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Case Report

Progressive osseous heteroplasia: A case report with an unexpected trigger

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ABSTRACT

Progressive osseous heteroplasia (POH) is a rare genetic disorder characterised by progressive heterotopic ossification (HO) within the skin and subcutaneous tissues. The condition is caused by heterozygous inactivating mutations of the *GNAS* gene and usually presents in infancy. We describe the case of a white male ex-preterm who was first referred because of subcutaneous calcium deposits along the right arm after extravasation of parenteral nutrition. As these lesions progressed, a skin biopsy was undertaken which revealed intramembranous ossification. Genetic testing revealed a constitutional, *de novo*, heterozygous, nonsense variant in the *GNAS* gene that has not previously been described, but which is consistent with patient's clinical diagnosis of POH. No endocrine abnormalities or other signs congruent with overlapping conditions were detected. To the best of our knowledge, this is the first case describing an inflammatory trigger in POH. Trials with intravenous bisphosphonate and glucocorticoid as well as with topical sodium thiosulphate were attempted without clinical improvement. Excision of the calcifications and physiotherapy seem to have provided a partial improvement on mobility of the elbow. This case widens the spectrum of phenotypes seen in *GNAS* mutation disorders and suggests that alternative anti-inflammatory treatments may be effective. Mutations in *GNAS* should be considered in cases of significant progressive calcium deposition after extravasation injury.

1. Introduction

Progressive osseous heteroplasia (POH) is a rare genetic disorder involving mesenchymal differentiation, which causes progressive ectopic bone formation within skin and subcutaneous tissues (OMIM 166350) (Adegbite et al., 2008; Stoll et al., 2000). The condition usually presents in early life with most cases caused by heterozygous inactivating variants of *GNAS*, the gene encoding the alpha subunit of the G-stimulatory protein of adenylyl cyclase (Gsα) (Ahmed et al., 1998). The *GNAS* gene has a key role in osteogenesis, thus, mutations in the gene, result in an impairment of bone development and regulation. POH is clinically distinguished from the other conditions associated with inactivating mutations of *GNAS* mutations due to differential patterns of heterotopic ossification (HO), the presence of normal endocrine function and the rapid and progressive course of calcification. However, overlapping syndromes are described with HO, and some papers suggest a possible overlap between POH and pseudohypoparathyroidism type I, pseudopseudohypoparathyroidism (PPHP) and osteoma cutis (OC) (Ahmed et al., 2002; Turan and Bastepe, 2013). POH can be observed in both sporadic cases or inherited in an autosomal dominant pattern with paternal imprinting (Lebrun et al., 2010) of which the underlying genetic mechanism is not fully understood. Maternally inherited *GNAS* mutations are also reported (especially among overlapping syndromes with endocrine abnormalities) (Happle, 2016). Key diagnostic criteria are well summarised in recent reviews (Mantovani et al., 2018; Pignolo et al., 2015) and include: 1) superficial HO with progression into deeper connective tissues 2) two or fewer features of Albright hereditary dystrophy, excluding HO 3) no parathyroid hormone (PTH) resistance.

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There is however wide variability in both phenotype and severity of progression. Here, we describe a case with a novel *GNAS* mutation and a new insight into the potential pathogenesis of HO, that has not previously been reported.

2. Case report

Our proband is a white ex-preterm boy born after a pregnancy complicated by intrauterine growth restriction (IUGR). He was born at 29 + 3 weeks of gestational age by emergency caesarean section secondary to IUGR and absent end diastolic flow on ultrasound. His birthweight was 920 g (13th centile) and he required resuscitation at birth with Apgar scores of 6 and 9 at 1 and 5 min respectively. His birth length was 49.5 cm (<0.4th centile) and head circumference was 36.8 cm (25th centile). His mother underwent several investigations regarding the cause of fetal growth restriction but they were all negative. His parents were not consanguineous. The neonatal period was mainly characterised by respiratory distress with a short course of ventilation and a prolonged period of non-invasive respiratory support. A patent ductus arteriosus was managed conservatively and he required treatment for suspected episodes of sepsis and necrotising enterocolitis during his neonatal admission. He was discharged at 45 weeks corrected gestational age with a weight of 3160 g (10th centile) on formula milk and regular vitamin D supplementation.

The boy was referred to the tertiary paediatric endocrine team at 16 weeks of age because of persistent subcutaneous calcium deposits which initially tracked from his antecubital fossa to his shoulder and then progressed by 5 months of age to his shoulder and around the top of his back and chest wall (Fig. 1). Calcification was first noted following extravasation of parenteral nutrition at the age of 8 weeks, which did not require any management and did not result in any tissue necrosis. The calcification subsequently progressed, prompting referral. By the age of 7 months the calcification has extended to his hand and around his thumb. On clinical examination a café-au-lait spot on the left side of his trunk was detected but there were no other clinical concerns. Family history was positive for renal stones on the maternal side but nil else of note. Endocrine biochemistry including calcium, phosphate, vitamin D and PTH were all normal. An abdominal ultrasound was performed and did not show any signs of nephrocalcinosis (Fig. 2).

A multi-subspecialty approach to the management of this cutaneous calcification has included input from paediatric dermatology, endocrine and plastic surgery. Trials with topical 10 % sodium thiosulfate, bisphosphonate (pamidronate 1 mg/kg/dose on 2 consecutive days on 2 occasions 6 months apart) and glucocorticoid (methylprednisolone 30 mg/kg/dose on 3 consecutive days on 2 occasions 1 month apart) were attempted, with the aim of improving physical appearance and function of his right arm, with no improvement and indeed ongoing extension of the calcification by the age of 2.5 years. At this stage, an excision of the calcification around the antecubital fossa was carried out, followed by multiple y-v plasties, with some initial improvement on mobility at the elbow. Unfortunately, despite medical and surgical treatment and physiotherapy, the lesions became more extensive and consequently were associated with greater functional impairment.

During multidisciplinary discussion (medical, surgical and radiological), it was suggested that a skin biopsy, for histological and genetic analysis, should be performed to aid diagnosis. Clinical Pathology reported histological findings of fibro-adipose tissue with intramembranous ossification not only in the skin but also in the subcutaneous and muscular tissues without evidence of atypia, malignancy or signs of inflammation. Analysis of this tissue by next generation sequencing revealed a heterozygous variant in *GNAS* resulting in a premature termination codon (NM_000516.7: c.831G>A; p.(Trp277*)) classified as pathogenic by the American College of Medical Genetics (ACMG) guidelines for interpretation of sequence variants 2015 (likely pathogenic: PVS1, PM2, PM6) (Richards et al., 2015). Subsequent sequencing of a lymphocyte-derived DNA sample revealed confirmed that this variant was constitutional and parental testing was in keeping with the variant being *de novo*. This variant has not previously been described, but is consistent with patient's diagnosis of POH, and as such is reported as likely to be pathogenic.

At most recent clinic review, aged 6.7 years, the boy is short (height SDS -2.79) and thin (BMI SDS -2.2). His height velocity has remained consistent but he is below his midparental height centile. He is currently in mainstream education with no neurodevelopmental delay. He has no sequelae secondary to his preterm birth and has no dysmorphic features, in particular no shortened metacarpals or round facies. He is reported to have difficulty with activities of daily living, including dressing, due to restrictions in movement and pain with limited flexion of his right shoulder, elbow and wrist. He is able to grasp a pencil but requires hand-over-hand support to use cutlery to eat food. Calcification of the right arm has progressed and currently there is functional impairment of his shoulder, elbow and wrist. Clinical and radiological assessments have

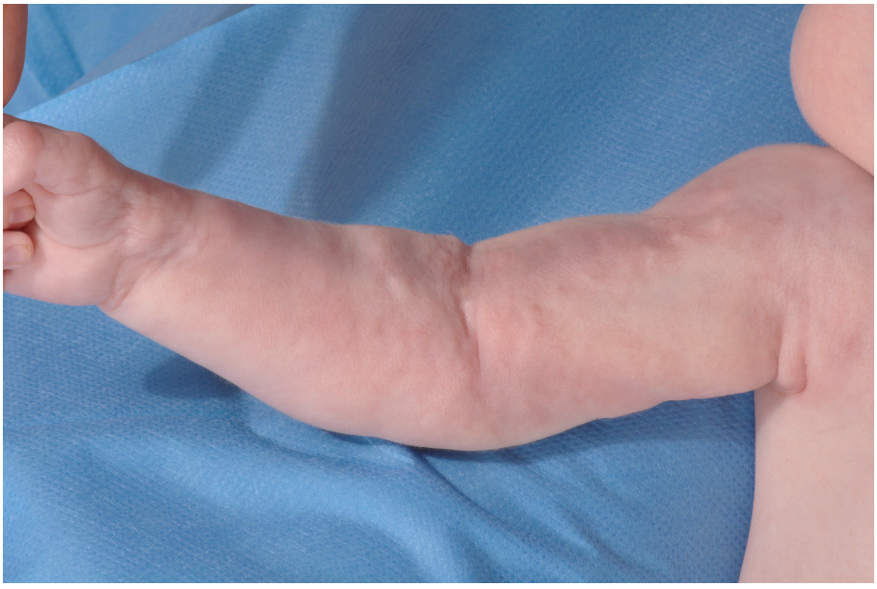

Fig. 1. Initial subcutaneous calcium deposits along the length of right arm. At initial development, these findings followed the same path of the catheter used for parenteral nutrition and as such, a local reaction to an extravasation was firstly hypothesized.

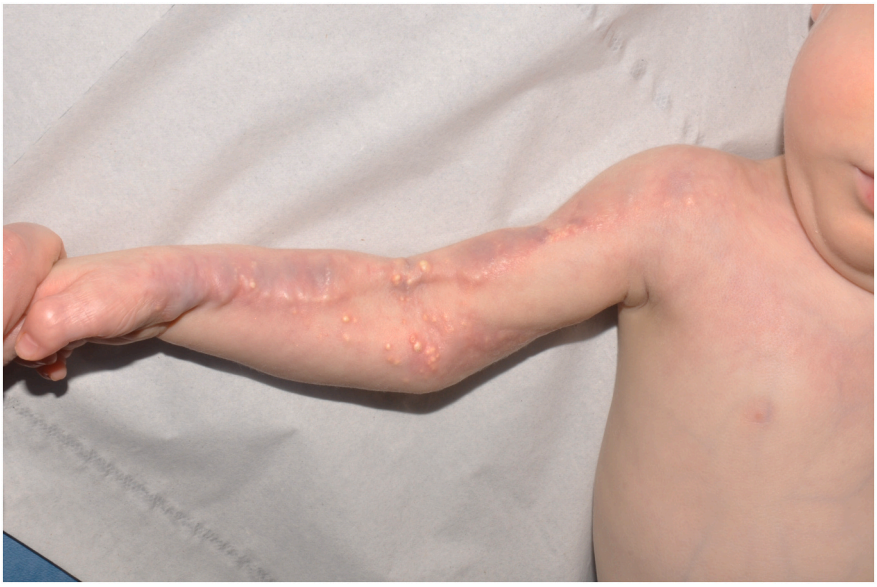

Fig. 2. Evolution of the calcifications along the right arm 4 months from the previous photograph. The lesion became more extensive both clinically and radiologically, prompting histological and genetic analysis. No surgical management had been performed by this stage.

demonstrated no new areas of calcification. Endocrine laboratory tests are normal: TSH 1.18 mIU/L (normal reference: 0.35–5.0 mIU/L), FT4 18.6 pmol/L (normal reference: 9.0–21.0 pmol/L), IGF1 42 μg/L (normal reference: 28-247μg/L), calcium 2.48 mmol/L (normal reference: 2.20–2.60 mmol/L), phosphate 1.30 mmol/L (normal reference: 0.90–1.80 mmol/L), 25-OH vitamin D 47 mmol/L (normal reference: >50 mmol/L), PTH 3.9 pmol/L (normal reference: 1.6–7.5 pmol/L), alkaline phosphatase 273 U/L (normal reference: 60–425 U/L). No calcium deposits have been identified on ophthalmic assessment. With the worsening of the condition, a trial of topical sodium thiosulfate was attempted with no benefit. Additional surgical excisions of the thickened calcification on the distal wrist are planned as surgical excisions in conjunction with physiotherapy have resulted in improvements in mobility previously. He has also been commenced on carbamazepine at 10 mg/kg for pain relief with good effect.

3. Discussion

Along with the genetic finding of a *GNAS* mutation, our case fits both with the major and many minor criteria of POH. However, the first evidence of heterotopic bone formations was discovered after an extravasation of parenteral nutrition with subcutaneous calcifications along the course of an intravascular line. To date, no other published cases of POH report an inflammatory event as a trigger for HO formation, although this has been seen in Fibrodysplasia Ossificans Progressiva (FOP) (Convente et al., 2015). On the contrary, the presence or absence of this correlation with trauma or inflammation triggers has been described as a helping feature to differentiate POH from FOP. Reports of connections between HO disorders and inflammatory components are important for researchers and clinicians attempting to better understand the pathogenesis of this group of conditions. Although inflammation is a common feature across many conditions that predispose to HO formation (Meyers et al., 2019), to the best of our knowledge, this trigger has not been described in the clinical presentation of POH. As such, this case is an important addition to the literature on POH. Unfortunately, the absence of inflammation in the pathology reports and the lack of response to anti-inflammatory drugs, suggests that anti-inflammatory treatments may not offer potential therapeutic benefits in other cases.

Interestingly, our case has not developed new lesions following incidental trauma nor after the standard intramuscular immunisations. In addition, his post-surgical healing has been good, again, with no heterotopic calcifications over the scar tissue. These findings are in line with the current criteria for POH diagnosis and highlight the well distinguished course of the disease in comparison with the consolidated pattern of FOP (Kaplan and Shore, 2000; Pignolo et al., 2011). Nonetheless, the link with the chemical insult from parenteral extravasation has been striking. This unexpected connection with an inflammatory trigger may alter POH clinical management recommendations in the care of these patients. Future studies should aim to investigate the possible relationship with inflammatory insults, such as extravasation. Consideration of *GNAS* analysis should be considered in those with significant, progressive calcium deposition, which appears out of context after extravasation injury.

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Declaration of competing interest

The authors have no conflicts of interest to disclose.

Data availability

Data will be made available on request.

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