Fibrodysplasia Ossificans Progressiva

Abstract

Fibrodysplasia ossificans progressiva (FOP) is a genetic disease known by its progressive bone formation in soft tissues. It has various symptoms and clinical indications; however, there are two being the most definitive for diagnosis of FOP: congenital malformed great toes and progressive heterotopic ossification. Radiographic modalities such as diagnostic x-ray, magnetic resonance imaging (MRI), and computed tomography (CT) have been known to be helpful and assist in the diagnosis of this disease. While FOP is untreatable at this time, early diagnosis is important to avoid excessive harm from unnecessary procedures.

Introduction

FOP also known as myositis ossificans progressiva is a rare genetic disorder of progressive heterotopic ossification.\(^1\)\(^-\)\(^5\) It is one of the most disabling forms of extraskeletal ossification known to humans; FOP ultimately leads to the formation of a second skeleton outside the original one, imprisoning the body.\(^5\) This disease is characterized by progressive bone formation outside of the skeleton in soft tissues such as: subcutaneous fat, muscles, ligaments, tendons, fascia, and aponeuroses.\(^2\)\(^-\)\(^4\),\(^6\) It can be defined by two classical clinical features: malformation of the great toes; and progressive heterotopic ossication.\(^2\),\(^5\),\(^7\),\(^8\) At the molecular level, FOP is caused by a heterozygous activating mutation of the gene encoding activin receptor A type 1/ activin-like kinase 2 (ACVR1/ALK2) due to a continual single nucleotide substitution at a specific position on that gene. The mutation in this gene activates bone morphogenetic protein (BMP) signaling without the binding of ligands.\(^1\),\(^4\) This knowledge provides great significance for diagnostic reasons in FOP.\(^4\) This disease is very rare with an incidence of one in every two million individuals.\(^3\),\(^8\) There is no racial, ethnic, sex, or geographic predisposition.\(^1\),\(^8\)

Symptoms and Clinical Indications

Patients with FOP appear normal at birth except for the characteristic malformations of the great toes (see Figure 1), which are present in all classically affected individuals.\(^5\),\(^7\) During
the first decade of life, children with FOP develop painful and highly inflammatory soft tissue swellings (or flare ups) usually in the neck or back, that transform the soft connective tissues into an armor like encasement of bone.\textsuperscript{7,8} While some flare ups regress spontaneously, most undergo pathological metamorphosis into mature heterotopic bone.\textsuperscript{8} Ribbons, sheets, and plates of heterotopic bone replace skeletal muscles and connective tissues through a process of endochondral ossification that leads to permanent immobility.\textsuperscript{7} Most patients with FOP are confined to a wheelchair by their third decade of life and require lifelong assistance in performing activities of daily living.\textsuperscript{1,3,7}

Heterotopic ossification in FOP progresses in characteristic anatomical and temporal patterns that mimic patterns of normal embryonic skeletal formation.\textsuperscript{7} FOP involvement is typically seen first in the dorsal (cervical paraspinal muscles), axial, cranial, and proximal regions of the body and later spreads to the ventral, appendicular, caudal, and distal regions.\textsuperscript{3,5,7} However; several skeletal muscles including the diaphragm, tongue, and extra ocular muscles are unexplainably spared from FOP. Cardiac and smooth muscle are also not involved in the process of FOP.\textsuperscript{3,7} Clinical features of early lesional involvement in the axial regions are often different from those seen in the appendicular regions. Axial lesions may appear very rapidly, more rapidly than almost any neoplasm. In the affected regions, swelling is often mistaken for tumors, as large bulbous anomalies may appear on the neck and back; whereas in the limbs, the swelling is often diffuse and may be mistaken for acute thrombophlebitis, which is a complication that can occur in patients with FOP due to generalized immobility and associated venous stasis.\textsuperscript{7} These ectopic osseous masses form bridges that abnormally connect sections of the skeleton, and impair normal functions. The progressive course of the disease leads to several complications including torticollis, scoliosis, deformity to the thorax, and joint immobilization due to contractures of muscles periarticular ossifications.\textsuperscript{3}

The development of rapidly growing masses, usually in the neck or paravertebral region is caused by fibroblastic proliferation and ossification of subcutaneous fat, fascia, muscles, tendons, aponeuroses, and ligaments.\textsuperscript{7} These soft tissue masses are not malignant and can grow spontaneously, but trauma can accelerate the growth and calcifications\textsuperscript{2,6} Minor trauma such as intramuscular immunizations, mandibular blocks for dental work, muscle fatigue, and blunt muscle trauma from bumps, bruises, falls, or influenza-like illnesses can trigger painful new flare
ups of FOP leading to progressive heterotopic ossification. While disease flare ups in FOP are episodic, disability is cumulative.

Clinically, there are some peculiar congenital defects of hands and feet that can suggest FOP, affecting 79-100% of patients who have this disease. These include: malformed (short) great toes, hallux valgus, short thumbs, synostosis, and hypoplasia of the digital phalanges. Other characteristic anomalies associated with FOP include adactyly, ankylosis of the IP joint, fusion of the facet joints in the cervical spine, short broad femoral necks, dysplasia of the hips, proximal medial tibial osteochondromas, and pseudoexostosis. Additional clinical manifestations include painful swelling of the soft tissues with subsequent ossification and restriction of movement on affected areas. These lesions usually affect areas of the spine, shoulder, and pelvic girdle. These initial symptoms are painful and hard soft tissue swellings that will lead to ossification. Knowing these clinical signs of FOP provide an opportunity for early suspicion and diagnosis of this disease.

**Diagnostic Radiology**

FOP can be evaluated using plain films, CT scanning and MRI. However, both plain films and CT imaging are the standard references to assess heterotopic ossification maturity. Joint malformations, deformities of the great toes, and soft tissue ossification are the characteristic radiographic features of FOP. Early in the course of this illness, radiographs generally appear normal with the exception of the joint malformations and deformity of the great toes. However, extraskeletal calcifications can be visualized in x-ray images if the disease has advanced as such. Subsequently, a radiographic skeletal survey may be performed, and ectopic ossifications may be seen in the affected regions. Also, radiographic and bone scan findings can reveal normal modeling and remodeling of heterotopic bone. Interestingly, the incidence of fractures is not increased in patients with FOP, although fracture healing is characteristically accelerated in heterotopic bone. Bone scans are generally abnormal before heterotopic ossification is even detected by conventional radiographs. Diagnostic imaging is important and can be helpful in differential diagnosis of malignant tumors and myositis ossification, especially in the intermediate and late stages of myositis ossification.
CT plays a crucial role in diagnosing FOP and identifying heterotopic ossification. CT is sensitive to detect calcifications and is helpful in assisting in characterization, localization, and histopathologic sampling of the soft tissue calcifications.\textsuperscript{12,14} This modality also provides a more accurate anatomic location of a pre-osseous lesions, which appear as swelling and edema of the muscular fascial planes and swelling of muscular bundles.\textsuperscript{11} Use of thick slab transverse slice reformatting is helpful for demonstrating the extent CT provided, with more detailed information on the distribution, pattern, and extension of lesions.\textsuperscript{14} To expand the range of diagnostic examinations contrast-enhanced CT scan helps reveal heterotopic ossification. Thanks to volume rendering techniques and 3D image reconstructions it is possible to precisely determine the position of ossifications in relation to the vessels and muscle attachment, which is important before commencing with any procedures. CT scans permit precise assessment of ossifications and their location in relation to other internal organs and vessels. Furthermore, CT scans allow visualization of even small lesions that are not noticeable in traditional x-ray images.\textsuperscript{6}

**MRI**

MRI is mostly useful for more subtle edema which would not generally show on other modalities.\textsuperscript{9} Like contrast enhancement CT, contrast enhancement MRI can detect pre-osseous lesions of FOP and help in early diagnosis.\textsuperscript{12} While plain radiographs are usually sufficient for following progression of the disease, changes have been described on MRI at different stages of lesional progreassion.\textsuperscript{8} MRI findings of a pre-osseous lesion and a unique feature of the appearance of spread along the fascial planes are sufficient for accurate diagnosis of FOP in an early stage, despite the absence of ectopic ossification.\textsuperscript{11}

**MRI/CT Integration**

Integrated imaging can be helpful whenever an ossifying process may be expected, especially in the pelvis and/or around the hip joints. Imaging can assist in the identification of three degrees of heterotopic ossification: amorphous calcifications, immature calcifications, and mature calcifications.\textsuperscript{10} MRI alone allows easy recognition of mature ossifications; however, amorphous calcifications or immature ossification shows non specific signal and contrast enhancement features making the differential diagnosis between heterotopic ossification and other soft tissue diseases problematic. These soft tissue diseases may include: soft tissue
infection, abscess, and septic bursitis. This is where integrating CT with MRI can be helpful in distinguishing heterotopic ossification from other soft tissue processes.\textsuperscript{10}

CT can aid in identifying the ossifying process showing peculiar morphological characteristics related to the degree of maturity.\textsuperscript{10} When MRI reveals a lesion with an indeterminate aspect, CT can assist with the diagnosis of heterotopic ossification by detecting amorphous calcifications or immature ossification inside the lesion. Whenever a certain degree of uncertainty is present in defining the nature of the calcifying lesion, and the clinical setting allows a “wait and see” behavior, carefully timed CT imaging can be helpful. In cases of sterile heterotopic ossification, follow up CT imaging can show the initial formation of a trabecular structure which is a typical aspect of heterotopic ossification in evolution to maturity.\textsuperscript{10} Contrary to immature heterotopic ossification, mature heterotopic ossification is easily recognizable by MRI since its signal intensity is similar to that of normal cancellous bone outlined by cortex. When these features of heterotopic ossification appear on MRI, CT is not required, as it offers no additional information.\textsuperscript{10} Radiologists should be aware of the different aspects of heterotopic ossification provided by MRI. Correlation between MRI and CT features is critical for accurate diagnosis. When curious or uncertain findings are present, CT scan follow up is advised.\textsuperscript{10}

**Iatrogenic Harm**

Iatrogenic harm is defined as any harm caused to a patient from a medical exam or treatment. Evidence has shown that microtraumas, intramuscular injections, and surgical procedures can contribute to the initiation of FOP.\textsuperscript{3} Traumas, surgical procedures, biopsies, and intramuscle injections can originate or exacerbate the inflammatory process of FOP, which precedes heterotopic ossification.\textsuperscript{3} Most patients with FOP are often misdiagnosed as having other soft tissue diseases before heterotopic ossification begins.\textsuperscript{15} Unfortunately, children with FOP frequently undergo unnecessary and harmful diagnostic biopsies that intensify the effects of this disease.\textsuperscript{7,8} This can be dangerous at any anatomical site, but especially so in the neck or back where symmetric heterotopic ossification can lead to rapidly progressive spinal deformity and increase the chance of thoracic insufficiency syndrome (TIS). Dental therapy, as well, must involve diligent attention to prophylaxis of cavities and must avoid intramuscular injection of local anesthetics, especially mandibular blocks and stretching of the jaw.\textsuperscript{7}
Misdiagnosis often results in unnecessary and harmful biopsies/surgeries or both that worsen the condition, resulting in permanent harm in over 50% of cases.² One in every three cases is mistaken for cancer, leading to unnecessary biopsies and iatrogenic harm. Kitterman et al⁴ performed a study of 138 patients with FOP and 92 of them had a biopsy shortly after initial presentation of symptoms. This number is significantly high and could be detrimental as it can induce rapid ossification of the affected area because of the unnecessary iatrogenic harm.

**Misdiagnosis/Diagnosis**

Despite the distinct defining clinical features; FOP is poorly recognized and often diagnosed late or misdiagnosed.²,³ FOP has been highly misdiagnosed and has reached about 90% of affected individuals worldwide.²,⁵,⁸ One main concern about misdiagnosis is that patients with FOP may undergo invasive procedures, such as biopsies, which lead to accelerated ossification and unnecessary iatrogenic harm.²,¹⁵ In a study of 138 FOP patients from 25 countries, 87% were initially given incorrect diagnosis. There was an average gap of 4.1 years between onset of symptoms and the ultimate diagnosis of FOP, with a median number of 6 physicians being consulted before correct diagnosis. Sixty seven percent of patients had unnecessary invasive procedures increasing the risk of iatrogenic harm.⁵

Clinicians often fail to associate the rapidly developing soft tissue swellings that appear on the head, neck, and upper back with the malformed great toes.⁷,⁸ When such associations are not made, FOP is commonly misdiagnosed as aggressive juvenile fibromatosis (skin bumps varying in size that appear on hands, neck, scalp, ears, nose, genitals, or in joint creases) lymphoedema, or soft tissue sarcomas before heterotopic ossification begins.⁷,⁸,¹⁵ The soft tissue swellings may also be accompanied by fever, mistakenly suggestive of infectious origin. The rapid formation of soft tissue swellings has led many physicians to consider neoplasms as the underlying diagnosis, because large bulbous lesions may appear on the neck and back. However, most neoplasms tend to grow in a slowly progressive manner. By contrast, FOP lesions appear suddenly and then change size and shape rapidly, often in a matter of hours. On the other hand, in the limbs, as previously stated in this article, the swelling is usually diffuse and may be mistaken for acute thrombophlebitis.³

Before the formation of heterotopic ossification, these readily detectable congenital malformations provide an opportunity for early suspicion and diagnosis of FOP.³ Awareness of
the clinical features of FOP by all physicians, but particularly pediatricians, is essential for timely diagnosis.\textsuperscript{2,8} However, the absence of these skeletal anomalies does not exclude the diagnosis, their presence individually or in combination further strengthens the clinical diagnosis of FOP.\textsuperscript{3} It has been suggested that for any child with malformed great toes, especially those associated with soft tissue swellings, FOP should be suspected.\textsuperscript{2,7}

Genetic confirmation can follow. Definitive genetic testing of FOP is available and can confirm a diagnosis of FOP prior to the appearance of heterotopic ossification. Clinical suspicion of FOP can lead to early clinical diagnosis, confirmatory diagnostic genetic testing, and the avoidance of iatrogenic harm and perhaps the chance to slow down the disease’s progression.\textsuperscript{2,8}

**Morbidity/Mortality Rate**

Kaplan et al\textsuperscript{1} undertook a comprehensive study to determine the lifespan and cause of death in individuals with FOP. They reviewed the comprehensive mortality records from the International Fibrodysplasia Ossificans Progressiva Association from its inception in 1988-2006, and from the International Fibrodysplasia Ossificans Progressiva Clinic at the University of Pennsylvania from its inception in 1973-2006.\textsuperscript{1} These two patient registries comprise more than 90% of the known patients with FOP in the world. All patients were well known to at least one of the investigators and had a confirmed history of FOP based on the presence of the two classical clinical criteria: congenital malformations of the great toes and progressive heterotopic ossification in characteristic anatomic patterns. Medical records were reviewed to establish the dates of birth and death and the cause of death for each individual.\textsuperscript{1}

The results showed there were 60 reported deaths (30 male/30 female) in the FOP study population during the 33-year period (1973-2006). Data were sufficient to establish an unequivocal cause of death in 48 (80\%) of the 60 individuals. Median age at the time of death for these 48 patients (24 male/24 female) was 40 years (range 3-60 years), the same median age (40 years; range 3-77 years) at the time of death for all 60 patients. Kaplan-Meir survival curve estimate from the combined data set of 371 living and 60 deceased individuals with FOP revealed an estimated median life expectancy of 56 years. Substantial excess mortality in patients with FOP began at about the age of 30 years, with only an estimated 30\% of patients with FOP surviving to the age of 60 years.\textsuperscript{1}
In this study Kaplan et al\textsuperscript{1} found the most common causes of death in patients with FOP were: cardio respiratory failure from TIS (54%; 26 [12 male/14 female] individuals, with a median age of 42 years; range, 8-58 years); pneumonia (15% 7 [3 male/4 female] individuals, with a median age of 40 years; range, 28-60 years); complications of falls (11%; 5 [2 male/3 female] individuals with a median age of 41 years; range, 32-46 years). All deaths from falls were ascribed to complications of head injuries, a well-known morbidity factor in patients with FOP. Surprisingly, there were no reports of complete autopsies for any patients. Median age at the time of death was 39 years for those with no clearly established cause of death, 42 years for those who had cardio respiratory failure from TIS, 40 years for those who had pneumonia, and 41 years for those who died from a fall. Deaths from cardio respiratory failure and pneumonia occurred within a 50 year range and a 32 year range, respectively, while deaths from falls occurred in a narrower 14 year range (between 32-46 years) most likely reflecting an age range in which some patients were still able to walk or able to transfer with assistance, but were at greatest risk of falls from progressive instability.\textsuperscript{1}

Lastly, two major findings from the study performed by Kaplan et al\textsuperscript{1} included: (1) FOP is not only an extremely disabling disease but also a condition of considerably shortened life span, and (2) the most common cause of death in patients with FOP is cardio respiratory failure from TIS. TIS and severe restrictive lung disease occur in all individuals with FOP. Individuals who died of cardio respiratory failure had a terminal course that was similar to patients with severe pulmonary hypertension. Greater awareness of FOP among clinicians, earlier diagnosis of the condition, and educational programs to avoid iatrogenic harm strongly suggest that mortality data should be stable, and perhaps even improving. Importantly, recent discovery of the FOP gene has provided critical insight into the development of medications that have the potential to alter the natural history of this disorder.\textsuperscript{1} Currently, definitive treatments and cures are not yet available for FOP, but there are some symptomatic treatments.\textsuperscript{1,8}

**Case Study: Still turning into stone**

A 39-year-old male presented with generalized stiffness and severe body restriction. He was unable to move his joints and incapable of sitting, due to his spine being completely fixed as a board (see Figure 2). His onset of symptoms began at age 8 when he noticed a bony protrusion on the medial side of his right knee (see Figure 3). The young man underwent surgical removal
of the lesion, which had been diagnosed as osteochondroma (benign noncancerous tumor). Following the surgery the prominence reappeared accompanied with swelling on the adjacent side, as well as progressive emergence of painful mass-like lesions in his back and neck. His jaw became stiff, decreasing his intake of food and diminishing his oral hygiene. Over a 10-year period, this patient underwent multiple surgeries to excise ectopic bones and release joint contractures. A physical exam revealed bilateral malformation of the great toes, ossified tendons, muscles, ligaments and bony prominences palpable throughout the skin, along with a plethora of other indications. Radiographic evaluations showed widespread heterotopic ossification of paraspinal ligaments and fusion of vertebral bodies giving the vertebral column a “bamboo spine” appearance (see Figure 4), which is a characteristic of Ankylosing Spondylitis (AS). AS was the suspected diagnosis of which the patient was referred to the rheumatology center; however, the patient’s preservation of his SI joints was not taken into account, a clue that makes this diagnosis highly unlikely. In this case, it is obviously shown how failure to connect the classic clinical features of FOP and make an accurate diagnosis early can lead to a terrible collection of iatrogenic harm, increasing the detrimental effects of FOP. Due to the rarity and lack of clinical awareness, this patient unfortunately underwent multiple invasive procedures experiencing repetitive iatrogenic harm, which has tragically turned him into stone.\textsuperscript{5}

**Conclusion**

FOP is a rare and seriously disabling disease. Clinicians should be aware of the two distinct characteristic clinical features that strongly suggest and allow suspicion for the diagnosis of FOP when a patient is presented with these symptoms. Lacking the awareness of these clinical indications, patients generally are misdiagnosed and undergo invasive procedures causing iatrogenic harm, which is known to increase the progression of the disease. The case study presented is a resourceful compilation of proof of the harm misdiagnosis or latent diagnosis can cause. While there is currently no cure and the life span of these patients are short, there are steps that can be taken to assist in early diagnosis, and avoid situations that can only worsen this horrible disease.
References


Figure 2. The spine was totally fixed. The patient was “frozen” in the demonstrated posture. Image courtesy of: Taslimi R, Jafarpour S, Hassanpour N. FOP: still turning into stone. Clin Rheumatol. 2013Nov. doi: 10.1007/s10067-013-2417-x.
Figure 4. Widespread ossification of soft tissue (asterisks); ossification of the paraspinal ligaments and fusion of the vertebral bodies give rise to a “bamboo spine” appearance. Image courtesy of: Taslimi R, Jafarpour S, Hassanpour N. FOP: still turning into stone. Clin Rheumatol. 2013Nov. doi: 10.1007/s10067-013-2417-x.