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Fibrodysplasia Ossificans Progressiva (FOP): Watch the great toes!

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Abstract

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disorder and the most disabling condition of heterotopic (extraskeletal) ossification in humans. Extraskeletal bone formation associated with inflammation preceding the osseous conversion usually begins in the first decade, predominantly in the head, neck and shoulders. All patients have malformed great toes. Most patients have a spontaneous mutation of the *ACVR1* gene. We report a 17-year-old girl with malformed great toes who had her first episode of heterotopic ossification and impaired mobility of the left hip at the age of 13 years. No inflammatory fibroproliferative masses preceded the onset of heterotopic ossification. Radiographic studies demonstrated myositis ossificans, but failure to associate the great toe malformation with heterotopic ossification led to a failure to diagnose FOP. She underwent repeated and unnecessary operative procedures to remove a recurrent lesion. FOP was finally suspected when the great toe malformation was correlated with the trauma-induced heterotopic ossification. Genetic analysis confirmed the presence of the classic FOP mutation (*ACVR1* c.617G>A; R206H).

Conclusion—This case highlights the importance of examining the great toes in anyone with heterotopic ossification. The association of malformations of the great toe with heterotopic ossification in all cases of classic FOP will lead to prompt clinical diagnosis and the prevention of iatrogenic harm.

Keywords

fibrodysplasia ossificans progressiva (FOP); heterotopic ossification; ACVR1; ALK2

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Conflicts of interest: none

Introduction

Fibrodysplasia ossificans progressiva (FOP) (MIM #135100) is a rare genetic disorder of heterotopic (extraskeletal) ossification in which skeletal muscles and connective tissue such as aponeuroses, tendons and ligaments progressively ossify (2, 3, 13, 19). The phenotype of FOP includes two defining features: congenital malformation of the great toes, and progressive heterotopic ossification in characteristic anatomic patterns (11). Additional common, but more variable, features include proximal medial tibial osteochondromas, orthotopic fusions of the posterior elements of the cervical spine, broad short femoral necks, and conductive hearing loss (8). The disease typically spares the tongue, diaphragm and extraocular muscles. Smooth muscles and cardiac muscles are not involved (3, 19).

Children with FOP appear normal at birth except for a malformation of the great toes, present in all affected individuals (3, 13, 19, 26). Although the time of onset is variable, progressive heterotopic ossification usually begins in the first decade of life, but not uncommonly initiates early in the second decade (2, 3, 16, 20).

The point prevalence of FOP is approximately 1 in 2 million of population (24). There are no differences in the distribution of FOP according to gender, race, ethnic background, or geographic location (13). Nearly all cases arise by spontaneous mutations with no previous family history, but autosomal dominant inheritance has been observed (19, 24, 26). Penetrance is complete. In all known patients with classic features of FOP, a recurrent heterozygous single nucleotide missense mutation (c.617G>A, R206H) has been identified in the glycine-serine activation domain of activin receptor A, type I/activin-like kinase 2 *(ACVR1/ALK2)* gene, a bone morphogenetic protein (BMP) type I receptor (7, 10, 26).

The rate of disease progression is variable. Nevertheless, most patients are wheelchair-bound by the third decade of life and require lifelong assistance in performing activities of daily living (3, 12, 19, 20, 22). There are no established curative treatment options for FOP.

Here, we report a girl who was born with great toe malformations and first presented with heterotopic ossification of the lower limb at the age of 13 years.

Case Report

The patient was born to healthy, non-consanguineous parents following a full term pregnancy and vaginal delivery. At birth, malformed great toes were noted in the absence of other malformations. There was no family history of neurologic or musculoskeletal abnormalities.

At the age of nine years, she was injured by a wooden splint at the proximal left thigh. At the age of 13 years, restricted mobility of the left hip and an impaired gait were noted. She was seen by an orthopaedic specialist. Plain radiographs led to the diagnosis of myositis ossificans, but no association was made with the malformation of the great toes.

She underwent operative resection of the myositis ossificans lesion and received indomethacin for the following two weeks. The diagnosis of myositis ossificans was confirmed histologically. Postoperative radiographs (six weeks after surgery) showed minimal ossification of the left hip. One year later she presented with a severe local recurrence of heterotopic ossification, which was resected again. Following surgery, she was free of pain and with normal hip function for three months, but again developed an impaired gait and recurrence of restricted mobility in the left hip. A second local recurrence of heterotopic ossification was confirmed a year later. Again, the lesion was resected and recurred. Due to the recurrence of heterotopic ossification following surgery, the diagnosis of isolated myositis ossificans was challenged.

Subsequent radiographic evaluation revealed short first metatarsals with bilateral monophalangism of the great toes [Figure 1]. Osteochondromas, a common phenotypic feature in nearly all FOP patients (4), were noted at the distal femoral metaphyses and at the proximal medial tibial metaphyses [Figure 2]. Although the patient lacked the typical anatomic progression of heterotopic ossification characterized by soft tissue swelling in the neck and back (2), an earlier diagnosis of FOP might have been suspected if the heterotopic ossification of the left hip [Figure 3] had been correlated with the malformed great toes noticed already at birth. Together, these radiographic findings were indicative of FOP. The diagnosis of FOP was confirmed by DNA sequence analysis [as described in (26)], which revealed the presence of the classical FOP mutation in the *ACVR1* gene (c.617G>A) [Figure 4].

Discussion

Here we report a girl who was diagnosed with FOP at the age of 16 years, three years after the first appearance of heterotopic ossification. She had congenital malformations of the great toes but lacked the classic early stage lesions with preosseous tumor-like swellings of soft connective tissues during the first decade of life. Furthermore, she did not exhibit the typical temporal and spatial patterns of episodic heterotopic bone formation (11, 15, 25). When myositis ossificans of the left hip was noticed, a surgical intervention was performed. The occurrence of a second relapse led to diagnostic reconsideration. Progressive heterotopic ossification along with congenital malformation of the great toes, the two major clinical features that define classic FOP, led to a suspicion of FOP and to the definitive screening of the *ACVR1* gene.

FOP usually affects patients during their first decade of life and leads to episodes of inflammatory fibroproliferative masses in skeletal muscles and aponeuroses (11, 15, 25) that progress to form heterotopic bone. Episodes of heterotopic ossification continue during childhood and adolescence both spontaneously and in response to soft-tissue injury (2, 3, 8, 18). Viral infections also can trigger the onset of FOP lesions (21).

The diagnosis of FOP is often delayed because of the rarity of the condition and the failure to associate the tumor-like soft-tissue swellings with the congenital malformations of the great toes (14, 17). Approximately 87% of individuals with FOP have a delay in diagnosis (17). The presentation of rapidly appearing tender masses at typical anatomic locations

(head, neck, shoulders) along with the classic malformations of the great toes should allow accurate and prompt clinical diagnosis (17) that can be confirmed by genetic testing (15). Routine laboratory parameters in calcium-phosphate metabolism are usually normal.

There are no established curative treatment options for FOP. The disorder's rarity, variable severity, and fluctuating clinical course hamper evaluation of experimental therapies. To date, no controlled clinical trials have been conducted to assess the relative efficacy of any potential therapy (1). None of the frequently used medications such as glucocorticoids, nonsteroidal anti-inflammatory drugs, chemotherapy agents, radiation therapy or amino-bisphosphonates have altered the natural history of FOP (5). Although there are common physical features shared by every person with FOP, there are differences among individuals that may alter the potential benefits or risks of any medication prescribed. Hematopoietic stem cell transplantation will not prevent ectopic skeletogenesis in patients with FOP (9).

Current approaches to FOP treatment are palliative and symptom-modifying. Prevention of soft-tissue injury and protection against the influenza virus remain a hallmark of FOP management since both can provoke flare-ups (13, 21). Intramuscular injections, biopsies and surgical procedures as well as injuries with soft tissue trauma can also result in exacerbation and should be avoided (3,6, 18).

Identification of the pathways regulated by the *ACVR1* gene and functional analyses of the proteins involved are needed to understand the underlying pathophysiology of the disease, and may accelerate the development of targeted therapeutic approaches (7, 9, 10, 23, 27). Signal transduction inhibitors (STI) of BMP-signaling, such as orally-available Dorsomorphin, may play a powerful role in inhibiting heterotopic ossification in future. Extensive testing in animal models of FOP will be necessary to evaluate potential efficacy and safety (27).

Ideally, the most effective way to prevent the exacerbation of FOP is by prompt diagnosis of the condition and by subsequent avoidance of iatrogenic harm. Malformations of the great toes are present in all classically affected individuals. Recognition of the malformed great toes in association with either soft tissue swelling or heterotopic ossification will promptly secure the correct diagnosis of FOP that can subsequently be confirmed with definitive genetic testing (15, 26).

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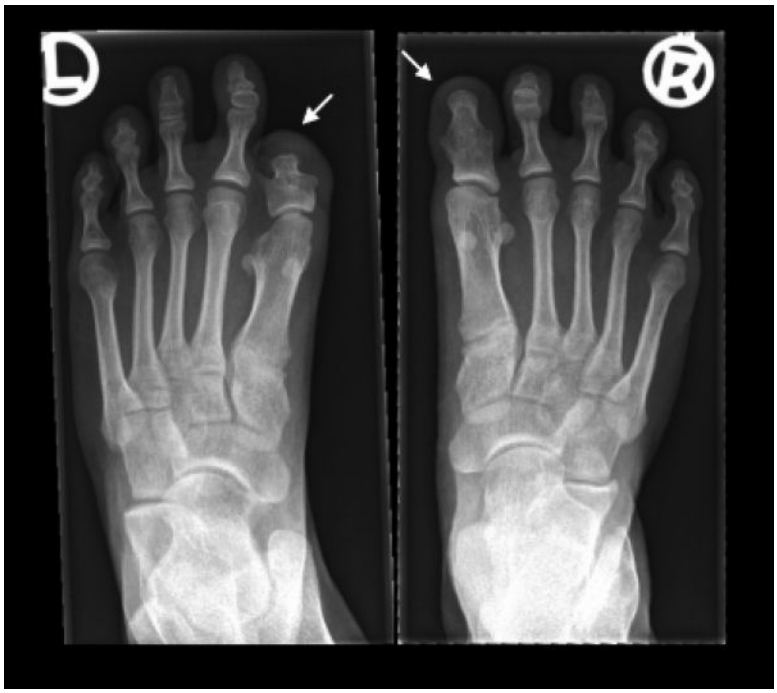

Figure 1.
Radiographic examination of the feet reveals malformations of the first metatarsals and monophalangism of both great toes.

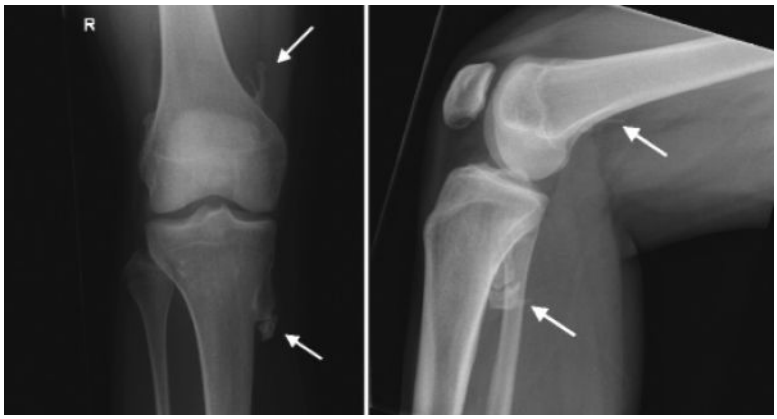

Figure 2.
Radiographic examination of the right knee shows osteochondromas of the distal femur and proximal tibia.

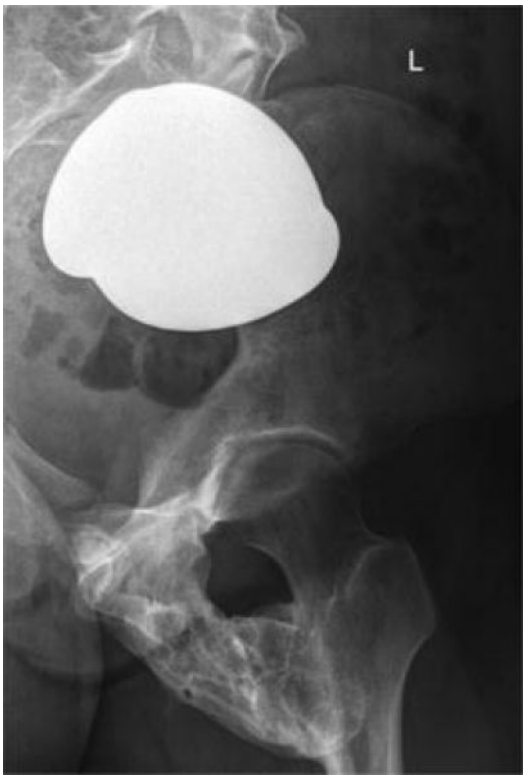

Figure 3.
Radiographic examination of the left hip exhibits extensive heterotopic ossification. The X-ray is taken after the third surgery and recurrence.

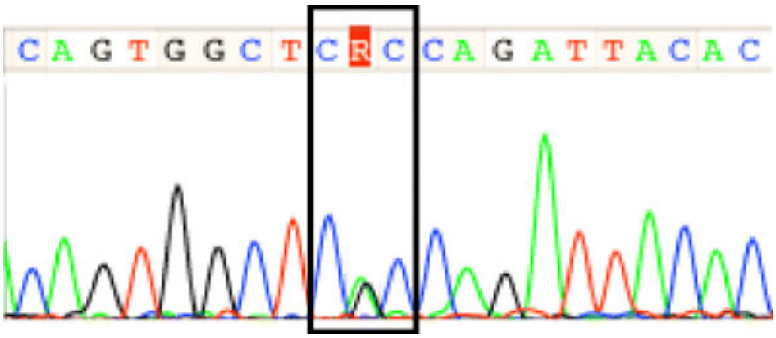

Figure 4.

Sequencing chromatogram of the patient, showing the classic FOP mutation within the *ACVR1* gene (c.617G>A; R206H). A G>A heterozygous substitution in nucleotide 617 of the protein-coding sequence of the ACVR1 gene was detected by direct DNA sequence analysis of genomic DNA. Nucleotides are represented by colored peaks in the electropherogram: A (green), C (blue), G (black), A (red). R = A/G. The mutation occurs in codon 206 (indicated by boxed area) and replaces arginine with histidine.