

# Fibrodysplasia Ossificans Progressiva: A Case Report

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**Abstract:** *Fibrodysplasia ossificans progressiva (Munchmeyer's disease, stoneman's disease, Myositis Ossificans Progressiva) is a very rare autosomal dominant genetic connective tissue disease, but most patients have a new mutation with a progressive ectopic ossification of muscle (intramuscular) or perimuscular connective tissue such as tendons or joint capsules. The osseous masses produced will form bridges that abnormally connect sections of the skeleton, causing disfiguration and normal motor function inhibition. We reported a 20-year-old female with few hard nodules on the back region which initially present as a painful soft mass on the back region. As the pain subsided, the mass hardened and also appeared in other parts of her back. Individuals are born usually following an uneventful gestation but the great toe abnormalities are almost invariably present at birth. These include hallux valgus, shortened great toes and sharpening of the first metatarsal bone. In the first decade of life, intermittent episodes of painful soft tissue swellings occur which progress to become the hard, bony lesions that characterize the disease. We decided not to do a biopsy or excisional surgery to prevent flaring up of the disease. Early diagnosis prevents catastrophic diagnostic and treatment procedures. The progressive nature of this disease is difficult to stop but we should delay it as much as possible by preventing muscle trauma, giving disease modifying agent and long-term physiotherapy to counter further disabilities which will eventually develop.*

**Keywords:** Fibrodysplasia ossificans progressive, Ectopic ossification, Painful soft mass, Early diagnosis, Preventing muscle trauma

## 1. Introduction

Fibrodysplasia ossificans progressiva (FOP) is a very rare autosomal dominant genetic connective tissue disease with a progressive ectopic ossification of muscle (intramuscular) or perimuscular connective tissue such as tendons or joint capsules. The osseous masses produced will form bridges that abnormally connect sections of the skeleton, causing disfiguration and normal motor function inhibition. Mutations in the cytoplasmic GS domain of the cell surface receptor **Activin A receptor type I (ACVR1)** were recently identified as the genetic cause of the rare human disease FOP. The inheritance is autosomal dominant, but that most cases are sporadic. The mutation in ACVR1 leads to over-activation of the bone morphogenetic protein signalling pathway.

This condition usually begins in childhood, which clinically present as painful swelling of the muscles and connective tissue. As the swelling subsides, after approximately 6 months or more, ossification starts at some sites at the mean age of 4-5 years. Congenital malformations which are characteristically observed in the great toes at birth in almost all cases of FOP are the diagnostic hallmark. A child with FOP will eventually develop disabilities starting from abnormal gait and joint movement until they are confined to a wheel chair at the third decade of life. Mortality is usually caused by the restricted chest expansion which leads to respiratory failure.

We are reporting a 20-year-old female presented with few hard nodules on the back region which initially present as a painful soft mass on the back region. As the pain subsided, the mass hardened and also appeared in other parts of her back. Based on the clinical and radiological examination, FOP was the most possible diagnosis. We decided not to do a biopsy or excisional surgery to prevent flaring up of the disease.

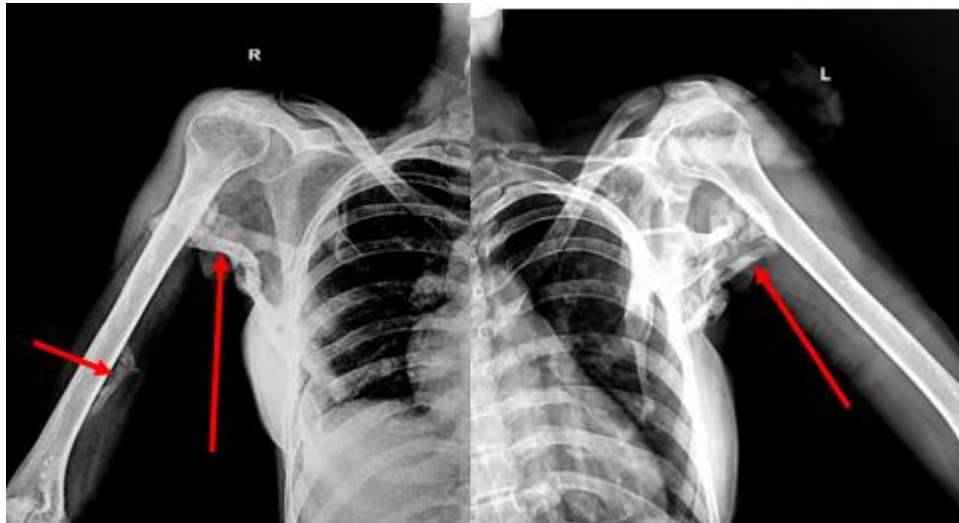
## 2. Case Report

An Asian female, the first child of healthy, non-consanguineous parents (father, 43 years; mother, 39 years old), was born in September 2000 by normal vaginal delivery after an uneventful full-term gestation was referred to our hospital with few soft nodules on back region which gradually becomes hard in consistency since 1 year, difficulty in movement of bilateral shoulder joint since 6 months associated with pain on attempt of movement, painful joint stiffness involving multiple joints of the body (especially bilateral shoulder joint, elbow joint, wrist joint) and recently developed difficulty in mouth opening. The parents do not have any obvious clinical skeletal malformation and a younger sister and two brothers of the patient is reported as normal.

## 3. Images



**Image 1:** In a 20 year old female, red arrow showing congenital hallux valgus deformity, hypertrophic nodule on back region and right arm



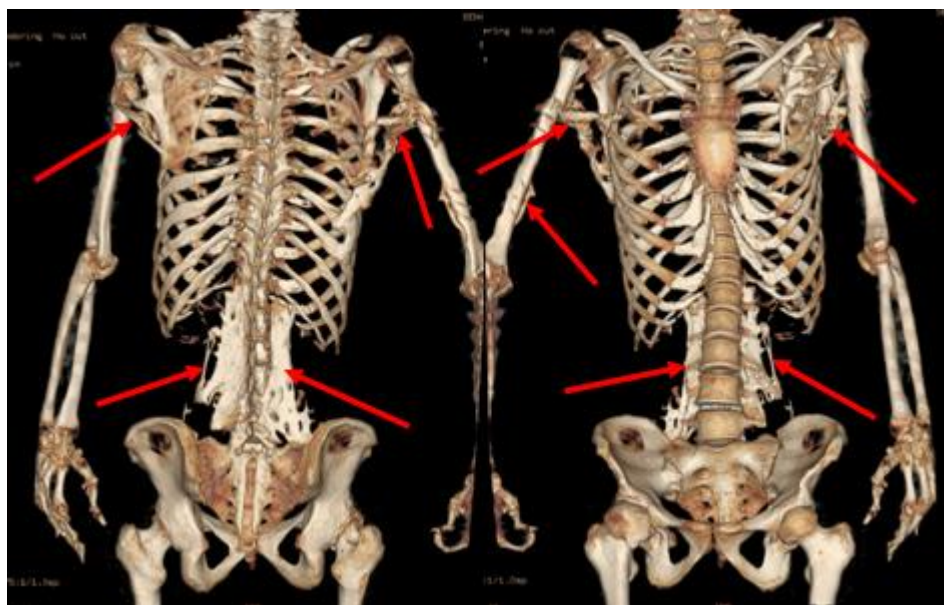
**Image 2:** In a X-ray of chest with bilateral arms of 20 years old female, red arrow showing heterotopic ossification involving left splenius muscle, bilateral subscapularis muscles, surrounding tendon of left shoulder joint, bilateral latissimus dorsi muscle and ossification of chondral cartilages on both side. There is fusion of heterotopic ossified tissue with adjacent scapula and few ribs



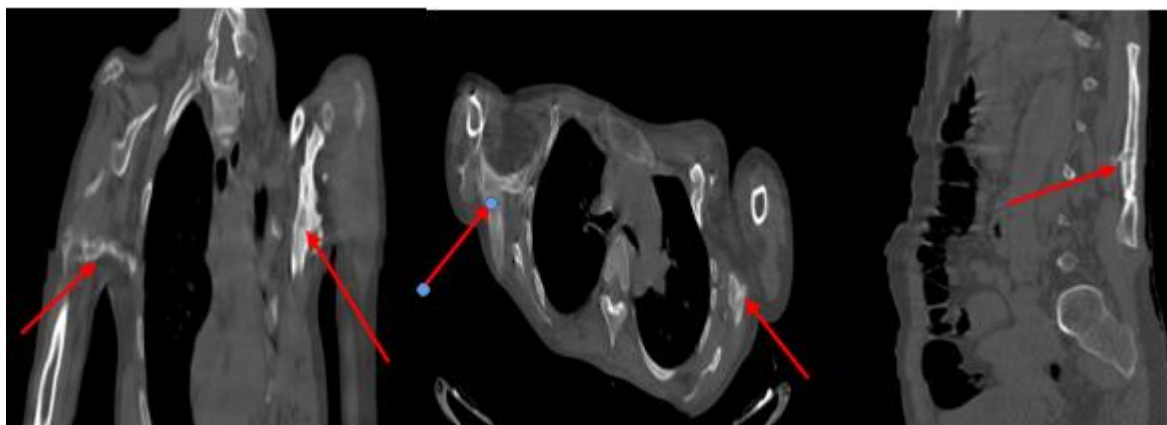
**Image 3:** In a X-ray of bilateral ankle with foot of 20 year old female showing abnormal 1<sup>st</sup> metatarsophalangeal angle consistent with hallux valgus



**Image 4:** In a X-ray of pelvis with both hips and thigh and knee with leg of 20 year old female, red arrow showing multiple loose zones involving shaft of femur and tibia bilaterally



**Image 5:** In a 3D reconstruction image of 20 year old female patient, red arrow showing heterotopic ossification



**Image 6:** In a CT scan of sagittal, axial and coronal images of 20 year old female patient showing heterotopic ossification

Based on the typical clinical and imaging findings for the FOP such as the congenital malformation of bilateral hallux valgus as a hallmark was enough for us to diagnose the patient as FOP without an unnecessary biopsy. We had informed the patient regarding the nature of this disease which may lead to disability and even death. We closely observed the development of the disease in this patient and prescribed the patient nonsteroid anti-inflammatory drugs. We carefully prevented flare-up by not doing any iatrogenic triggers such as biopsy, excisional surgery, or any intramuscular injection. We also educated the parents to be

more careful and not to accept intramuscular injection (such as for immunization) and prevent injury since these might also trigger a flare-up.

#### 4. Discussion

Awareness across a wide spectrum of practitioners is key to early diagnosis and prevention of injurious diagnostic or therapeutic interventions. Although it is a rare disease, the clinical features are unique and unambiguous and genetic testing has recently become available.



A biopsy is contraindicated due to risk of catastrophic explosive new bone formation. Disease flare-ups may be precipitated by trauma including intramuscular injections, lesion biopsies and nerve blocks especially around the temporomandibular joint.

There is presently no cure for the disease. A multitude of therapeutic agents have been tried without success but some selected agents like palovarotene currently undergoing clinical trials have shown some promise.

Currently analgesia with non-steroidal anti-inflammatory drugs and a short course of steroids started at the onset of a flare-up are the mainstay of treatment during "flare-ups."<sup>2</sup>

Support groups such as IFOPA offer up to date advice and invaluable information concerning the disease.

**History and Prevalence**

Guy patin first described this entity (FOP) in 1648 as a case who "turned to wood". Prevalence is approximately 1/2.000.000 and over 700 cases have been reported in the world literature to date. FOP is a rare and disabling genetic condition characterized by:

- 1) Congenital malformation of the great toes and
- 2) Initial soft tissue swelling which spontaneously subsides, but leads to progressive heterotrophic ossification in specific anatomic patterns. The patients are confined to a wheel chair by the third decade.

**Clinical and Radiological Findings:**

Our case also started with this pattern. One year before, spontaneous swelling occurred in the back region. The radiological evidence of ectopic ossification is not usually detected until 6 months (sometimes up to one year). Bony bridge causes skeletal contracture (the lumps decrease in size after a few weeks, but the inflammatory tissue which is replaced first by cartilage and then by bone causes restricted joint movement)

In our case, the onset of symptoms with the typical anatomic pattern occurred at twenty year of age and spread at the subsequent year. Ossification in the radiologic exam and CT scan was detected. In addition, ossification of thoracic soft tissue causes restrictive pulmonary disease. As a result of this event, the patient will be predisposed to chest infection and consequently death in the third or fourth decade prevalently.

**Diagnosis:**

FOP should be diagnosed as early as possible based on history, clinical and imaging findings. The guide of diagnosis is bilateral anomaly of the great toes present from birth, reported almost in 100% of the patients. Therefore, clinical and radiological examination is important.

Roentgenogram aid demonstrates minor osseous dysmorphism such as hallux valgus, clinodactyly, microdactyly, phalangeal shortening, metacarpal and metatarsal shortening, shallow acetabulum, short widened femoral neck, medial cortex thickening of the tibia, long small vertebra, fusion and segmentation of the spine,

increased incidence of exostosis and long bone metaphyseal widening.

When the ectopic ossification occurs, in plane radiography, bony bridges running from the bones to the muscles spreading also along the fascial planes are seen.

**CT Scan**

In early disease before ossification, CT demonstrates fascia plane edema and swelling and mesenchymal mass like lesion in the muscle that moderately enhances with IV contrast. In late disease after ossification and calcification, these findings could be seen in the muscles, fascia and connective tissue, especially near the bones.

**Differential Diagnosis**

In the early phase, these patients may be misdiagnosed with malignant tumors especially sarcoma, rhabdomyosarcoma, aggressive fibromatosis, post traumatic myositis, lymphadenopathy, TB, scleroderma, dermatomyositis of childhood, RA, nodular fasciitis and Klippel-Feil syndrome.

In the late phase, the differential diagnoses are osteosarcoma, progressive osseous heteroplasia (POH), Albright hereditary osteodystrophy (AHO), osteoma cutis, ankylosing spondylitis, Still's disease, calcinosis interstitialis ossificans, Weber-Christian disease, pseudohypoparathyroidism, hypervitaminosis D, traumatic myositis ossificans and multiple exostosis.

FOP has many differential diagnoses. This disease may be misdiagnosed in the early stage most importantly and most commonly as sarcoma and other cancers, aggressive fibromatosis and vascular masses.

In summary, in review of case series and case reports and articles of diagnostic errors, and our case, we conclude that FOP is often misdiagnosed and the correct diagnosis happens very late. Early diagnosis prevents catastrophic harmful diagnostic and treatment procedures. For early correct diagnosis we propose:

- 1) Family physicians, paediatricians and radiologists should be aware of the early feature of FOP before development of heterotrophic ossification. The most important and best key is great toe malformation which must be noticed clinically and radiologically as an early pattern of involvement.
- 2) Early clinical and radiological diagnosis must lead to an MRI study or molecular genetic study, which depends on the accessibility and cost. Both of them proved the diagnosis.

**Table 1: Classes of medications**

Class	Description	Drugs
I	Have been widely used to control symptoms of the acute flare-up in FOP, with anecdotal reports of favorable clinical results and generally minimal side effects	Short-term use of high-dose corticosteroids, and use of nonsteroidal anti-inflammatory drugs including the new anti-inflammatory and anti-angiogenic cox-2 inhibitors
II	Have a theoretical application to FOP, are approved for the treatment	Leukotriene inhibitors, mast cell stabilizers, and aminobisphosphonates

	of other disorders, and have limited and well-described effects.	(Pamidronate; Zoledronate)
III	Investigational new drugs	Signal transduction inhibitors, monoclonal antibodies targeting ACVR1, and retinoic acid receptor gamma agonists (presently under development)

## 5. Conclusion

FOP is an extremely rare disease and often misdiagnosed thus the correct diagnosis sometimes happens late. General practitioners, paediatricians, orthopaedics as well as radiologists should be aware of the early feature of FOP. Early diagnosis prevents catastrophic harmful diagnostic and treatment procedures. The progressive nature of this disease is difficult to stop but we should delay it as much as possible by preventing muscle trauma, giving disease modifying agent and long-term physiotherapy to counter further disabilities which will eventually develop.

## References

- [1] KA Bhagwat, R Khanapur, VM Patil, HS Gill Stone man syndrome: a case report and review of literature J Pub Health Med Res, 2 (2) (2014), pp. 47-51
- [2] J Hashemi, A Shahfarhat, A Beheshtian Fibrodysplasia ossificans progressiva: report of a case and review of articles Iran J Radiol, 8 (2) (2011), pp. 113-117
- [3] AF Kamal, R Novriansyah, Prabowo Y Rahyussalim, NC Siregar Fibrodysplasia ossificans progressiva: difficulty in diagnosis and management. A case report and literature review JOrthop Case Report., 5 (1) (2015), pp. 26-30
- [4] EM Shore, MQ Xu, GJ Feldman, DA Fenstermacher, TJ Cho, IH Choi, *et al* .A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressive Nat Genet, 38 (2006), pp. 525-527
- [5] M Puszczewicz, A Kołczewska, I Zimmermann-Górska, D Majewski, A Ogrodowicz Fibrodysplasia ossificans progressiva: case report Pol Arch Med Wewn, 117 (1-2) (2007), pp. 53-56