FIBRODYSPLASIA OSSIFICANS PROGRESSIVA: CASE REPORT

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ABSTRACT

Fibrodysplasia ossificans progressiva is a very rare inherited connective tissue disease characterized by progressive heterotopic ossification in soft tissues of the trunk and extremities with associated congenital malformation of great toes and thumbs. Episodic flare-ups of pre-osseous soft tissue swelling usually begins during early childhood and progress throughout life causing progressive ankylosis of joints with resultant severe disability. Literature review reveals that there are more than 600 reported cases so far and presently there is no prevention or effective treatment for this disorder. Imaging plays a major role in the diagnosis to prevent unnecessary harmful biopsies. We present a case of a 2-year-old boy with extensive heterotopic ossification with classical radiological findings.

Key Words: Fibrodysplasia ossificans progressiva, Myositis ossificans, Munchmeyer disease, Multidetector Computed Tomography

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INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP) is very rare autosomal dominant condition and is also known as myositis ossificans progressive or Munchmeyer disease. It mostly begins in childhood with presenting mean age of 4-5 years. In this disease, there is abnormal proliferation of the connective tissue in the skeletal muscles, fascia and ligaments. Patient presents with painful swelling and when the swelling subsides after few months, ossification and heterotopic bone formation starts at same site. Eventually, this new heterotopic bone formation interferes with normal movements of the patient and most of these patients are then immobile by the third decade. Mortality in these cases is related to restrictive lung disease due to involvement of thoracic wall soft tissues causing inability to expand the chest. There is an association with characteristic congenital malformation observed in the great toes at birth in almost all cases of FOP[1,2].

CASE REPORT

A 2-years-old boy presented with right gluteal, para ischial, shoulder girdle and paraspinal tender hard masses. He had bossy swellings on his forehead and deformed big toes (Figure 1). He was born of a full term pregnancy via normal vaginal delivery and attained developmental milestones normal for his age. There was no history of consanguineous marriages in the family and no history of similar illnesses. These swellings in the back, forehead, right hip and shoulder girdle region were noted after trivial trauma from the last one year.

On examination, he had paraspinal (upper thoracic and lower neck) and peri-scapular swellings which were painful, tender but no associated skin changes. He had significantly restricted movements at the neck, shoulders and right hip. Radiological investigations in the form of plain radiography and multidetector computed tomography (MDCT) were performed on 128 slice CT machine using low dose technique (80kVp). 1-3mm images in bone and soft tissue window were reviewed on vitrea workstation. Multiple axial and reformatted images of CT in different window settings revealed ectopic ossifications in soft tissues of neck, paraspinal muscles and sublingual region and along the forehead.

Similarly, extensive heterotopic ossification were seen in anterior chest wall muscles, along medial aspect of humeri bilaterally and along lateral chest wall. In the pelvic region, there were extensive ossifications in right gluteal soft tissues (Figures 1, 2 & 3). No other visceral abnormality was seen in the abdomen and pelvis. Large arachnoid cyst was seen in posterior fossa of brain, however, no brain parenchymal abnormality was observed. Hallux valgus was seen in X ray of both feet with abduction of first metatarsophalangeal joint (Figure 4), first metatarsal bone was angled away from the second (metatarsus primus varus).

Figure 1: Multiplanar reconstructed and axial CT images in different window settings reveal heterotopic ossifications (arrows). Axial Bone window of skull (lower larger sagittal bone window image) shows soft tissue swelling in frontal region with tiny early small ossifications (small arrow). Lower right photograph of back of patient showing visible bony bumps

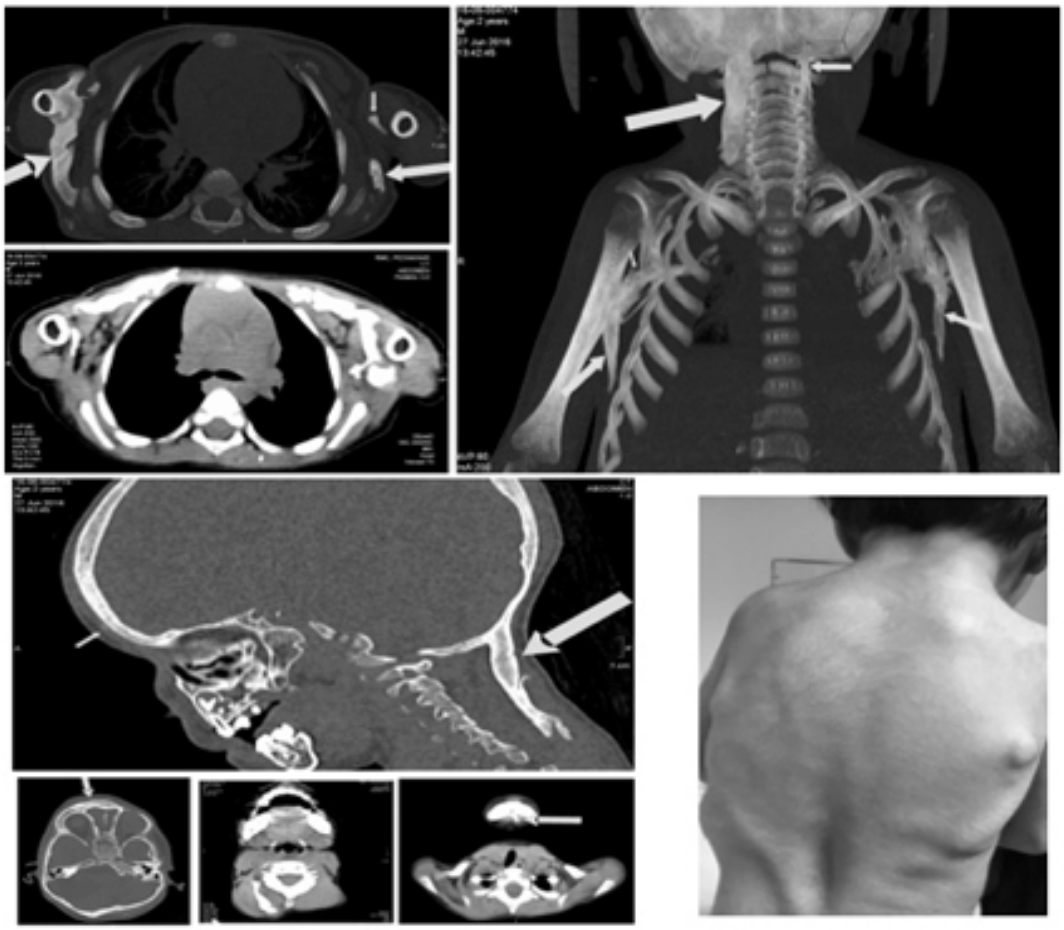


Figure 2: Axial CT scan image in bone window setting shows extensive ossification in right gluteal soft tissues

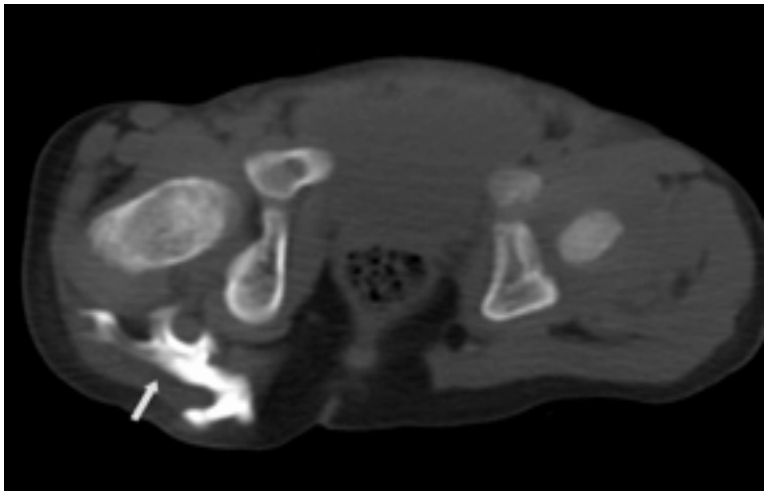
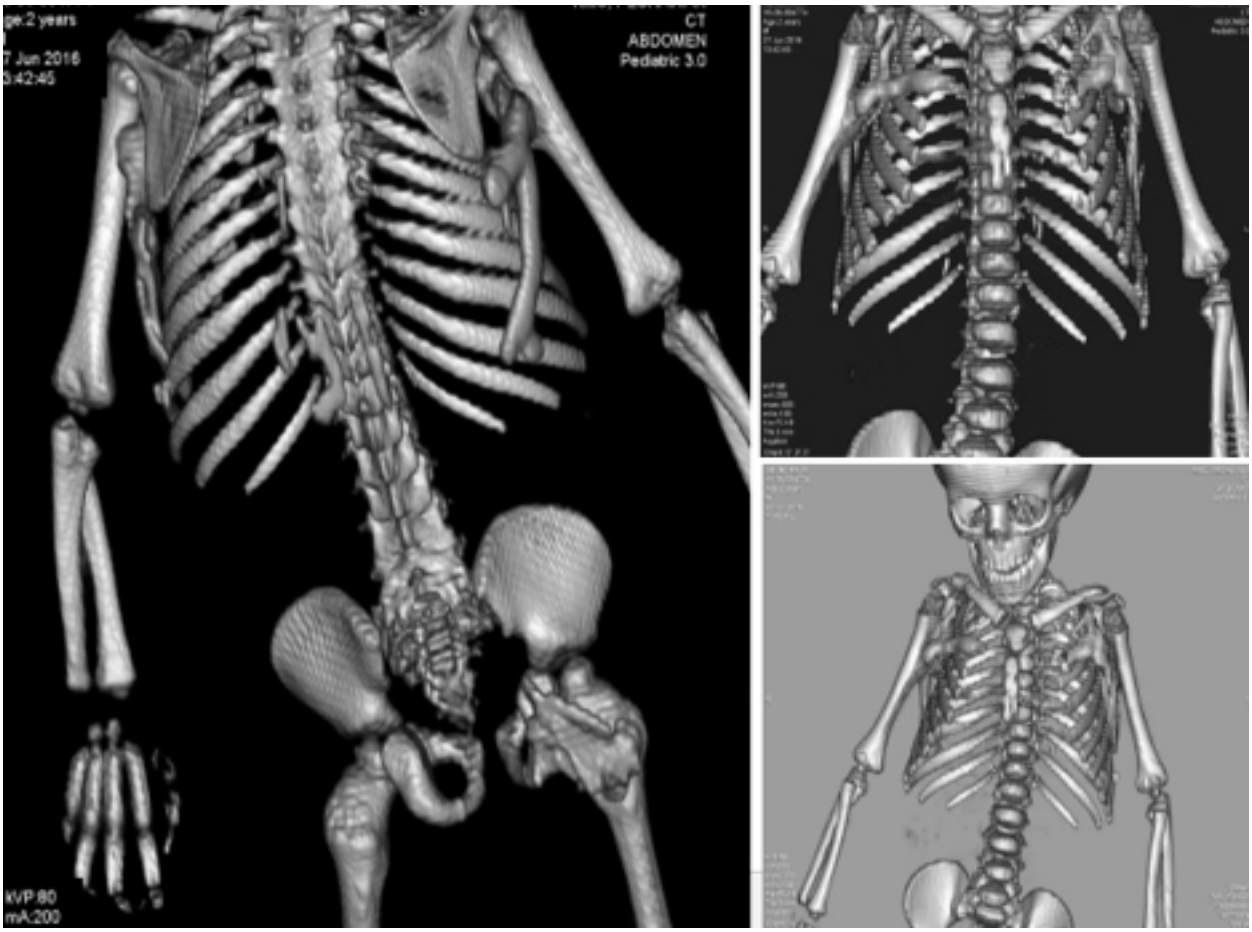


Figure 3: 3D reformatted and volume rendered images showing abnormal bone formation (green shaded) along chest cage, paraspinal soft tissues and along ischial bone



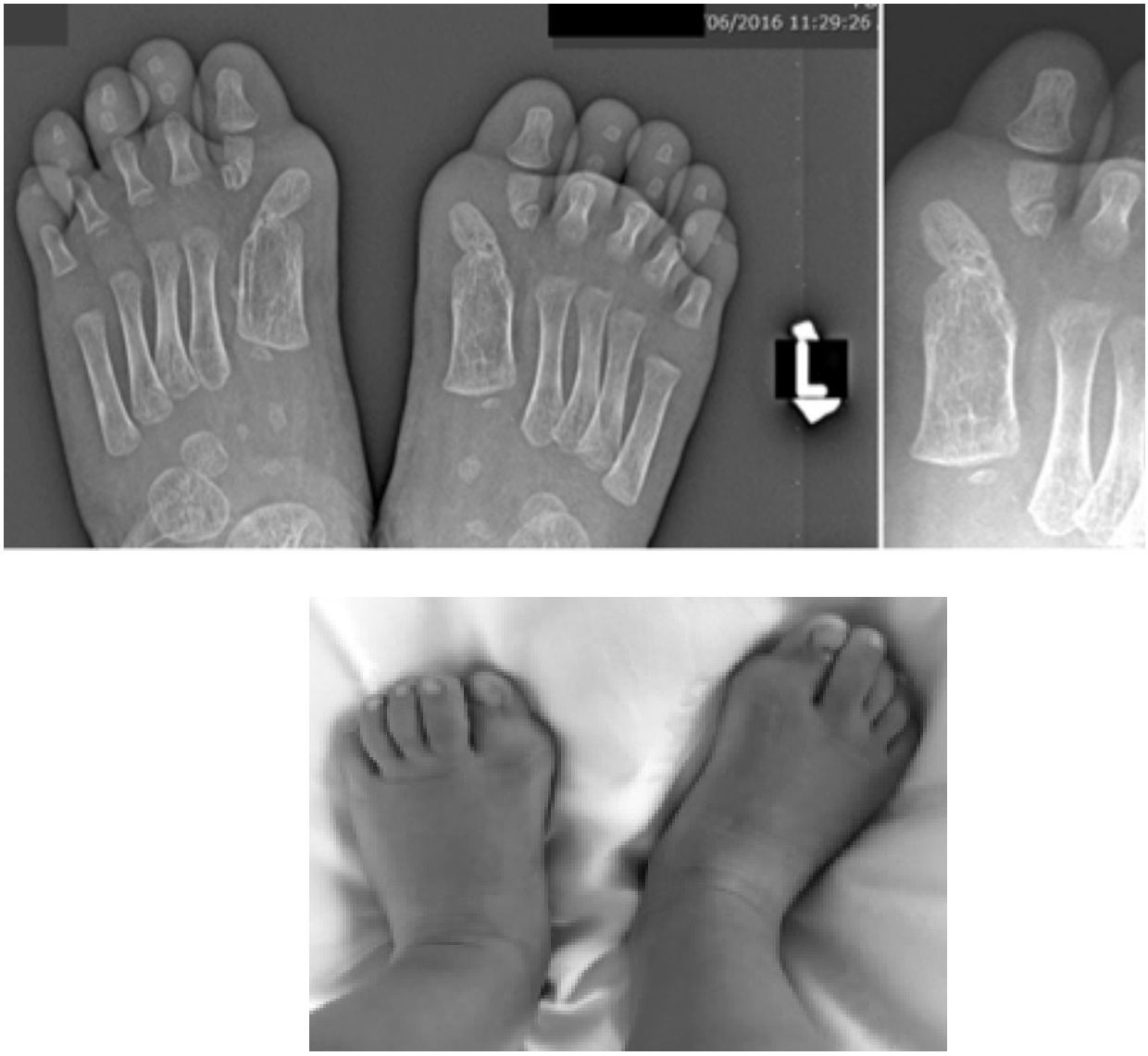
DISCUSSION

FOP is a catastrophic heterotopic ossification genetic disorder. Genetic analysis has revealed that the FOP gene is located on chromosome 4 and mutation causes over-expression of bone morphogenetic protein (BMP4)[2]. This disabling condition of progressive skeletal malformations is characterized by heterotopic ossification. The disease flare-ups are episodic being precipitated by trauma to soft tissues. Clinical features which define classic FOP are progressive heterotopic ossification in specific spatial pattern and big toes abnormality. At birth, other than the big toe abnormality, these individuals appear normal[3]. During the first decade of life, painful soft tissue swellings develop and transform into bone (skeletal muscles and connective tissue are replaced by ribbons, sheets, plates of heterotopic bone) through endochondral ossification process[4]. This, later on, leads to permanent immobility[5]. Later in life, even minor trauma like intramuscular injections, blunt trauma causing bumps or bruises, illnesses and even muscle fatigue can trigger painful new flare-ups of FOP leading to further progressive new bone formation[6].

Typically, the FOP involvement is first evident in the dorsal axial, cranial and proximal body regions and later on seen in the ventral, appendicular, caudal and distal regions[4]. In the axial region, large bone lesions may appear on the neck and back and these swellings can be mistaken for tumour. It has been observed that axial lesions appear rapidly (even more rapid than any neoplasm). In the limbs, the swelling is mostly diffuse, where misdiagnosis of thrombophlebitis/DVT with edema can be made, which can be seen as a complication in patients with FOP owing to venous stasis due to generalized immobility[7]. The muscles usually spared from FOP are of tongue, extra-ocular muscles and diaphragm. Smooth and cardiac muscles are also spared.

In patients with FOP, there is no evidence of increased risk of fractures, however if fractured, the healing is accelerated in the heterotopic bone. Bone formation is episodic, but the disability is cumulative. Individuals

Figure 4: Hallux valgus seen with abduction of first metatarsophalangeal joint. X ray images show first metatarsal bone rotated and angled away from the second metatarsal bone (Metatarsus primus varus)



with FOP present with severe weight loss when there is involvement of jaw (ankylosis) and sometimes pneumonia or even right heart failure complicates rigid fixation of the chest wall. Death in these individuals often results from complication of thoracic insufficiency syndrome[8]. Regarding the surgical excision of these heterotopic bone masses, it has been shown in literature that surgical attempts for removal have commonly reulted in painful new bone growth episodes (surgery itself acting as soft tissue trauma). In cases where symmetrical big toes malformation association is not checked, FOP can be misdiagnosed as aggressive juvenile fibromatosis (extra-abdominal desmoid tumors), lymphedema or even malignancy like soft tissue sarcomas leading to unnecessary diagnostic biopsies in children that prove harmful and cause further disease progression[9]. Biopsy attempt at any site is harmful, especially in the neck or back where the later asymmetric ossification can lead to spinal deformity and further exacerbating the thoracic insufficiency syndrome.

The correct diagnosis of FOP is confirmed with radiological findings. Plain X ray of the swelling site along with X ray of bilateral feet should be the initial imaging modality. This should be followed by skeletal survey. Any swelling site in FOP can be seen as either soft tissue exaggeration, ossified foci or bands of ossified dense bone. X ray image of the swelling site shows heterotopic

bone formation in form of ribbons, bands and sheaths of abnormally located bones. X ray of feet shows Hallux valgus with abduction of first metatarsophalangeal joint (Figure 4). The first metatarsal bone can be seen as rotated and angled away from the second metatarsal bone. X ray chest usually shows abnormal ossified bone along the posterior and lateral thoracic ribs, usually forming ankylosis with the humerus, thus limiting the mobility. Computed tomography (CT) and magnetic resonance imaging (MRI) of axial and appendicular skeleton further gives a detailed overview of the extent of heterotopic bone and its detail (Figures 1 and 2). Multidetector CT with multiplanar reconstruction (MPR) and 3D reformation shows the abnormal soft tissues and bone formation (Figure 3), giving a generalized overview of the disease process. MRI is useful to detect early soft tissue lesions, even before ossification has started. Nephrolithiasis can be seen on x ray abdomen or ultrasound and is more common in older patients with FOP (could be due to immobilization and dehydration).

Diagnosis of FOP, although radiologically suggested with above findings, can be further confirmed by diagnostic DNA testing of the ACVR1 gene. It is not easily available in our setting. The routine biochemical evaluation of bone mineral metabolism is usually normal. Urinary basic fibroblast growth factor and serum alkaline phosphatase can be increased during flare-ups.

So far no medical treatment has shown any benefit but there is limited evidence for the use of steroids in acute flare ups. Non-steroidal anti-inflammatory drugs, leukotriene inhibitors and cyclo-oxygenase-2 inhibitors have been used but there is no clear evidence for their use. Bone marrow transplantation has been attempted but has failed to show any benefit in the management of FOP. Long term immunosuppression may have some role, but its use is debatable[10]. It has been shown that prevention and treatment of heterotopic ossification in FOP should be based on at least one of four principles: i) suppressing the immunological and/or inflammatory triggers; ii) disrupting the relevant inductive signaling pathways; iii) altering the relevant osteoprogenitor cells in the target tissues; and iv) modifying the tissue environment conducive to heterotopic osteogenesis.

Traumatic insult or surgical intervention is a trigger for progressive heterotopic ossification at the site of insult. For this reason, till present, no surgical treatment can be offered to these patients. Our patient has been advised routine follow up with an orthopedic surgeon and it has been advised to the parents to avoid physical trauma.

CONCLUSION

Fibrodysplasia ossificans progressiva is a rare catastrophic disorder with two classic features i.e. progressive heterotopic ossification and malformation of great toes. The extent of which can be easily diagnosed by reformatted CT images.

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