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Case Report

Progressive osseous heteroplasia in a five-month-old boy with a mutation in exon 9 of *GNAS*: a case report

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Abstract: Progressive osseous heteroplasia (POH) is an ultrarare hereditary disease that begins with cutaneous ossification, and progressive heterotopic ossification involves subcutaneous and deep connective tissues. We reported a case of POH in a five-month-old boy with clinical, pathological, and genetic features of POH. Most POH cases are caused by GNAS inactivating mutations, and the mutation of GNAS is also found in some other related heterotopic ossification conditions. A discussion of the clinical and laboratory features of these disorders is made in our case report.

Keywords: Mutation, GNAS, progressive osseous heteroplasia

Introduction

Progressive osseous heteroplasia (POH) is an ultrarare genetic disorder of progressive extraskeletal bone formation (number 166350 in Mendelian Inheritance in Man). POH was initially identified in 1994 and characterized by cutaneous ossification and progressive heterotopic ossification of subcutaneous and deep connective tissues, including muscles, tendons, ligaments, and fascia, in early life [1]. Most cases of POH are caused by heterozygous inactivating mutations in the GNAS gene, which encodes the alpha subunit of the G-stimulatory protein of adenylyl cyclase (Gsα) [2, 3].

POH is one of several related inactivating mutations of GNAS illnesses that have common features of heterotopic ossification (HO), including pseudohypoparathyroidism (PHP), Albright hereditary osteodystrophy (AHO), and pseudopseudohypoparathyroidism (PPHP). In addition, POH should be distinguished from fibrodysplasia ossificans progressiva (FOP), another genetic disorder of abnormal bone formation [2-5].

Case

A five-month-old boy presented with a two-month history of a hard, non-tender bump on his left wrist and three and a half months of growing maculopapular lesions on his arms, legs, and back. The bump began as a reddish maculopapular lesion, then calcified into a freely moveable cutaneous nodule. This bump on his left wrist measured 20 × 5 mm in diameter (**Figure 1**). The boy was born normally following a full-term gestation and had no family history of heterotopic ossification or hereditary conditions. Hematoxylin-eosin-stained slices of the nodule revealed mature bone with osteocytes and osteoblasts (**Figure 2**). The blood biochemical examination revealed normal renal function, serum calcium, phosphate, parathormone (PTH), cortisol, ACTH, and gonadotropin levels. The autoimmune antibodies screening examination and hormonal tests showed nothing abnormal. Whole exon sequencing revealed a GNAS1 mutation that was not detected in his parents, notably a missense mutation in exon 9 (**Figure 3**). Given his lack of laboratory abnormalities or Albright's hereditary osteodystrophy (AHO) phenotype suggesting pseudohypoparathyroidism and inactivating GNAS mutations, the patient was diagnosed as progressive osseous heteroplasia (POH).

Discussion

Cutaneous ossification (CO) is a rare dermatological feature that can be manifested in a vari-

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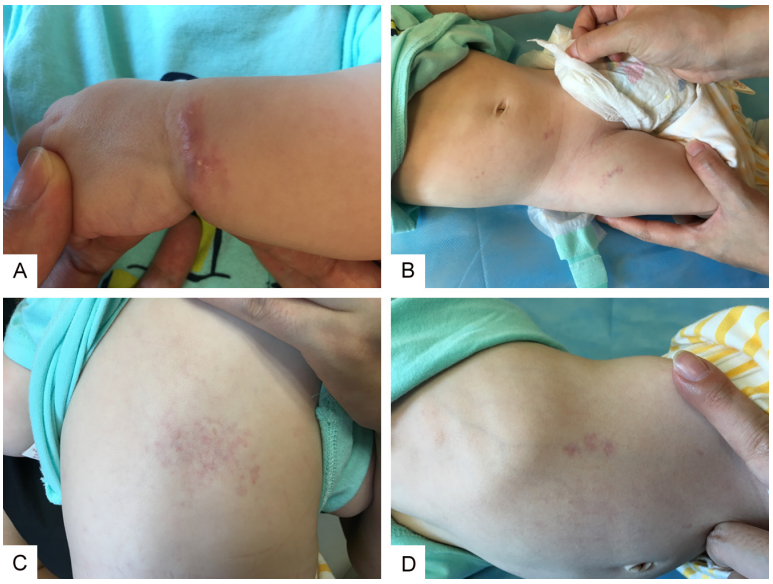

Figure 1. Multiple congenital papular rashes with varying sizes on the back, legs, and left subcostal (B-D), and hard nontender bump on his left wrist (A).

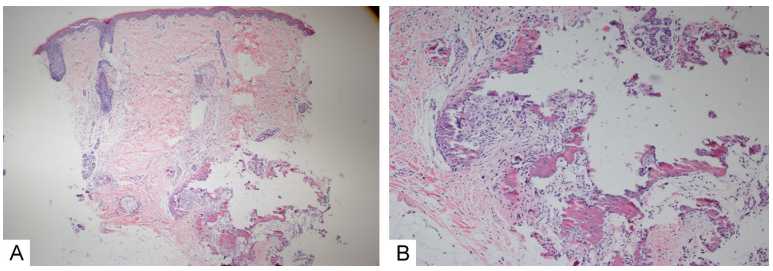

Figure 2. Histological examination of the parasternal nodule shows lamellated bone in the dermis (A). At higher magnification, the bony tissue is composed of osteocytes and osteoblasts (B).

ety of diseases. The hereditary form of OC is prevalently connected with GNAS mutations [6]. Furthermore, several other hereditary forms of CO, such as fibrodysplasia ossificans progressive (FOP), which is associated with mutations in the ACVR1 gene (located on chromosome 2q23-24), are unrelated to GNAS mutations and should be differentiated from POH [7].

POH is an ultrarare genetic disease of invasive progressive cutaneous ossification, and heterotopic ossification involves subcutaneous and deep connective tissues, including muscles, tendons, ligaments and fascia in early life. POH initially manifests in children as a patchy growth of bones in the skin. It eventually affects the muscles and joints, leading to joint contractures and impaired mobility. POH always reveals normal renal function as well as serum calcium, phosphate and PTH levels and shows no parathormone resistance [8].

AHO is a clinical condition distinguished by complicated dysmorphology and endocrine characteristics such as HO, fat body habitus, round faces, short stature, brachydactyly, mental retardation, and developmental delay. The heterotropic bone formation of AHO is only revealed in the skin [9, 10]. For AHO feature combined with PTH resistance, along with resistance to other hormones such as thyroid stimulating hormone (TSH), gonadotropin (Gn), and growth hormone-releasing hormone (GHRH), the condition is termed PHP-Ia (OMIM 103580). The heterotropic bone formation of AHO is only visible in the skin. There are three subsets in PHP: PHP-Ia, PHP-Ib, and PHP-Ic. PHP-Ia (OMIM 103580) is a disorder characterized by AHO and PTH resistance, as well as resistance to other hormones such as thyroid stimulating hormone (TSH), gonadotropin (Gn), and growth hormone-releasing hormone. If some of the hormone resistance found in PHP1a occurs in the absence of the physical features typical of AHO, the condition is referred to as PHP1b (OMIM 603233). HP-Ia and PHP-Ic have essentially an identical clinical phenotype, including the manifestation of AHO features and hormone resistance. However, no patients with PHP-Ic have been found to show a defect in the activity of the erythrocyte stimulatory G (Gs) protein (where the PTH receptor is coupled to, and thereby activates the cAMP formation), whereas patients with PHP-Ia have a variety of deficiency of Gs activity in the membranes of various cell types. PPHP (OMIM 612463) refers to cases in which AHO features in the absence of hormone resistance. In addition to PHP-I and PPHP, PHP-II is found to have a normal cAMP response to PTH infusion, whereas with a defi-

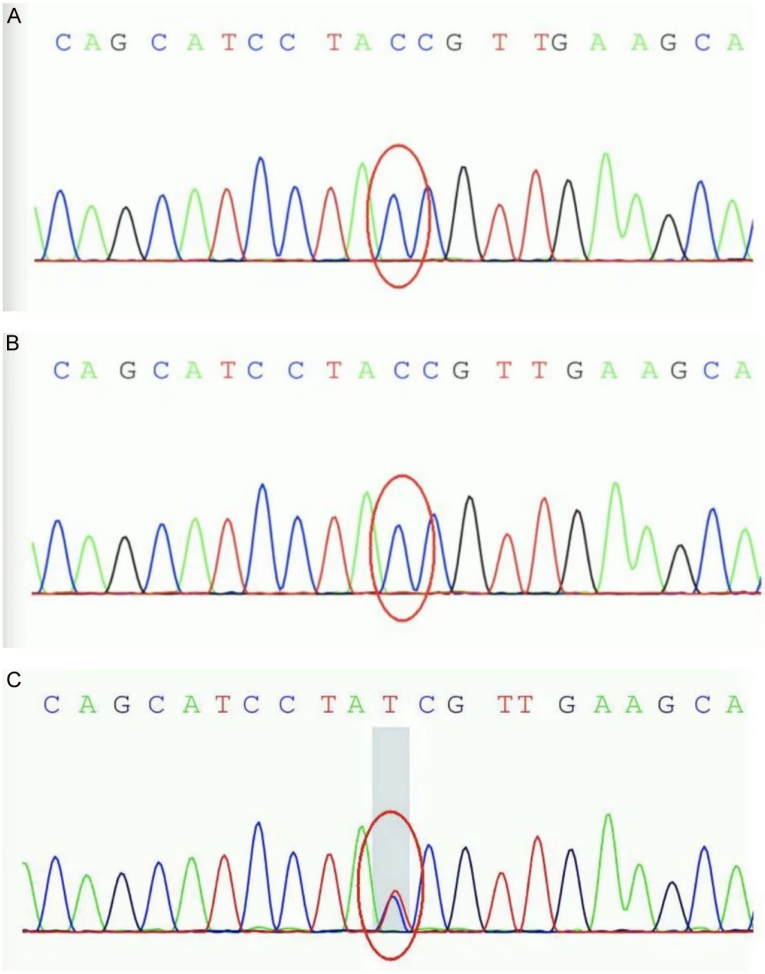

Figure 3. The genetic sequence of the patient's father (A) and mother (B) did not observe mutation in exon 9 of GNAS1. The patient's sequences show a missense mutation in exon 9 of GNAS1 (C).

cient phosphaturic response, the renal cells reveal a defect distal to cAMP generation, which distinguishes PHP-I from PHP-II. In addition, patients with PHP type II lack AHO features [9, 11]. FOP is a rare ACVR1 gene heterozygous mutation disease with progressive ossification of skeletal muscle; this disease is characterized by progressive heterotopic ossification and big toe malformation [7, 12].

POH is diagnosed based on the three major criteria: superficial HO that progresses to deep connective tissues, two or fewer AHO features excluding HO, and no PTH resistance [8]. In this case, the patient met all three major diagnostic criteria. Hormonal tests showed no PTH resistance, so we ruled out the diagnosis of PHP. POH is distinguished from FOP by the presence of cutaneous ossification congenital papular rash and the lack of congenital malformation of the first toes (**Table 1**). By literature review, other similar cases are summarized in **Table 2**.

There are no viable theraputic approaches for POH as of currently. Surgical excision frequently results in recurrence in widespread lesions but leads to successful long-term results in areas of clear border [2, 8]. Bisphosphonates have been shown to effectively cure osteoporosis and heterotopic bone growth in children [26]. However, another case report revealed that attempts with intravenous bisphosphonate and glucocorticoids were attempted without clinical improvement [27]. It therefore remains controversial. Everolimus treatment had a minor impact on the osseous turnover biomarker pattern, and empirical rescue treatment with Everolimus failed to change the clinical course of POH [28]. Retinoic acid receptor γ agonists have been demonstrated to effectively reduce HO in mouse models [29], however, their effect on individuals with HO remains uncertain [29]. Because there are limited treatment options, several children have had their limbs amputated [13].

In some POH cases, the disorder causes severe disability, which has been connected with the degree of morbidity that depends on the extent and location of HO. Furthermore, congenital papular rash, prone to misinterpretation, could be the only clinical sign in the early stages of POH. Consequently, to provide an early diagnosis and appropriate counseling, pediatricians and dermatologists must be knowledgeable about the clinical and radiological characteristics of POH.

Disclosure of conflict of interest

None.

Table 1. Differential diagnosis for distinguishing among GNAS-based and ACVR1-based conditions of heterotopic ossification

Features	POH	FOP	PHP				PPHP
			PHP-Ia	PHP-Ib	PHP-Ic	PHP-II	
Congenital malformation of great toes	-	+	-	-	-	-	-
Congenital papular rash	+	-	-	-	-	-	-
AHO	-	-	+	-	+	-	+
Cutaneous ossification	+	-	+	-	+	-	+
Subcutaneous ossification	+	-	+	-	+	-	+
Muscle ossification	+	+	-	-	-	-	-
Superficial to deep progression of ossification	+	-	-	-	-	-	-
Severe limitation to mobility	+	+	-	-	-	-	-
Ectopic ossification after intramuscular injections	-	+	-	-	-	-	-
Ectopic ossification after traumas	+/-	+	-	-	-	-	-
Parathormone resistance	-	-	+	+	+	+	-
Hypocalcemia and hyperphosphatemia	-	-	+	+	+	+	+
Genetic mutations	See PHP and PPHP	Activating mutation of the gene encoding the BMP type 1 receptor ACVR1/ALK2	Heterozygous inactivating mutations of the maternal allele of the GNAS gene, encoding the a-subunit of G-stimulatory protein adenylyl cyclase				

Differential diagnosis for distinguishing among GNAS-based and ACVR1-based conditions of heterotopic ossification.

Table 2. Literature review of similar cases

Similar cases to the current case			
Year	Researchers	Case	GNAS mutation
1994 [13]	Kaplan, F.S. et al.	POH was first described.	Unknown*
2004 [14]	Chan, I. et al.	A 9-year-old female, with progressive osseous heteroplasia, with small stature started to develop skin lesions at the age of 9 months.	Exon 11
2007 [15]	Gelfand, I.M. et al.	A 4-month-old boy with clinical features of both POH and PHP Ia.	Exon 7
2008 [16]	Kumagai, K. et al.	A boy with typical clinical, radiographic, and genetic features of POH.	Exon 7
2009 [17]	Schimmel, R.J. et al.	Here are two girls, one girl's left arm with contractures and retardation in the deep connective tissue, and the other girl had AHO with widespread, superficial heterotopic ossification.	Exon 13; exon 5
2010 [18]	Goto, M. et al.	A 6-year-old boy with short stature developed soft tissue masses in the right heel and right elbow.	Nonsense mutation p.R342X of GNAS
2011 [19]	Gk, S. et al.	A 10-year-old boy with developed progressive ossification of the skin and deep connective tissue.	Unknown
2014 [20]	Schrander, D.E. et al.	A 7-year-old female with a painful swelling on the left foot, without congenital hallux valgus.	Heterozygote mutation c.565_568del of GNAS1
2015 [21]	Lin, M.H. et al.	A 4-year-old boy with obesity, speech delay, and expanding subcutaneous masses on buttock/forearm.	Not found
2016 [22]	Birjandinejd, A. et al.	A twenty-four-year-old male with a complaint of ankylosis of the entire upper left limb and digital cutaneous lesions and sparing of the other limbs and the axial skeleton.	Unknown
2020 [23]	Sahu, K. et al.	A 3-year-old child who presented with bone formation on cutaneous and subcutaneous planes.	Unknown
2021 [24]	Zhang, K. et al.	A 9-year-old girl 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, and so on.	Not found
2023 [25]	Ryabets-Lienhard, A. et al.	A 15-year-old boy presented with generalized calcific nodules, progressive contractures, and muscle weakness leading to immobility, beginning at 6 years of age.	FAM118 gene*
2023 [3]	Ma, J. et al.	A 5-year-old boy with a growing mass in his right foot, radiographic imaging revealed severe ossification in his right foot and smaller areas of intramuscular ossification in his arms and legs.	Exon 2

*Note: Unknown is that the article did not mention relevant mutations. FAM111B gene located in chromosome 11q12.1 has been associated with a rare, autosomal-dominant disorder of POIKTMP. It is the first case of POH phenotype associated with a frameshift pathogenic variant of FAM111B.

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