

Progressive osseous heteroplasia (POH): an Egyptian patient

Ezzat El Sobky and Solaf M. El Sayed

Genetics Unit, Children's hospital, Ain Shams University

ABSTRACT

Progressive osseous heteroplasia is a rare genetic disorder characterized by cutaneous ossification during infancy and progressive ossification of subcutaneous and deep connective tissue including muscle and fascia during childhood. It is at the severe end of a spectrum of Guanine Nucleotide-binding protein, Alpha-Stimulating activity polypeptide (GNAS) associated ossification disorders that include osteoma cutis and Albright hereditary osteodystrophy. Here we describe a five year old boy with progressive ossification of skin and subcutaneous tissue and progressive limitation of movement of all joints. X-rays revealed extensive calcification of cutaneous and subcutaneous tissues involving nearly the whole body. As far as our knowledge, no cases have been reported before in the Middle East. Here we describe the first Egyptian child affected with this disorder.

Key Words:

Progressive osseous heteroplasia, GNAS1 mutations, Heterotopic ossification.

Corresponding Author:

Ezzat Elsobky

E-mail: elsobkyezzatt@hotmail.com

INTRODUCTION

Progressive osseous heteroplasia (POH) is a rare disorder of mesenchymal differentiation characterized by dermal ossification beginning in infancy and consists of maculopapular rashes at sites of future ossification, followed by increasing and extensive bone formation in deep muscle and fascia. Dermal lesions coalesce rapidly to form extensive ossified plaques.¹

CASE REPORT

Our case is a five year old boy, the first born after uncomplicated pregnancy to non-consanguineous healthy parents. The patient has a younger normal 4 year old brother and no similar affected family members.

His condition started at the age of 2 years when he developed hardened cutaneous lesions that coalesced into plaques and extended rapidly all over his body with subsequent ulcerations through the epidermis. This was associated with progressive loss of motor skills. On examination, the patient had ossified plaques and ulcers all over the trunk and limbs and limited movement of nearly all joints with flexion deformity. He was unable to walk or to move his upper limbs. Neurological examination revealed no abnormalities. There was no facial dysmorphism or digital malformation

Serum levels of calcium and phosphorus were normal as well as parathyroid hormone level. X-rays showed extensive

diffuse cutaneous and subcutaneous web-like calcification surrounding all the upper and lower limbs and sparing only the soft tissue areas around hands and feet, (Figs. 1: A, B, C).

Unfortunately, the condition of the patient progressed rapidly with extensive ulceration of the skin and subcutaneous tissue that was associated with secondary infection which ended by his death shortly after presentation to our clinic.

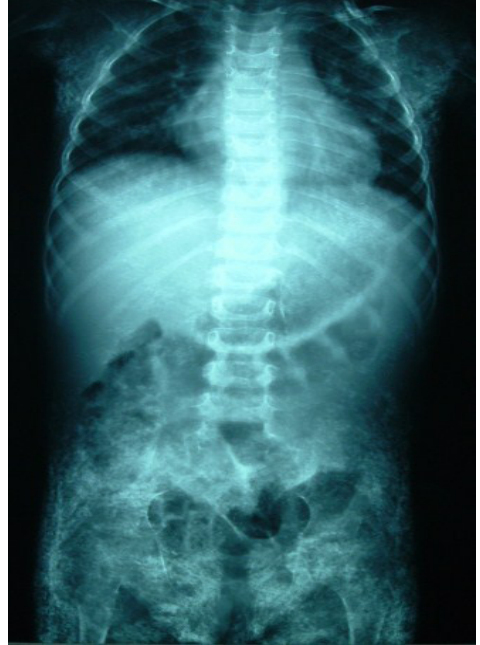


Fig. 1 (A, B, C): Radiographs of the patient showing tiny radiodensities seen in skin and soft connective tissues of nearly all body extending from the dermis down through the skeletal muscle sparing only the hands and feet.

DISCUSSION

Our patient has typical features of POH described by Kaplan, et al. 1994 with heterotopic ossification involving subcutaneous and deep connective tissues, including muscle and fascia, in the absence of multiple features of Albright hereditary osteodystrophy (AHO) or hormone resistance¹. Usually, the first symptoms occur in childhood (Birth to 3 years) and girls appear to be more affected than boys.²

Differential diagnosis include fibrodysplasia ossificans progressive (FOP), which is another rare autosomal dominant condition of heterotopic ossification and can readily be distinguished by the absence of cutaneous ossification, the congenital malformation of the great toes and the presence of preosseous tumor-like inflammation or "Flare-ups"³. Triggering factors such as trauma, infection or needle punctures do not seem to occur in POH as they do in FOP.¹

The heterotopic ossification of POH is predominantly intramembranous and involves subcutaneous and deep tissues but not the viscera⁴. In contrast, the heterotopic ossification in FOP is predominantly enchondral.³

Although differential diagnosis may include pseudopseudohypoparathyroidism (PPHP) or Albright hereditary osteodystrophy (AHO) because it is caused by mutation of the same gene, patients with PPHP have a constellation of physical findings that is often not seen in patients with POH. It has been suggested that POH may be an extreme end of the spectrum of the AHO features seen in PPHP.⁵

The results of laboratory studies in our patient were normal and he had normal height, normal phenotype and normal great toe with no flare ups or tumour like inflammations supporting the diagnosis of POH and excluding other diagnoses such as PPHP, AHO and FOP.

Most of POH cases are caused by heterozygous inactivating mutations of *GNAS*¹, the gene encoding the alpha subunit of the G-stimulatory protein of adenylyl cyclase. The defective allele in POH is inherited exclusively from fathers, a result consistent with a model of imprinting for *GNAS*¹. The same mutation can cause either POH or AHO features depending on the parental origin of the mutant allele⁶. Faust, et al. (2003) identified a heterozygous germline mutation in the *GNAS*¹ gene causing POH of the face in an Albanian girl.⁷

Cases of patients with combined features of POH and AHO have been reported⁸. Stoll, et al. reported the clinical and radiologic features of a patient with POH who was 20 years old at presentation. In addition to abnormal ossifications, she had short metacarpals at the fourth and fifth rays and short metatarsals at the second rays. Her parents were unaffected.⁹

POH has been observed in sporadic cases and in an autosomal dominant pedigree pattern with widely variable expression¹¹. In this present family with healthy parents, the disease is most probably due to new mutation with rare recurrence risk.

There are no specific genotype-phenotype correlations that distinguished the more progressive forms such as POH, from the nonprogressive forms, such as PPHP.¹⁰

Physiotherapy to preserve movement and the prevention of skin breakdown is the only currently acceptable therapy. There is no reliable treatment or prevention for POH³. Although areas of well-circumscribed heterotopic ossification can sometimes be removed successfully, the surgical removal of POH tissue has led to recurrence in most patients, notably when the heterotopic ossification is diffuse and web-like rather than focal⁴. Amputations have been done in some children.³

The present patient had a severe progressive course that ended eventually by his death at the age of 5 years. The long-term prognosis of POH is uncertain because only few patients have been followed-up beyond adolescence, but, in these cases, the disease has followed a course of slower progression during adulthood^{11,12}. Kaplan, et al. mentioned that, in patients with an early onset of the disease, progression had generally ceased by adulthood.³

Early diagnosis is important for genetic counseling and for prevention of iatrogenic harm. Patients and relatives should be given adequate counseling particularly with regard to education as the patients are not mentally impaired and because the disease does not seem to progress rapidly in the adult.

REFERENCES

1. Kaplan FS, Craver R, MacEwen GD, Gannon FH, Finkel G, Hahn G, et al. 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(3):425-36.
2. Seror R, Job Deslandre C, Kahan A. Progressive osseous heteroplasia: A rare case of late onset. *Rheumatology (Oxford)* 2007;46(4):716-7.
3. Kaplan FS, Shore EM. Progressive osseous heteroplasia. *J.Bone Miner.Res.* 2000;15(11):2084-94.
4. Schmidt AH, Vincent KA, Aiona MD. Hemimelic progressive osseous heteroplasia. A case report. *J.Bone Joint Surg.Am.* 1994;76(6):907-12.
5. Bastepe M, Juppner H. GNAS locus and pseudohypoparathyroidism. *Horm. Res.* 2005;63(2):65-74.
6. Shore EM, Ahn J, Jan de Beur S, Li M, Xu M, Gardner RJ, et al. Paternally inherited inactivating mutations of the GNAS1 gene in progressive osseous heteroplasia. *N.Engl.J.Med.* 2002 10;346(2):99-106.
7. Faust RA, Shore EM, Stevens CE, Xu M, Shah S, Phillips CD, et al. Progressive osseous heteroplasia in the face of a child. *Am.J.Med.Genet.A.* 2003 1;118(1):71-5.
8. Eddy MC, Jan De Beur SM, Yandow SM, McAlister WH, Shore EM, Kaplan FS, et al. Deficiency of the alpha-subunit of the stimulatory G protein and severe extraskeletal ossification. *J.Bone Miner.Res.* 2000;15(11):2074-83.
9. Stoll C, Javier MR, Bellocq JP. Progressive osseous heteroplasia: An uncommon cause of ossification of soft tissues. *Ann.Genet.* 2000;43(2):75-80.
10. Adegbite NS, Xu M, Kaplan FS, Shore EM, 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;146(14):1788-96.
11. Urtizbera JA, Testart H, Cartault F, Boccon Gibod L, Le Merrer M, Kaplan FS. Progressive osseous heteroplasia. Report of a family. *J.Bone Joint Surg. Br.* 1998;80(5):768-71.
12. Ahmed SF, Barr DG, Bonthron DT. GNAS1 mutations and progressive osseous heteroplasia. *N.Engl.J.Med.* 2002 23;346(21):1669-71.