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Case Report

A 24-year-old man with fibrodysplasia ossificans progressiva: clinical challenges and management

Syed Jamil Abdal[1]*, Sabrina Yesmin[2], M. Abu Shahin[1], M. Ariful Islam[1], Syed Atiqul Haq[3], Sharmin Nahar[4]

[1]Department of Rheumatology, Bangladesh Medical University (Formerly Bangabandhu Sheikh Mujib Medical University), Shahbag, Dhaka, Bangladesh
[2]Department of Rheumatology, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Shahbag, Dhaka, Bangladesh
[3]Green Life Center for Rheumatic Care and Research, 32 Green Road, Dhaka, Bangladesh
[4]Department of Rheumatology, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh

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***Correspondence:**
Dr. Syed Jamil Abdal,
E-mail: sjabdal@gmail.com

ABSTRACT

Fibrodysplasia ossificans progressiva (FOP) is a rare, disabling genetic disorder characterized by progressive heterotopic ossification of skeletal muscles and connective tissues. It is recognized as the most disabling condition of extraskeletal bone formation. The worldwide prevalence is approximately 1 in 2,000,000, with no ethnic, racial, gender, or geographic predilection. The hallmark clinical features include congenital malformation of great toes (commonly bilateral hallux valgus) and recurrent episodes of heterotopic ossification, often triggered by trauma or occurring spontaneously. Pathogenesis involves dysregulated bone morphogenetic protein (BMP) signaling due to mutation in the ACVR1 gene. Here we report a case of 24-year-old male with classical FOP, presenting with bilateral deformities of the big toes and progressive ectopic ossification. Despite advances in understanding the molecular mechanisms of the disease, there are currently no definitive preventive treatments. Early recognition of FOP, particularly by pediatric clinicians, is critical to avoid exacerbating factors, such as invasive procedures or trauma that may accelerate disease progression. This case report highlights the importance of clinical vigilance and continued research into therapeutic options for this devastating condition.

Keywords: Fibrodysplasia, Heterotopic ossification, ACVR1 gene mutation, Bone morphogenic protein

INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP) is a rare and progressively disabling genetic disorder having the hallmark of progressive heterotopic ossification. It is considered one of the most disabling extra-skeletal conditions in human history.[1]

Mr. John Freke described the first documented case of FOP in 1740 through a letter to the Royal Society, highlighting similarities with current cases, such as early childhood onset of multiple swellings at their back.[2]

Subsequent historical contributions to the understanding of FOP include Fränkel's description of characteristic malformations of the great toe in 1871, Helferich's identification of brachydactyly associated with FOP in 1879, and Bauer and Bode's naming of the condition in 1940.

Later, Mr. McKusick's work in 1960 FOP as a primary connective tissue disorder affecting tendons, ligaments, fascia, and aponeuroses.[3]

CASE REPORT

A 24-year-old male presented with swelling across his neck and back that had persisted for 20 years. He also experienced rigidity in his right knee, leading to difficulties in walking and cycling over the past six months, significantly affecting his daily activities.

He was born to non-consanguineous parents after an uneventful full-term pregnancy. There was no history of similar joint swellings in other members of his family.

The symptoms began when he was four, with his parent's noticing swellings in the paraspinal and scapular regions. These swellings often followed minor trauma, were initially soft, mildly painful, and later became hard and painless over time.

Subsequently, he developed stiffness in his spine, hips, and left knee, causing further challenges in walking and cycling. His parents also recalled a hardened area at the vaccination site on the lateral aspect of his left thigh since nine months of age, which they had overlooked at the time.

Clinical records revealed that, at the age of six, he was diagnosed with multiple exostoses and was being treated with non-steroidal anti-inflammatory drugs (NSAIDs), which alleviated the pain but did not reduce the persistent swellings. Physical examination revealed as shown in Figure 1. There was loss of neck lordotic curvature, kyphoscoliosis in the thoracolumbar region, and restricted spinal movement in all directions.

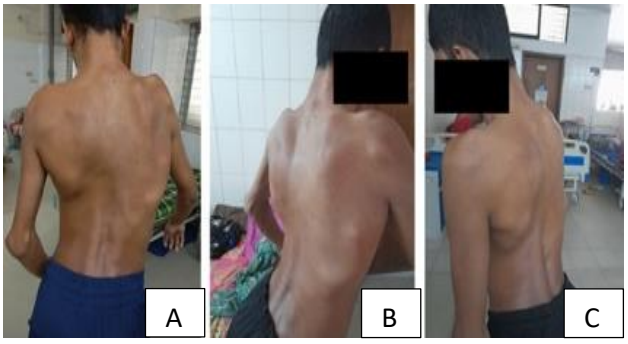

Figure 1 (A-C): Hard bony swelling on the nape, parascapular region, and thoraco-lumbo-sacral area.

The patient exhibited a fixed flexion deformity with a reduced range of motion (ROM) in the right shoulder, left elbow, hips, and left knee. Bilateral significant toe malformation of both great toes as shown in Figure 2 and shortened thumbs were observed since birth.

Laboratory investigations revealed normal cell counts, inflammatory markers, and renal and hepatic functions. Radiographs of the affected joints revealed extensive extra-skeletal ossification in the soft tissues of the neck, elbows, thoracolumbar region, pelvis, knees, and feet (Figures 3-8).

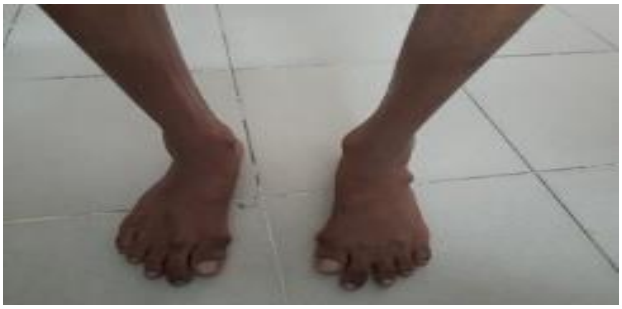

Figure 2: Bilateral significant great toe malformation (hallux valgus).

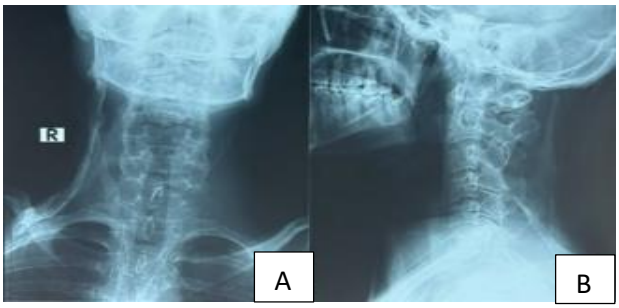

Figure 3 (A and B): X-ray cervical spine (both views) showed extra-skeletal ossification in the sternocleidomastoid muscles, subcutaneous tissue on the right side, and cervical curvature straightening.

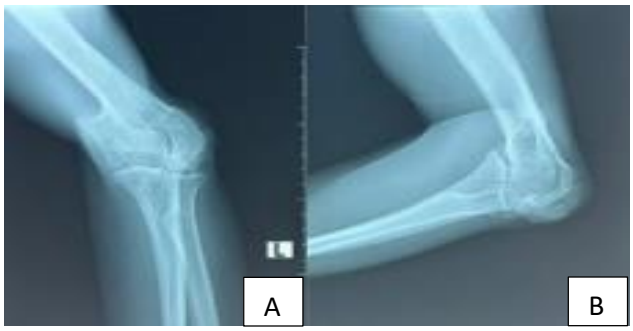

Figure 4 (A and B): Left elbow X-rays revealed joint deformity with ossification at the lateral epicondyle and capitulum of the humerus.

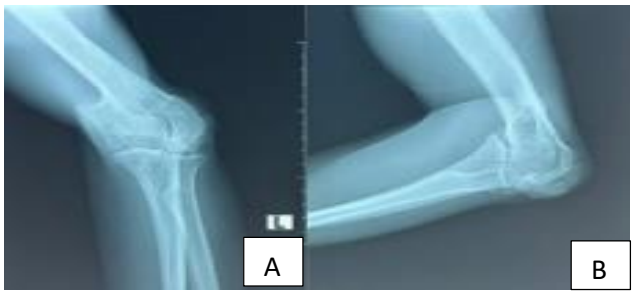

Figure 5 (A and B): Right shoulder X-rays showed ossification involving part of the subscapularis muscle.

The hallux valgus deformity was seen in both feet (Figure 9). The patient and his attendant were counselled about the cause, course, prognosis of the disease and advised to avoid biopsy, excision, injections and trauma. In addition to physiatrists care, analgesics were recommended for flare-ups.

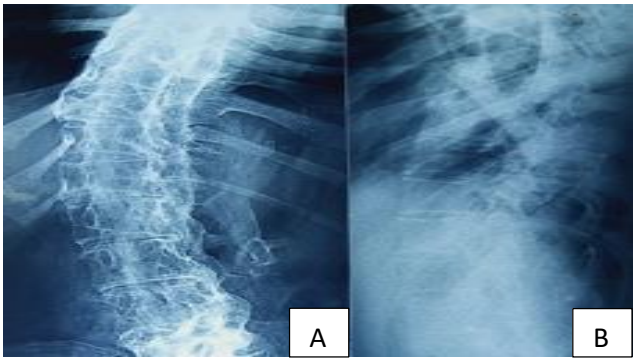

Figure 6 (A and B): Thoracolumbar spine X-rays showed generalized osteopenia, scoliosis and ossification of the lateral collateral ligament on the left side, along with ossification in some paravertebral muscles.

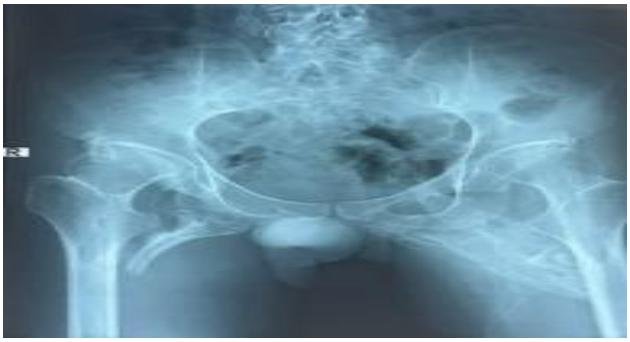

Figure 7: Pelvic X-ray revealed ossification at the proximal insertion of the right adductor brevis muscle distal to the inferior pubic ramus and in the adductor magnus muscle on the left side loose bodies were observed around right hip joint.

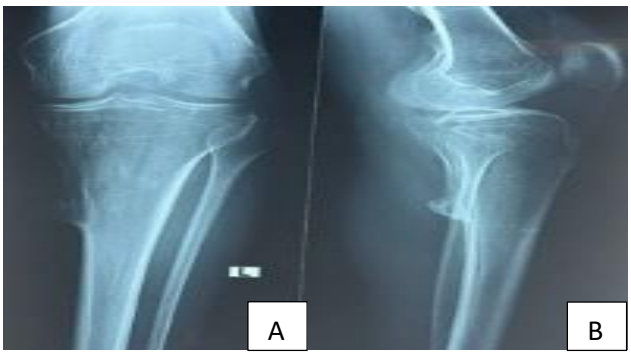

Figure 8 (A and B): X-ray images of the left knee, including part of the left leg, revealed periosteal ossification noted in the posterior aspect of distal third of both the femur and tibia on the lateral view.

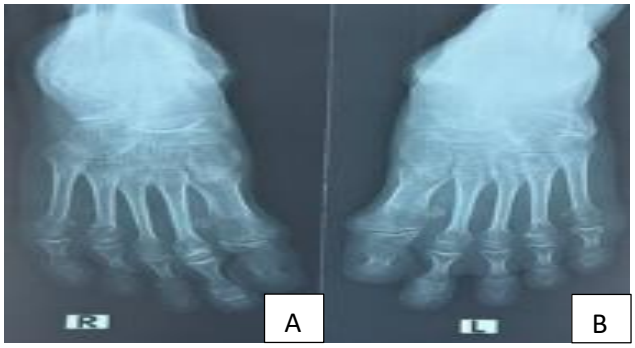

Figure 9 (A and B): X-ray of both feet showed a short, dysplastic hallux with an unusual malformation of the proximal phalanx, leading to a distinctive hallux valgus.

DISCUSSION

Worldwide, approximately one in 2,000,000 is the prevalence rate. To date, no ethnic, racial, gender, or geographic predilection to FOP is reported. The etiology of the disorder was hunting phase for long time. In practice, sporadic cases are reported mostly. However, autosomal dominant inheritance with complete penetrance and variable expression has been also found. Our patient did not give any history of such features in his past and existing family members suggestive of autosomal dominant inheritance. FOP is caused by heterozygous mutations in the activin A type I receptor (also known as activin-like kinase 2). The mutation in the activin A type I receptor leads to abnormally activation of bone morphogenetic protein (BMP) signaling that cause heterotopic bone formation and other osseous abnormalities along with osteochondromatosis. There is also evidence that suggests that involvement of the inflammatory component of the immune system plays a vital role in the pathogenesis of FOP, proven by the presence of macrophages, lymphocytes, and mast cells in early FOP lesions, intermittent flare-ups following viral infections, and the glucocorticoids response of early flare-ups. Except for congenital malformations of the great toes, children having FOP usually appear normal at birth. The most common clinical sign is a congenital malformation of the hallux valgus (often bilateral).

The clinical features are generally prototypes. The classical clinical features of FOP are malformation of the great toes and progressive heterotopic ossification in different joints of the affected individual, which presents with painful soft tissue swellings. Sometimes, scalp nodules can be an early sign of the disease found in infants. The first decade of the affected children is crucial during this time of life. The heterotopic ossification is the hallmark of the disease, where skeletal muscles and connective tissues, such as tendons, ligaments, and aponeuroses, progressively ossify. Though trauma incites recurrent episodes of heterotopic ossification, spontaneous heterotopic ossification may occur. The symptoms of our case were also preceded by trauma.[4-7]

During childhood, misdiagnosis of FOP affected individuals worldwide (approximately 90 percent). FOP is commonly misdiagnosed as aggressive juvenile fibromatosis, lymphedema, or soft tissue sarcoma. Clinicians should be vigilant, consider the rapidly developing soft tissue swellings on the head, neck, and upper back with the malformed great toes, and diagnose FOP.[8] Unnecessary and harmful diagnostic biopsies can exacerbate the condition's progression.[9]

Histology reveals different stages of FOP lesions. Early FOP lesions contain an intense perivascular B-cell and T-cell lymphocytic infiltrate followed by migration of mononuclear inflammatory cells into affected muscle, which precedes widespread myonecrosis. Following a brief inflammatory stage, an intense fibroproliferative reaction starts, producing robust neoangiogenesis. These early lesions are microscopically indistinguishable from aggressive juvenile fibromatosis. As time passes, fibroproliferative tissue undergoes an avascular condensation into cartilage, followed by a revascularization stage and osteogenesis in a characteristic process of endochondral ossification (Kaplan et al).

At present, no proven effective prevention or treatment for FOP is available. Global apex body guideline-based treatment is nonexistent. Prophylaxis of dental caries and avoidance of intramuscular injection of local anesthetics, especially mandibular blocks and jaw stretching, are useful. All intramuscular injections and sustaining of trauma must be avoided. Prophylaxis against respiratory infection and cardiopulmonary complications of restrictive chest wall disease is crucially important to help minimize flare-ups. Such measures include prophylactic pneumococcal pneumonia, influenza vaccinations (subcutaneously administered), and chest physiotherapy. The antibiotic treatment at the early stages of chest infection is warranted. Efforts to reduce swelling, including therapy with glucocorticoids and respiratory support, are also recommended. Appropriate specialists should address the management of learning disabilities. Upper abdominal surgery interferes with diaphragmatic respiration and should be avoided whenever possible. The patients with FOP have approximately two-fold higher chances of kidney stones than the general population. A low fiber diet, deficient water intake, excess animal protein intake, and history of urinary tract infections increase the risk of developing kidney stones in FOP.[10] Recently, a trial with gene therapy was conducted by adeno-associated virus (AAV) vectors to transfer healthy copies of the ACVR1 gene to FOP-affected cells.[11]

CONCLUSION

As a very rare case, we report a classical FOP with bilateral deformity of the big toes and progressive ectopic ossification. Clinicians should be watchful to diagnose FOP, especially our pediatric colleagues, since the disorder starts in childhood.

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