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### Fibrodysplasia ossificans progressiva; A rare case report & review of literature

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#### Abstract

Fibrodysplasia Ossificans Progressiva (FOP) or Myositis Ossificans Progressiva is a rare Disorder. It is characterised by progressive heterotopic ossification in the skeletal muscle and the connective tissues which leads to severe disability. Abnormality of great toe is the most characteristic finding and often the only sign present at birth. Gradually, soft tissue enlargement precipitated by minor trauma develop, which may spontaneously resolve or gradually form an ectopic bone. Due to relative rare prevalence of the disease and gross neglect of this condition in textbooks, physicians remain unaware of the condition leading to missed diagnosis. The purpose of this paper is to sensitise the physicians to the severity of this condition.

We report a case of advanced FOP in a 21 yr old male with the aim that it will help health care providers to diagnose this disease early and to manage it better.

**Keywords:** Fibrodysplasia Ossificans Progressiva, Ossification, Myositis.

#### Introduction

Fibrodysplasia Ossificans Progressiva (FOP) or Myositis Ossificans Progressiva is a rare autosomal dominant disorder with a prevalence of 1 in 2 million individuals with no ethnic, racial, gender, or geographic predisposition<sup>[1, 2]</sup>. It is characterised by progressive heterotopic ossification in the skeletal muscle and the connective tissues which leads to severe disability. At present, more than 300 years after the first report by Patin in 1648 in which he described the woman who "turned to wood", its pathogenesis remains largely unknown and its therapy is limited to symptom-modifying trials. The average age of patients is 28.7 year old<sup>[3, 4]</sup>, though a few reach old age also.

Abnormality of great toe is the most characteristic finding and often the only sign present at birth<sup>[5]</sup>. Gradually, soft tissue enlargement precipitated by minor trauma develop, which may spontaneously resolve or gradually form an ectopic bone. Due to relative rare prevalence of the disease and gross neglect of this condition in textbooks, physicians remain unaware of the condition leading to missed diagnosis. The purpose of this paper is to sensitise the physicians to the severity of this condition.

We report a case of advanced FOP in a 21 yr old male with the aim that it will help health care providers to diagnose this disease early and to manage it better.

#### Case History

A 21-year-old male presented to our orthopaedic clinic, with chief complaint of difficulty in mouth opening for the last few days. On eliciting further details it was revealed that this man had been to various peripheral hospitals for the last 15 years with complaints of nodular swelling all over the body. His parents reported that his birth was uneventful and only difficulty he faced in childhood was difficulty in crawling. His appearance was also normal at birth except for strikingly short great toes bilaterally. As he was growing up, multiple painful nodular swellings cropped up in succession over the limbs and back, which characteristically coincided with a preceding minor trauma. He started having limitation of neck and back movements almost 11-12 years back. Gradually he started having difficulty in walking because of contracture of both his knees and had been wheel-chair bound for the last 3 years. His condition was managed only at a primary health centre till he developed difficulty in opening his mouth and was not to take meals, for which he was brought to our tertiary care centre.

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There was no history of similar disease in his family. There was no history of hearing impairment and learning disabilities. On physical examination, general condition was debilitated may be because of poor oral intake and restricted mobility. He had a typical facies (Fig.3) and the temporomandibular joints appeared to be fused. There were multiple bony prominences varying in size at paravertebral region from cervical to lumbar and posterior thoracic wall. The masses including those over the limbs were non-tender, hard in consistency and fixed to bone. We could palpate bone bridges starting from inferior occipital bone to cervical spine and also between inferior scapula and humerus definitely restricting their movement. Both shoulder joints were dislocated and both the knee joint had flexion deformity (Fig.2) (right knee- 45 degrees and left knee -15 degrees). The characteristic finding of short great toes (Fig.1) was present. He also had an ulcer over the left lower leg possibly due to trauma. Fortunately, his cardiopulmonary functions were not compromised and he had adequate vital capacity with no evidence of chest infection. Skeletal survey was done to find out the extent of involvement and the radiograph of the cervical spine showed characteristic anomalies of the cervical spine i.e large posterior elements, tall narrow vertebral bodies, and fusion of the facet joints between C2 and C7 with new bone bridging occipital bone to upper thoracic spine (Fig.6). The x-ray of the skull revealed thickened calvarium and ankylosed temporomandibular joints (Fig.6). Chest and shoulder radiographs also showed heterotopic ossification at both the humerus bridging to inferior angle of scapulae, with posterior subluxation of left humeral head (Fig.5). The lumbo-sacral spine also showed ankyloses of posterior elements with mild scoliosis towards right. (Fig.4) There was extensive new bone formation around right femur investing the quadriceps and hamstrings. (Fig.7) Because of the characteristic picture obtained with radiograph, no other imaging was undertaken. Blood investigations including CBC, ESR, CRP, ALP etc were essentially normal. Because the patient presented so late that the disease had progressed significantly, the diagnosis of Fibrodysplasia Ossificans Progressiva (FOP) was easily made on clinic-radiological basis without resorting to the harmful procedure of biopsy. Extensive literature research did not yield any satisfactory medical or surgical therapy. The main concern at presentation was his inability to take oral feeds and hence, it was managed by surgery department. Corticosteroids were administered to decrease flareup and any possible inflammation of the food pipe hindering swallowing. Surgical release of joint contractures, osteotomy of heterotopic bone or surgical removal of heterotopic bone is generally counter-productive and risks new, trauma-induced HO. Spinal bracing is ineffective and surgical intervention is associated with numerous complications<sup>[6]</sup>. Hence, physiotherapy is the only viable option for orthopaedic disabilities. Patient was discharged 2 weeks later when he started taking oral feeds again. It was known from the last telephonic enquiry that the patient had succumbed to chest infections and had died 1 year later.

### Discussion

Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disorder with a prevalence of 1 in 2 million individuals with no ethnic, racial, gender, or geographic predisposition<sup>[1,2]</sup>. Malformations of the great toes and progressive heterotopic endochondral ossification (HEO) in characteristic anatomic

patterns are the two diagnostic features of FOP. The natural course of the disease is quite predictable with symptoms of painful nodular swellings starting in the first decade of life, patient becoming wheel chair bound by the third decade and succumbing to the disease by the 4<sup>th</sup> decade. The only diagnostic clue at birth may be shorter, malformed great toes but soon neck stiffness develops making it difficult for the neonates to crawl. In the first decade, inflammatory soft tissue swellings (or flare-ups) crop up which may regress spontaneously or transform the soft connective tissues into mature heterotopic bone by endochondral ossification. It has been observed that the flare ups are triggered by minor traumatic events such as intramuscular injections, surgical procedures like biopsy or excision influenza-like viral illnesses, mandibular blocks, muscle fatigue, blunt muscle trauma from bumps or falls etc. which eventually lead to characteristic anatomic and temporal patterns of HEO. Heterotopic bone replaces skeletal muscles (excluding extraocular muscles, tongue and diaphragm) and connective tissues and encase the normal bone in a pattern similar to normal embryonic skeletal formation, so that the dorsal, axial, cranial, and proximal regions of the body are affected first followed by ventral, appendicular, caudal, and distal regions<sup>[7]</sup>.

HEO in FOP is episodic following traumatic events, but disability is cumulative<sup>[8]</sup>. The most serious complications of severe weight loss due to jaw ankylosis and that of pneumonia or right-sided heart failure due to thoracic insufficiency, eventually prove fatal<sup>[9]</sup>.

Radiography is the first line of imaging study and many a times, the only study required. Sheets, ribbons and plates of heterotopic bone encasing the long bones like armaments, can be seen almost anywhere in the body. The anomalies of the cervical spine include large posterior elements, tall narrow vertebral bodies, and fusion of the facet joints between C2 and C7. Proximal tibial osteochondromas, clinodactyly, short broad femoral necks etc. may also be present. Bone scans are useful for early diagnosis as they become abnormal before radiographs. Computed tomography and magnetic resonance imaging of early lesions do not provide any extra input. Hematological and biochemical studies are essentially normal except during flare-ups when ESR, CRP and ALP may be increased<sup>[10]</sup>. Urinary basic FGF levels may be elevated during disease flare-ups coinciding with the pre-osseous angiogenic phase of early fibroproliferative lesions<sup>[11]</sup>. The possible diagnoses of juvenile fibromatosis, lymphedema, or soft tissue sarcomas should be ruled out.

The histopathology of FOP lesion varies according to the stage of the disease<sup>[12-15]</sup> viz. inflammatory stage, fibroproliferative stage, revascularization stage and osteogenesis stage. Early lesions show intense perivascular infiltration of macrophages, mast cells, and lymphocytes, likely inflammatory response to the triggering event. This is followed by the fibroproliferative phase with lesions showing angiogenesis and neovascularity, similar to aggressive juvenile fibromatosis. Finally fibroproliferative tissue condenses into cartilage and the maturation starts with the characteristic osteogenesis, where ossicles of new heterotopic bone appear histologically normal with mature lamellar bone. A single FOP lesion can have all 4 stages, suggesting that different regions within the lesion mature at different rates.

Heterozygous activating mutations in activin receptor IA/activin-like kinase-2 (ACVR1/ALK2), a bone morphogenetic protein (BMP) type I receptor, exist in all sporadic and familial cases of FOP<sup>[16]</sup>. The FOP gene is a highly conserved therapeutic target in the BMP signaling

pathway.

FOP has always remained a diagnostic challenge in the early stage of the disease, mainly because of rarity of the condition and relative ignorance among the clinicians about the existence of such a disease. The rate of misdiagnosis reaches as much as 90% [17] which has serious consequences, as seen in our case. The children are put to unnecessary and counter-productive tests like diagnostic biopsy which is particularly dangerous in the neck, back, and jaw regions because of development of rapidly progressive spinal deformity, exacerbation of thoracic insufficiency syndrome, or rapid ankylosis of the temporomandibular joints. Also, timely diagnosis can help prolong and improve the quality of life by avoiding injuries and by taking conservative therapy. The definitive diagnosis of FOP can be made by simple clinical evaluation that associates rapidly appearing soft tissue lesions with malformations of the great toes [18, 19]. Definitive genetic testing of FOP is available for research purposes mainly and can confirm a diagnosis of FOP prior to the appearance of heterotopic ossification that too without triggering it.

### Management of Fop

Medical intervention is only supportive and for symptomatic relief, with no therapy available to alter the natural history of the disease [20]. Hence, preventive and rehabilitative therapy assume special importance. Avoid all intramuscular injections [21] including mandibular block for the dental treatment and prevent falls to avoid flare-ups. Complications like respiratory infections and cardiopulmonary compromise can be prevented by immunization against influenza and pneumonia and chest physiotherapy.

Guidelines for symptomatic management of disease flare-ups have been published which support the anecdotal utility of glucocorticoids in managing new flare-ups involving major joints [20]. Besides, NSAIDs, COX-2 inhibitors, leukotriene inhibitors and mast cell stabilizers are useful anecdotally in managing chronic discomfort and ongoing flare-ups. Experimental therapies include Bone marrow transplantation, Chronic immunosuppression and Gene therapy aimed at blocking activity of the mutant FOP receptor or diverting the responding mesenchymal stem cells to a soft tissue fate.

Management of complications range from hearing aid application for conductive hearing loss to ESWL or PCNL for renal stones. Though respiratory support becomes necessary during episodes of pulmonary infection and right sided hear failure (Thoracic Insufficiency Syndrome), patients given unmonitored oxygen have a high risk of death due to sudden correction of oxygen tension and suppressed respiratory drive. With the disease progression, joint movement is progressively lost leading to nearly complete immobility. Surgical interventions like contracture release and osteotomy or removal of heterotopic bone are rarely indicated. Infact, it is better to refrain from these invasive procedures as they trigger more abnormal ossification. The best available remedy is occupational therapy and vocational education consultations.

### Conclusion

Fibrodysplasia Ossificans Progressiva is a rare but disabling disease, with no definitive treatment available currently [22]. Because the management is largely preventive, it is very important to identify the disease early and to take the precautions like avoiding intramuscular injections and preventing falls. Another important message is that we should avoid procedures like biopsy on such patients, unless diagnosis is unclear and some other diagnosis is more likely. A surgeon

should avoid the temptation to do surgical releases or osteotomies for joint deformities and should make maximum use of rehabilitation.



**Fig 1:** Characteristic short great toes seen in FOP



**Fig 2:** Flexion contracture of right knee along with proximal tibial osteochondromas



**Fig 3:** Decreased mouth opening due to fused TM joint



**Fig 4:** Lumbo-sacral spine showing ankyloses of posterior elements with mild scoliosis towards right



**Fig 7:** Extensive new bone formation around right femur investing the quadriceps and hamstrings and around pelvic bones



**Fig 5:** X- ray showing heterotopic ossification around the humerus with posterior subluxation of left shoulder joint



**Fig 6:** X-ray skull showing thickened calvarium, fused TM joint and large posterior elements, tall narrow vertebral bodies, with fusion of the facet joints between C2 and C7

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