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Case Report Open Access

First Reported Case of Fibrodysplasia Ossificans Progressiva in Saudi Arabia

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Abstract

Fibrodysplasia Ossificans Progressiva (FOP) is a rare Autosomal Dominant disease that is characterized by deep ossification that ankyloses joints. The diagnosis confusion and the treatment dilemma are discussed in this case report of a 3 year old Saudi male. Literature review revealed that no FOP cases reported in Saudi Arabia. This case report is the first documentation of FOP in Saudi Arabia and reviews the literature for the latest treatment protocol.

Case Report

A 3 year old boy was born full-term with normal milestones. The boy was healthy until 6 months prior to presentation, when he had a minor trip at home and noticed to have subcutaneous swellings on the back and stiff neck. He was gradually progressing into a stiff neck and shoulders. He had no lower limb involvement; the child is still active and playing. Parents are concerned and anxious.

Past medical history: There was no fever or upper respiratory tract infection, no other anomalies. Currently he is not taking any medication. Has no allergies and his immunization is up to date.

Family history: he is the 7th born; all siblings are alive and healthy. There is no family history of similar disease.

Physical Examination: Active child with low set ears and wide nasal bridge.

The patient has flat spine; flat with no normal sagittal spine curvatures (Figure 1). He has multiple subcutaneous hard swellings in the back (Figure 2), arms and axilla, with no skin discoloration over the swellings, the swellings are non-tender and they are fixed to underlying structures. Patient has neck and whole spine stiffness to active and passive movement.

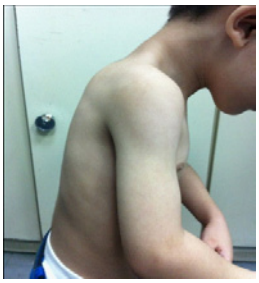

Figure 1: Lateral Picture of the patient with no sagittal balance.

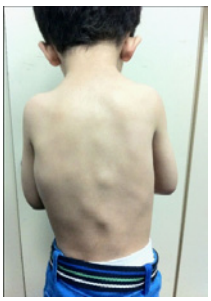

Figure 2: Picture of the patient's back with appearance of the deep nodules.

The shoulder joints are held in 10° abduction has active and passive abduction 10° to 60° bilaterally; elbows are limited in active and passive flexion extension from 20° to 90°. The wrists and hands are normal. Lower limbs examination is normal, except for bilateral Hallux Valgus and short first metatarsal (Figure 3).

Investigations: Blood profile is within normal limits. Plain X-rays showed soft tissue ossification in the axilla from the humerus to the scapulae, linear with small branching (Figure 4). The spine X-ray shows linear ossification from mid-thoracic to lower lumbar dorsal to the spinous processes, in the paraspinal muscles (Figures 5 and 6).

Foot X-ray: deformed first metatarsal head and fused to a delta shaped proximal phalanx of the big toe, with varus mal-alignment, the middle phalanx is also delta shaped and short. The big toe is in hallux valgus interphlalngus (Figure 7).

Discussion

Fibrodysplasia Ossificans Progressiva (FOP) is a rare Autosomal

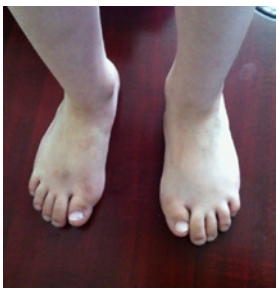

Figure 3: Foot picture shows the characteristic big toe deformity (short metatarsal and Hallux valgus).

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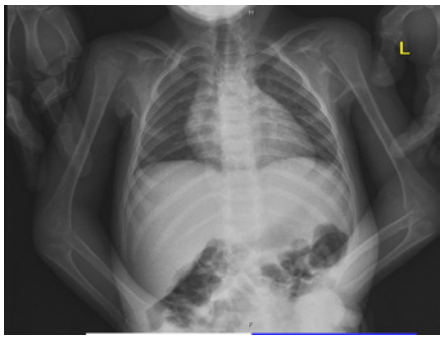

Figure 4: Chest radiograph with upper limbs shows deep nodules in the axilla.

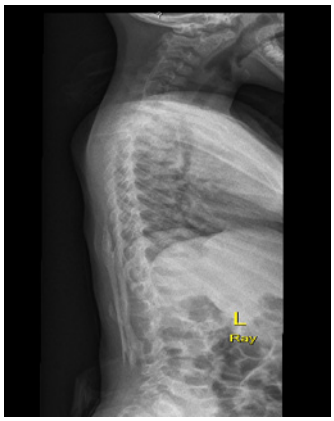

Figure 5: Lateral spine radiograph, shows longitudinal muscular ossification.

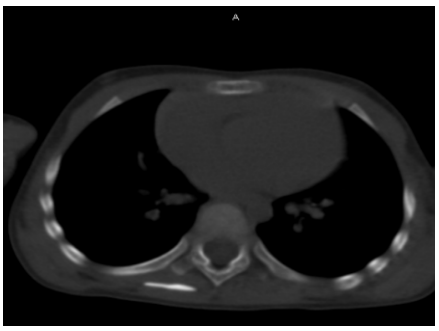

Figure 6: Chest CT scan, shows the posterior spine muscle ossifications.

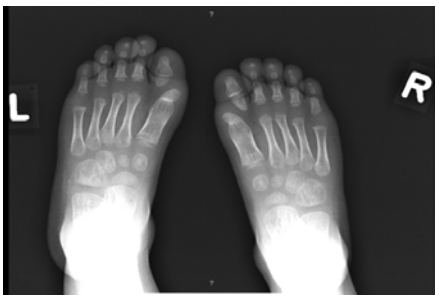

Figure 7: Foot radiograph, shows the typical delta first metatarsal, hallux valgus and hypoplastic middle phalanx, and absent proximal phalanx.

Dominant disease [1]. No case has been reported in the literature from Saudi Arabia, and no known registry for such cases.

The patient's presentation was typical of FOP as swelling and progressive stiffness of the neck and joints. But this patient has stiff neck and back by the age of 3 year, with fast progression, which is earlier than other cases in the literature.

Common differential diagnoses are: klipple Fiel syndrome, aggressive juvenile fibromatosis, lymphoma, and thoracic insufficiency syndrome.

The diagnostic deformity is the big toe deformity that is present in all patients [2].

He is the 7th born in the family, with all healthy siblings, which is explained by spontaneous mutation in the patient.

The treatment algorithm that the patient was given was first to follow guidelines in table 1, then to contact the pediatric orthopedic unit whenever the patient has new painful subcutaneous nodule to come to the hospital within the first 24 hours to start Prednisone 2 mg/kg/day for 4 days, and Ibuprofen 10 mg/kg/day for 1 week. If the flares are 48 hours old, then Ibuprofen alone.

The course of the disease, the expected symptoms, complications and the gravity was explained to the parents.

The patients continued to have occasional flares around 4 per year, unfortunately patient lost follow up at the age of 5 years.

Literature review

There are 150 cases of FOP reported in the United States of America. Point prevalence is one in 2 million populations [3]. Most cases of FOP appear to arise by spontaneous mutation [2].

The incidence in the United Kingdom is 1 per 1.64 Million [1].

In Saudi Arabia there are no official reported cases. There is no registry in the country to know the exact incidence and prevalence. The population of Saudi Arabia in the last sensuous in 2011 was 30 million (29,195,895) with children below 15 are 42.3% which is around 12 million, and with a yearly increased live births of around 600,000 per year, taking into consideration the world's incidence we should have at least 20 cases that are misdiagnosed or unreported.

There was no age of presentation definition, most reports states first decade of life, and most cases present at 8-10 years [4-6]. Our case was full clinical picture by the age of 3 years, which states the aggressiveness and the poor prognosis of the disease and that will be the earliest age reported in literature [7].

FOP is characterized by painful inflammatory soft tissue swelling that later transform most connective tissue to mature heterotopic

Activity	Rules
Falls	Should be avoided, no contact sports
anesthesia	General should be by a senior consultant
Injections	Subcutaneous is allowed Intravenous superficial is allowed No intramuscular injection
Immunization	Not during the flare ups, change the intramuscular to subcutaneous
Physiotherapy	Should be avoided
Occupational therapy	Done to help the patient with the daily activity
Procedures	Avoid biopsies, elective procedures

Table 1: General Guidelines in treating FOP patients.

ossification. Ribbons, sheets and plates of heterotopic bone replace skeletal muscles and connective tissue through endochondral ossification that leads to armament-like encasement of the bone and permanent immobility [4,8]. Those episodes are unpredictable, and non-preventable. The diagnostic deformity is shortened great toe with a single or delta shaped phalanx in all patients [2].

Several skeletal muscles are spared including the diaphragm, tongue, extra-ocular muscles [8], heart and smooth muscles [2].

Bone formation is episodic, but the disability is progressive, most patients are wheelchair bound by the third decade [8]. The functional changes happen due to the joint stiffness as the ribbons of heterotopic ossification cross the joints, commonly shoulders, hips, and knees.

Other skeletal anomalies are known in FOP like the stiff neck and shoulder, cervical spine anomalies, short malformed thumb, and short broad femoral neck [8].

Conductive hearing impairment is a common feature associated with this condition and it probably occurs due to the fusion of the ossicles of the ear [4].

Common complications are malnutrition due to ankylosed jaw, pneumonia and heart failure due to rigid thoracic wall [8].

FOP gene has been detected, and screening can be done for patients with abnormal big toe at birth. The gene is on the chromosome 2q23-24 region. The gene encoding activin receptor type IA/activin-like kinase2 (ACVR1/ALK2), a BMP type I receptor [7,8].

The biomolecular discovery is the over-activity of BMP 2 and 4, which is responsible for the enchondral ossification program [2,4].

Unfortunately all treatments provided are symptomatic, and surgery for removal of the heterotopic ossification will cause bleeding and more aggressive heterotopic ossification in the soft tissues, the wounds, and more stiffness, as reported in most literature in cases where a diagnostic biopsy was done before diagnosing the patients [9].

There is no treatment algorithm for FOP patients except following the general guidelines (Table 1). Treatment is by injury prevention mainly then by inhibition of inflammation [4].

Medical treatment has been classified by a panel of reviewers to three classes [8], Class I: Medications for control of symptoms of the acute flare-up in FOP (swelling and pain), like short-term use of high-dose corticosteroids, and use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and anti-angiogenic cox-2 inhibitors. The prednisone dose is 2 mg/kg/day (up to 100 mg) used as a single daily dose for a maximum of four days, within 24 hours of the onset of a flare-up. If the flare-up is more than two days old, prednisone is generally less effective [8]. If the flare-up responds to the medication but recurs when the prednisone is discontinued, a repeat 4-day course with a subsequent 10-day taper can be considered. Prednisone should generally not be used for flare-ups on the chest or trunk, as it is difficult to judge the exact onset of a new flare-up. Prolonged or chronic use of corticosteroids is of no benefit, and may accelerate heterotopic ossification. After the steroid use or if the flare-up is older than 48 hours then NSAIDs are used, or a cyclooxygenase-2 (cox-2) inhibitor can be used as early as two years, with gastrointestinal precautions.

Class II: Medications that have theoretical application to FOP, are approved for the treatment of other disorders, and have limited and well-described effects. Examples: Leukotriene inhibitors, mast cell stabilizers, and aminobisphosphonates (Pamidronate; Zoledronate).

The leukotriene inhibitor montelukast (Singulair) used at a dose of 5 mg or 10 mg per oral daily (starting age is 6 year). The combined use of montelukast and a non-steroidal anti-inflammatory agent or a cox-2 inhibitor can be considered as a long term treatment, following the discontinuation of a single 4-day steroid burst [8].

Trial of bisphosphonate use in FOP patients was written by Hickey et al. and they concluded that the use of etidronate in high dose in children did not stop the flare ups and had harmful but reversible effect on the growth plate in all the 7 patients in the trail [10].

Class III: Investigational new drugs. Examples: Signal transduction inhibitors, monoclonal antibodies targeting ACVR1, and retinoic acid receptor gamma agonists (presently under development) [8] are under development and are not yet available [8].

Trail of radiation therapy for FOP is done by Sodic et al. in 2011. They used small dose of radiation to impend ossification in a 35 year-old patient and concluded that the treatment is successful. We think that the method of treatment is valid, but more studies are needed before implementing this as a method of treatment [11].

Summary

FOP is a rare but devastating disease. It ossifies all muscles except the smooth muscles, and ankylose most joints.

A registry should be started in Saudi Arabia and in all countries to calculate the incidence and prevalence.

Unfortunately no treatment protocol has been effective, but avoiding any type of trauma to the muscles, and once flare up is diagnosed, except in the trunk, high dose of steroids in a short period of time seems the only evidence based treatment available. Other experimental drugs are in the literature but are yet to publish a long term result with statistical significance for those to be followed.

With the gene discovery, revolutionary treatment is awaiting a discovery.

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