

Rare Genetic Cases of Heterotopic Ossification

Ashwini Mallappa^{1*}, Anu Vishwanath^{1*}, Marsha C Pratt², Klaas J Wierenga² and Sowmya Krishnan¹

*Equal Contribution

¹Section of Diabetes and Endocrinology, Department of Pediatrics, University of Oklahoma Health Sciences Center, Oklahoma City, USA

²Section of Genetics, Department of Pediatrics, University of Oklahoma Health Sciences Center, Oklahoma City, USA

Abstract

Heterotopic Ossification (HO) is formation of normal bone in extraskeletal tissues, such as skin, subcutaneous tissue and deep connective tissue. Heterotopic ossification can be hereditary or nonhereditary in nature. We report two cases of rare hereditary forms of heterotopic ossification namely Fibrodysplasia Ossificans Progressiva (FOP) and Progressive Osseous Heteroplasia (POH). Hereditary forms of heterotopic ossification are progressive and severely debilitating in nature. Though these disorders are rare, awareness and knowledge about these disorders will help in early identification of such unique cases, leading to appropriate referral and management.

Case Presentations

Case 1

A 4 year old Caucasian female was admitted with history of painful soft tissue swelling and induration on her right upper back, posterior neck and torso following an all-terrain vehicle accident that occurred a few weeks before her admission. Patient also reported trouble sitting up and increasing stiffness with ambulation. She had been evaluated in orthopedic clinic a few months previously for scoliosis and suspected Klippel-Feil anomaly. Physical examination revealed extensive tender indurated swellings over upper back and neck. She was also noted to have bilateral hallux valgus (Figure 1). Laboratory data revealed normal electrolytes, blood cell counts, liver enzymes, alkaline phosphatase and LDH levels. CT of her shoulder revealed a bony extension of the left anterior/inferior clavicle (Figure 1) and was reported as exostosis of the clavicle with nonspecific soft tissue stranding through the lower neck and chest wall musculature, findings inconsistent with Klippel-Feil syndrome. Genetic testing for FOP was done because of a strong clinical suspicion and due to the presence of hallux valgus, which revealed a c.617G>A transition in *ACVR1* gene, resulting in a missense mutation (p.R206H), commonly associated with FOP [1].

Case 2

A 17 year old Caucasian male presented to our endocrinology/bone clinic for evaluation of subcutaneous nodules. The lesions were first noted on his right index finger at two years of age. Over time similar lesions were noted on his right extremity. In the previous year he had noted more lesions in his right hand with extension into the forearm. He also had complaints of mild right wrist joint pain and stiffness with activity. He had undergone surgical removal of the lesions repeatedly (seven times). Family history was negative for ectopic ossifications,

Labs	Results
Calcium	9.8 mg/dL (8.4-10.2)
Phosphorus	3.8 mg/dL (2.5-4.5)
Intact Parathyroid Hormone (PTH)	21 pg/ml (7-53)
Alkaline Phosphatase	100 Units/L (65-260)
Albumin	4.7 g/dL (3.4-5.0)
Vitamin D 25-OH	34 ng/mL (10.0 - 55.0)
Vitamin D 1,25-(OH) ₂	47 pg/mL (15-90)
Urine Calcium/Creatinine ratio	0.02

Table 1: Case 2 - Progressive Osseous Heteroplasia. Laboratory data.

rickets, hormone deficiencies or other bone disorders. There was no history of consanguinity.

Physical examination showed a well appearing Tanner V adolescent, with no features of Albright Hereditary Osteodystrophy (AHO). Extremity examination was remarkable for 2-4 mm sized bony lesions palpable in the inter-digital space of right index and middle finger and also extending along the radial aspect of the forearm. He was noted to have decreased mobility of the index and middle fingers. Similar lesions were noted on the dorsal aspect of the second digit of the right foot and mid-plantar aspect of the same foot.

Laboratory evaluation for disorders of mineral metabolism was essentially within normal limits (Table 1). Plain X-rays showed sheet-like disorganized and scattered ossifications centered around the right metacarpal, metacarpophalangeal joints, proximal and distal forearm as well as along the phalanges. A nuclear medicine scan revealed

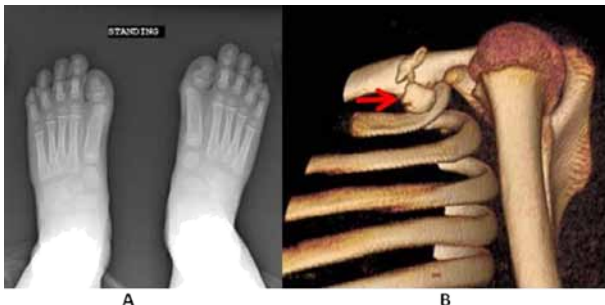


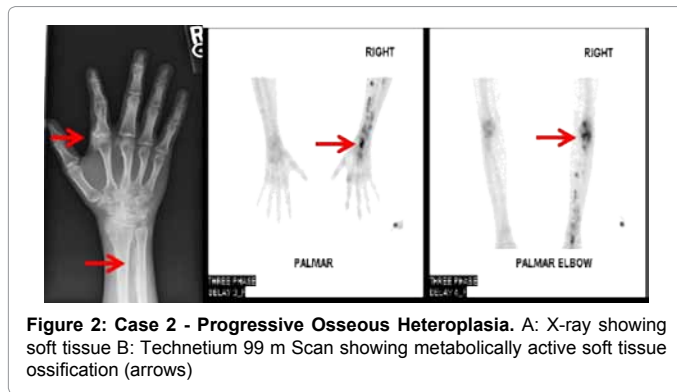
Figure 1: Case 1 - Fibrodysplasia Ossificans Progressiva. A : X-ray feet demonstrating Hallux Valgus deformity. B: 3D CT reconstruction noting a bony projection extending off of the anterior and inferior surface of the clavicle, at the junction of medial two third and lateral one third of the clavicle.

*Corresponding author: Anu Vishwanath, Section of Diabetes and Endocrinology, Department of Pediatrics, University of Oklahoma Health Sciences Center, USA, E-mail: anu-vishwanath@ouhsc.edu

Received August 22, 2012; Accepted September 17, 2012; Published September 19, 2012

Citation: Mallappa A, Vishwanath A, Pratt MC, Wierenga KJ, Krishnan S (2012) Rare Genetic Cases of Heterotopic Ossification. Endocrinol Metab Syndr 1:105. doi:10.4172/2161-1017.1000105

Copyright: © 2012 Mallappa A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.



metabolically active soft tissue ossifications localized to right forearm, elbow and hand, posterior lateral border of the left scapula and the mid aspect of the left tibia (Figure 2). Guanine nucleotide binding protein alpha stimulating activity polypeptide (*GNAS*) gene sequencing identified a previously described mutation in the exon 7 of the *GNAS* gene, predicted to result in a frameshift and loss of function.

Discussion

Heterotopic ossification is a pathological condition where bone formation occurs in extra skeletal tissues (skin, soft tissues, muscle). The two known genetic forms of heterotopic ossification are FOP and POH.

FOP is a very rare disorder with a prevalence of about 1 in 2 million individuals [2]. It is a progressively debilitating condition characterized by extra skeletal bone formation. Most cases are due to sporadic mutations but autosomal dominant inheritance has been observed in a small number of families [1]. The most common mutation is a heterozygous single nucleotide substitution c.617G>A in *ACVR1* (located on chromosome 2q23–24) which encodes activin receptor type 1 (*ACVR1*) also known as activin like kinase 2 (*ALK2*), a bone morphogenetic protein (BMP) type I receptor. This mutation leads to a R206H substitution in the glycine-serine region of the cytoplasmic domain of *ACVR1*, which is highly conserved [1,3,4]. This gain-of-function mutation leads to dysregulated enhanced BMP signaling, responsible for the new bone formation in connective tissue, as occurring in this condition.

Patients with FOP have congenital malformations of the great toes such as hallux valgus, malformed first metatarsal or monophalangism. Painful episodes of soft tissue swellings typically occur in the first decade of life, often before age five, precipitated by soft tissue injury, intramuscular injections, viral infection, muscular stretching, falls or fatigue. These flare-ups can initiate ossification and heterotopic bone formation in skeletal muscles, tendons, ligaments, fascia, and aponeuroses leading to restricted mobility, progressive deformity of spine and eventually to respiratory decline. Progressive episodes of HO occur in specific anatomic patterns, and are typically seen first in the dorsal, axial, cranial, and proximal regions of the body and later in the ventral, appendicular, caudal, and distal regions [1,5].

A four day course of high-dose corticosteroids (prednisone 2 mg/kg/day, administered as a single daily dose) is recommended starting within the first 24 hours of a flare up that affects major joints, the jaw, or the submandibular area. A second course of corticosteroids may be necessary. For symptomatic relief, NSAIDs or cox-2 inhibitors (in conjunction with a leukotriene inhibitor) may be used. Bisphosphonates and muscle relaxants are other treatment options.

Emphasis should be on palliative or preventive measures such as prevention of injuries and infections, appropriate immunizations while avoiding intramuscular injections, appropriate occupational therapy for kyphosis, scoliosis and limb swelling to facilitate activities of daily living, preventive oral care, monitoring of cardiorespiratory function and audiology screening. Family and patients need to be counseled about the progressive nature of the disease and the measures to minimize the flare-ups [2,6].

POH is caused by a mutation in the *GNAS* locus. Loss or gain-of-function mutations in G proteins have been identified in several endocrine disorders. The *GNAS* locus is a transcriptionally complex imprinted locus located on chromosome 20q13.11 [7]. Heterozygous inactivating mutations of *GNAS* have been identified as the cause in most cases of POH, and the mutation in exon 7 identified in our patient has been described as a 'hotspot' [8]. Intrafamilial inheritance analysis of POH indicates that the mutation tends to be paternal in origin [9]. Family pedigree analyses document the wide clinical and phenotypic variability among affected individuals carrying the same gene mutation, and some patients with POH exhibit features of AHO [9,10].

Clinical presentation of POH is characterized by progressive cutaneous ossification beginning in childhood and progressive involvement of the subcutaneous and deep connective tissue, with no features of AHO or parathyroid hormone (PTH) resistance as seen in Pseudohypoparathyroidism type 1a or 1c (PHP1a/1c). There is a subset of patients with progressive HO who present with multiple features of AHO or with both AHO and PTH resistance (POH/PHP1a/1c) [8]. Given that POH overlaps with features of AHO (Pseudopseudohypoparathyroidism), and also PHP1a/1c, it is suggested that all these conditions are part of a similar pathophysiologic group of disorders of extra skeletal ossification caused by inactivating mutation of *GNAS*, with POH at one end of the phenotypic spectrum [8]. *GNAS* mutations seen in POH have previously been identified in patients with PHP1a, thus raising the question of parental origin of the mutation [8,10].

The basic pathophysiology behind the extra-skeletal ossification in POH is still to be elucidated. Factors contributing to the complexity of pathophysiology include the ubiquitous nature of *GNAS* expression and several downstream signaling pathways mediated through *GNAS* products, as well as genomic imprinting occurring at this locus. Alpha subunit of the stimulatory G-protein (*Gsa*) mediated mechanisms are thought to be involved in osteoblast and chondrocyte differentiation [11]. Further research and studies in this area may provide better options for treatment of this rare but debilitating disease.

Therapeutic options for POH at this time are limited owing to the complexity of the gene mutation and dearth of knowledge about the pathophysiology involved. Surgical removal is an option for well-circumscribed lesions interfering with mobility, but the risk of recurrence has been noted to be higher in diffuse lesions. Again, emphasis and education on preventive measures is of utmost importance to avoid unnecessary therapies and procedures leading to further progression of the disease and complications. Affected members and families benefit from customized occupational therapy to assist with activities of daily living, psychological support, genetic counseling and access to support groups [12].

Both patients described here had seen multiple care providers before the diagnoses were made. The patient with FOP had undergone extensive physical therapy to improve shoulder joint mobility before the diagnosis was made. Similarly the patient with POH had undergone multiple surgeries to remove the 'calcifications' without a definitive

diagnosis which may have led to recurrence or increased severity of the lesions.

In conclusion, both FOP and POH have a progressively debilitating course, causing families tremendous amount of anxiety. Having a clinical suspicion leads to early diagnosis with appropriate referrals, preventing unnecessary interventions and providing families with necessary support.

References

1. Kaplan FS, Xu M, Seemann P, Connor JM, Glaser DL, et al. (2009) Classic and atypical fibrodysplasia ossificans progressiva (FOP) phenotypes are caused by mutations in the bone morphogenetic protein (BMP) type I receptor ACVR1. *Hum Mutat* 30: 379-390.
2. Shore EM, Kaplan FS (2010) Inherited human diseases of heterotopic bone formation. *Nat Rev Rheumatol* 6: 518-527.
3. Shore EM, Kaplan FS (2011) Role of altered signal transduction in heterotopic ossification and fibrodysplasia ossificans progressiva. *Curr Osteoporos Rep* 9: 83-88.
4. Kaplan FS, Lounev VY, Wang H, Pignolo RJ, Shore EM (2011) Fibrodysplasia ossificans progressiva: a blueprint for metamorphosis. *Ann N Y Acad Sci* 1237: 5-10.
5. Pignolo RJ, Shore EM, Kaplan FS (2011) Fibrodysplasia ossificans progressiva: clinical and genetic aspects. *Orphanet J Rare Dis* 6: 80.
6. http://www.ifopa.org/en/component/docman/doc_download/52-the-medical-management-of-fibrodysplasia-ossificans-progressiva-current-treatment-considerations.html
7. Kelsey G (2010) Imprinting on chromosome 20: tissue-specific imprinting and imprinting mutations in the GNAS locus. *Am J Med Genet C Semin Med Genet* 154C: 377-386.
8. Adegbite NS, Xu M, Kaplan FS, Shore EM, Pignolo RJ (2008) Diagnostic and mutational spectrum of progressive osseous heteroplasia (POH) and other forms of GNAS-based heterotopic ossification. *Am J Med Genet A* 146A: 1788-1796.
9. Shore EM, Ahn J, Jan de Beur S, Li M, Xu M, et al. (2002) Paternally inherited inactivating mutations of the GNAS1 gene in progressive osseous heteroplasia. *N Engl J Med* 346: 99-106.
10. Lebrun M, Richard N, Abeguilé G, David A, Coëslie Dieux A, et al. (2010) Progressive osseous heteroplasia: a model for the imprinting effects of GNAS inactivating mutations in humans. *J Clin Endocrinol Metab* 95: 3028-3038.
11. Weinstein LS, Xie T, Zhang QH, Chen M (2007) Studies of the regulation and function of the Gs alpha gene Gnas using gene targeting technology. *Pharmacol Ther* 115: 271-291.
12. <http://www.pohdisease.org>