*Case Report*

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# Fibrodyplasia Ossificans Progressiva (FOP)

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## Abstract

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic condition of abnormal ossifications of body tissues. It is an autosomal dominantly inherited condition or can be sporadic. It is a severe musculoskeletal disease characterized by extensive new bone formation within soft connective tissues and unique skeletal malformations of the big toes which represent a birth hallmark for the disease. Most of the isolated classic cases of FOP showed heterozygous mutation in the ACVR1 gene on chromosome 2q23 that encodes a bone morphogenetic protein BMP (ALK2).

**Keywords:** Fibrodysplasia ossificans progressiva; Autosomal; Heterozygous; Subcutaneous.

## Introduction

Children are usually active, playful and prone for injuries. Usually the injuries heal by themselves, but sometimes there are conditions of genetic origin which may make a child crippled with calcifications following trauma. Here we report a rare condition of heterotopic calcifications occurring over soft tissues in a girl which has puzzled her parents, family and her family physician. The condition known as Fibrodysplasia Ossificans Progressiva (FOP) is being presented here for rarity and precautions in avoiding trauma and surgery.

## Case report

A 6 year old girl presented to our OPD with complaint of swellings over body for last 2 years. The mother visited the Obstetrics & Gynecology department for advice for her next pregnancy and wishes to know whether her daughter condition is genetic. The girl was apparently well about 2 years back when she started having subcutaneous swellings over body, chest, spine and limbs. The patient presented with episodes (flare-ups) of soft tissue swellings which become painful; these episodes used to be triggered by trauma and occasionally ulcerate (Figure 1).

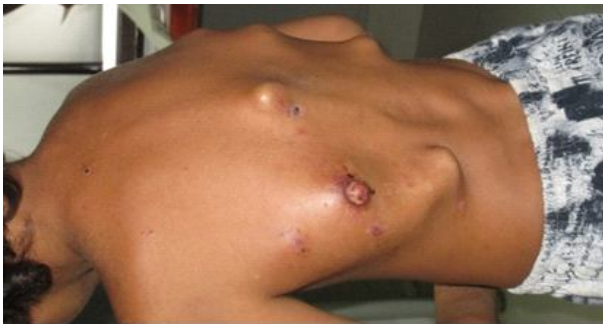

**Fig. 1:** Girl showing heterotopic calcifications with ulcerations.

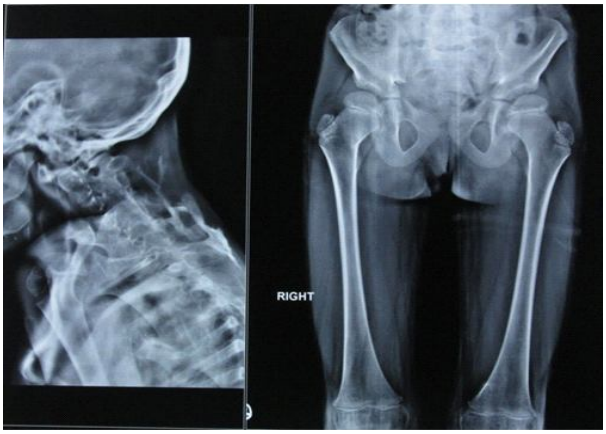


**Fig. 2:** Calcifications of tissue of chest wall and back of spine.

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Detail family history was not significant and there was no consanguinity. She weighed 17 KG and was 106 cm tall. She had bilateral hallux valgus deformity. She had multiple bony swellings as seen in figure 1. Rest of physical examination was within normal limits.

The hematological and biochemical investigations including Serum Calcium, phosphorus and alkaline phosphatase were within normal limit. The radiological investigations showed widespread calcifications of soft tissue over chest, spine, back and abdomen (Figure 2). The child was not subjected to biopsy as it is known to cause further calcifications.

She was counseled to avoid trauma, surgery or injections and advised for the genetic evaluation for mutations. However, the family was lost to follow up after the 2nd visit.

## Discussion

The condition is an Autosomal dominant with complete penetrance and having variable expression. Gonadal mosaicism has also been suggested. Most cases are *de novo* mutations. However, it can be caused by mutation in the bone morphogenetic protein type 1 receptor ACVR1 (OMIM 102576) gene located on chromosome 2q24.1. It is a rare, congenital disorder with onset in infancy or childhood. The disease manifests with progressive heterotopic ossification. The heterotopic ossifications are common and if appears in the spine or thoracic area, trunk deformity and severe respiratory problems may occur. In general, heterotopic ossification first occurs during infancy and later childhood, following subcutaneous swelling and sclerosis (flare-ups) often triggered by trauma, invasive wounds such as bruising, and surgery. They may also results in trismus. Additionally patients have hallux valgus deformity [1].

*Classic FOP* have congenital malformations of the great toe (short and malformed, often with only one phalanx) and progressive heterotopic ossification. Painful inflammatory swelling and subsequent calcification and ossification of fasciae, tendons and muscles, in tissues of neck, trunk, limbs, lead to progressive immobilization. The *FOP-plus* (classic defining features of FOP plus one or more atypical features) and *FOP variants* (major variations in one or both of the two classic defining features of FOP) have been described. All these cases had heterozygous ACVR1 missense mutations in conserved amino acids. Severe cases with widespread, rapidly progressive ectopic calcifications detected shortly after birth have been described. The disease needs to be distinguished from the familial ectopic ossification which is benign and without additional symptoms; and from myositis ossificans which occurs following trauma. X-ray in FOP shows soft tissue calcification, short broad femoral necks, and small and abnormal cervical vertebral bodies. Frequently there may be microdactyly or adactyly of thumbs and great toes. Cases from India have been reported and most have been screened positive for ACVR1 gene mutations [2, 3].

The cases have been reported from other places also [4]. Currently there is no effective treatment for the condition. Short course of prednisone could be used in extremely early symptomatic treatment of flare-ups that affect major joints, the jaw, or the submandibular area. A brief course of well-monitored narcotic analgesia in addition to the use of NSAIDs, COX-2 inhibitors or glucocorticoids could be used to manage painful flair-ups. However, there is no definitive treatment preventing the development of heterotropic ossifications in FOP till now [5]. Based on the findings about the central role of uninhibited activity of mutant ALK2 receptors in the heterotropic ossification, specific inhibitors of BMP receptors have been developed to block this uninhibited intracellular signaling. A specific small chemical inhibitor of BMP type I receptors called dorsomorphin is found to block the induction of osteoblastic differentiation *in vitro* in myoblasts expressing ALK2 (p.Arg206His) and ALK2 (p.Gly356Asp) [6].

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