



Fibrodysplasia Ossificans Progressiva in an Adult Indian Male

Yetişkin Bir Hintli Erkekde Progresif Ossifikan Fibrodizplazi

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ABSTRACT

Following its first description by Guy Patin in 1692 as a disease that turned a woman into wood, Fibrodysplasia Ossificans Progressiva has maintained its low profile that too mainly in textbooks and rarely does one encounter a live walking individual affected by this entity. The hall marks of this deadly disease are the short size of only the big toes and uninhibited progressive ossification of soft tissues. It can have a sporadic occurrence or may even be inherited through autosomal dominant pattern and has a wide range of expression. A wrong clinical diagnosis exposes the patient to unnecessary surgical excision and even harmful radiotherapy.

Hence a case of Fibrodysplasia Ossificans Progressiva in an adult Indian male is being reported here for the benefit of one and all.

Key Words: Munchmeyer's disease, Fibrodysplasia Ossificans Progressiva, Calcifications, Short Big toes, Paraspinal ossification, Microdactyly, Synphalangism.

ÖZET

İlk olarak 1692 yılında Guy Patin tarafından kadınları ahşaba dönüştüren hastalık olarak tanımlanmasını takiben Progresif Ossifikan Fibrodizplazi, bir çok kitapta genelde olarak düşük bir profil muhafaza etmiş ve nadiren bu durum tarafından etkilenen yaşayan bireylere rastlanmıştır. Bu ölümcül hastalığın işaretleri sadece büyük ayak baş parmağının kısalığı ve yumuşak dokuların engellenemeyen progresif kemikleşmesidir. Sporadik oluşuma sahip olabilir, hatta otozomal dominant pattern yoluyla kalıtılabilir ve geniş bir ifade yelpazesine sahip olabilir. Yanlış bir klinik tanı hastayı gereksiz cerrahi eksizyona ve hatta zararlı radyoterapiye maruz bırakır. Yetişkin Hintli erkeklerdeki Progresif Ossifikan Fibrodizplazi vakasına bağlı durum, herkesin yararı için burada rapor edilmiştir.

Anahtar Kelimeler: Münchmeyer hastalığı, Progresif Ossifikan Fibrodizplazi, Kalsifikasyonlar, Kısa, büyük ayak baş parmağı, Paraspinal kemikleşme, Mikrodaktili; Simfalangizm.

INTRODUCTION

FibrodysplasiaOssificansProgressiva (FOP) is a rare progressive diseasehallmarked byexcessive calcifications or ossification of soft tissues. Its sporadic (95%) form is more common than the autosomal dominant (5%) variant. The reported

incidence is 0.5 per million, but not more than 700 confirmed cases are known globally. This case report emphasizes the diagnostic imaging findings, in presence of which biopsy is totally contraindicated as it may further deteriorate the patient.

CASE REPORT

An Indian male of around 39 years of age, presented with multiple swellings over the back which he had been noticing for the past 5 years. The swellings over the back were insidious in onset, progressive in nature, painless. He had a bowed posture as his spinal movements were restricted. There was no history of any significant trauma. Laboratory investigations were essentially normal. On examination, there were multiple, non-tender, hard (bone like) swellings varying in size from 3 cm to over 12 cm. The swellings had indistinct edges and there were no signs of active inflammation. What was unique in this patient was that the great toes of both feet very significantly and symmetrically short.

As shown in Figure 1A, clinical photograph revealed multiple swellings over the back. Figure 1-B demonstrates coronal CT reconstruction showing sheets of ossification in paravertebral soft tissues. As in Ultrasound of the swellings (figure 2A) shows hyperechoic foci within the soft tissues over the back associated with posterior acoustic shadowing suggestive of dense calcification / ossification inside it. The Axial CT image (figure 2B) better depicts the location and extent of these ossifications.

Clinical photograph (figure 2C) showing small size of the great toe-a characteristic of this entity. Plain Radiograph (figure 2D) of left foot showing the small sized great toe. Based upon these classical imaging findings a diagnosis of FOP was put forth.

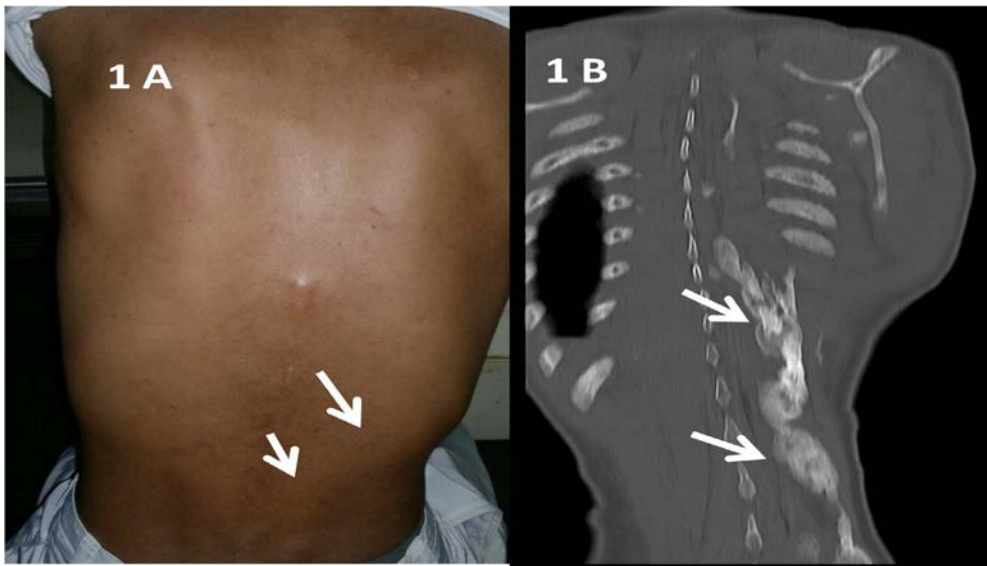


Figure 1.

1-A. Clinical photograph showing multiple swellings over the back.

1-B. Coronal CT reconstruction showing sheets of ossification in paravertebral soft tissues.

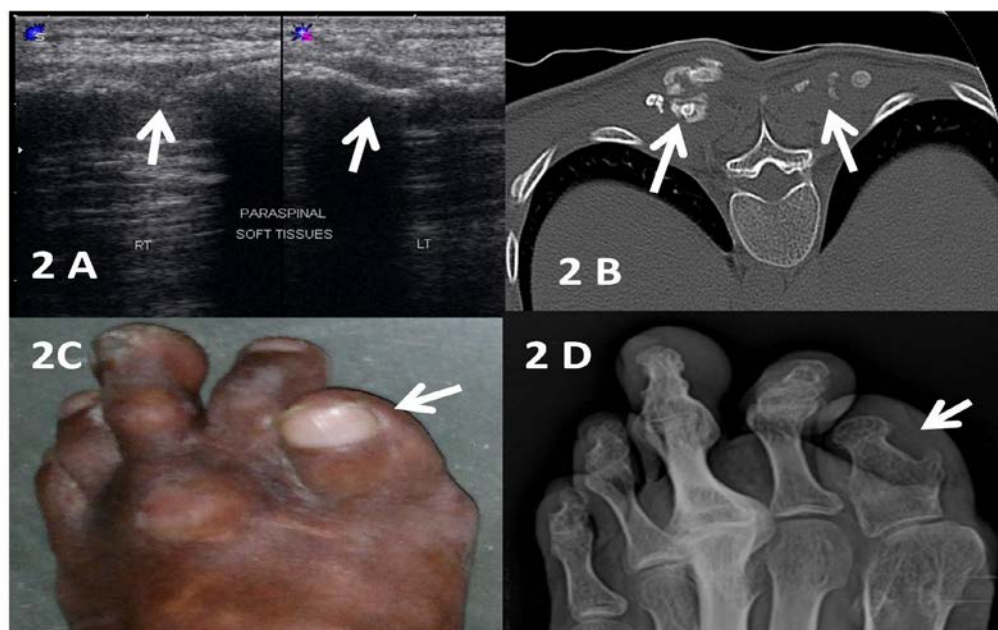


Figure 2.

2A. Ultrasound of the swellings showing hyperechoic foci within it associated with posterior acoustic shadowing suggestive of dense calcification / ossification inside it.

2B. Axial CT image better depicts the location and extent of these ossifications.

2C. Clinical photograph showing small size of the great toe-a characteristic of this entity.

2D. Plain Radiograph of left foot showing the small sized great toe.

DISCUSSION

The original description of this entity is credited to Guy Patin who in 1692 wrote about the woman who turned to wood¹. Later in 1869, Munchmeyer first gave a comprehensive description of the disease with an account of 12 cases-hence the eponym 'Munchmeyer's disease'. The name was officially modified to Fibrodysplasia ossificans progressiva in the 1970s by in order to acknowledge that other soft (or fibrous) tissues in addition to muscle (for example tendons and ligaments) are replaced by bone².

Clinical and Imaging findings are sufficient to reach the final diagnosis. Clinical criteria include

acute episodes of swellings that flare up usually after minor trauma or surgery in males or females usually in the first or second decade of life. Sites of primary involvement include the neck (50%), dorsal

paraspinal region (30%), head (10%), or limbs (10%)^{3,4}.

The other very distinct clinical features for FOP is the congenital malformation of the great toes, with shortening of the first metatarsal and proximal phalanx which is the earliest phenotypic feature of FOP and is present in nearly all the affected individuals at birth⁵.

There is early onset of endochondral bone formation with ankylosis of temporo-mandibular joint (in which case the patient dies of starvation) & rib cage (in which case the patient dies of respiratory distress)⁵. Remissions and exacerbations are characteristic.

The heterotopic bone formation progresses in specific well defined pattern & mimics normal embryonic skeletal formation i.e. follows dorso-ventral, axio-appendicular, cranio-caudal and proximo-distal gradients. Heart, diaphragm, larynx, tongue, sphincter and eye muscles are not

involved⁴. Laboratory and haematological work-up is essentially normal.

Radiological criteria include microdactyly of the great toe associated with synphalangism, heterotopic ossification of soft tissue with temporal progression of osteogenesis in characteristic anatomic patterns^{6,7}. Other associations include synostosis of phalanges (Monophalangitic), exostoses, broad neck of femur and malformed cervical vertebrae⁸.

All patients with classic clinical features of FOP (great toe malformations and progressive heterotopic ossification) have previously been found to carry the same heterozygous mutation (c.617G4A; p.R206H) in the glycine and serine residue (GS) activation domain of activin A type I receptor/activin-like kinase 2 (ACVR1/ALK2), a bone morphogenetic protein (BMP) type I receptor. All patients examined have heterozygous ACVR1 missense mutations in conserved amino acids.

No specific biological or genetic markers are available to date. BMP4 (Bone Morphogenetic Protein type 4) Type 1 receptor ACVR1 has been found in some FOP patients but can't be reliably used routinely. Genetic nature of the disease is difficult to establish since 95% cases are sporadic, thereby suggesting a high rate of de novo mutations. Autosomal dominant inheritance in 5% cases has been observed and is supported by observations of 2 to 3 successive affected generations^{9,10}.

The deadliest health impact of FOP is that it slowly and steadily impairs individual's ability to eat as well as to breathe, until finally the patients succumb to it.

Surgical removal of heterotopic bone formation or muscle biopsy, given its potential risk of inducing heterotopic osteogenesis, is strictly contraindicated. All invasive procedures should therefore be avoided^{9,10}.

There is no known effective treatment for FOP. Reviews have shown that since any surgical or even anaesthetic intervention incites reactive,

heterotopic new bone formation and exacerbation of the soft tissue ossifications if removed, management includes mainly supportive and preventive care. The patients are advised to avoid any sort of soft tissue injury or any intramuscular injections. Short term steroids within 48 hours following an acute flare-up to suppress or abort the early lymphocytic infiltration into skeletal muscle has been tried with some results but long term use is potentially deleterious^{9,10,11}.

Average life span of an individual is reduced to about 45 years. Risk of transmitting FOP genetic defect to next generation is 50% in theory. Risk is higher if one of the parents exhibits classic malformation of the great toe. Transmission is through autosomal dominant inheritance pattern. Rate of de novo mutations is particularly high being 95%¹².

Symptomatic treatment includes short term Prednisone within 48 hours following an acute flare-up to suppress or abort the early lymphocytic infiltration into skeletal muscle. Long-term use of steroids is deleterious. Drugs under trials are IV Etidronate, Interferon, Squalamine, Genetically engineered Anti-Noggin agents.

There is a definitive role of Genetic Counselling in FOP; as the risk of transmitting FOP genetic defect to next generation is 50% in theory. Risk is higher if one of the parents exhibits classic malformation of the great toe. Rate of de novo mutations is particularly high (95%). Prenatal testing is yet not available.

There have been instances of FOP being misdiagnosed on histopathology as tumors for which radiotherapy has been given. The diagnosis of this rare disease needs to be made as early as possible to avoid any inadvertent treatment like radiotherapy or surgical interventions like removal of heterotopic bone formations so as to prevent rapid descent on the path to death.

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