

Hypertrophic osteoarthropathy: Case report and literature review

Leila Mahmoudieh¹, Zahra Zakeri², Yas Shahbakhsh^{3*}

¹Department of Internal Medicine, Shahid Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; ²Rheumatology Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran; ³Medical student, Iran University of Medical Science, Tehran, Iran

Hypertrophic osteoarthropathy manifests as digital clubbing, subperiosteal new bone formation in tubular bone and diffuse skin hypertrophy. It could be either primary or secondary. We report a 31-year-old man presenting with digital clubbing and diffuse skin thickening which started at puberty. X-rays showed subperiosteal new bone formation. All examinations for secondary causes were negative.

Keywords: digital clubbing, primary hypertrophic osteoarthropathy, subperiosteal new bone formation.

Introduction

Hypertrophic osteoarthropathy (HOA) manifests as changes in the bone and skin. It is characterized by digital clubbing, arthralgia, periostitis and subperiosteal new bone formation in tubular bone. It could be either primary or secondary. The primary familial form can be inherited in an autosomal dominant pattern with variable penetrance or infrequently as an autosomal recessive. Different mechanisms have been suggested, but the exact mechanism is yet to be explained. The disorder more commonly affects skin and bones and most commonly starts at puberty. Like other inherited diseases, there is no exact treatment. We present our patient with primary HOA and review the literature about this disorder.

Case report

A 31-year-old man presented with a long history of distal phalanges enlargement of the hands and feet along with prominent thickening of skin folds on his face. He also complained of polyarthralgia, especially in the knees and ankles, and severe acne on his face and arms. All these problems began gradually at puberty and had continued over the subsequent 13 years. He had visited several physicians and had done many evaluations with no result. Watery diarrhea and exuberant sweating of the palms and soles had been additional symptoms for the last three years.

On examination, his vital signs were stable with no sign of cyanosis. The skin on his face was pletoric. Forehead

ridges and nasolabial folds were prominent along with thickness of the eyelids, ptosis and severe acne. No sign of head enlargement, separated teeth or other signs of acromegaly were observed. Clubbing was evident in all fingers and toes, along with erythematous skin. No signs of arthritis were found (Figs. 1 and 2). The patient has a younger brother who is about 20 years of age who has similar, but milder, symptoms.

Laboratory tests, including IGF-1 (for evaluation of acromegaly), were unremarkable except for Alk-p, which was slightly above normal range (Table 1). Skin biopsy revealed pachydermoperiostosis. Forearm and leg x-rays showed subperiosteal new bone formation (Fig. 3).

A chest radiograph done after a diagnosis of HOA to evaluate possible secondary causes was normal. Echocardiography showed no signs of structural heart disease. In line with the history of diarrhea for one year, inflammatory bowel disease as a secondary cause of HOA was evaluated by endoscopy, colonoscopy and biopsy, which showed mild nonspecific chronic inflammation.

In line the diagnosis of familial HAO, treatment was started with indomethacin (225 mg daily), octreotide (beginning with 150 µg daily and gradually increased to 300 µg) and sulfasalazine (1500 mg daily gradually increased to 3 g daily). The patient's symptoms, including the diarrhea and polyarthralgia, improved gradually; thus, the dosage of indomethacin was decreased in line with the decrease in symptoms. Acne and skin erythema also

* Corresponding Author: Yas Shahbakhsh, E-mail: Yas.shahbakhsh@gmail.com, Tel: +98- 9394023784

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subsided. Unfortunately, economic considerations of the patient prevented performance of vascular endothelial

growth factor (VEGF) and platelet-derived growth factor (PDGF).



Fig. 1. Symptoms of thickened eyebrow, prominent nasolabial and forehead folds and acne



Fig. 2. Digital clubbing

Table 1. Laboratory data

Variable	Value	Normal range	Variable	Value	Normal range
T4	1.4	0.7-2 ng/dl	ESR	10	Upto 15
TSH	2.1	0.27-4.2 mIU/ml	CRP	Neg.	
Ca	9.6	8.1-10.4 mg/dl	IGF-1	92	87-415 ng/ml
Alb	4.8	3.5-5.1 mg/dl			
P	4.2	2.5-4.5mg/dl			
Alp	458	80-306 IU/l			
PTH	32	15-65 pg/ml			



Fig. 3. Subperiosteal new bone formation in left tibia (arrow)

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HOA manifests as changes in bone and skin. It was introduced in the late 1800s and was believed to be a pulmonary disease manifestation known as hypertrophic pulmonary osteoarthropathy (HPOA) [1]. HOA could be either primary or secondary. The primary familial form is also known as pachydermoperiostosis (PDP), is hereditary (autosomal dominant and autosomal recessive) and manifests in different ways [2]. Although the exact prevalence is unknown, one study reported a prevalence of 0.16% [2]. It predominates and is exhibited in greater intensity in males [3]. A gene mutation on chromosome X is hypothesized as being responsible for the gender variation.

The secondary form of HOA can be caused by a variety of diseases, including cystic fibrosis, cyanotic heart disease and inflammatory bowel disease. The exact mechanism of HOA is unknown, but possible mechanisms have been suggested. The observed increase and decrease in cytokines such as prostaglandin E2 have suggested hormonal, immunological, neurological and thrombotic mechanisms [4-6]. It appears that the most accurate suggested pathogenesis is activation of endothelium through inflammatory mediators and generation of abnormally large platelets. Normally inactivation of the inflammatory mediators and fragmentation of platelets take place in the lungs, a mechanism which appears to be impaired in HOA [7, 8].

Megakaryocyte fragments and inflammatory mediators at the distal sites of systemic circulation activate vascular endothelial cells and releases the growth factors of VEGF and PDGF from the platelets. These factors have angiogenic and trophic effects which lead to new bone formation, angiogenesis and edema [9, 10].

In the primary form, mutation of the gene encoding hydroxyprostaglandin dehydrogenase (HPGD) 15 located on chromosome 4q33-4q34 has been shown to be responsible. The enzyme encoded by this gene is responsible for prostaglandin degradation. This mutation would cause high concentrations of prostaglandin E2 in the body which, in turn, causes overexpression of VEGF and the cascades explained above [11, 12]. HOA is usually asymptomatic and is usually initially noticed as a change in the shape and size of the fingers and toes [2]. Symptoms usually appear gradually in puberty and slowly progress

over time [13, 14].

The disorder more commonly affects the skin and bone, but can manifest as rare abnormalities such as patent ductus arteriosus, wide cranial sutures and hypertrophic gastropathy [15, 16]. The most common clinical manifestation is clubbing of the digits [17]. Skin changes are more common in the idiopathic form of the disease as skin thickening with prominent skin folds. This is mostly noticeable on the face and is known as leonine face and bilateral or unilateral eye ptosis (blepharoptosis). Other manifestations are acne, seborrhea, oily skin and palmoplantar hyperhidrosis [18, 19]. Arthralgia and bone pain are part of the complaints in some patients. Although articular effusion, especially in the lower extremities, could be present, arthritis is not present and the synovial fluid is non-inflammatory. Affected patients are prone to inflammatory bowel disease and myelofibrosis [20].

There is no definite diagnostic test for this condition. X-rays of tubular bones reveal periosteal new bone formation which supports the diagnosis. The presence of characteristic facial features along with clubbing and evidence of periostosis on x-rays are the main criteria which support the diagnosis and indicate the need for an intensive search for secondary causes. Without evidence of secondary causes, it is considered to be primary [21, 22].

Erythrocyte sedimentation rate and alkaline phosphatase as markers of bone turnover are elevated in some cases. These markers can be useful for follow-up and disease monitoring [23]. Because mutation of the HPGD gene is present in most PDP cases, it could be used as a tool for diagnosis [24].

There is no exact treatment and all the medication is palliative. Non-steroidal anti-inflammatory drugs (NSAIDs) are used for the arthralgia and bone pain. Bisphosphonates which inhibit osteoclasts and have anti-resorptive effects have been shown to alleviate pain [20]. Limited reports suggest a combination of octreotide and pamidronate as being more helpful in relieving pain, both of which have an inhibitory effect on VEGF [25]. Retinoids are used for acne, seborrhea and folliculitis. Other medications have been suggested, including corticosteroids, colchicine, sulfasalazine and methotrexate [26].

Conflicts of interest

The authors declare no conflict of interest.

References

- Martínez-Lavín M, Matucci-Cerinic M, Jajic I, Pineda C. Hypertrophic osteoarthropathy: consensus on its definition, classification, assessment and diagnostic criteria. *J Rheumatol* 1993 Aug; 20(8):1386-7.
- Castori M, Sinibaldi L, Mingarelli R, Lachman RS, Rimoin DL, Dallapiccola B. Pachydermoperiostosis: an update. *Clinical Genetics* 2005; 68(6): 477-86. doi: 10.1111/j.1399-0004.2005.

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- Kowalewski M, Urban M, Gorska A. Familial occurrence of primary hypertrophic osteoarthropathy: Acase report. *Med Sci Monit* 1997; 3: 229-34.
 - Ginsburg J, Brown JB. Increased oestrogen excretion in hypertrophic pulmonary osteoarthropathy. *Lancet* 1961 Dec 9; 278(7215): 1274-6. doi: 10.1016/s0140-6736(61)91139-4.
 - Schumacher HR Jr. Articular manifestations of hypertrophic pulmonary osteoarthropathy in bronchogenic carcinoma. *Arthritis Rheum* 1976; 19(3): 629-36. doi: 10.1002/art.1780190317.
 - Matucci-Cerinic M, Martinez-Lavin M, Rojo F, Fonseca C, Kahaleh BM. von Willebrand factor antigen in hypertrophic osteoarthropathy. *J Rheumatol* 1992 May; 19(5): 765-7.
 - Fam AG, Chin-Sang H, Ramsay CA. Pachydermoperiostosis: scintigraphic, thermographic, plethysmographic, and capillaroscopic observations. *Ann Rheum Dis* 1983 Feb; 42(1): 98-102. doi: 10.1136/ard.42.1.98.
 - McGuire MM, Demehri S, Kim HB, Kamin D. Hypertrophic osteoarthropathy in intestinal transplant recipients. *J Pediatr Surg* 2010 Nov; 45(11): e19-22. doi: 10.1016/j.jpedsurg.2010.07.019.
 - Miller RE, Illing RO, Whelan JS. Lung carcinoma with hypertrophic osteoarthropathy in a teenager. *Rare Tumors* 2011 Mar 30; 3(1): 25-27. doi: 10.4081/rt.2011.e8.
 - Martinez-Lavin M. Hypertrophic osteoarthropathy. *Curr Opin Rheum* 1997 Jan; 9(1): 83-6. doi: 10.1097/00002281-199701000-00016.
 - Uppal S, Diggle CP, Carr IM, Fishwick CW, Ahmed M, Ibrahim GH, et al. Mutations in 15-hydroxyprostaglandin dehydrogenase cause primary hypertrophic osteoarthropathy. *Nat Genet* 2008; 40(7): 927.
 - Harada S, Nagy JA, Sullivan KA, Thomas KA, Endo N, Rodan GA, Rodan SB. Induction of vascular endothelial growth factor expression by prostaglandin E2 and E1 in osteoblasts. *J Clin Invest* 1994; 93(6): 2490-2496. doi: 10.1172/jci117258.
 - Auger M, Stavrianeas N. Pachydermoperiostosis. *Orphanet Enciclopedia* 2004: 1-8.6.
 - Sinha GP, Curtis P, Haigh D, Lealman GT, Dods W, Bennett CP. Pachydermoperiostosis in childhood. *Br J Rheumatol* 1997; 36: 1224-7. doi: 10.1093/rheumatology/36.11.1224.
 - Kabashima K, Sakabe J, Yoshiki R, Tabata Y, Kohno K, Tokura Y. Involvement of Wnt signaling in dermal fibroblasts. *Am J Pathol* 2010 Feb; 176(2): 721-32. doi: 10.2353/ajpath.2010.090454.
 - Seifert W, Beninde J, Hoffmann K, Lindner TH, Bassir C, Aksu F, et al. HPGD mutations cause cranioosteoarthropathy but not autosomal dominant digital clubbing. *Eur J Hum Genet* 2009; 17(12): 1570-6. doi: 10.1038/ejhg.2009.104.
 - Vazquez-Abad D, Pineda C, Martinez-Lavin M. Digital clubbing: a numerical assessment of the deformity. *J Rheumatol* 1989; 16: 518-520.
 - Alves AP, Holanda Filha JG, Jerônimo FT. Eyelid ptosis associated with pachydermoperiostosis: case report. *Arq Bras Oftalmol.* 2005 May-Jun; 68(3): 401-4. doi: 10.1590/s0004-27492005000300025.
 - Matucci-Cerinic M, Lotti T, Jajic I, Pignone A, Bussani C, Cagnoni M. The clinical spectrum of pachydermoperiostosis (Primary hypertrophic osteoarthropathy). *Medicine* 1991; 70(3): 208-14. doi: 10.1097/00005792-199105000-00005.
 - Martinez-Lavin M, Pineda C. Digital clubbing and hypertrophic osteoarthropathy. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. *Rheumatology*. 5th ed. Philadelphia. Mosby. 2011: 1701-5. doi: 10.1016/b978-0-323-06551-1.00168-8.
 - Manger B, Lindner A, Manger K, Wacker J, Schett G. Hypertrophic osteoarthropathy. Bamberger-Marie disease. *Z Rheumatol* 2011 Sep; 70(7): 554-60. doi: 10.1007/s00393-011-0813-7.
 - Zanon AB, Faccin MP, Alvarenga Anti SM, Silva Melo Cruz FJ, Rosa RF. Primary hypertrophic osteoarthropathy: case report and literature review. *Bras J Rheumatol* 2009; 49(4): 447-55. doi: 10.1590/s0482-50042009000400010.
 - Altman RD, Tenenbaum J. Hypertrophic osteoarthropathy. Kelley W, Harris ED Jr, Ruddy S, Sledge C, eds. *Textbook of Rheumatology*. 5th ed. Philadelphia, Pa: WB Saunders. 1997: 1514-20
 - Diggle CP, Carr IM, Zitt E, et al. Common and recurrent HPGD mutations in Caucasian individuals with primary hypertrophic osteoarthropathy. *Rheumatology* 2010 Jun. 49(6): 1056-62. doi: 10.1093/rheumatology/keh048.
 - Terrier B, Lavie F, Miceli-Richard C, Azria A, Mariette X. Painful hypertrophic osteoarthropathy successfully treated with octreotide. The pathogenetic role of vascular endothelial growth factor (VEGF). *Rheumatology* 2005; 44(10): 1326-1327. doi: 10.1093/rheumatology/keh720.
 - Nguyen S, Hojjati M. Review of current therapies for secondary hypertrophic pulmonary osteoarthropathy. *Clin Rheumatol* 2011 Jan; 30(1): 7-13. doi: 10.1007/s10067-010-1563-7.