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CASE REPORT

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Presentation of pseudohypoparathyroidism and pseudopseudohypoparathyroidism with skin lesions: Case reports and review

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Abstract

We report three cases of patients with pseudohypoparathyroidism or pseudopseudohypoparathyroidism. These diseases are considered *GNAS* inactivating mutation syndromes that are characterized by a diversity of alterations among which a particular phenotype and specific endocrine or ossification abnormalities may be found. These patients may present with hard cutaneous nodules, which can represent osteoma cutis. The presence of these lesions in pediatric patients should prompt the dermatologist's consideration of this group of diseases when reaching a diagnosis. A multidisciplinary team of pediatricians, endocrinologists, geneticists, and dermatologists should carefully evaluate these patients.

KEYWORDS
GNAS, imprinting, inactivating mutation, pediatrics, pseudohypoparathyroidism, pseudopseudohypoparathyroidism

1 | INTRODUCTION

Pseudohypoparathyroidism (PHP), pseudopseudohypoparathyroidism (PPHP), and progressive osseous heteroplasia (POH) are syndromes caused by inactivating mutations of *GNAS*, a gene that codifies the subunit G_s-alpha of the G-protein-coupled receptors. Some of these syndromes are related to a particular phenotype known as Albright's hereditary osteodystrophy (AHO) while some have a normal phenotype. We describe three patients who were diagnosed with syndromes related to *GNAS* inactivating mutations after presenting with dermatologic lesions (Table 1).

2 | CASE REPORT

2.1 | Patient 1

A 13-year-old boy with congenital craniosynostosis and cryptorchidism, along with hypothyroidism and growth hormone deficiency, was on hormone replacement therapy. He was referred to our department for a lesion on his heel that appeared 1 month prior to presentation. Physical examination revealed a 2 cm, subcutaneous, mobile, tender nodule on his right heel and bilateral shortening of his fifth fingers. Radiographs of the lesion showed a calcium-density lesion in the area of the nodule. Upon removal of the nodule, histologic examination showed bone formation in the hypodermis, representing osteoma cutis (Figure 1). Blood tests showed normal calcium, phosphorus, and vitamin D levels and increased levels of parathyroid hormone (PTH). A heterozygous mutation of uncertain significance (c.128T>C) was detected on exon 1 in the *GNAS* gene. Genetic testing of the patient's parents did not detect any *GNAS* mutations. The patient was diagnosed with spontaneous PHP Ia.

2.2 | Patient 2

A 10-year-old girl with hard cutaneous plaques on her abdominal and pretibial skin was referred for a lesion on her left sole that had

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TABLE 1 Patient characteristics

Patient	1	2	3
Age (years)	13	10	13
Sex	Male	Female	Male
AHO phenotype	Brachydactyly Rounded face Osteoma cutis	Brachydactyly Rounded face Short stature Overweight Osteoma cutis	Brachydactyly Short stature Osteoma cutis
Other phenotypes	Craniosynostosis Cryptorchidism	—	Language delay
Calcium-phosphate metabolism	Nonaltered	Mild hyperphosphatemia Vitamin D deficiency	Nonaltered
PTH	Increased	Non-altered	Nonaltered
Other endocrine alterations	Hypothyroidism GH deficiency	Increased TSH[a]	Nonaltered
GNAS exon 1 mutation	c.128T>C	c.103C>T	c.2T>G
Diagnosis	Spontaneous PHP 1a	Spontaneous PHP 1a	Spontaneous PPHP

AHO, Albright's hereditary osteodystrophy; PTH, parathyroid hormone; GH, growth hormone; TSH, thyroid-stimulating hormone; PHP, pseudohypoparathyroidism; PPHP, pseudopseudohypoparathyroidism.
[a]During follow-up.

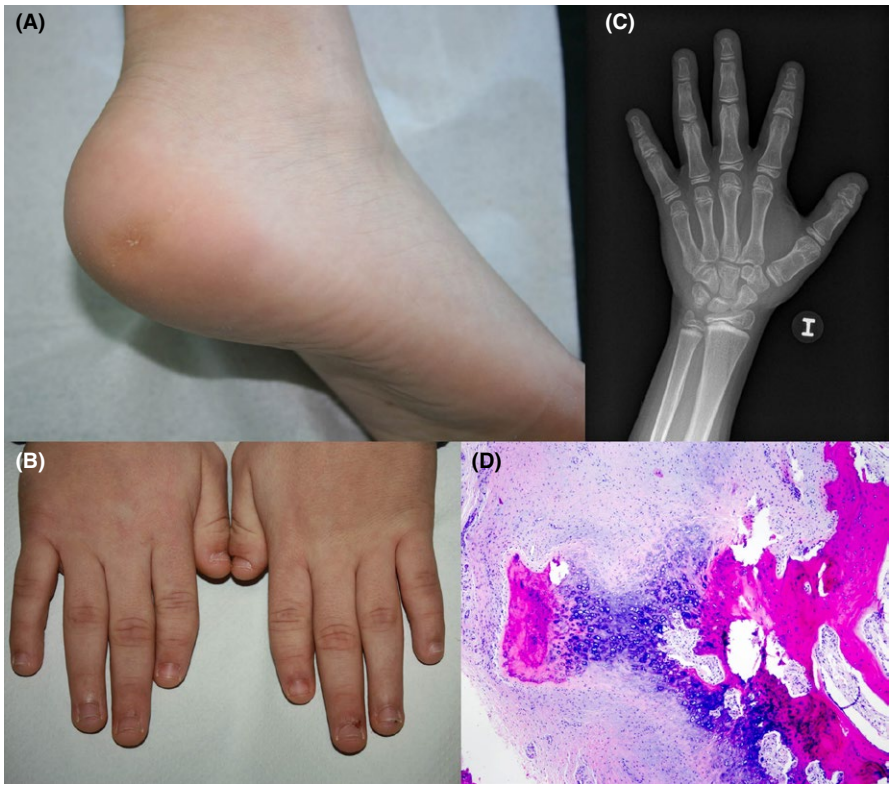

FIGURE 1 Clinical, radiological, and histopathology findings in patient 1. (A) Hard, firm nodule on heel. (B) Radiography of patient's right foot, where calcium is visible. (C) Bilateral shortening of fifth fingers. (D) Histology of the nodule on toe, on hematoxylin-eosin 4×, where cartilage and bone formation in subcutaneous tissue are visible

been growing in the last 3 months. Physical examination revealed a subcutaneous, tender, mobile, 2 × 1 cm nodule on the sole and a rounded face, short stature, and bilateral shortening of the fifth fingers. Radiological tests showed shortened fourth and fifth left metacarpal bones. Ultrasound of the abdominal, pretibial, and sole lesions showed hyperechoic structures at the hypodermis, with posterior acoustic shadow suggesting bone (Figure 2). Blood tests with calcium, phosphorus, magnesium, vitamin D, thyroid-stimulating hormone (TSH), free T4, and PTH were normal. A heterozygous pathological mutation (c.103C>T) was found on exon 1 in the *GNAS* gene. Genetic tests of her parents and brother revealed no *GNAS* mutations. The patient was firstly diagnosed as a PPHP, due to

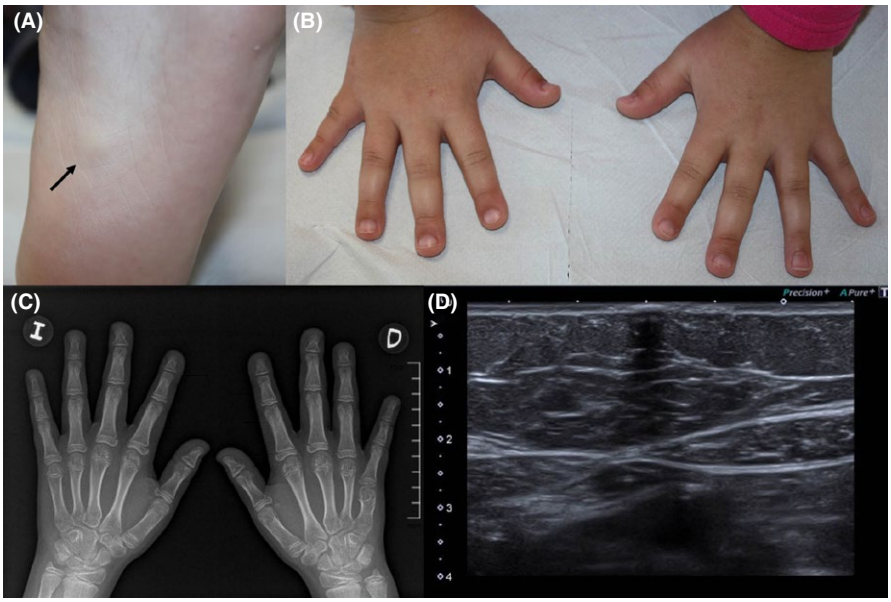

FIGURE 2 Clinical, radiological, and ultrasound findings in patient 2. (A) Hard nodule on patient's left sole (arrow). (B) Bilateral shortening of fifth fingers. (C) Radiography, where right fifth metacarpal shortening and left fifth metacarpal hypoplasia are visible. (D) Ultrasound of nodule on left sole, showing hyperechoic structures at dermo-hypodermis level with posterior acoustic shadowing

the absence of endocrine alterations; later, after blood tests showing an increased TSH, despite normal levels of PTH, her diagnosis was changed to PHP 1a as PPHP is not related to endocrinologic abnormalities.

2.3 | Patient 3

A 13-year-old boy with a history of language delay and short stature was referred for a lesion on the first toe of his left foot. In the 3 years of having the lesion, he received unsuccessful treatment with keratolytic substances and cryotherapy. On physical examination, the patient showed a tender, subcutaneous, mobile nodule on the left foot and bilateral shortening of the fifth fingers, which was confirmed on radiological tests (Figure 3). Blood tests showed normal levels of calcium, phosphorus, PTH, TSH, and vitamin D. A heterozygous pathological mutation (c.2T>G) was found on exon 1 in the *GNAS* gene. Genetic testing of his parents and brother showed no *GNAS* mutations. The patient was diagnosed with spontaneous PPHP.

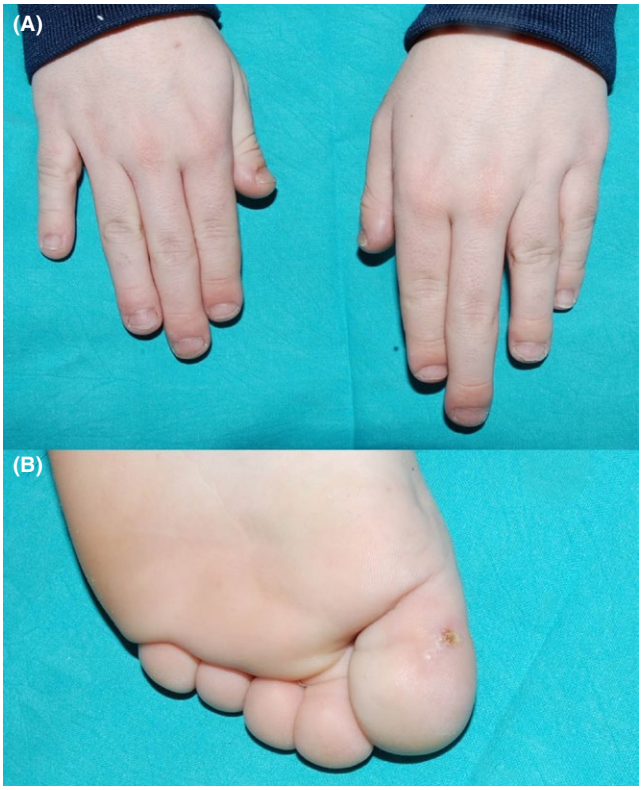

FIGURE 3 Clinical findings in patient 3. (A) Bilateral shortening of fifth fingers. (B) Hard nodule on big toe of left foot

3 | DISCUSSION

The *GNAS* gene is located on the long arm of chromosome 20 and codifies the alpha subunit of G-protein-coupled receptors. The transcript of this gene is regulated by an alternative splicing process, allowing it to express different proteins: G_s-alpha, extra-large (XL) αs (an alternative version of G_s-alpha), and the chromogranin-like protein, which represents G_s-alpha subunit in neuroendocrine tissues.[1-3] Expression of *GNAS* is determined by imprinting, through which the paternal and maternal alleles encode different proteins by varying methylation of their exons (NESP55 in the paternal allele[1] and A/B and XLαs in the maternal allele) that will not be expressed.[1,4] Due to methylation of exon 1 from the paternal allele, all the G_s-alpha protein in neuroendocrine tissues (hypophysis, thyroid gland, ovaries, testicles) and renal tubules is encoded in the maternal allele.[5,6] Clinical manifestations of this autosomal dominant disease will be different depending on whether the father or the mother transmits the mutation. Paternal inactivating *GNAS* mutations will reduce by half G_s-alpha protein in all tissues, except in the

endocrine tissues, which will continue expressing the usual amounts of this protein from the maternal allele. Maternal inactivating mutations will reduce by half G_s-alpha protein expression in all tissues with the exception of the neuroendocrine tissues, where it will be completely suppressed. There exists a 50% risk of transmission to offspring of the syndromes without endocrine alterations (PPHP, POH, osteoma cutis [OC]) if the mutation comes from the father or with them (PHP 1a/c) if it comes from the mother.[7] Moreover, spontaneous mutations are also possible, as in our three patients.

There are five diseases related to *GNAS* inactivating mutations:

1. PHP 1a/1c: These patients have a particular phenotype known as AHO, characterized by a rounded face, short stature, central obesity, brachydactyly, ossifications, and sometimes a certain degree of mental retardation. Brachydactyly, described as shortening of III, IV, and V metacarpals and I distal phalanx, and heterotopic ossifications are the most specific features of AHO. PHP 1a/1c is also associated with endocrine diseases due to end-organ resistance such as hypothyroidism, hypogonadism, or growth hormone (GH) deficiency, and hypoparathyroidism due to PTH resistance, which in turn can increase serum PTH levels, causing hypocalcemia and hyperphosphatemia. The 1a and 1c subtypes are differentiated through the determination of G_s-alpha activity in vitro, which is low in the 1a subtype and normal in 1c.[8]
2. PHP 1b: Patients with this disease only present with PTH resistance and potentially elevated PTH. Some of them may show altered calcium and phosphate in blood tests. PHP 1b is not related to the AHO phenotype or heterotopic ossifications.[8]
3. PPHP: These patients only exhibit the AHO phenotype, without any endocrine alteration.[8]
4. PHP 2: This subtype is related only to increased PTH resistance, without AHO or other endocrine problems.[8]
5. POH and isolated OC: These diseases manifest with heterotopic ossifications in soft tissues.[8]

Some authors hypothesize that these diseases are on a continuum of endocrine and ossification abnormalities, and the clinical manifestations determine the specific syndrome.[9] Craniosynostosis has been also described as related to these syndromes.[10] AHO is a particular phenotype that should not be confused with the McCune-Albright syndrome, which is produced by a hyperactivating mutation in the *GNAS* gene that leads to excess production of GH and TSH and is characterized by the clinical triad of dysplastic fibrous bones, café au lait spots, and precocious puberty.

Pediatric patients with cutaneous lesions of ectopic ossification should undergo a thorough physical examination to identify physical features that could resemble the AHO phenotype. Radiological tests can be performed to confirm metacarpal shortening, and ultrasound can confirm the presence of calcium in the lesions. Blood tests for calcium, phosphate, PTH, TSH, luteinizing hormone, and follicular-stimulating hormone should be performed in order to identify endocrine diseases related to these syndromes.[11] Biopsy of the cutaneous lesions is not always mandatory, but it can be helpful in cases where the diagnosis is in question. Definitive diagnosis requires genetic testing of the *GNAS* gene. Mutations detected may be recognizable and described as pathological or unknown and of uncertain significance, as in patient 1. In those cases, if laboratory and especially clinical findings are suggestive of these syndromes, clinicians can assume the mutations are pathological.

Differential diagnosis of firm lesions within the skin should include other cutaneous calcifications and ossifications. Cutaneous calcifications consist of amorphous deposits of calcium within the dermis and/or subcutaneous fat, and four different types have been described. Dystrophic calcifications are caused by cell membrane damage, such as in autoimmune connective tissue diseases, panniculitides, infections, genetic disorders, or neoplasms. Metastatic calcifications are those caused by dysfunction of the calcium regulatory system, like renal disease, milk-alkali syndrome, or hypervitaminosis D. Iatrogenic calcifications are secondary to extravasation of intravenous solutions containing calcium or phosphate, topical application of calcium-rich substances or after organ transplantation. When these conditions are excluded, lesions can be classified as idiopathic calcifications.[12] On the other hand, cutaneous ossifications or osteoma cutis lesions are characterized by calcium and phosphorus deposits in a proteinaceous matrix as hydroxyapatite crystals. Lesions with endochondral mechanism of bone formation are usually secondary to fibrodysplasia ossificans progressiva,[13] an autosomal dominant disorder of bone formation, while those with intramembranous ossifications are included in POH, AHO, OC, or milliary osteomas of the face.[14]

In conclusion, we present three cases of cutaneous ectopic ossification associated with GNAS inactivation, two of which also had endocrinologic abnormalities. It should be noted that, upon diagnosis of lesions of osteoma cutis or ectopic ossification, it is important to consider referral to endocrinology and genetics departments and to follow these patients over time in order to screen for endocrinologic abnormalities.

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