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Unilateral progressive osseous heteroplasia

A 50-year-old male patient presented with firm subcutaneous nodules and plaques with a gritty texture, unilaterally affecting the left side of the trunk and the left limbs. These lesions had had a progressive course since early childhood and caused functional impairment. There was no family history of similar disorders. No phospho-calcium metabolism abnormalities were observed. Biopsies of the affected areas demonstrated osteoma cutis. Analysis of DNA showed no mutation of the GNAS gene. The clinical features were consistent with progressive osseous heteroplasia, atypically presented in a unilateral form, probably revealing a mosaic distribution.

Key words: progressive osseous heteroplasia, heterotopic ossification, GNAS mutation

Progressive osseous heteroplasia (POH) is a distinct disorder of mesenchymal differentiation, described by Kaplan in 1994 in children initially thought to have atypical progressive fibrodysplasia ossificans [1]. It may either be sporadic or inherited as an autosomal dominant trait [1]. POH is characterized by dermal ossification during childhood with progressive heterotopic ossification of cutaneous, subcutaneous and deep connective tissues [1, 2]. Fewer than 60 cases have been identified worldwide [3]. Recently, Shore *et al.* reported that paternally inherited, inactivating mutations in the GNAS gene are implicated in the pathogenesis of POH [4]. GNAS encodes for the alpha subunit of the stimulatory G protein of adenylyl cyclase and is thought to be a critical negative regulator of osteogenesis in non-osseous connective tissues, especially in skin, fat, and skeletal muscle [4, 5].

Case report

A 50-year-old male patient was observed with subcutaneous nodules and plaques which had been noticed since infancy, below the age of 1. These lesions had progressively expanded in number and size. On examination they were firm, relatively well-demarcated, skin-coloured or slightly blue, with a gritty texture. Only the left side of the body was affected, predominantly the scapular region, arm, forearm, digits I-III, thigh, leg, dorsal aspect of the foot and heel (*figure 1*). The patient complained of functional impairment in the tibio-tarsic joint. No acute flares of the disease were reported, nor exacerbation with trauma or intramuscular injections.

He was otherwise healthy, mentally normal and attended normal school. There was no family history of skeletal disorders, nor were the parents consanguineous. He had no facial dysmorphism, nor musculoskeletal deformities. The patient was of normal weight and height. Serum and urine levels of calcium and phosphate were normal, as were those of parathyroid and thyroid hormones and vitamin D metabolites. Lactate dehydrogenase and alkaline phosphatase levels were also within the normal ranges.

A skin biopsy revealed islands of well-differentiated bone in the reticular dermis, typical of osteoma cutis (*figure 2*). Skeletal radiological imaging of the affected areas showed extensive ossification involving the subcutaneous and deep tissues and pronounced at the ankle with continuity within the muscular plane (*figure 3*). Genomic DNA was extracted from peripheral blood samples and subsequent analysis showed no mutations in the gene encoding for the alpha subunit of the stimulatory G protein of adenylyl cyclase (GNAS).

The final diagnosis was unilateral POH, based on clinical features, clinical evolution, normal phospho-calcium metabolism, skin biopsy findings and radiological imaging.

Discussion

This case report corresponds to a rare ossifying disorder with few other cases previously reported, particularly if we take into account that it exists in a sporadic and uni-



Figure 1. A, B) Subcutaneous nodules and plaques along the left forearm and leg.



Figure 2. Skin biopsy compatible with osteoma cutis. Haematoxylin and Eosin stain; original magnification $\times 40$.

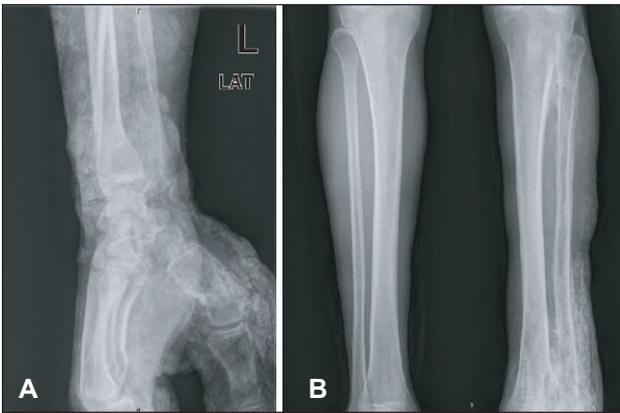


Figure 3. A, B) Radiographs showing extensive ossification of the forearm, hand and left leg. Right leg with no lesions.

lateral form in a male patient [6-10]. Furthermore, the absence of mutation in the protein coding region of the *GNAS* gene is a relevant event. However, this mutation seems to be present in only 64% of POH patients, as found in a recent study [5]. It is interesting to note that individuals without detectable mutations were clinically indistinguishable from those with mutations. The occurrence of mutations in a regulatory region of the *GNAS* gene, or in another gene, is probable in those cases but has never been reported until now.

Not only most cases of POH, but also plate-like osteoma cutis and Albright's hereditary osteodystrophy (AHO), can result from heterozygous inactivating germ-line mutations of *GNAS* localized to 20q13, causing abnormal expression or function of the alpha subunit of the stimulatory G protein of adenylyl cyclase [4]. *GNAS*-alpha is imprinted in a tissue-specific manner: maternal inheritance of a mutation in *GNAS* leads to an AHO phenotype with hormonal resistance, whereas paternal inheritance leads to AHO phenotype without hormonal resistance or POH [4, 11, 12]. However, the mechanism by which a mutation in the paternally derived *GNAS* gene results in heterotopic ossification originating in the fat cells, which would seem to require the conversion of fat cells to osteoblasts, remains unknown [12]. *GNAS* somatic (postzygo-

tic) activating mutations play a role in another skeletal disease: the McCune-Albright syndrome [12].

The asymmetric mosaic distribution of lesions is an important feature of POH and some unilateral cases have already been reported [1, 7, 8]. The anatomical distribution of lesions suggests that the pathogenesis may involve a variable expression of the mutant gene in mesenchymal stem cells destined for widespread mosaic distribution [1, 2]. In addition to the highly variable phenotypic expression present in POH, non-penetrance cases have also been observed in some families. These could be due to epigenetic modifications, complex regulatory mechanisms, influences from other genetic loci, or environmental factors [4]. Many questions about the genotypic complexity and phenotypic variability in POH are waiting for answers, however studies are being conducted to complete the puzzle.

Finally, to our knowledge, this is the first case of unilateral POH reported in Portugal, even though a case of heterotopic cutaneous ossification in a 12-month-old child was described in 2006 [13]. ■

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