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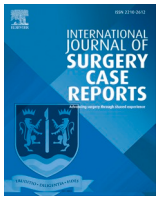

Case report

Fibrodysplasia Ossificans Progressiva: A rare disease due to unawareness, case report and literature review

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ABSTRACT

Introduction and importance: Fibrodysplasia Ossificans Progressiva is an ultra-rare genetic disorder of progressive soft tissue ossification. Due to unawareness and poor clinical suspicion, the rate of misdiagnosis, delay in diagnosis, and unnecessary diagnostic procedures leading to permanent injury and lifelong disability is common. Here we report this rare genetic disorder in a six years old child who was initially misdiagnosed as multiple exostoses and operated on.

Case presentation: A 6 year old child presented with swellings over the posterior neck and back for four years. The patient was misdiagnosed as a case of multiple exostoses and an excisional biopsy was done a year back. The swelling worsened after the excision; currently, she cannot move her neck from side to side, and flex and extend. Examination revealed multiple hard and slightly tender masses over the posterior neck, para scapular and thoracolumbar para spinal region. She also has hallux valgus deformity that had been present since birth. CT (computed tomography) scan confirmed extensive extra-skeletal soft tissue ossification.

Clinical discussion: The progression of heterotopic ossification is characteristically anatomic and orderly, typically initially involving the body's dorsal, axial, cranial, and proximal regions and later in the ventral, appendicular, caudal, and distal regions. Skeletal muscles of the tongue, diaphragm, extra-ocular muscles, cardiac muscles, and smooth muscles are inexplicably spared.

Conclusion: Early diagnosis prevents potentially harmful diagnostic and therapeutic procedures. The characteristic big toes malformation is the most important and best key for the early suspicion of the diagnosis.

1. Introduction

Fibrodysplasia Ossificans Progressiva (FOP) is an extremely rare, heritable disorder of connective tissue. It is characterized by congenital malformation of the great toes and progressive postnatal heterotopic ossification of skeletal muscles, tendons, ligaments, aponeurosis, and fascia [1,2]. It was first described by Guy Patin in 1648, but Munchmeyer reported the first case series in 1869, hence the eponym Munchmeyer's disease [2]. The estimated prevalence is 1 in 2 million with no ethnic, racial, gender, or geographic predisposition. The majority of FOP cases are due to sporadic de novo mutations. However, autosomal dominant transmission with complete penetrance but variable expression has been established [3]. Lack of awareness often results in misdiagnosis and unnecessary treatment. We report a case of FOP in a 6-year-old female child.

This work has been reported in line with the SCARE criteria [4].

2. Presentation of a case

A six years old female child presented with swellings over the posterior neck and back of 4 years. The swelling initially appeared over the posterior neck at the age of 2 years and progressively increased in size and number to involve the whole back. The swellings are intermittently painful. She has severely reduced side-to-side movement of her neck and bending of the back otherwise can move other joints. She is the 4th child in her family born from non-consanguineous parents after term pregnancy. Neither her siblings nor her extended family had a similar illness. She has no history of trauma. A year back she was misdiagnosed with multiple exostoses and excision was attempted. The pain and neck swelling worsened after the surgery.

On examination, there was a midline scar involving the posterior cervical and upper thoracic region. She has multiple hard and slightly tender masses over the posterior neck, para scapular, and thoracolumbar

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para spinal regions (Fig. 1). There were also small hard slightly tender masses on the left parasternal area. Further examination revealed a bilateral big toe malformation (hallux valgus) that had been present since birth (Fig. 2).

Laboratory studies were normal and genetic testing was not done because of the availability and parents' financial problem. Spine CT scan revealed extraskeletal ossification of the soft tissues of the posterior neck, parascapular and thoracolumbar regions (Fig. 2). X-ray of the foot confirmed bilateral hallux valgus deformities, which were revealed on clinical examination (Fig. 3).

Based on the above information the clinical diagnosis of the classic form of Fibrodysplasia Ossificans Progressiva was made. The parents were counseled regarding the cause, course, and prognosis of the disease and precautions to avoid any invasive procedure and physical trauma as much as possible. She is currently on follow-up and intermittent courses of non-steroidal anti-inflammatory drugs. During the last 6 months after the diagnosis, she was adherent to the instructions and precautions. There was no gross progression of the disease.

3. Discussion

Fibrodysplasia Ossificans Progressiva is an ultra-rare genetic disorder of progressive soft tissue ossification, which is usually the result of spontaneous de novo mutations, although familial cases of autosomal dominant inheritance have been described [5]. Our patient has no family history of FOP or similar illness, suggesting acquired mutation and the more prevalent sporadic form described in most other studies. The gene responsible for FOP is located on chromosome 2q23–24, a locus containing the Activin A receptor type 1 (ACVR1) gene encoding a BMP type 1 receptor. A recurrent heterozygous missense mutation in the glycine-serine (GS) activation domain of ACVR1 was identified in all affected individuals with classic features of either sporadic or inherited FOP, establishing mutation of this gene as the definitive cause of FOP and making molecular confirmation possible [1,2,6].

The prevalence of Fibrodysplasia Ossificans Progressiva is 1 in 2 million populations. However, only about 700 cases have been reported worldwide, indicating a lack of awareness among healthcare professionals [6]. In Ethiopia, a country with a population of over 120 million, only one case has been reported [7]. FOP patients appear normal at birth except for characteristic malformations of the great toes that are present in all classically affected individuals [1]. In addition to malformations of the great toes, other less common skeletal malformations include proximal medial tibial osteochondromas (~90 % of patients), orthotopic fusions of the posterior elements of the cervical spine (~80 % of patients), malformations of the thumbs (~50 % of patients), short broad femoral necks (~50 % of patients) [1,2]. Although the absence of these skeletal anomalies in a patient with malformed great toes does not exclude the diagnosis of FOP, their presence individually or in combination further strengthens the clinical diagnosis of FOP. FOP has been classified into three types based on clinical criteria [8]: The Classic FOP is defined as patients having the two defining clinical features of FOP (characteristic congenital malformation of the great toe and progressive heterotopic ossification). The second type is FOP plus, defined as patients having the classic clinical features of FOP plus one or more atypical features (normal or minimal changes of great toes, childhood glaucoma, Marfan's syndrome, and cryptorchidism). Lastly, the FOP variant is diagnosed in individuals having major variations in one or both of the classic defining features of FOP. Our patient has bilateral hallux valgus deformities and progressive and characteristic heterotopic soft tissue ossification. During the first decade of life, most children with FOP develop episodic, painful inflammatory soft tissue swellings. Some of these swellings regress spontaneously, while most transform soft connective tissues — including aponeurosis, fascia, ligaments, tendons, and skeletal muscles into mature heterotopic bone [2,9]. The progression of heterotopic ossification is characteristically anatomic and orderly, typically initially involving the body's dorsal, axial, cranial, and proximal regions and later in the ventral, appendicular, caudal, and distal regions. Skeletal muscles of the tongue, diaphragm, extra-ocular muscles, cardiac muscles, and smooth muscles are inexplicably spared from HO [1,2,9]. In our patient, the HO (heterotopic ossification) initially appeared over the posterior neck and progressed to the parascapular area and lumbar paraspinal regions respectively. Recently two small swellings appeared on the left side of the parasternal area. The clinical presentation of rapidly appearing soft-tissue swelling in FOP has led many physicians to consider neoplasm as the underlying diagnosis. Cancer and other tumors were the most common initial diagnosis in a recent study of FOP patients worldwide who had undergone a biopsy of a soft tissue lesion [1,10]. Our patient was initially misdiagnosed as having multiple exostoses and operated on. Several triggering factors have been identified and include minor trauma such as intramuscular immunizations, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises, falls, or influenza-like viral illnesses, resulting in painful new flare-ups of FOP leading to progressive HO (heterotopic ossification) [1,10]. Attempts to surgically remove heterotopic bone often provoke explosive and painful new episodes of bone growth, which was exactly what happened in our case. Scoliosis is a common finding because of asymmetric heterotopic bones connecting the trunk and pelvis [11]. The fusion of ossicles of the middle ear leads to conductive hearing loss, which is a common feature associated with this condition [6,12]. The typical onset is early

Fig. 1. Clinical photography showing multiple hard masses over the posterior neck and thoracolumbar spinal paraspinal region.

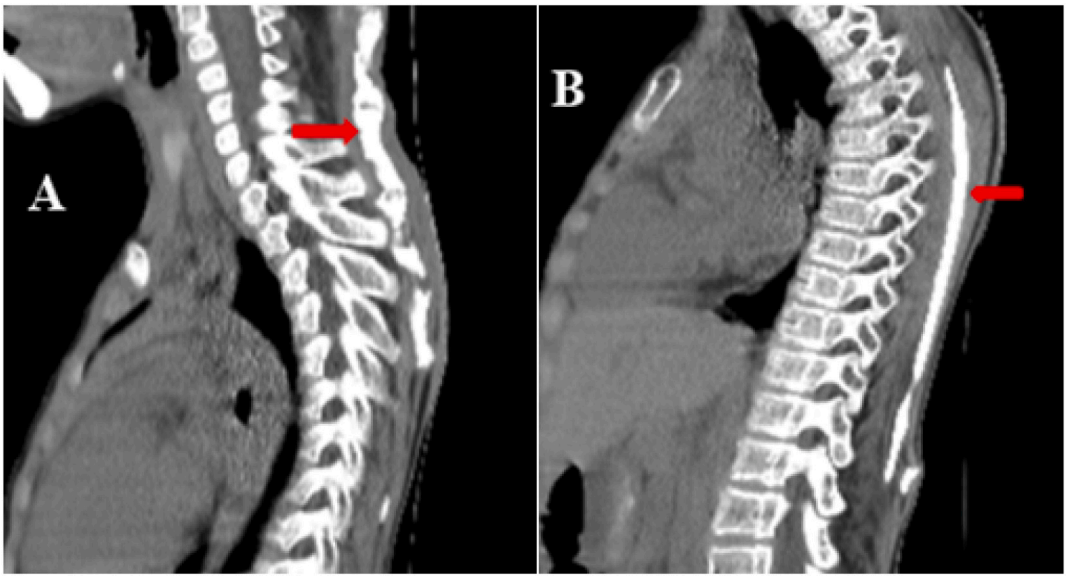

Fig. 2. A and B) Sagittal computed tomography showing posterior neck and thoracic paraspinal soft tissue ossification (red arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

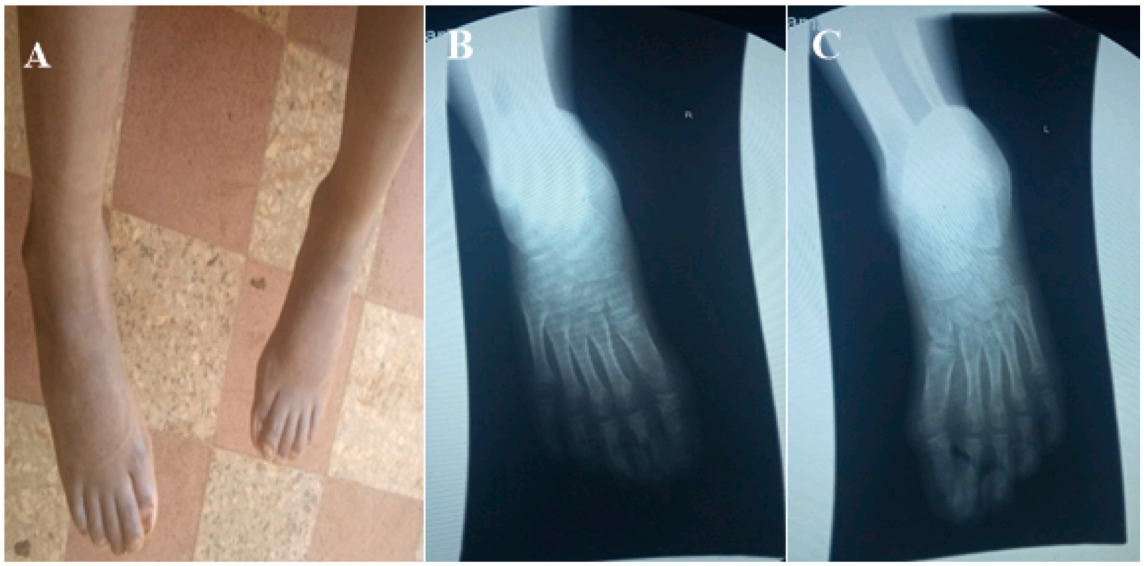

Fig. 3. Photograph (A) and foot X-ray showing bilateral hallux valgus deformity (B, C).

childhood or adolescence and progresses slowly. Progressive episodes of heterotopic ossification result in ankylosis of all major joints of the axial and appendicular skeleton, rendering movement impossible. In the second decade of life, most patients with FOP are confined to a bed or wheelchair [9,13]. In addition to the disability and suffering of the patient, there is a huge burden on their families, both emotionally and financially. FOP is not only an extremely disabling disease but also considerably shortens lifespan. The most common cause of death in FOP is cardiorespiratory failure resulting from kyphoscoliosis, costovertebral malformations, and ossification of intercostal muscles. The terminal course of patients who died of cardiorespiratory failure was similar to that of severe pulmonary hypertension [10,14,15].

Due to unawareness and poor clinical suspicion, the rate of misdiagnosis and delay in diagnosis is high. About 90 % of cases are misdiagnosed, and 67 % undergo unnecessary diagnostic procedures leading to permanent injury and lifelong disability in more than 50 % [8,16,17]. In underdeveloped countries where diagnostic procedures are expensive and not easily accessible, clinical suspicion based on great toe findings alone can be sufficient in assisting the initial diagnosis. Subsequent confirmatory testing (genetic analysis of ACVR1 mutation) though not available in Ethiopia, can later be arranged before heterotopic ossification (HO) and the appearance of severely restricted joint mobility but its use is not of any therapeutic value to the patient yet.

The ultimate treatment of FOP will likely be based on integrated knowledge of the cellular and molecular pathophysiology of the condition. The rarity of FOP and the unpredictable nature of the condition make it extremely difficult to assess any therapeutic intervention previously. A multitude of therapeutic agents has been tried without success. Currently, analgesia with non-steroidal anti-inflammatory drugs and a short course of steroids started at the onset of a flare-up is the mainstay of treatment. Our patient has been treated with intermittent courses of non-steroidal anti-inflammatory drugs. Research to develop treatments for FOP has focused on targeted inhibition of the ACVR1 receptor, ACVR1 ligands, BMP pathway signaling, the pre-osseous

chondrogenic anlagen of HO, and inflammatory triggers of disease activity [10]. These offer hope for the future. To date, there is no proven effective prevention or treatment for FOP.

4. Conclusion

FOP is an extremely rare disease that is often misdiagnosed despite its distinctive features. Awareness of this condition is the key to making an early diagnosis and avoiding unnecessary invasive diagnostic and therapeutic procedures which may promote progression. Thus, General physicians, pediatricians, and radiologists should be aware of the characteristic features of FOP before or even after the development of heterotopic ossification. The characteristic big toe malformation is the most important and best key for the early suspicion of the diagnosis.

Abbreviations

ACVR1 Activin A receptor type 1
BMP bone morphogenetic protein
FOP Fibrodysplasia Ossificans Progressiva
HO heterotopic ossification

Ethics approval

Not applicable.

Consent for publication

Written informed consent was obtained from the patient's legal guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief.

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CRediT authorship contribution statement

YH: Writing original draft, Conceptualization, Data curation, Review, and editing. FT: Conceptualization, Review, and editing. AJ: Radiology data collection, interpretation, and manuscript review. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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