Genetic disorders with heterotopic ossificans

Ruthiramurthy Sankar, Kalpana Gowrishankar, Saraswati Viswanathan

ABSTRACT

Fibrodysplasia ossificans progressiva (FOP) and progressive ossific heteroplasia (POH) are rare genetic disorders characterized by heterotopic bone formation leading to progressive loss of mobility and function. We report three cases of these rare disorders (two cases of FOP and one case of POH), which were clinically diagnosed and underwent genetic analysis. The aim of this report is to highlight the clinical features and the differences between these two conditions. We would also like to emphasize on the morbidity that can arise from unnecessary invasive investigations for diagnostic purposes.

Key words: Fibrodysplasia ossificans progressiva, heterotopic ossification, progressive ossific heteroplasia, genetic analysis

MeSH terms: Ossification, heterotopic, genetic predisposition to disease

INTRODUCTION

Heterotopic ossification is a pathological condition in which bone forms at nonskeletal sites. It is formed due to abnormal activation of endochondral or intramembranous osteogenesis and develops through processes similar to the events that occur during normal embryonic bone and skeletal formation and hence, it is qualitatively a normal bone. Nonhereditary forms of heterotopic ossification are associated with injury to the spinal cord and brain, hip replacement surgeries, severe burns and high-energy wounds with severe tissue damage. The usual presentations in genetic disorders of heterotopic ossificans are multiple bony hard lesions in soft tissues in childhood. There are two distinct genetic forms of heterotopic bone formation: Fibrodysplasia ossificans progressiva (FOP) and Progressive Ossific Heteroplasia (POH).

Children with FOP appear normal at birth except for a tell tale malformation of the great toe, a finding present in >95% of cases. Ossifications usually begin in the first decade of life with rapid appearance of painful preosseous swellings with a waxing and waning history, followed by bony lesions. There is temporal pattern of involvement which is generally seen first in the dorsal, axial, cranial and proximal regions of the body and later in the ventral, appendicular, caudal and distal regions. This pattern is similar to those seen during embryonic skeletal development. Although the rate of disease progression is variable, most patients develop ankylosis of all major joints of the axial and appendicular skeleton by the third decade.

POH is characterized by the appearance of islands of dermal bony lesions that appear during infancy. Over time, the islands of heterotopic bone coalesce into plaques with subsequent involvement of the deeper connective tissues including fascia, skeletal muscle, tendon and ligament. Extensive ossification of the deep connective tissues results in ankylosis of affected joints and focal growth retardation of involved limbs. There is no temporal pattern and it is not associated with congenital toe anomalies.

Although they are two distinct clinical entities, reports of misdiagnosis of POH as FOP are reported as both these disorders have bone formation in nonskeletal tissues leading to progressive loss of mobility and function. We report three cases of heterotopic ossification (two FOP and one POH case). These cases were clinically diagnosed and genetic analysis for mutation study was performed. The emphasis is on clinical diagnosis and differences between these cases.
**CASE REPORTS**

**Case 1**
A 2 year old male child, first born child of nonconsanguineous parents, with no significant family history was brought with bony lesions in the upper back. Examination revealed bilateral hallux valgus, bony hard swellings in the nape of the neck and left supraclavicular region. Parents gave a history of small painful swellings appearing and resolving in the back. Genetic counseling was obtained and provisional diagnosis of FOP was made. No clinical photographs were taken during the initial visit. The child was lost to followup after the first visit.

**Case 2**
A 3 year old male child presented with progressive stiffness of both the shoulders and the neck. There was no significant family history. Multiple bony hard lesions in the back, bilateral hallux valgus and torticollis were noted (Figure 1). Both shoulders were stiff with complete absence of movements. Both elbows had restriction of flexion beyond 40° with no fixed flexion deformity. Forearm rotations, wrist and hand movements were within normal range. Lower limb movements were normal. Diagnosis of FOP was made clinically. Deoxyribonucleic acid sequence analysis showed the classic mutation R206H in activin receptor type-1 (ACVR1) gene. This child is on a 6 monthly followup and has been advised to do gentle exercises. Parents have been counseled regarding the condition and precautions to be undertaken to prevent exacerbations. Inj. Pamidronate 0.75 mg/kg/day slow i.v infusion was administered for 3 consecutive days as a prophylactic measure.

**Case 3**
A 5 year old girl child presented with recurrent bony swellings with past history of two open biopsies for the same. There was no significant family history. History of multiple small nontender lesions in early infancy which grew with age was noted. Biopsy of the wrist nodule was done at the age of 1 year followed by physiotherapy. The lesion recurred within 6 months with progression along the forearm. Lesion of the back in the right paraspinal region became prominent by 2 years of age. Parents gave a history suggestive of biopsy of the lesion at 2.5 years of age but recurred. Examination revealed surgical scar on the dorsum of the left wrist with a flat bony lesion in the entire forearm extending proximally until the elbow joint. Nodular swelling was noted in the elbow joint. All the lesions were fixed to the overlying skin. No facial asymmetry, midline lesions in the back or toe deformities were noted. Left elbow was fixed in 90° of flexion, forearm in 30° of pronation and wrist was fixed in neutral position [Figure 2]. Hand movements and shoulders were relatively free. Genetic consult was obtained and clinical diagnosis of POH was made. Genetic analysis was noncontributory. Child is on a yearly followup. There is a flat bony lesion on the left thigh which has become prominent in the last 1 year but there is no worsening of upper limb involvement [Table 1].

**DISCUSSION**

Inherited human disorders of heterotopic ossificans are FOP and POH.3 They are distinct from each other clinically and genetically. FOP is associated with skeletal deformities like hallux valgus, occasionally short thumbs, fifth finger clinodactyly, malformed cervical vertebrae and short broad femoral neck. It has a typical cranial to caudal progression pattern.4 On the contrary POH has predominantly cutaneous ossifications with asymmetric mosaic pattern of distribution.5 The genetic association of these two conditions is also distinct. FOP is associated with mutation in ACVR1 gene whereas inactivating mutations in guanine nucleotide binding protein, alpha stimulating polypeptide 1 (GNAS1 gene) have been identified as causative in POH.4,5 Only 60% of POH cases have the mutation in the gene. Our case of POH also had a negative genetic study, indicating that clinical examination is the mainstay in diagnosis of this condition. It is worth noting that inactivation of GNAS Gene mutation is also seen in pseudopseudohypoparathyroidism or albright hereditary...
osteodystrophy (AHO). AHO is an endocrine disorder with dysmorphic “moon” facies, obesity, short stature, brachydactyly and end-organ resistance to parathyroid hormone. We did not consider this differential diagnosis as our patient had no facial dysmorphism or other physical findings of AHO.

The mechanism of new bone formation is also different in these two disorders - enchondral ossification in FOP and intramembranous ossification in POH. Kaplan and Shore have elaborated the genetic, molecular, histologic and clinical differences and have suggested clinical diagnostic criteria for these disorders [Table 2].

There are case reports of FOP and POH from the Indian subcontinent. This indicates that though these conditions are rare, one may encounter these cases in clinical practice. Hence it is important to note that early clinical diagnosis is a must. Excisional biopsy of these lesions for diagnosis leads to recurrence and increases the morbidity. Kaplan has reported that nearly 90% of FOP patients world-wide are misdiagnosed and 67% undergo dangerous and unnecessary diagnostic procedures that lead to permanent harm and lifelong disability in >50% of all affected individuals. Trauma accelerates the formation of new bone in these conditions. Minor trauma such as intramuscular immunizations, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises, falls or influenza-like viral illnesses can trigger painful new flare-ups of FOP leading to progressive heterotopic ossification. Corticosteroids and NSAIDs have been recommended for prophylaxis to prevent exacerbation during necessary invasive procedures.

Intravenous pamidronate injections have antiangiogenic property and inhibits proliferation of rapidly dividing cells. The recommended dose is 0.75-1.0 mg/kg/day for 3 days and every 3-4 months.

Unlike FOP, POH patients do not have an exaggerated inflammatory response to trauma. Case reports of biopsies,
surgical procedures in POH patients leading to recurrences and exacerbations have been reported. Gentle range of motion exercises, although has a limited role, is advocated to prevent contractures."}9

There is no definitive treatment for these conditions. Although the average life span of an FOP patient is 45 years, patients having survived longer have been reported. Mortality is mainly due to restrictive cardiopulmonary function. Natural history of POH cases is not well documented in literature. This could be due to the fact that this condition was identified as separate entity only since 1994 and long term followups are awaited.

These rare disorders can be encountered by general orthopedic surgeons mainly due to the bony lesions. History of skin rashes and lesions appearing superficially and involving deep structures, without skeletal or hormonal abnormalities with sheath like ossification on radiographs are diagnostic of POH. Waxing and waning lesions with congenital great toe abnormalities with temporal progression of bone lesions are pathognomonic of FOP.

These children should be on regular followup. Biopsy should never be done. Any other invasive procedures, if inevitable, should be undertaken under antiinflammatory cover. Gentle range of motion exercises and breathing exercises, although has a limited role, should be advised to prevent contractures and maintain pulmonary function.

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