

Fibrodysplasia Ossificans Progressiva in a Four year Old Child

Mayur Kardile¹, Sidhartha Nayak¹, Nagaraja H S¹, Abani Kanta Mishra¹

Abstract

Introduction: Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disorder characterized by bone formation within muscles tendons and ligaments. It has an incidence of one in two million. We hereby report a case of FOP in a four year male child from a tribal family in Orissa.

Case Report: 4 yr old male child presented with gradual development of stiffness of neck and hard nodules on his body for which his parents had sought all sort of indigenous treatment and manipulations by traditional bone setters. Patient returned to our hospital at the age of four years with widespread ossification and stiffness of neck, shoulders and back. He also had upper tibial osteochondromas and scalp nodules and valgus deformity of bilateral great toes. A diagnosis of FOP was made on clinical and radiological examination.

Conclusion: Though rare, diagnosis of Myositis ossificans progressiva should be considered in a child with heterotopic bone formation and valgus deformities of great toes. Being a rare condition, treatment guidelines are not clear and this condition need further research.

Keywords: Fibrodysplasia ossificans Progressiva, tibial osteochondromas, scalp nodules.

Introduction

Fibrodysplasia ossificans Progressiva (FOP) is also known as Myositis ossificans progressiva, Stone man disease, Munchmeyer's disease. FOP is an extremely rare and most crippling form of heterotopic ossification in humans with an incidence of 1 in 2 millions [1]. Kitterman et al reported that it takes atleast six physician evaluations to reach the diagnosis and 90% of these individuals will have received some wrong or hazardous treatment before appropriate diagnosis [2]. We hereby report a case of FOP in a 4 year old boy coming from tribal family in Orissa. The diagnosis of this patient was delayed due as the parents tried all sorts of indigenous medications and even manipulations by traditional bonesetters whose influence has been deep rooted in minds of the tribal population in this part of the country.

¹Dept Of Orthopedics, MKCG Medical College, Berhampur, Orissa 760004

Address of Correspondence

Dr Mayur Kardile
PGT, Dept Of Orthopedics, MKCG Medical College, Berhampur, Orissa 760004
Address: Room no 79, PG Hostel 2, MKCG Medical College Campus, Berhampur, Orissa 760004
Mayur_kardile@hotmail.com

Case Report

Our patients was a four year old boy who presented with chief complains of stiffness of neck, decreased movements in bilateral shoulders and had bony hard swellings in his back. Patient had hypoplastic great toes with valgus deformity. At the age of three years, his parents noticed that he had stiffness of neck and had developed nodules at his scalp, which gradually subsided without any treatment. Coming from a tribal background, parents consulted many indigenous medicine practitioners and child was subjected to repeated manipulations of the neck by traditional bone setters. Child developed painful swellings on his back a day following such manipulations. These swellings hardened over a period of few days and the child developed stiffness of spine. He was subjected to further manipulations and gradually developed stiffness of bilateral shoulders and left elbow. On examination, the patient had bony hard swellings in cervico-thoraco-lumbar spine, bilateral axillae and left elbow and left 3rd costochondral junction along with hypoplasia and valgus deformity of great toes (Fig. 1a,b). His hearing was normal.

Radiographs revealed hallux valgus and hypoplasia of proximal phalanges of great toes with short widened first metacarpals bilaterally (Fig. 2a), ectopic ossifications in





Fig 1-a Frontal view of the patient showing ankylosis of bilateral shoulders and left elbow with bony swelling at left 3rd costo chondral junction. b-Photograph showing multiple bony swellings on back and paraspinous area.

bilateral axillary region (Fig. 2b,c) extensive ossification overlying both side of the neck and in the Para vertebral tissues in dorsolumbar area (Fig. 2d,e) broad femoral necks (Fig. 2f) and bilateral symmetrical proximal medial tibia osteochondromas (Fig. 2g). Diagnosis of FOP was made in basis of all these radiological and clinical findings

Discussion

Our case once again highlights the deleterious effects of trauma in the form of manipulations and massage that can aggravate the ossification process in case of FOP. Trauma as trivial as intramuscular injections, mandibular block during dental procedures, muscle fatigue, muscle trauma due to bumps, falls and influenza like illness can aggravate the process of heterotopic ossification in these patients [1]. A sporadic mutation in the gene encoding bone morphogenetic protein (BMP) activin receptor type IA/activin-like kinase 2 (ACVR1/ALK2) located on chromosome 2q23-24 region has been identified as the main genetic abnormality in FOP [1,3]. Recently, additional mutations have been identified in the GS-domain and kinase domain of ACVR1 in individuals with

atypical forms of FOP [1]. Inheritance is in autosomal dominant manner but less than 10 cases of familial transmission have been reported [1]. In vitro experiments with use of cells derived from patients with fibrodysplasia ossificans progressiva show a markedly attenuated response of Noggin (BMP-4 antagonist) expression to BMP4 stimulation. An inadequate BMP-antagonist response following soft-tissue trauma would permit the rapid expansion of a BMP4 morphogenetic gradient in a patient with fibrodysplasia ossificans progressiva and could explain the explosive bone induction seen during flare-ups [4]. A new research by Quen et al interpreted that in addition to the above, the mutation also induces chondrogenesis by signaling in a BMP independent and BMP responsive manner [5]. This mutation may also sensitize mesenchymal cells to BMP-induced osteoblast differentiation, and stimulates new bone formation [6].

Individuals with FOP are normal at birth except for having valgus deformity of great toes. Heterotopic ossification is heralded by the rapid appearance of large painful swellings of highly vascular fibro-proliferative tissue involving tendons, ligaments, fascia, and skeletal muscle. These preosseous swellings progress along a pathway of endochondral ossification to form mature heterotopic bone. Heterotopic ossification in FOP progresses in specific anatomic and temporal patterns. Typically, the dorsal, axial, cranial, and proximal regions of the body are involved early, and the ventral, appendicular, caudal, and distal regions are involved later [1,7]. Conductive deafness occurs in 50% of these individuals [1,8]. Several skeletal muscles including the diaphragm, tongue, and extra-ocular muscles are spared from FOP. Cardiac muscle and smooth muscle are spared from heterotopic ossification [1]. Histological examination of early FOP lesions reveals an intense perivascular lymphocytic infiltrate followed by lymphocyte-associated death of skeletal muscle and robust development of fibro proliferative tissue with

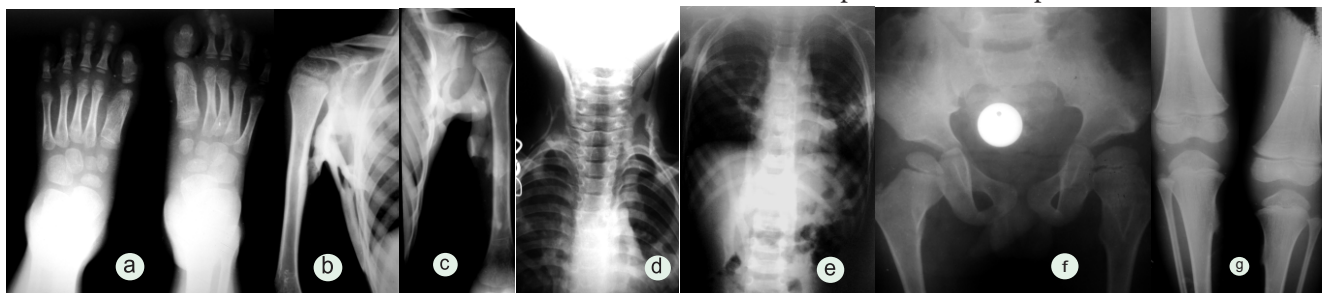


Fig 2. Radiological Findings. a- bilateral hallux valgus and hypoplastic proximal phalanx of great toe with short and widened first metatarsal. b,c-Ectopic ossification in both axilla. d-Extensive ossification on either sides of cervical spine. e-Extensive ossification in paravertebral tissues in dorsolumbar area. f-Bilateral broad femoral neck. g-Proximal medial tibial osteochondromas

extensive neovascularity and mast cell infiltration. Tissues from FOP lesions at later stages of maturation exhibit characteristic features of endochondral ossification that support ectopic hematopoiesis [5]. However biopsies from these lesions should be avoided as it aggravates the ossification process [1]. Definitive genetic testing for FOP is now available however is not essential for diagnosis which is purely clinical [1]. This condition needs to be differentiated from Progressive osseous hyperplasia (POH), which presents with heterotopic ossification. POH is distinguished from FOP by the absence of congenital skeletal malformations, the absence of predictable regional patterns of heterotopic ossification, the pre-dominance of intramembranous rather than endochondral ossification, and the presence of heterotopic ossification in skin and subcutaneous fat—findings never seen in FOP [9]. There is a high association of scalp nodules in patients with FOP. Piram et al noted 40% incidence of scalp nodules in patients of FOP in their retrospective study on 43 patients [10]. Proximal tibial osteochondromas are a common phenotypic feature of fibrodysplasia ossificans progressiva. Deirmengian et al reported 90% incidence of upper tibial osteochondromas in a study on 96 patients [11]. Our case had this particular finding and cases with combined heterotrophic ossifications with osteochondromas should be considered for this diagnosis. Based on these typical and commonly found characteristics, Mutlu et al described diagnostic criterias for FOP [12]. The Great toe malformations along with rapidly developing and waxing/waning soft tissue lesions over head, neck and upper back are characteristics for FOP. Kaplan et al commented that failure to make such association is the commonest cause of misdiagnosis of FOP [13]. Misdiagnosis may lead to inadvertent managements like manipulations, biopsies and surgery. As in our case, these strategies just help the disease to flare and make the life of patient much difficult. Kitterman et al reported incidence of misdiagnosis to be >90%, with 68% receiving inappropriate treatment which lead to permanent disability in about 50% of cases [2]. Early diagnosis and high index of suspicion will not only prevent the itrogenic harm but may also slow the disease progress and avoid rapid and early deterioration in patients quality of life [14]. In our case, ignorance was more of an issue than misdiagnosis. The practice of treatment by local bone setter is still prevalent in our country. This lead to rapid progression of disease in our case with early development of deformities.

Various treatment modalities have been reported in literature. Short course of steroids are used in during acute flare-ups in large joints and submandibular area. Other drugs tried are NSAIDs and COX-2 inhibitors, bisphosphonates like etidronate and pamidronate, rosiglitazones, Mast cell inhibitors, retinoic receptor agonists etc [15, 16]. However a statement made by Julius Rosenstirn in 1918 still holds true: “The disease was attacked with all sorts of remedies and alternatives for faulty metabolism; every one of them with more or less marked success observed solely by its original author but pronounced a complete failure by every other follower. In many cases, the symptoms of the disease disappear often spontaneously, so the therapeutic effect (of any treatment) should not be unreservedly endorsed” [17]. The rare incidence of this disease and unpredictable nature of flare-ups makes it difficult to formulate an ideal treatment for it [1].

Kaplan et al reported that Bone marrow transplant for replacement of hematopoietic cells was not sufficient to prevent ectopic skeletogenesis in the patient with fibrodysplasia ossificans progressiva but pharmacologic suppression of the apparently normal donor immune system following transplantation in the new host modulated the activity of the fibrodysplasia ossificans progressiva and diminished the expression of skeletal ectopia. However regular use of such strategy is still under investigation [18]. Glaser et al reported BMP4-induced heterotopic ossification can be prevented in vivo either by local delivery of wild-type Noggin or after somatic cell gene transfer of a Noggin mutein in murine model of FOP [4]. Recently, Dorsomorphin has been identified as a powerful orally-available signal transduction inhibitor of BMP signaling and preliminary data suggest that this category of STIs may play a powerful role in inhibiting heterotopic ossification in animal models but its safety and efficacy in animal models of FOP is still to be determined [1].

Although the rate of disease progression is variable, most patients are confined to a wheel- chair by their early twenties and require lifelong assistance with activities of daily living. Patients with FOP usually succumb later in adulthood at mean age of 40 years to cardiopulmonary complications secondary to thoracic insufficiency syndrome and severe restrictive pulmonary disease due to ossification and ankylosis of the joints of thoracic cage [7,19]. Reproductive fitness is low therefore familial transmission has a very rare incidence [1].



Conclusion

Thus in conclusion clinical suspicion, early diagnosis and expectant treatment are the main management strategy in cases with FOP. FOP demands further research to treat individuals suffering from this dreaded form of heterotopic ossification.

Clinical Message

Valgus deformity of great toes and neck stiffness are important pointers towards diagnosis of FOP and this condition needs further research to find an effective treatment modality for it

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