Am J Transl Res 2021;13(12):14109-14114
www.ajtr.org /ISSN:1943-8141/AJTR0138575

Case Report

Progressive osseous heteroplasia: a case report and literature review

Keyun Zhang*, Hairong Tang*, Renming Zhang, Yongchao Wang, Qin Su, Xin Lin, Qiang Tian, Sheng Cao, Meichun Fu, Jian Zhu, Xiaoqing Shen, Feng Li

*Department of Orthopedics, The First Affiliated Hospital of Hunan Medical College, Huaihua 418000, Hunan, China. *Equal contributors.*

Received August 25, 2021; Accepted November 2, 2021; Epub December 15, 2021; Published December 30, 2021

Abstract: Objective: To investigate the clinical features and pathogenesis of progressive osseous heteroplasia (POH) in children. Methods: The clinical features and imaging findings of a child with POH are described, and family investigations and gene comparisons were performed, followed by a literature review. Results: A 9-year-old female with no relevant family medical history initially presented with ectopic ossification of the skin and subcutaneous tissue of the right face that developed slowly. The ossification area extended to the right waist, back, and right knee. The unilateral body (limbs) was gradually invaded. The patient exhibited limited movement of the head, neck, and left shoulder joint, and experienced difficulty in opening her mouth. She also exhibited deformity of the toe, delayed development, insufficient language skills and behavioral ability, and difficulty in communicating with others, but had no apparent endocrine disorders. Blood calcium, phosphorus, and alkaline phosphatase levels were normal, and DNA sequencing did not yield a positive result. Conclusion: The clinical manifestations of POH include hard plaques, which can develop deep into the bone; however, there are currently no effective preventive or treatment measures.

Keywords: Progressive dysplasia of bone, children, plaques

Introduction

Progressive osseous heteroplasia (POH) is a rare congenital disease characterized by heterotopic ossification of the skin and subcutaneous tissue at birth or in infancy, with progressive development in childhood and a high disability rate [1]. The disease was first described by Kaplan et al. [2]. The lesions mainly involve the limbs, face, and trunk, and heterotopic ossification is asymmetric. The etiology is unknown and cases are sporadic, and a few studies have reported familial associations. In 1998, Urtizberea et al. reported that POH is an autosomal dominant disease [3]. In 2002, Kaplan et al. identified an inactivation mutation in the guanine nucleotide binding protein α-stimulating activity polypeptide (*GNAS*) gene [4]. In 2008, Degbit et al. found that only 64% of POH patients harbored mutations in *GNAS*, although there was no significant difference in clinical manifestations between patients with and without gene mutations [5]. Herein, we report a case of POH without a *GNAS* gene mutation.

Case data

The patient was a 9-year-old female, who visited the our hospital on September 20, 2017 for treatment with the primary goal of improving dietary habits. The patient's mother complained that the patient's right cheek was light blue in color after birth, and her sucking ability was weak approximately 1 month after birth. Some areas of the right side of her face hardened 3 months after birth, and gradually appeared as a sclerotic mass on the right side of the neck. Subsequently, her head became tilted to the right side, with limited movement of the head and neck. Later, a mass was found on the right side of her back. In October 2011, she was treated in the dermatology department of a provincial tertiary hospital. Soft tissue calcification was observed in a biopsy specimen without any special treatment. Subsequently, a

hard mass appeared in the right knee, although the knee joint was mobile. In more recent years, mouth opening became limited, thus affecting normal dietary patterns; as such, only a liquid diet was allowed. Since the onset of the disease, however, there was no systemic pain, feeling of cold and fever, or abnormal urine and stool. She rarely laughed and cried with her mouth widely open, and she ate very slowly. When eating, water and food flowed out from the right corner of her mouth. Her speech was vague and difficult to understand. She was born at full-term, with a birth weight of 2.9 kg. The patient was breastfed and weaned in August. At 2 years of age, she could ambulate without a transitional period of crawling and standing while leaning on a wall, although she walked unsteadily and fell easily. At 7 years of age, she attended preschool and is currently in the third grade of primary school. She earned poor grades, had poor memory and low computational power. She denied any history of surgery, trauma, blood transfusion, poison exposure, or major mental trauma. Moreover, there was no family history of similar conditions.

Physical examination revealed a smaller right face than left, hardened skin with disappearing skin lines, and a stiff face. Although her right eye was open, the upper and lower eyelids could not be opened and closed, and the double sclera was blue. The right side of her mouth could not be opened and closed, and the left side could be opened <1 cm. Opening and closing of the mouth were limited, and the upper and lower teeth could not be occluded. The subcutaneous layer of the right head and face were palpable, with varying sizes of indurations and mobility. There was no skin ulceration, and skin temperature was not elevated. A large number of nodular protrusions were visible on the right side of the neck and the back of the right shoulder. Her head tilted to the right, and her neck was fixed and tilted to the left. Along the course of the ride trapezius muscle, a strip of hard skin was palpable and movement of the neck was limited: the range of left rotation was approximately 10°, right rotation was approximately 20°, and the range of flexion and extension virtually disappeared. The right shoulder was on the stage, abduction was approximately 100°, flexion and extension were extended, rotation was not limited, left shoulder abduction was approximately 170°, and movement was not limited. There was no scoliosis. Approximately 10×5 cm above the iliac spine at the right waist was approximately 10×5 cm, with local protrusions and indurations of varying sizes under the skin. The bilateral thumbnails exhibited dysplasia without deformity, and the movement of each finger was not limited and there was no obvious abnormality in the toes of both feet (**Figure 1**).

Auxiliary examinations including routine laboratory investigations and seven items of nail function were normal, and serum alkaline phosphatase (ALP) levels were increased. Imaging revealed ossification of the right face, straightening of the cervical curvature, ossification of the nuchal ligament, and diffuse calcification. Ossification of the sacroiliac joint was also observed. No obvious abnormality was found in the bilateral phalangeal bones (**Figure 2**). There were no significant abnormalities in gene alignment between the child and her parents (**Figure 3**).

The child was diagnosed with progressive bone dysplasia. The family desired to improve the child's food intake given the large number of ectopic ossifications in the face, the maxilla and mandible were essentially fixed by "adhesions", and opening and closing of the mouth were limited. Accordingly, compression surgery was performed to remove the central and lateral incisors to artificially increase the size of the oral cavity to facilitate food passage. The postoperative effect was not statistically significant. Although the oral cavity was enlarged by approximately 1.5×1.5 cm after the operation, and approximately 300 ml of liquid food was administered every day before the operation, food intake after surgery was unchanged and her weight did not increase. Her nutritional status was not improved six months later. Informed written consent was obtained from the patient for the publication of anonymized case details and accompanying images.

Discussion

Case characteristics

This case involved a 9-year-old female with neonatal onset disease and no relevant family history. The initial manifestation was heterotopic ossification of the skin and subcutaneous tissue on the right side of the face, which

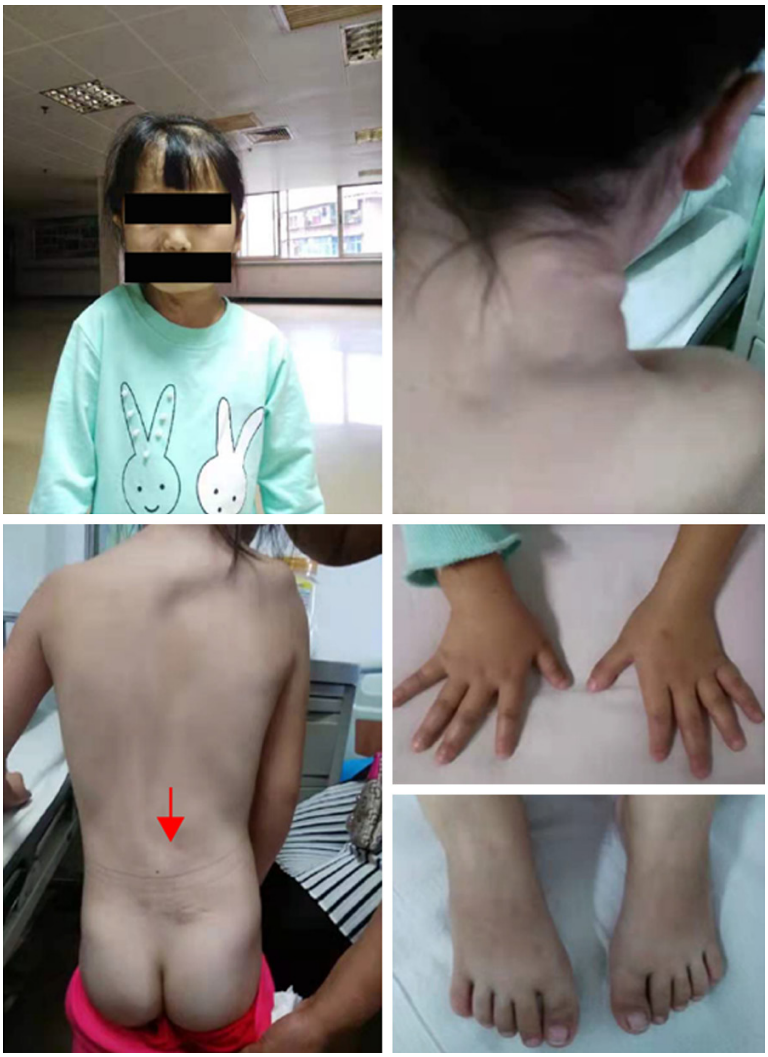

Figure 1. A 9-year-old female with bilateral facial asymmetry, small right side, and uneven skin. Subcutaneous nodules of different sizes were palpable on the right head and face without movement. The right eye could not be opened and closed. A large number of nodular protrusions are visible on the right side of the neck and right shoulder and back. The head and neck tilt to the right, with limited movement. The subcutaneous tuberosity of sacrum (shown by the arrow) is hard. No deformity was found in the fingers and toes.

developed slowly. The ossified area extended to the right waist, back, and right knee, exhibiting unilateral body (limb) invasion. Head and neck movement gradually became limited, accompanied by difficulty with mouth opening. Left shoulder joint movement was limited, although there was no congenital deformity of the fingers and toes, and no internal secretion disorders. The child exhibited growth retardation compared with normal children of the same age, a lack of language skills and behavioral ability, and difficulty in communicating with others. Laboratory investigations revealed normal blood calcium, phosphorus, and ALP levels, and DNA sequencing yielded no significant findings.

In 2003, Russell et al. [6] described a similar patient, an 8-year-old female, with a large number of heterotopic ossifications of the left mandible, severe dysphagia and sleep apnea. After birth, local macular papules gradually hardened and the disease progressed. There was no relevant family history, and pathological examination revealed extensive heterotopic ossification of the dermis, subcutaneous tissue, and deep connective tissue. The patient was ultimately diagnosed with POH. In contrast to the present case, however, DNA examination revealed a *GNAS1* gene mutation. In 2016, Birjandinejad et al. described a case of extensive heterotopic ossification of the left upper limb in a woman without a first toe deformity who was also diagnosed with POH [7]. Similar descriptions were reported by Singh et al. [8, 9]. Other similar cases are summarized in **Table 1**.

Characteristics of POH

Although POH can be sporadic, there have been family reports of autosomal hereditary disease, with an age at onset of 6 weeks old to 9 years old. Claude et al. cited 14 cases of POH reported in 2000, 11 of which involved females [10]. POH is characterized by progressive heterotopic ossification of the skin, subcutaneous fat, and deep connective tissue [10]. Most of the initial symptoms include maculopapular skin in infancy, and ossification appearing at sites of rash. Skin ossification often exhibited a fragmented distribution, and lesions fused into larger patches. The initial ossification occurred in the dermal tissue and heterotopic ossification of the skin developed

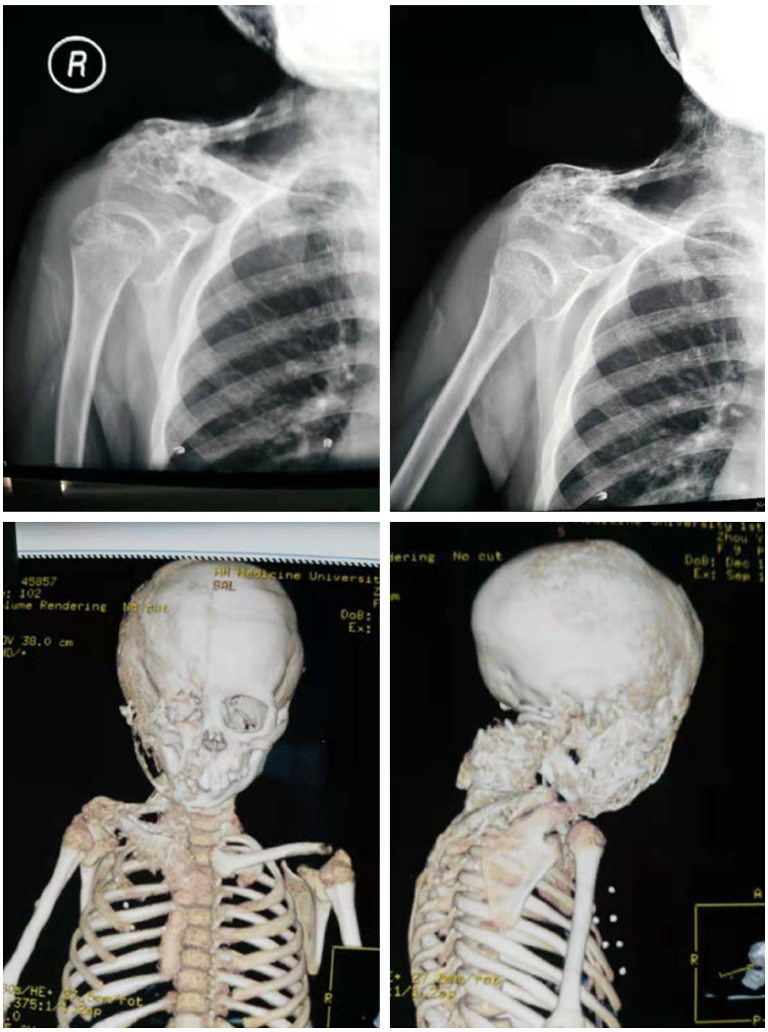

Figure 2. Diffuse ossification shadow on the right side of the face. Despite a normal skull, the structure of maxilla and mandible is indistinct. The curvature of the cervical spine becomes straight, the nuchal ligament ossifies, and the acromioclavicular joint is ossified and deformed. An ossification belt is formed from the cervical spine to the acromion, and resembles a bone.

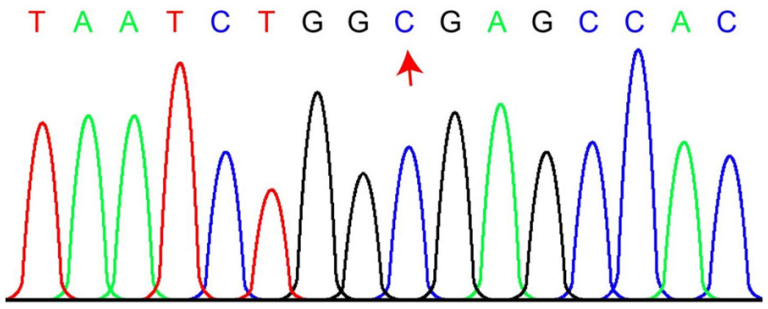

Figure 3. Sequence of exon (part).

gradually, with widespread heterotopic ossification of skeletal muscle and deep connective tissue gradually appearing [4]. Bone lesions mainly involve the limbs, but also involve the trunk (lumbar spine, back, abdominal wall, and chest) and asymmetry at the site of heterotopic ossification, with unilateral limb involvement. Extensive ossification of the deep connective tissue can lead to limited joint movement and local growth and development disorders of the affected limbs.

Serum ALP levels have been reported to be elevated in patients with heterotopic ossification, although serum parathyroid hormone (PTH) and vitamin D levels were normal. Transient abnormalities have been observed in only a few patients. Increases in serum lactate dehydrogenase and creatine kinase levels indirectly reflect the deposition of bone in the skin and skeletal muscle. The histopathological manifestation of POH is progressive ossification of the dermis or deep connective tissue, including the muscle and fascia.

Relationship between GNAS gene mutation(s) and POH

The etiology of POH remains unclear; however, it is considered to be closely related to an inactivation mutation of the *GNAS1* gene [11, 12], which leads to a decrease in the Gαs level, resulting in an increase in hedgehog signal peptide levels, which activates the Hedgehog signaling pathway and leads to ectopic bone formation [13]. Mutations in the *GNAS* gene have been detected in most patients with POH. The specificity of the *GNAS* gene mutation for POH is not high. Heterotopic ossification associated with *GNAS* gene inactivation mutations was found in a series of familial pedigree

Table 1. Similar cases to current case

Year	Researcher	Case
1994	Kaplan	The disease was proposed in this study.
2003	Russell	An 8-year-old female patient, with a large number of heterotopic ossification of the left mandible, with severe dysphagia and sleep apnea, But DNA examination showed GNAS1 gene mutation.
2016	Ali Birjandinejad	A case of extensive heterotopic ossification of the left upper limb in a female without first toe deformity.

hereditary diseases. In addition to POH, *GNAS1* plays an important regulatory role in the osteogenesis of connective tissue in Albright hereditary osteodystrophy (AHO), pseudohypoparathyroidism, and primary osteoma cutis (POC). With regard to POH, *GNAS1* mutation leads to osteosynthesis in damaged cells [14].

Diagnosis of POH

Pignolo et al. [15] proposed diagnostic criteria for POH, including three main criteria and several clinical manifestations supporting the diagnosis. The main criteria included: ectopic ossification of superficial and deeper layers; no more than two features of AHO, except for heterotopic ossification, including short stature, obesity, round face, short finger/toe deformity, and neurobehavioral problems (including intellectual disability) in adulthood; and no PTH resistance. Other evidence supporting diagnosis includes *GNAS* gene mutation, paternal genetic evidence, X-ray revealing ossification as a reticular structure, in which the mechanism of osteogenesis is only intramembranous osteogenesis or both intramembranous and intrachondral osteogenesis, intrauterine growth retardation, emaciation, and age at onset <1 year. However, the authors did not report the need to fulfill several of the diagnostic criteria simultaneously. In the case described, the diagnosis of POH was confirmed by signs and symptoms combined with imaging data and laboratory investigations. No mutation in the *GNAS* gene was found in this case. Although mutation of the *GNAS* gene is one factor supporting the diagnosis of POH, it is not essential.

Differential diagnosis

The differential diagnosis of POH mainly includes fibrodysplasia ossificans progressiva (FOP), AHO, and primary osteoma (POC). POH, FOP, AHO, and POC are all autosomal dominantly inherited diseases with low incidence rates. They have a background of heterotopic ossification disease caused by abnormal bone formation.

FOP is also known as myositis ossificans progressiva (MOP). Compared with POH, FOP is more likely to occur in children, with progressive ossification of the fascia and connective tissue and secondary dysfunction. The difference is that FOP exhibits a characteristic skeletal deformity, and more specifically, hallux deformity, with short toe, only one phalanx, lack of skin wrinkles, and eversion at the metatarsophalangeal joint. The developmental direction of heterotopic ossification of FOP is from the body axis to the limbs, from the head to the foot, from the proximal end to the distal end, exhibiting symmetry. In terms of gene mutation, FOP is a glycine serine-activated region mutation of the bone morphogenetic protein type I receptor.

GNAS1 is a compound imprinted gene. Due to the different allelic functions of some genes in paternal and maternal lines, *GNAS1* mutation(s) can result in different clinical phenotypes. Inactivation mutation of the *GNAS1* gene causes POH if inherited paternally, and AHO if inherited maternally [16]. At five months of age, the deformity of the short toe (AHO) and phalanx, especially the short toe and full face, are found; it can also be accompanied by pseudohypoparathyroidism, which is characterized by incomplete or no response of the PTH receptor to PTH. Laboratory investigations have revealed increased levels of PTH and blood phosphorus levels, and decreased blood calcium levels [17].

POC is characterized by superficial ectopic bone formation, no hormonal resistance, and AHO. Although POC and POH have much in common, a significant difference is that the heterotopic ossification in POH exhibits progressive development, while in POC, it does not.

Treatment

Currently, there are no effective prevention and/or treatment strategies for POH. Large areas of skin ossification and irreversible deep heterotopic ossification represent challenges

to treatment. Some investigators have sought new treatment methods for heterotopic ossification. The activation of the hedgehog signaling pathway is due to inactivation of the *GNAS* gene. Therefore, hedgehog signaling peptide inhibitors are anticipated to be a new class of drugs to treat heterotopic ossification [18]. Ectopic follow-up in a small number of patients has revealed that the disease slows in adulthood [12]. Due to the small number and sporadic nature of cases, no specific time and exact follow-up period have been reported in the literature, and the exact rate of progression cannot be predicted.

Disclosure of conflict of interest

None.

Address correspondence to: Feng Li, Department of Orthopedics, The First Affiliated Hospital of Hunan Medical College, 225 Yushi Road, Huaihua 418000, Hunan, China. Tel: +86-13684651668; E-mail: lifeng_001111@163.com

References

[1] Aynaci O, Mujgan Aynaci F, Cobanoglu U and Alpay K. Progressive osseous heteroplasia. A case report and review of the literature. J Pediatr Orthop B 2002; 11: 339-342.

[2] Kaplan FS, Craver R, MacEwen GD, Gannon FH, Finkel G, Hahn G, Tabas J, Gardner RJ and Zasloff MA. Progressive osseous heteroplasia: a distinct developmental disorder of heterotopic ossification. Two new case reports and follow-up of three previously reported cases. J Bone Joint Surg Am 1994; 76: 425-436.

[3] Urtizberea JA, Testart H, Cartault F, Boccon-Gibod L, Le Merrer M and Kaplan FS. Progressive osseous heteroplasia. Report of a family. J Bone Joint Surg Br 1998; 80: 768-71.

[4] Kaplan FS and Shore EM. Progressive osseous heteroplasia. J Bone Miner Res 2000; 15: 2084-2094.

[5] Adegbite NS, Xu M, Kaplan FS, Shore EM and Pignolo RJ. Diagnostic and mutational spectrum of progressive osseous heteroplasia (POH) and other forms of GNAS-based heterotopic ossification. Am J Med Genet A 2008; 146A: 1788-1796.

[6] Faust RA, Shore EM, Stevens CE, Xu M, Shah S, Phillips CD and Kaplan FS. Progressive osseous heteroplasia in the face of a child. Am J Med Genet A 2003; 118A: 71-75.

[7] Birjandinejad A, Taraz-Jamshidi MH and Hosseinian SH. Total ankylosis of the upper left limb: a case of progressive osseous heteroplasia. Arch Bone Jt Surg 2016; 4: 285-288.

[8] Singh GK and Verma V. Progressive osseous heteroplasia in a 10-year-old male child. Indian J Orthop 2011; 45: 280-282.

[9] Zhang SD, Xie ZL, Zhang KQ, Nh-Tseung K and Zhao JJ. Progressive osseous heteroplasia in a Chinese infant and a novel mutation in the GNAS gene. J Eur Acad Dermatol Venereol 2018; 32: e209-e211.

[10] Stoll C, Javier MR and Bellocq JP. Progressive osseous heteroplasia: an uncommon cause of ossification of soft tissues. Ann Genet 2000; 43: 75-80.

[11] Pereda A, Martos-Tello JM, Garin I, Errea-Dorronsoro J and Perez de Nanclares G. Progressive osseous heteroplasia caused by a mosaic GNAS mutation. Clin Endocrinol (Oxf) 2018; 88: 993-995.

[12] Shore EM, Ahn J, Jan de Beur S, Li M, Xu M, Gardner RJ, Zasloff MA, Whyte MP, Levine MA and Kaplan FS. Paternally inherited inactivating mutations of the GNAS1 gene in progressive osseous heteroplasia. N Engl J Med 2002; 346: 99-106.

[13] Corrales JD, Blaess S, Mahoney EM and Joyner AL. The level of sonic hedgehog signaling regulates the complexity of cerebellar foliation. Development 2006; 133: 1811-1821.

[14] Goto M, Mabe H, Nishimura G and Katsumata N. Progressive osseous heteroplasia caused by a novel nonsense mutation in the GNAS1 gene. J Pediatr Endocrinol Metab 2010; 23: 303-309.

[15] Pignolo RJ, Ramaswamy G, Fong JT, Shore EM and Kaplan FS. Progressive osseous heteroplasia: diagnosis, treatment, and prognosis. Appl Clin Genet 2015; 8: 37-48.

[16] Bastepe M. GNAS mutations and heterotopic ossification. Bone 2018; 109: 80-85.

[17] Sarathi V, Patil A, Wade R, Bandgar TR and Shah NS. Intraarticular heterotopic ossification as the initial manifestation in a child with pseudohypoparathyroidism 1a. Indian J Pediatr 2011; 78: 745-748.

[18] Pacifici M. Acquired and congenital forms of heterotopic ossification: new pathogenic insights and therapeutic opportunities. Curr Opin Pharmacol 2018; 40: 51-58.