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A rare encounter: A case report of fibrodysplasia ossificans progressive (Stone Man syndrome) in an adolescent

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Keywords: Fibrodysplasia ossificans progressive; Heterotopic ossification; Acvr1/Alk2 mutation; Bony swellings; Stone Man syndrome.

Abbreviations: FOP: Fibrodysplasia Ossificans Progressive; HTO: Heterotopic Ossification; POH: Progressive Osseous Heterolalia.

Abstract

Purpose: This case report aims to illustrate the clinical presentation, diagnosis, and management of Fibrodysplasia Ossificans Progressive (FOP), a rare genetic disorder characterized by heterotopic ossification, through a detailed analysis of a specific patient case.

Background: Fibrodysplasia Ossificans Progressive (FOP), also called Munchmeyer disease or myositis ossificans progressive or stone man syndrome, is an extremely rare genetic disorder in which fibrous connective tissue such as muscle, tendons, and ligament gradually ossify into bone tissue. It is a severely disabling genetic condition that can occur due to sporadic mutation or autosomal dominant inheritance. FOP is caused by a mutation of the gene ACVR1/ALK2 that induces osteoblast activation. The mutation affects the body's repair mechanism, causing fibrous tissue, including muscle, tendons, and ligaments, to become ossified. Minor injuries can cause joints to become permanently fused as new bone forms, replacing the damaged muscle tissue that brides the joint space. This new bone formation, also known as "heterotopic ossification", eventually forms a secondary skeleton and progressively restricts the patient's ability to move.

Case summary: A case of a 12-year-old male presenting with progressive joint immobility, bony swellings, and malnutrition over 2 years was examined. The classical appearance of the great toe helps to differentiate this disorder clinically from other causes of heterotopic ossification like Progressive osseous heteroplasia, aggressive juvenile fibromatosis, and fibrous dysplasia, etc. Many drugs failed to show improvements in patients with FOP. Hence, the disease remains without a cure; however, recently, palovarotene has shown some promising results. Still, palliative management is the only treatment available at present. In our patient, pain was managed with a short course of non-steroidal anti-inflammatory drugs. Hager mouth opening gag was used to open the mouth sufficiently for feeding assistance. Surgical intervention is contraindicated as it may result in extensive ectopic bone formation.

Conclusion: Early Diagnosis and tailored supportive care are pivotal in managing FOP. Clinicians should be aware of this rare entity, as it can mimic with other causes of heterotopic ossification and misdiagnosis may result in unnecessary biopsies that often hasten disease progression, which may have catastrophic implications for patients. Advancements in understanding FOP pathogenesis offer hope for future pharmacological treatments, emphasizing the significance of continued research and clinical vigilance in optimizing patient outcomes.

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Introduction

Fibrodysplasia Ossificans Progressive (FOP), also known as myositis ossificans progressive or Machmeter disease, is an extremely uncommon genetic disorder wherein connective tissues like skeletal muscles, tendons, ligaments and fascia progressively transform into bone, forming an abnormal secondary skeleton that severely disables patients. Prevalence is roughly 1 in 2 million worldwide without gender, ethnic or geographic predilection [1]. FOP arises from activating mutation in activin receptor 1A/ activin-like kinase 2 (ACVR1/ALK2) inducing osteoblast activity [2]. This mutation causes connective tissues to heterotopically ossify following injury. Children who have FOP appear normal at birth except for classical congenital malformations of the great toes. During the first decade of life, Minor trauma leads to inflammation causing painful soft tissue swelling that resolves spontaneously initially; but in later phases of disease, activation of bone formation process transforms soft tissue like tendon, ligament, fascia and muscle into bone. If Heterotopic Ossification (HTO) involves the muscle that is bridging the joint, it leads to ossification of muscle and thus decrease in range of motion of joints to complete fusion-like state. This newly deposited bone is structurally similar to normal bone. Joint degeneration may happen independently due to disuse and systemic inflammation. Heterotopic ossification typically develops in a centrifugal pattern, beginning at the axial skeleton and extending outward to the extremities, with the lower limbs being the last to be affected. The muscle, ligaments, fascia and tendons are progressively replaced by bone due to HTO forming sheets, ribbons and rope like heterotopic bone that covers the body like armament and causes progressive immobility. Most patients with FOP become wheelchair-dependent by their third decade of life. Median age of survival is 40 years and patients often develop life-threatening complications, including severe weight loss due to ankylosis of the temporomandibular joints and thoracic insufficiency syndrome. Diagnosis depends substantially on clinical features of characteristic great toe deformity and progressive HTO, family history is rarely positive. If clinical suspicion is high, targeted genetic testing can confirm ACVR1 mutation. In this case report we report clinical and radiographic findings of this rare disease to make clinicians aware of this condition.

Case report

A 12-year-old male, apparently alright 2 years ago, presented with complaints of hard painful swelling first noticed on the back of neck, for which treatment was taken from a local hospital but with no benefit. Later on, he developed another swelling on back and decreased mobility of the cervical spine. After 6 months he developed swelling over right wrist joint that increased progressively over 3-4 months leading to redistricted mobility of wrist joint. In the next few months, he developed multiple bony swellings and progressive joint immobility causing complete restriction in movements of most of the joints including wrist, ankle, knee, spine, and temporomandibular joint over the next 2 years making him bedridden for the last 6 months. He had bony swellings bridging over the joints causing restriction in mobility of all limbs as well as his jaw, involving Temporomandibular Joint (TMJ) which led to impaired mouth opening and inability to eat solid foods. He was only able to take in semi-solid feeds and liquids as a result, which had weight loss, generalized weakness and malnutrition. He was born at term following an uncomplicated vaginal delivery. There was no family history of similar symptoms, no history of parental consanguinity and his siblings were reportedly unaffected. Milestones in early childhood were normal. There was a past history of a penile surgery at age 4.5 years though records of it were unavailable.

On examination, he appeared conscious, well-oriented and afebrile. Vitals signs were normal with palpable distal pulses. He had evidence of muscular wasting with signs of malnutrition. On skeletal examination, there were fixed flexion deformities of both elbow and knee joints bilaterally and restricted spine mobility. Shoulder and wrist movements were also reduced bilaterally. His temporomandibular joints showed reduced mobility. The jaw could open up to 2-3 mm to allow passage of one finger only. Multiple firm subcutaneous lesions were noted over the joints, along the upper thoracic spine, signifying ectopic bone formation (Figure 1). Examination of feet showed bilateral hallux valgus deformities (Figure 2). All the routine biochemical examinations including serum (S) calcium, S. phosphorus, S. albumin, S. alkaline phosphatase, 25(OH)vitamin D and iPTH were normal. Non-Contrast Computed Tomography (NCCT) head, spine, thorax, and abdomen were done to evaluate the extent of the disease and relevant complications. NCCT head revealed a thick band of heterotopic ossification within soft tissues of the left temporal region, extending over the mandibular condyle (Figure 3). No abnormal calcification was seen in the brain parenchyma. NCCT cervical spine showed facet joint fusion from C2-C7 (red arrow in Figure 4a), irregular ossification foci in the superficial soft tissues of the dorsal region (green arrow in Figure 4b), and the extent of heterotopic ossification from occiput to preliberal junction traversing through superficial soft tissues of drozitumab region (highlighted by yellow arrows in 3-D VRT image in Figure 4c). Bizarre-shaped thick osseous bands were also extending along the iliopsoas muscle down to its insertion onto the lesser trochanter of the femur on both sides (red arrows in Figure 5a and 5b). Muscles, fascia, and intermuscular planes of upper and lower extremities also showed irregular heterotopic ossification (Figures 6 and 7). With above mentioned clinical and radiological features, diagnosis of FDO was made. Supportive therapy was initiated, including air mattress and frequent change in posture to prevent pressure sores, nutritional supplementation, pain control using non-steroidal anti-inflammatory medications as needed, Hager mouth-opening gag was utilized to adequately open the mouth for assisted feeding along with psychological support to promote emotional health and coping skills in dealing with this challenging diagnosis. He was managed conservatively with physiotherapy, pain control, and nutritional support, to optimize his quality of life while avoiding surgical risks.

Discussion

Fibrodysplasia ossificans progressive typically shows autosomal dominant inheritance, but most cases are sporadic from de novo mutations as suspected in our patient, in absence of family history. Diagnosis is clinical, cantered on characteristic features like childhood onset extra-skeletal ossification, great toe malformations and joint immobilization progressing centrifugally from axial skeleton into appendages [3]. A defining clinical feature of FOP, malformation of the big toe was seen in our case

Table 1A: Differentiating features between Traumatic Heterotopic Ossification (THO) and Fibrodysplasia ossificans progressive (FOP).

Condition	Traumatic Heterotopic Ossification (THO)	Fibrodysplasia ossificans progressiva (FOP)
Site	Ossification at site of injury or surgery; esp. hip replacement or spinal cord injuries	Centrifugal, progressive axial to appendicular ossification
Initiating trigger	Specific inciting event present	Can be spontaneous, or after minor or major trauma
Site	localized	Generalized
Progression	Non progressive	Progressive

Table 1B: Differentiating features between Progressive Osseous Heterolalia (POH) and Fibrodysplasia Ossificans Progressive (FOP).

Condition	Progressive osseous heteroplasia (POH)	Fibrodysplasia ossificans progressiva (FOP),
Site	Bone growth may develop on the surface of the skin (Dermal osseous plaques)	No cutaneous ossification
Defect	Mutation in GNAS gene	ACVR1/ALK2 mutation
Presentation	Pre osseous tumor-like inflammation or "flare-ups" absent	Pre osseous tumor-like inflammation or "flare-ups" Present
Deformities	Congenital skeletal malformations like short stature, round faces, short fourth metatarsal may be present. No great toe malformation	Characteristic great toe malformation present

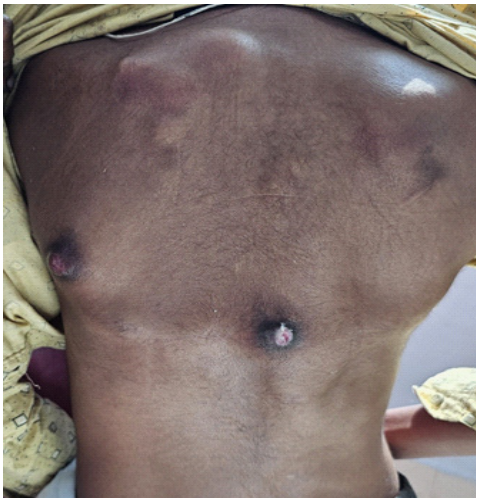

Figure 1: New bone swelling palpable under skin with bed sores over bony prominences.

consolidating the diagnosis [4]. Lab reports are typically normal and imaging studies like X-rays, CT and MRI complement the clinical diagnosis.

Heterotopic Ossification (HO) refers to the abnormal formation of bone in soft tissues, where bone normally does not exist. While Fibrodysplasia Ossificans Progressive (FOP) is a well-recognized genetic form of HO, other causes and conditions also lead to similar phenomena. Thus, other causes of heterotopic ossifications and how to differentiate from FOP should always be kept in mind, especially Traumatic Heterotopic Ossification (THO) and Progressive osseous heteroplasia (Table 1A and 1B).

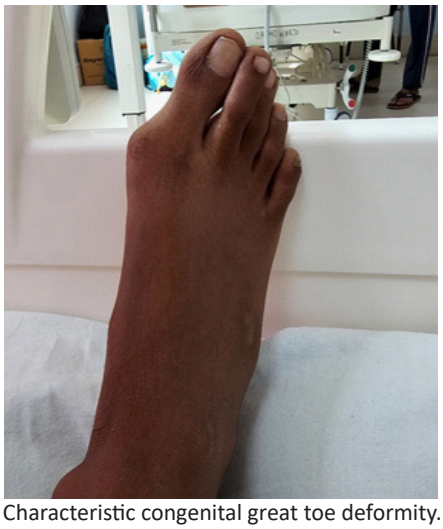

Figure 2: Characteristic congenital great toe deformity.

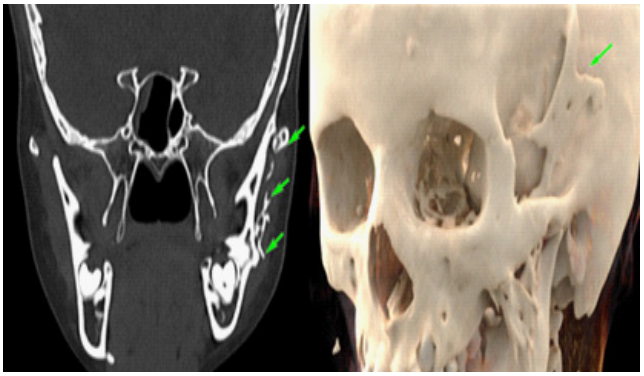

Figure 3: (a) CT (bone window) face in coronal view and (b) VRT image in oblique view show an irregular band of heterotopic ossification within soft tissues of the left temporal region, extending over the mandibular condyle (highlighted by green arrows).
CT: Computed Tomography, VRT: Volume Rendering Technique

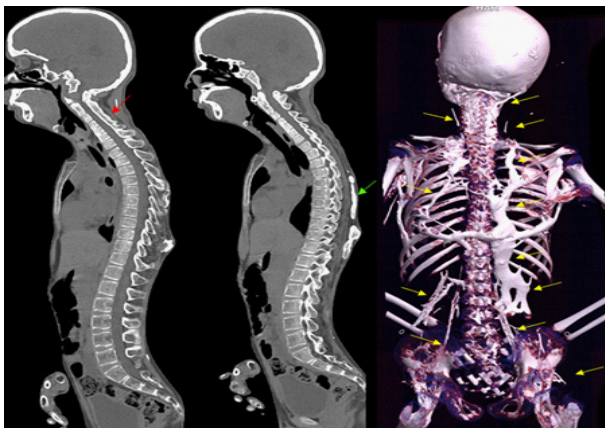

Figure 4: **(a)** CT (Bone window) whole spine in sagittal view show C2-C7 facet joint fusion (red arrow), **(b)** irregular ossification foci in the superficial soft tissue of the dorsal region (green arrow), **(c)** 3-D VRT image in posterior view shows the extent of heterotopic ossification from occiput to pelvifemoral junction traversing through soft tissues of thorax and back (highlighted by yellow arrows).
CT: Computed Tomography, VRT: Volume Rendering Technique.

Differentiating these conditions is crucial for appropriate management and treatment. Aggressive juvenile fibromatosis results in fibroblasts overgrowth and invasion in tendons, ligaments and other connective tissues, resembling the tissue swelling lesions of FOP. However, fibromatosis does not have the HTO or toe malformation. Other causes of heterotopic calcification or ossification that should be differentiated are pseudohypopara-

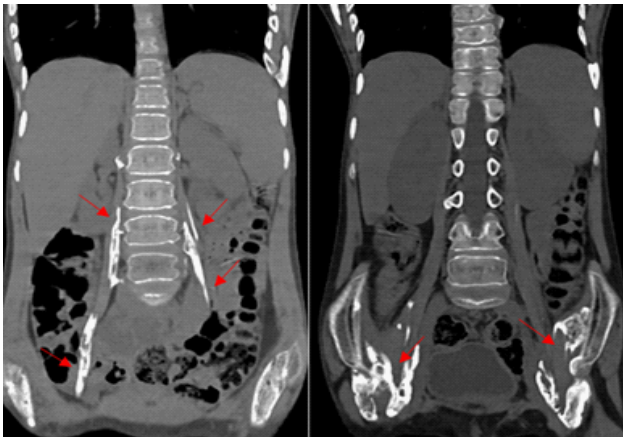

Figure 5: (a and b) CT (bone window) paravertebral region in coronal view shows a bizarre-shaped thick osseous band extending along the iliopsoas muscle down to its insertion onto the lesser trochanter of the femur on both sides (red arrows).
CT: Computed Tomography.

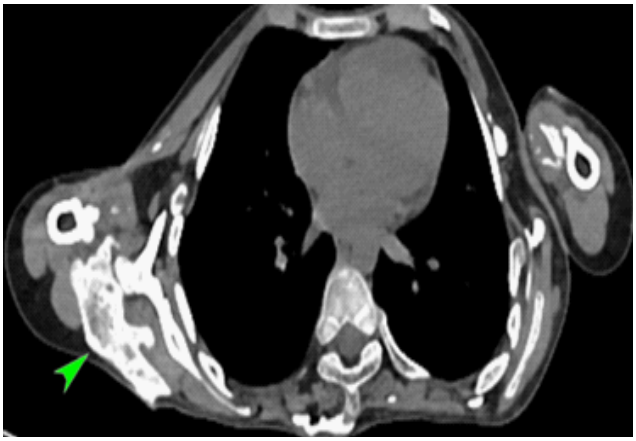

Figure 6: CT thorax (bone window) in axial view shows irregular massive heterotopic ossification extending along the teres major muscle extending to triceps muscle (green arrowhead). Similar abnormal osseous tissue is also evident in right paravertebral soft tissues adjoining the spinous process and along muscles of the left posterolateral chest wall.

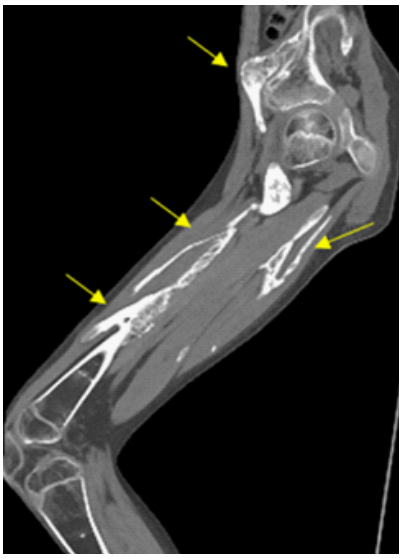

Figure 7: CT thigh (bone window) in sagittal view shows massive heterotopic ossification extending along the iliopsoas muscle, muscles, and intermuscular planes of the anterior, posterior, and medial compartment of the thigh with resultant contracture and flexion deformity of the left knee (yellow arrows).

thyroidism (hypocalcaemia, hyperphosphatasaemia and raised parathyroid hormone), tumoral calcinosis (hyperphosphatemia, FGF23, GALNT3 or KLOTHO gene mutation, characteristic radiology of amorphous, multilobulated periarticular calcification), and chronic kidney disease (raised creatinine, hyperphosphatemia etc). Disease course of FOP is chronically progressive and debilitating. Biopsies should be avoided when FOP is suspected because these tests may result in rapid bone formation in those areas where tissue is removed and may give false impression of osteo fibrosarcoma. Surgery accelerates progression of disease and is thus contraindicated. If surgery is done, explosive bone formation at the site of trauma is warranted preoperatively. Currently, conservative management remains mainstay, concentrating on physiotherapy for retained mobility, assistive devices to aid independence, optimized nutrition, preventative dentistry, and emotional health support. Genetic counselling assists family planning. NSAIDs and COX-2 inhibitors provide symptomatic relief for episodic flare-ups while corticosteroids show minimal benefit Advances in elucidating molecular pathways promise future pharmacologic treatments. Promising emerging options include mast cell stabilizers like cromolyn [5]. Recent studies, such as the randomized, double-blind, placebo-controlled phase 2 trial of Grantsman, have shown promising results in reducing these abnormal bone formations, offering new hope for management and treatment of FOP [6]. Palovarotene is a selective retinoic acid receptor gamma (RAR)γ agonist that reduces the number of new bony formations in muscle and soft tissue. MOVE trial, a global Phase III trial, assessed the efficacy of palovarotene in reducing the volume of new HO in patients with FOP, demonstrating a 62% reduction in mean annualized new HTO volume in treated participants compared to untreated ones from a natural-history study [7]. Thus, Palovarotene has been approved by the U.S. Food and Drug Administration (FDA) for use in adults and children (females aged 8 or older, or male aged 10 or older) with FOP [8]. Palovarotene reduces HO in FOP but risks physeal closure in young patients [9]. Despite these promising results, the drug has faced regulatory challenges in Europe, where the European Commission did not grant marketing authorization following a negative opinion by the Committee for Medicinal Products for Human Use (CHMP). Early diagnosis is critical for managing the progression of FOP and improving patient outcomes. Early detection through clinical vigilance and imaging studies is crucial. Radiographs are most often the first imaging study used to detect non genetic HO [10]. Computed Tomography (CT) scans are particularly useful for diagnosing and monitoring the extent of heterotopic bone formation. Currently, tailored supportive care alongside precautions to prevent iatrogenic harm provides optimal quality of life. Goals of management are early diagnosis to promptly initiate occupational and physical therapy, provide emotional support, and avoid medications/procedures that can worsen progression. In sum, while the clinical presentation of HO can be similar across different etiologist, key differences such as the trigger event, location of bone formation, and associated conditions help in differentiating them. Management strategies need to be tailored according to the specific type and underlying cause of HO.

Conclusion

By reporting this rare case of FOP with characteristic features-heterotopic ossification and great toe malformations, we want to highlight this uncommon cause of HTO. As early clinical suspicions and diagnosis may halt the disease progression by preventing minor and major trauma and use of newer drugs like

palovarotene. Later in the course of disease only conservative therapies like pain management, support, dental care and psychosocial counselling are the only treatment options we have till now.

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