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Role of radiotherapy in management of Fibrodysplasia ossificans progressiva

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Abstract
Fibrodysplasia ossificans progressiva (FOP) is an extremely rare genetic disorder with widespread extra-skeletal bone formation. This disease usually begins with typical ossification pattern in early childhood, causing increasing disability and making patients totally disabled by the age of 30 years. Ectopic ossification can be triggered by any trauma as small as intramuscular injections, with no effective cure. Radiotherapy can be helpful in impeding ossification, although this treatment is not yet supported by strict evidence. Here in, we present a clinically diagnosed case of Fibrodysplasia Ossificans Progressiva managed with radiotherapy for symptomatic relief. This case indicates that radiotherapy can be useful in these patients.

Keywords: Fibrodysplasia ossificans progressiva, genetic condition, rare disease, palliative care

Introduction
Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant genetic disorder of the connective tissue characterized by extensive extra-skeletal enchondral bone formation leading to progressive disability [1, 2]. It affects approximately one in two million individuals [1]. It is associated with progressive heterotopic ossification of the connective tissue structures including skeletal muscles causing permanent disability due to contractures and joint fusions [3]. Heterotopic bone formation is episodic, occurring in a predictable sequence, starting in the upper back and neck region [5]. Attempting biopsy or surgical removal of heterotopic bone may provoke even more, sudden and painful new bone growth [4]. Treatment of FOP is multifactorial and is primarily based on injury prevention apart from appropriate clinical therapy [6]. Radiotherapy treatment might have some therapeutic effect by heralding new bone formation although literature referring to radiotherapy as a treatment modality in patients with FOP is extremely scarce.

Materials and Methods: A 35 years old male presented with the chief complain of diffuse inflamed hard swelling of the left arm (Fig. 1), with restricted movement at the left shoulder and elbow joint since 6 months. The patient had a history of fall over the left shoulder before the onset of symptoms. Initially a diffuse redness and swelling appeared over the affected area leading to progressive hardening of soft tissue and muscle in the left arm. He (inadvertently) underwent excision of bone mass with release of soft tissue around the shoulder region. Post surgery he developed increased stiffness and swelling in the left arm with complete loss of movement at the shoulder joint. Histopathological examination of the bone specimen was suggestive of fibrous tissue along with cartilage and bone, consistent with myositis ossificans.
Patient had a past history of developing multiple bony hard swellings since the age of 12 years. The swellings first started to appear in the back, progressing to involve various sites of the body like arms, hands and toes (Fig.2, 3). Swellings are associated with pain, especially those present in the back.
On physical examination multiple tender bony swellings were present all over the body with malformations of the toes. Chest X-ray including left shoulder joint and pelvis showed multiple abnormal fibro-calcific bands (Fig. 4,4.1). MRI left upper arm showed multiple

bridging osseous slings and plaque of soft tissue ossifications suggestive of Fibrodysplasia Ossificans. Patient was referred for radiotherapy. Simulation CT scan of left shoulder was done for radiotherapy planning and treatment (Fig. 5). He received radiotherapy to a total dose of 10Gy in 5 fractions to the left shoulder region (Fig. 6). On follow up after 1 month the swelling and pain over the left arm had reduced with regain of motion. At 6 months follow up patient was still maintaining the improved range of motion over the left shoulder joint, with reduced firmness over the left arm. After a follow up of 15 months the patient has sustained relief at the irradiated site with reduced pain, increased mobility and no swelling (Fig. 7). The patient is on continued the systemic treatment, with increased precaution to avoid trauma. Poor prognosis of the disease and lack of permanent cure has been explained to the patient.

Results and Discussion

Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant genetic condition causing progressive heterotopic ossification of the connective tissues leading to permanent disability. Studies have concluded that the estimate incidence of FOP is one in two million births [1]. The genetic mutation leading to FOP has been linked to chromosome 2q23-24 with heterozygous mutation in the glycine-serine activation domain of ACVR1, a bone morphogenetic protein (BMP) type 1 receptor [8, 9].

Initially, patients present with painful and hard, soft tissue swellings leading to heterotopic ossification. It usually occurs from birth up-to the age of 16 years (mean age 4.6 years), following spontaneous or trauma-induced "flare-ups" [3, 10]. Heterotopic ossification usually follows a typical pattern beginning in the cervical para-spinal muscles and later spreading from axial to appendicular, cranial to caudal and proximal to distal sites [5]. Scoliosis often results from asymmetric heterotopic bones connecting the trunk and pelvis [1], conductive hearing loss is a common feature associated with this condition, probably due to the fusion of the ossicles of the ear [11, 12]. Progressive episodes of heterotopic ossification lead to ankylosis of all major joints, rendering movement impossible [13]. Most patients with FOP are non-ambulatory by the third decade of life, and require lifelong assistance in performing daily activities. The median age of survival is approximately 41 years, with thoracic insufficiency as most common cause of death [13, 14].

In the presented case also symptoms developed at the age of 12 years beginning in the back and progressive to the whole body, making the patient non-ambulatory. Flare-up episodes were seen with trauma, like the attempted surgery.

Diagnosis of FOP is mainly clinical and it is usually made based on the presence of three major criteria [12]:

(a) Congenital malformation of the great toes,

(b) Progressive heterotopic enchondral ossification

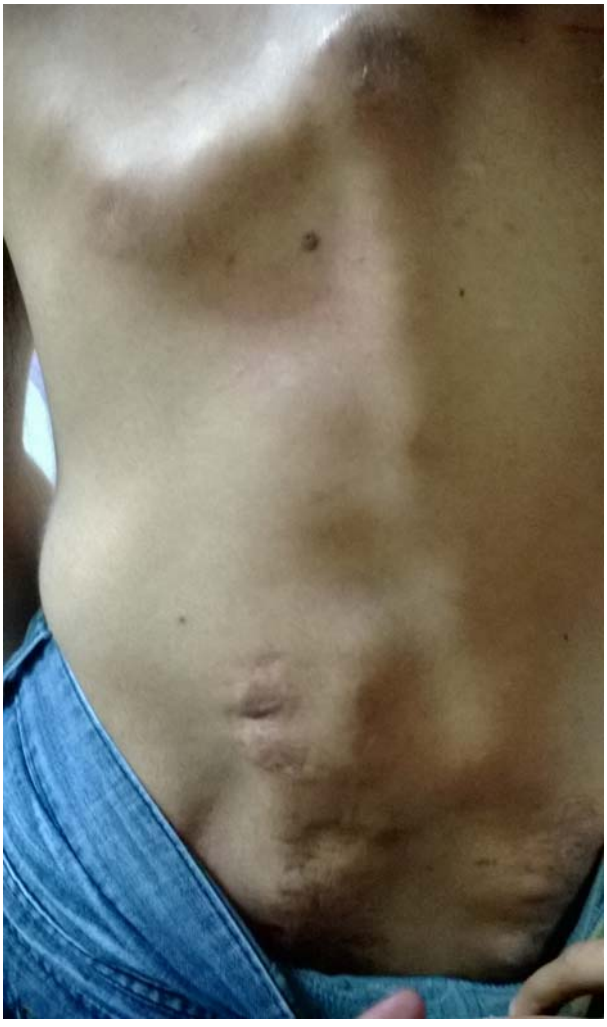
(c) Progression of the disease in well-defined anatomical and temporal patterns.

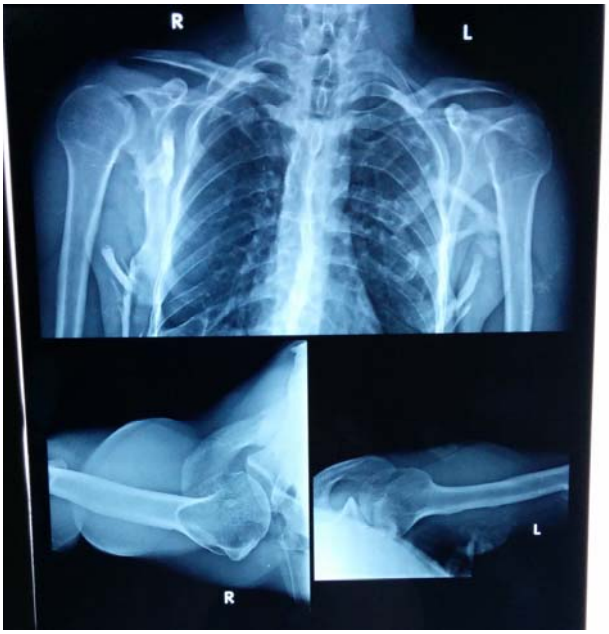
Laboratory tests may show raised ESR during the "flare-ups". On Imaging, radiographs and CT scan/MRI scan shows the heterotopic bones at various sites. Biopsy (although not advised) reveals monocytic, lymphocytic infiltration into skeletal muscles followed by myocyte degeneration, fibroproliferation, chondrogenesis and osteogenesis [15].

Prevention of trauma forms an important part of the treatment of patients with FOP [6]. Early diagnosis and avoidance of trauma are the basic principles treatment. Medical management is based on the guidelines published by Kaplan *et al* [6, 7]. In the acute phases of the disease corticosteroid like prednisolone is useful and for maintenance a combination of a leukotriene inhibitor and a Cox-2 inhibitor is used [6, 7].

Radiotherapy has been used in few cases based on the fact that radiotherapy is effective in preventing new bone formation and is used for prophylaxis of post-operative ossification and for spinal injuries (with no serious side-effects) [16]. Radiotherapy is efficient in killing proliferating cells and induction of bone re-modelling, two of the elements that are crucial in pathophysiology of FOP lesions [19].

Only few case reports are available indicating the role of radiotherapy in impending heterotopic ossification [17, 18]. Thus, the most effective fractionation schedule and dose is unknown and still a matter of debate.

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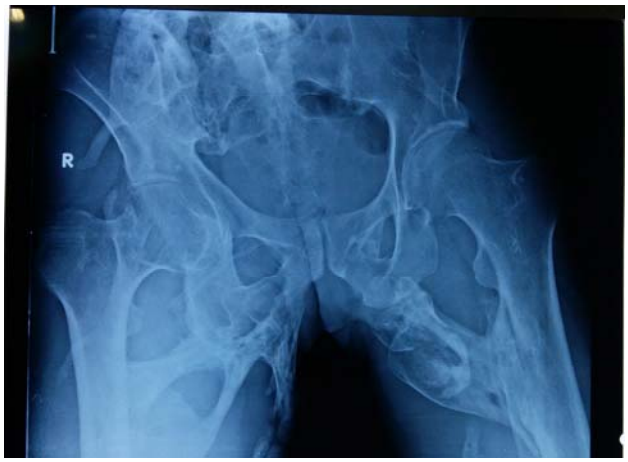
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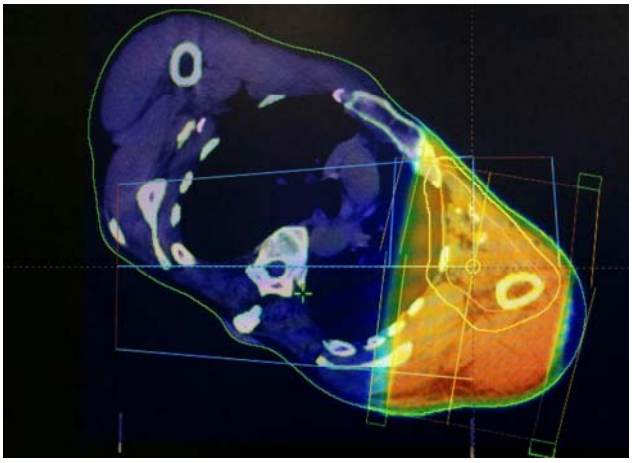

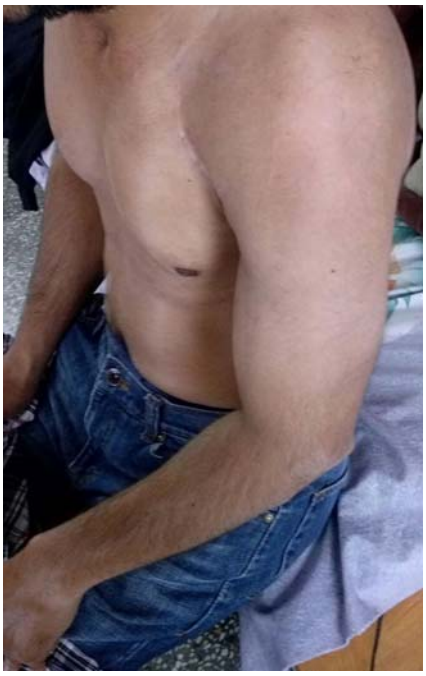

Conclusion

Fibrodysplasia ossificans progressiva is a rare disease with no effective treatment. The best approach is early diagnosis and prevention of trauma. Radiation therapy should be considered, to herald heterotopic ossification and improve quality of life. This treatment should be tested in larger number of FOP patients to evaluate its efficacy and establish standard treatment regimens.

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