M. Primary hypertrophic osteoarthropathy in a patient with rheumatoid arthritis. J Clin Rheumatol, 13 4 (2007), pp. 242–3.
17. Shinjo SK, Borba EF, Goncalves CR, Levy-Neto M. Ankylosing spondylitis in a patient with primary hypertrophic osteoarthropathy. J Clin Rheumatol, 13 3 (2007), 175.
18. Burson JS, Grana J, Varela J, Atanes A, Galdo F. Laminar periostitis and multiple osteonecrosis in systemic lupus erythematosus. Clin Rheumatol, 9 4 (1990), pp. 535–8.
19. Kim JE, Kolh EM, Kim DK. Takayasu's arteritis presenting with focal periostitis affecting two limbs. Int J Cardiol, 67 3 (1998), pp. 267–70.
20. Martinez-Lavin M, Vargas A, Rivera-Vinas M. Hypertrophic osteoarthropathy: a palindrome with pathogenic connotation. Current Opinion in Rheumatology. 2008; 20:88-91.
21. Zhang H, Yang B. Successul treatment of pachydermoperiostosis patients with etoricoxib, aescin, and arthroscopic synovectomy: Two case reports. Medicine. 2017;96(47):e8865.
22. Jojima H, Kinoshita K, Naito M. A case of pachydermoperiostosis treated by oral administration of a bisphosphonate and arthroscopic synovectomy. Mod Rheumatol. 2007;17(4):330–2.
23. Lee J, Kim H, Hwang JW, Noh JW, Ahn JK, Koh EM, Cha HS. Arthroscopic synovectomy in a patient with primary hypertrophic osteoarthropathy. J Korean Rheum Assoc. 2008;15(3):261–7.
24. Beauregard S. [Cutis verticis gyrata and pachydermoperiostosis. Several cases in a same family. Initial results of the treatment of pachyderma with isotretinoin] [Article in French]. Ann Dermatol Venereol 1994;121(02):134–7.
25. Ghosn S, Uthman I, Dahdah M, Kibbi AG, Rubeiz N. Treatment of pachydermoperiostosis pachydermia with botulinum toxin type A. J Am Acad Dermatol 2010;63(06):1036–41.
26. Taichao D, Fuling L, Hengguang Z. Comprehensive Surgical Strategies for the Management of Pachydermoperiostosis. Facial Plast Surg. 2018 Jun;34(3):330-4. doi: 10.1055/s-0038-1653992. Epub 2018 May 15. PMID: 29763941.