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# A REVIEW ON STONEMAN SYNDROME

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**Abstract**

Fibrodysplasia Ossificans Progressiva (FOP), better known as Stone Man Syndrome (SMS), is a rare genetic condition characterised by progressive heterotopic ossification that severely limits mobility. Misdiagnosis and mishandling of FOP are relatively common. Even harder to identify, atypical manifestations of FOP might result in iatrogenic harm that causes lasting disability. We describe the case of a 10-year-old girl who presented with complaints of a spine deformity and several back swellings that had been present for a year without any prior medical history. Upon examination, many hard bone swellings of varying sizes were observed on the back, along with a right sided mid-dorsal scoliosis that was accentuated when the patient bent forward. A skeletal survey identified the following abnormalities: bilateral short and broad femoral neck, pseudo-exostosis over the distal femur and proximal tibia, fusion of the lower cervical spinous process, and hallux valgus deformity in the left foot. The ACVR1 gene's p.R206H mutation was linked to FOP by sequencing. In this unusual presentation of SMS/FOP, the danger of misdiagnosis and mismanagement has been avoided thanks to the confirmation of the diagnosis through genetic investigation. Future therapeutic strategies for FOP may benefit from understanding the varying phenotypic expressivity of the condition.

**Keywords:** Myositis ossificans progressiva, Fibrodysplasia ossificans progressiva, Heterotopic ossification,

## Introduction

Fibrodysplasia ossificans progressiva (FOP), commonly referred to as Munchmeyer disease, is another name for the sporadic autosomal dominant illness known as Stoneman syndrome. brought induced by heterozygous missense of connective tissue alteration in the type I of the bone morphogenetic protein (Type I ACVR1 for activin A).Most FOP cases are 1, 2, and 3 is caused by the type's unique R206H amino acid substitution ACVR1, also known as the I BMP/TGF- cell surface receptor, ALK2, which activates R-mediated signalling too strongly,Smad1/5/8.4which eventually becomes heterotopic Obssification (HO).5,6 No proven remedy exists for Future events may determine the course of treatment for FOP.

Fibrodysplasia ossificans progressiva is an extremely rare autosomal dominant disorder and debilitating syndrome characterised by postnatal progressive heterotopic ossification of the connective tissue and congenital deformity of

the big toes. Around 1 in 2 million babies globally are affected by fibrodysplasia ossificans progressiva. Almost 90% of patients with fibrodysplasia ossificans progressiva receive the incorrect diagnosis and care, leading to unnecessary procedures. Around 700 documented active cases have been found so far in the world. Confirmatory methods for an early diagnosis of the condition include clinical examination, radiographic assessment, and genetic testing for ACVR1 gene mutation. We believe this is the first report of postsurgical excessive reaction in fibrodysplasia ossificans progressiva, which is well known to be associated with heterotopic ossification.

Such patients present with difficult airway management because to developing axial and appendicular skeleton fusion, temporomandibular joint (TMJ) ankylosis, concomitant restrictive lung illness, and sensitivity to even little oral trauma. [3] The term "Stone man disease" has also been used to characterise this disorder in which painful, stony-hard swellings develop that significantly increase morbidity and disablement.1 Only roughly 600 cases have been documented in medical literature.2 Given that FOP is so uncommon, many medical professionals misdiagnose patients who have the condition. Due to its rarity and clinicians' lack of knowledge with it, diagnosing FOP can take months or even years. Since diagnostic mistakes have been reported in up to 87% of FOP cases globally, with cancer being the most frequent wrong diagnosis, we believe that the case we are presenting here may be of interest to the readers of BMJ.

In-progress ossification, anatomical details, and preosseous lesions that are likely to be missed on traditional radiographs can be better and earlier visualised on a CT scan using three-dimensional multiplanar postprocessed pictures. Since this technique can confidently detect and differentiate this uncommon condition, we would like to place emphasis on it. In-progress ossification, anatomical details, and preosseous lesions that are likely to be missed on traditional radiographs can be better and earlier visualised on a CT scan using three-dimensional multiplanar postprocessed pictures. Since this technique can confidently detect and differentiate this uncommon condition, we would like to place emphasis on it.[4] The formation of extra bones can be noticed as early as infancy because the disease is inherited, commencing at the neck and moving down the body into the limbs. Patients with FOP typically have large, deformed toes when they are born. This is a very distinctive symptom because no other skeletal and muscle-related disorders exhibit huge, deformed toes, shortened thumbs, and other skeletal anomalies and growths.

**History**

Beginning with Dr. Guy Patin in 1692, medical records have described people with FOP.FOP was first known as myositis ossificans progressiva, and it was believed that this condition was brought on by a muscular inflammatory condition (myositis) that led to the production of bones. After learning that soft tissues other than muscles (including ligaments) were also impacted by the illness process, Victor A. McKusick termed the condition in 1970.

Harry Eastlack's FOP case, which spanned 1933–1973, is the most well-known. His illness started to worsen when he was 10 years old, and at the time of his death from pneumonia in November 1973—six days before he turned 40—his body had entirely ossified, leaving him with just the ability to move his lips. In all of Eastlack's years of living with FOP, he never encountered anotherThe skeleton of Eastlack, whose corpse was donated to science and is now

on display at the Mütter Museum in Philadelphia, has proven to be a priceless source of knowledge for the research of FOP. Carol Orzel, who also had FOP and died in February 2018, also donated her corpse to the museum. In February 2019, her skeleton was displayed there next to Eastlack's.[1] The term "soft connective tissue that gradually turns to bone" is referred to as FOP, or fibrodysplasia ossificans progressiva (fibro-dis-play-sha os-sih-fih-cans pro-gress-ev-a). The 17th and 18th centuries contain the earliest recorded cases. Research attempts to find therapies and a cure have escalated after the FOP gene was discovered in 2006. Future therapeutic research now has a highly targeted target in the FOP gene, which holds potential for changing not just the disease's symptoms but also the disease itself. Furthering research and medicine development, it made it possible to create animal models that can express the mutant gene.[2]

**Epidemiology**

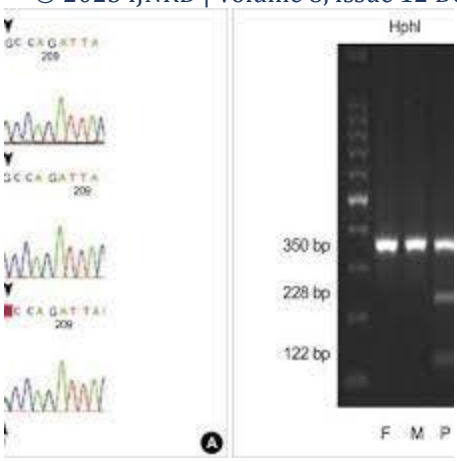
FOP is an incredibly uncommon genetic condition that affects roughly 1 in 2 million people worldwide. It has no regard for race, gender, or ethnicity, and it affects all geophysical propensity. Occurs frequently sporadically illustrates how varied autosomal dominant trait transmission occurs expression. Early in life, the disease develops postnatally. Life moves forward unavoidably[1]. The Japanese Ministry of Health, Labour, and Welfare about 500,000 people are affected worldwide. FOP does not favour any one ethnicity, race, gender, or location. [2] With only one instance per two million people worldwide, FOP is extremely uncommon. No predisposition related to race, ethnicity, or location has been mentioned.[3] As of 2017, there were about 800 verified cases of FOP worldwide, making it one of the rarest diseases ever identified. All ethnic groups are impacted by the estimated 0.5 cases per million population incidence of FOP.

**Pathophysiology**

Fibrodysplasia ossificans progressiva (FOP), also known as stone man syndrome, is a severely disabling and catastrophic-inherited disorder of connective tissue characterised by congenital malformation of the great toes, thumbs and vertebrae associated with progressive ossification of striated muscles. FOP is a disorder in which congenital abnormalities of the big toes are associated with progressive heterotopic ossification of the connective tissue structures, including those related to the striated muscles, leading to permanent disability.

**Mechanism of stone man syndrome**

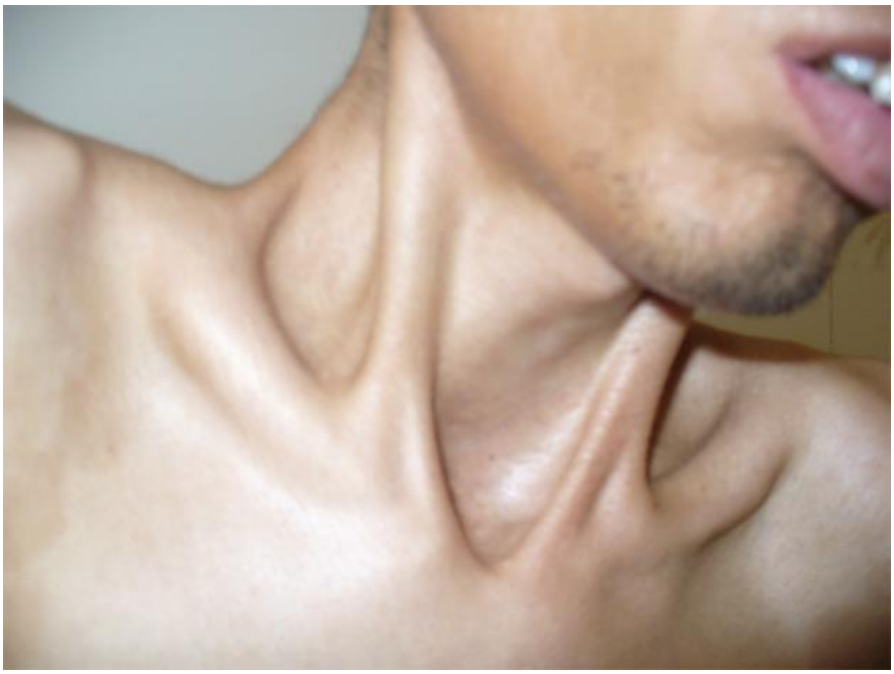
Stone Man syndrome or fibrodysplasia ossificans progressiva (FOP) is an extremely rare (1 in 2 million) genetic disorder characterised by ectopic ossification of the skeletal and connective tissues leading to progressive fusion of axial and appendicular skeleton. FOP is caused by a mutation of the gene ACVR1. The mutation affects the body's repair mechanism, causing fibrous tissue including muscle, tendons, and ligaments to become ossified, either spontaneously or when damaged as the result of trauma.




**Case report**

An oral abscess at the Dental Faculty in Mashhad, Iran, led to the referral of a 28-year-old man (33.5 kg and 1.68 cm in height) with increasing ossification of the muscles (Figure 1). His condition was identified as FOP. He first displayed the signs of FOP as a painless tumour on the scapula when he was three years old, according to medical records and history. He reported stiffness and a gradually limiting of his neck motion following the surgical excision of this tumour. Two months later, his issue reappeared, necessitating additional surgery in the same area. His issues eventually got worse over the next 20 years, leading to neck, knee, jaw, shoulder, and hip restrictions.(Figure 2) He was more disabled functionally at the age of 28. He had a blood pressure reading of 130/60 mmHg, a heart rate of 75 beats per minute, and a respiratory rate of 20 breaths per minute during his most recent physical, which was performed a week before the dentist appointment. The neck, chin, spine, shoulders, hips, and elbow were all immobile, and the elbow's full extension was only partially visible during the musculoskeletal examination (Figure 3). Lab results for calcium, PT, PTT, urinalysis, and blood cell count were within normal bounds. Hereditary ossification was visible on radiographs of the foot, neck, spine, head, and shoulder. The initial phalynx of the thumb was shorter in the patient's hands, as seen in the hand radiograph and photo (Figure 4). In addition, the trapezius muscle had ossified on the lateral neck radiograph, and the spine had fused entirely (Figure 5). A CT scan of the paranasal sinuses, mandible, and maxilla revealed no soft tissue mass lesions, focal bone lesions, or aberrant calcification. No signs of lymphadenopathy in the parapharyngeal area were visible on the neck MRI, according to the report. On the paraspinal muscles, the MRI of the spine revealed many ossifications of various sizes. His lateral jaw movement was around 0 mm and his maximal mouth openness was 5 mm throughout the dental evaluation. Poor oral care and several dental decays were present in the patient. He had a significant infection in the right mandibular second tooth when he saw his dentist nine months prior. Antibiotics alone were used to treat it, however after After many days, the infection spread to the buccal area and resulted in an abscess there. We could not pull the tooth in our department, but the abscess was drained and antibiotic medication was administered.

**Figure 1 A 28-year-old man with progressive ossification of neck muscles.**



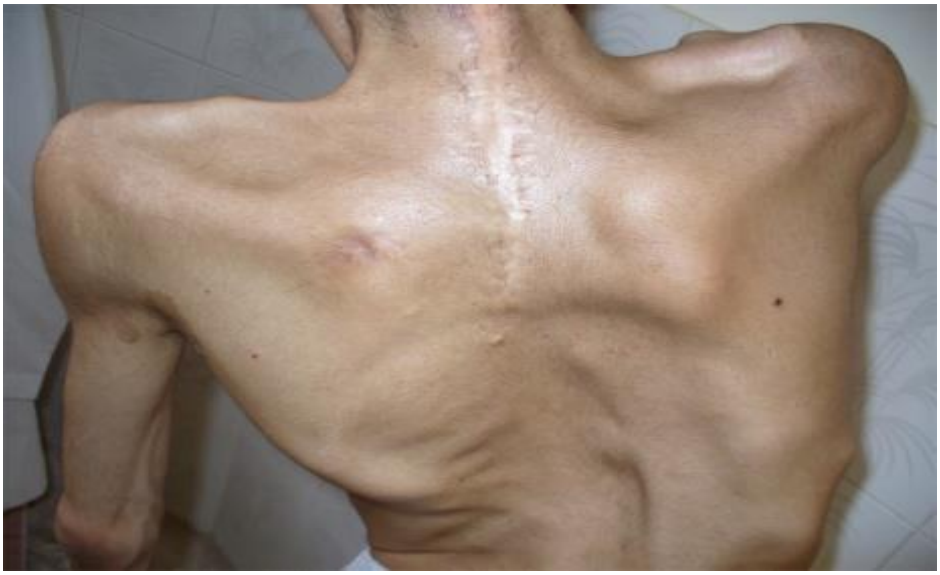


**Figure 2** Body deformities ayjjnd scarring from surgery might be seen on the patient's back.

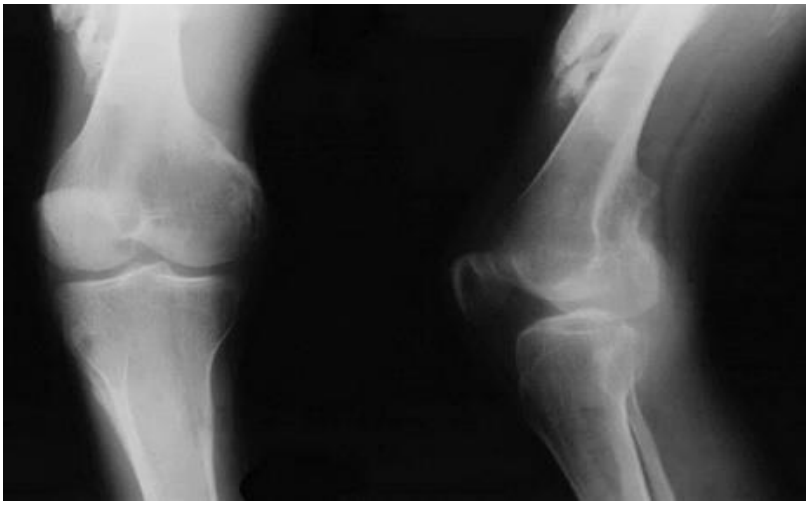


**Figure 3** Radiographs of the lower limbs revealed ectopic ossification in the quadriceps muscle.

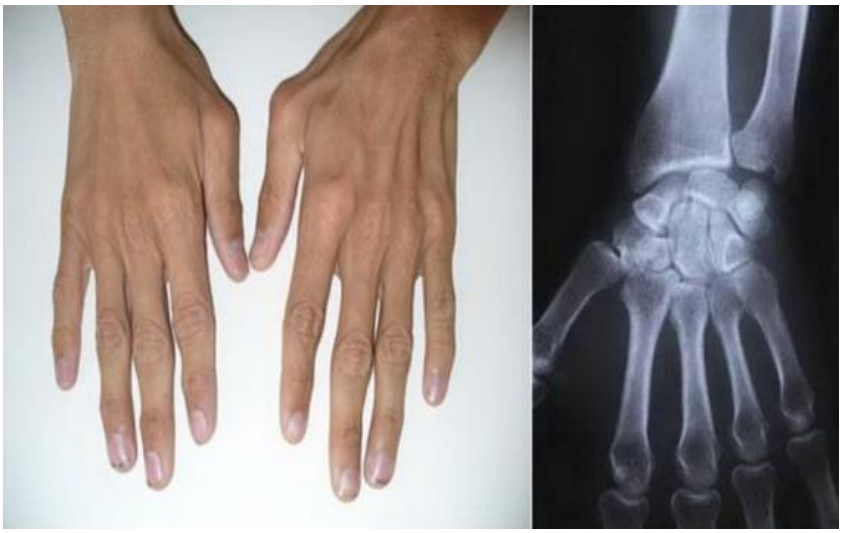


**Figure 4** The first phalynx of the thumb was shorter, as evidenced by a hand radiograph and picure.

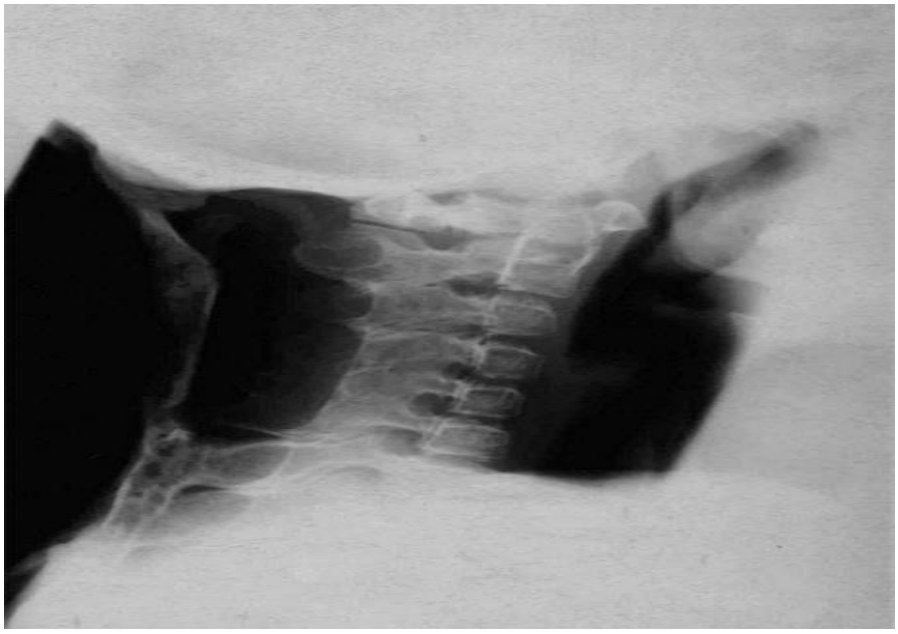


**Figure 5** Lateral radiography of the neck showed ectopic ossification in the trapezius muscle.

**Symptoms**

The genetic condition is both easy and difficult to identify due to its nature. Because FOP is very uncommon and poorly understood by the general population, it might be mistaken for less serious muscular illnesses. However, it is simple to detect due to its unique characteristics.It is quite likely that this rare genetic illness will be passed on to your offspring if you are connected to someone who has it through blood.

Examining their newborn child's thumbs and toes closely will reveal it. Babies affected by this disease are born with deformed large toes and, occasionally, thumbs.

- Limited joint motion, primarily in the neck and shoulders in the early stages.
- Deformed spine.
- Moving with irregularity and often experiencing low-grade fever, inflammation, and joint pain.
- All over the body, with the exception of the tongue, diaphragm, extraocular muscles, cardiac muscle, and smooth muscle, is a surface reflection of aberrant bone formation.

**Diagnosis**

FOP is extremely rare, making diagnosis extremely challenging. Misdiagnosis as fibrosis or cancer is increasingly frequent and potentially fatal. This is due to the possibility that misdiagnosis-related biopsies may worsen the growth of the additional bones. On the other hand, FOP patients' deformed thumbs or toes can aid in differentiating the condition from other bone issues. Elevated levels of bone-specific alkaline phosphatase and alkaline phosphatase can also be used clinically to identify the condition. Simple X-rays can be used to identify more subtle anomalies of the

great toe. Normal radiography can identify abnormal results from the bone scan. Additionally beneficial is confirmatory genetic testing, which is currently offered by a number of labs.

**Treatment**

There is currently no recognised treatment or cure for FOP (Stoneman syndrome). Even while research is ongoing. It is nevertheless challenging due to the patient's fragility and the illness. Because there is a risk of fast bone development, it is not advantageous to have surgery to remove the extra bone. Restrictive pulmonary disease and alterations in the heart's electrical conduction system are further reasons not to undergo anaesthesia. On the other hand, supportive therapy might be used to temporarily relieve symptoms. This involves using corticosteroids at high dosages.

**Discussion**

Fibrodysplasia/Stone Man Syndrome Ossificans Progressiva is a terrible condition that causes the connective tissues to skeletonize, severely restricting movement. It was first described in 1648 by "Gay," who said that the case had "turned to wood."

Bone morphogenetic proteins (BMPs) are a class of highly conserved signalling molecules that control endochondral ossification and cell differentiation. They are intimately related to the pathophysiology of FOP. Complexes of transmembrane receptors mediate BMP signalling. Among the three BMP type 1 receptors, activin receptor 1 A (ACVR1)/activin like kinase 2 (ALK2) is one1,3, 4. It is divided into four domains: the transmembrane domain, the ligand-binding domain, the GS-rich domain, and the protein kinase domain. When it comes to binding and SMAD signalling activation, the GS rich domain is important. Moreover, it is a binding site for the protein FKBP12, which prevents leaky receptor activation when a ligand is not present3,5. The majority of FOP cases are caused by a single nucleotide change at codon 206 of the ACVR1 gene (p.R206H) between histidine and arginine. Zhang et al. found that 97% of the 72 FOP cases they looked at had this mutation.

Numerous cases have been documented where surgical interventions were considered for cases misdiagnosed as adolescent idiopathic scoliosis, Klippel Feil syndrome, hereditary multiple exostosis, etc. This led to an acute flare-up and rapid progression of the disease process2,3,6,8. The potential for diagnostic and treatment errors has been avoided in this instance thanks to the confirmation of the diagnosis through genetic analysis of the ACVR1 gene mutation (p.R206H). Despite sharing the same ACVR1 gene mutation, classical and atypical instances of FOP range significantly in terms of phenotypic presentation and severity, with some experiencing a more aggressive and florid illness phase while others have a delayed and milder one. Although the exact cause of this varied expressivity is unknown, modifier genes3 are thought to have an impact. Future FOP therapy efforts may be more successful if these moderating factors are well understood.

## Conclusion

Fibrodysplasia Ossificans Progressiva is a rare genetically based musculoskeletal illness that is frequently misdiagnosed and mistreated. The gold standard method for diagnosing tumours and tumor-like lesions is a biopsy or histological examination, yet both methods are not reliable for FOP. Such intrusive operations can result in unintentional iatrogenic harm, which accelerates the severe disease's course. While mutation analysis of the ACVR1 gene is the gold standard test for the identification of atypical SMS/FOP, clinico-radiological features may help in the diagnosis of classical cases of FOP. In order to prevent the trend of incorrect diagnoses and inadequate treatment, it is imperative to raise awareness of this illness. The preferred course of treatment is secondary prevention of damage. In the future, gene treatment is the aim.

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