Case Report of a Kid with Fibrodysplasia Ossificans Progressiva (FOP) and Literature Review for Management of FOP

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Authorship and contribution Declaration:
Each author of this article fulfilled ALL 04 Criteria of Authorship:
1. Conception and design of or acquisition of data or analysis and interpretation of data.
2. Drafting the manuscript or revising it critically for important intellectual content.
3. Final approval of the version for publication.
4. All authors agree to be responsible for all aspects of their research work.

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ABSTRACT

Fibrodysplasia ossificans progressiva is a connective tissue disorder in which connective tissues (ligaments, tendons) are gradually ossified and replaced by bone, there is extra skeletal bone formation. Any trauma can aggravate ossification in soft tissue. This condition usually is noticed at childhood. There is restriction of movements in major joints.

We report a case of 2 years old boy with fibrodysplasia ossificans progressiva, who was brought by his parents to our OPD with history of swelling on back, scapular region and forehead for last 4 months. Parents also reported limitations of movements in spine and bilateral shoulders. Radiographs shows heterotrophic ossification in paraspinal muscles of dorsolumbar spine, and latissimus dorsi and trapezius muscle. Clinical and radiological evidence was of Fibrodysplasia ossificans progressiva. Treatment strategy is mainly based on prevention of trauma or injury, educating parents about the disease and medical management for acute painful episodes.

Keyword: Fibrodysplasia ossificans progressiva (FOP), Heterotrophic ossification (HO), Myosotis ossification, Stone man disease Management

This article may be cited as: Wahab H, Khan A, Ibrahim M, Qadir RI. Case Report of a Kid with Fibrodysplasia Ossificans Progressiva (FOP) and Literature Review for Management of FOP. J Pak Orthop Assoc.2023;35(1):62-66.

INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP) also known as myositis ossificans progressiva is a rare connective tissue disorder. FOP is characterized by extra skeletal ossification of connective tissue (muscles, Ligaments, tendons and fascia). Any trauma can cause inflammation which leads to ossification of muscle/ connective tissue.[1]

Patient with FOP is normal at birth, with typical bilateral big toes deformity and microdactyly (hallux valgus and short metatarsals). The disease starts with sporadic painful swelling, usually presents as nodules at head or back. Typically attacks occur in 1st decade of life (at the ages of 3 or 4 years).[2,3] This condition usually is noticed at childhood, usually starts with neck movements restriction and the shoulders and proceeding down to limbs. FOP typically start in head and neck region and progress from cranial to caudal and dorsal to ventral and from truck to limbs. [2,4]

There is significant movements restriction, progressive loss of mobility. Disability is cumulative.[5]

In advance stages there is difficulty in opening the oral cavity which leads to difficulty in eating and talking. Osseous bridging between appendicular and axial skeleton is also reported in advance stages of the disease, there is also difficulty in breathing due to heterotrophic ossification (HO) around the rib cage that restricts lungs expansion. Leading to cor-pulmonale from thoracic insufficiency. [4]

Fibrodysplasia ossificans progressiva is an autosomal dominant, which means one altered gene in each cell is sufficient to cause the disorder.

The prevalence of the FOP is 1 in 2 million with no gender or regional predisposition. There are no known risk factors.[1]

FOP is caused by mutations in the activin A receptor type I (ACVR1)/activin-like kinase II (ALK2) gene on chromosome 2q24 that encodes the membrane type I receptor for bone morphogenetic proteins (BMPs).[6]

CASE REPORT

We present a case of 2 years old boy with fibrodysplasia ossificans progressive, who was brought by his parents to our OPD with history of swelling on back and forehead for last 4 months. According to parents this swelling was preceded with history of minor trauma. Parents initially noticed these swelling on dorsolumbar spine, bilateral scapular regions and now for last 4 months on forehead. It is associated with limitations of movements.

On examination an active and alert kid with bilateral short great toes (1st brachymetatarsia). There is a diffuse swelling on left side of forehead (frontal region), another swelling on left side occipital region. There was also a swelling on left side at inferior angle of scapula and a similar swelling on right side just distal to inferior angle of scapula and dorsolumbar spine. Shown in image 01. There is significant restriction in movements of dorsolambar spine and bilateral shoulder movements.

The child was the first-born of a non-consaguinous couple with no family history of the same disease.

Plan radiographs were taken which shows heterotrophic ossification in dorsolumbar spine, bilateral hallux valgus with microdactyly of the big toe. There was Heterotrophic Ossification (HO) in latissimus dorsi on left side and at HO at inferior angle of right scapula.

DISCUSSION

FOP is a rare disease 1 in 2 million population. It is estimated that FOP is misdiagnosed most of the time (About 90% of patients suffering with FOP are misdiagnosed), among these patients a large proportion undergo invasive diagnostic procedure (Approximately 67%). [7]

Literature review was done to look for recent advances in management of FOP.

Pediatricians and orthopedic surgeons are the first one to encounter patients with FOP with congenital deformity of great toes. Restriction of neck movements is one of the early signs in patients with FOP, due to heterotrophic ossification in neck region. [1,7]

The two classical features for diagnosis of FOP is congenital great toe deformity and progressive soft tissue mass (due to heterotrophic ossifications).

Diagnosis is confirmed with genetic analysis showing mutation in ACVR 1 gene.[6,7] Invasive diagnostic or therapeutic interventions are harmful for patient and leads to more aggressive HO and life-long disability.

Many approaches have been tried to treat FOP, but there is no proven strategy to treat FOP. For management of FOP patients one of the most effective and essential approach is to follow the "Primum non nocere" principle which means "First do no harm". [7]

The treatment of FOP is supportive. Prevent progression by avoiding invasive procedures, intramuscular injections, invasive biopsies and excision of FOP masses, manipulation of stiff joints and prevention of fall injuries should be prioritized. Acute flare ups should be managed with short term steroids, NSAIDs, Bisphonates, leukotriene inhibitors and mast cell stabilizers or radiotherapy. Scientist are trying to do targeted gene therapy in near future as this could be the only solution for this disease.[7,8,9,10]

Some studies suggest that use of Bisphosphonates (Etidronate) in high dose showed good results, however its side effects can't be completely ignored when given in high doses. In a study conducted in 2014 it was shown that Pamidronate is more potent as compared to Etidronate.

Surgical excision of FOP masses is contraindicated. If surgery is inevitable, short-term use of corticosteroids is recommended to inhibit ossification in the surgical site.[11,12]

Kardelen Gencer-Atalay in 2019 reported a case of 18 years old female with FOP and with 5 years follow up. He reported that short-term use of corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) is recommended for acute attacks and bisphosphonates for chronic disease. Treatment with low-dose steroids and bisphosphonates was continued because of joint limitation and pain increased after the steroid dose was stopped. Significant walking improvement (hip and trunk movement) was observed after 10 sessions of radiation therapy. [11]

In 2019 a literature review was done, case reports and clinical trial published between 2009 and 2018 were included.

Total 95 articles were reviewed only 14 were included (8 with non-interventional and 6 with interventional therapy)

36-years-old female patient with FOP having 13 years follow up was reported by Rogoveanue et al.

NSAIDs, physical therapy modalities, cyclo-oxygenase inhibitors and breathing exercises were used. During follow up pain was improved however, joint limitations remained same. [14]

According to report published by Bouvard et al. a patient who started treatment at the age of 12. NSAIDs and high-dose steroids were administered during the pain episodes and was followed up for up to 17 years while continuing to use various bisphosphonates.

29-year-old patient with painful swelling of soft tissue that turned into ossification was reported by Ulusoy. FOP was suspected clinically, oral etidronate treatment was initiated to prevent new ossification. General condition and ability to walk did not deteriorate during the one-year follow-up.

48-year-old patient with frequent flare-ups is reported by Gatti et al. Each flare up lasted a few weeks and resulted in new calcifications. There was no significant improvement with corticosteroid and bisphosphonate treatments, then the patient was started on rosiglitazone (an antidiabetic drug in the thiazolidinedione class) therapy. After a year and a half of treatment with rosiglitazone no new flares were detected but rather significant clinical improvements were noticed.

Palhares et al. reported two pediatric cases, with FOP before the age of 3. During flare-up periods Patients was given intravenous Clodronate (a non-nitrogen-containing bisphosphonate) along with continuous oral ascorbic acid. The frequency and severity of Flare-ups decreased significantly during treatment.[11]

Two patients with FOP who received Rapamycin were reported by Kaplan et al. Although Rapamycin is reported to be successful in animal models, but in both cases it in no way affected disease progression.

According to a case series by Kaplan et al. there was no response to corticosteroids, NSAIDs, cyclooxygenase inhibitors or bisphosphonates in seven patients with FOP. Flare-up intensity and frequency was significantly decreased with Imatinib (kinase inhibitors) therapy.

A clinical trial was published by Kitoh et al., It was included in it as case-based review designed to investigate Perhexiline maleate (a coronary vasodilator) efficacy and safety of in the treatment of FOP.

Author treated 5 patients for 12 months with Perhexiline maleate and followed for 2 years. As a treatment strategy for FOP Perhexiline maleate was not effective as 2 patients developed new heterotrophic ossifications.[13]

Current management of FOP is to avoid any trauma, for acute flares steroids, non-steroidal anti-inflammatory Drugs (NASIDs), Cyclooxygenase inhibitors (COX inhibitors), Mast cell stabilizers, or Bisphosphonates. Because of high-risk surgical complications that may trigger flares and intubation associated complications until very necessary surgical intervention should be avoided. In a high need most minimal invasive approach should be taken in practice.

Six cases with interventional therapy have been reported in the literature.[11]

Report generated by Ozkan et al. presents 21-year-old female with chest pain in left side and shortness of breath. The mass in left hemithorax was surgically removed and no recurrence was detected at 1-year follow-up.[15]

A case of 10 years old boy who presented with a painful mass on the chest wall was reported by Seok et al. there was progressive limitation in movement at his right shoulder. Active ROM exercises were taken into practiced with Naproxen given orally. After surgically removing of HO between pectoralis minor and major on 5th POD full range of motion was achieved.[16]

47-year-old male with limitations of both hips and shoulders movements in a period of 1 year was reported by Jayasundara et al. Four surgical resections were done with in two year timeframe targeting one joint at a time. Indomethacin after 4 surgeries and radiotherapy was given after the 5th surgery. [17]

17-year old boy with ankylosis of both temporomandibular joints and the right hip is reported by Duan et al. Hos from these joints were removed at the same session. Postoperative oral doses of NSAIDs and etidronate were given. During 2-years follow up there was significant improvement.[18]

Three FOP cases with significant deformities around neck region (chin-on-chest deformities) were reported by Moore et al. Because of treats of high risk complication one patient was followed without surgery while other two patients were successfully operated. Satisfactory long-term results of defect correction were observed in both patients.[19]

A 34-year old patient with FOP who had Difficulty in walking and progressive myelopathy was reported by Grobelny et al. Thoracic laminectomy and short-term use of corticosteroids showed significant improvement in walking and muscle strength.[12]

In 2020 Sukhmani Singh and colleagues reported the case of a 32-year-old man enrolled in a study evaluating palovarot (selective agonist of retinoic acid receptor gamma) to prevent formation of HO in patients with FOP. A year post starting palovarotene, patient had a fall resulting in intertrochanteric fracture of left femur. Intramedullary nailing (IM Nail) of the femur shaft was performed. 12 weeks post op x ray showed bridging HO at site of IM nail, although patient was on palovarotene during this time. Nine months after the left hip fracture patient had a second fall, for which intramedullary nailing of the right hip was done. Patient was again on Palovarotene. Post op x ray showed HO formed near the insertion site of the intramedullary rod. After each surgical procedure patient had prolonged recurrent flare-ups around the hips. The author reported that the efficacy of palovarotene in prevention HO could not be assessed, with no negative impact on Skin or fracture healing.[20]

Esmée Botman et al reported a systematic review 6 cases. One case received high dose radical treatment and 5 cases received low dose radiotherapy to prevent HO or treat patients with FOP. 4 out of 5 cases there was improvement in flare

up symptoms and reduction in HO formation. 2 out of 5 cases along with radiotherapy additional treatment modalities were also reported, NSAID in both cases and Bisphosphonate in one case.[5]

CONCLUSION

FOP is a rare disease. Early diagnosis is important in order to avoid iatrogenic injury caused by invasive procedure for diagnosis of the disease. Congenital deformity of the great toe in a child with microdactyly is considered a tool for early diagnosis of FOP.

The principle of "primum non nocere" should be followed, and injury prevention by all means is recommended. Acute flare ups should be controlled with short term use of high dose steroids, Bisphosphonates, Leukotrienes inhibitors, non-steroidal anti-inflammatory medications (NASIDs) and low dose radiotherapy.

Parents counselling and community awareness regarding the disease and its progression and avoiding vaccination and intra-muscular injections and iatrogenic injury should be avoided by all means.

Conflict of Interest: None

Grants/Funding: None

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