A CASE OF FIBRODYSPLASIA OSSIFICANS PROGRESSIVA WITH PRIMARY AMMENORRHOEA

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ABSTRACT

Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant hereditary disorder affecting around one in two million people. It is characterized by heterotopic calcification in muscles, tendons, ligaments, membranes and aponeurosis. It is the only known disorder in which one kind of tissue is converted into another. There is no gender, ethnic or geographical preference. We describe the case report of fibrodysplasia ossificans progressiva in 28 years old female with primary amenorrhoea, first of its kind from Pakistan.

Key Words: *Fibrodysplasia ossiificans progressiva, heterotopic ossification, primary amenorrhoea, sclerosis, corticosteroids.*

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INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP) first reported by Patin in 1648, is an extremely rare and disabling autosomal dominant hereditary disorder affecting 1 in 2 million population.[1] There is no gender, ethnic or geographical preference. Recent studies have shown that ACVR1 (activin A receptor, type I; OMIM 102576) gene, which encodes the bone morphogenetic protein (BMP) type I receptor protein, is responsible for this disease.[2] Fibrodysplasia ossificans progressiva was formerly called myositis ossificans till it was realized that besides muscles other connective tissues such as membranes, tendons, ligaments and aponeuroses are also involved in the disease process.

Several subtypes of FOP (myositis ossificans) exist including post-traumatic myositis ossificans (PTMO), non traumatic/pseudo malignant myositis ossificans and myositis ossificans progressiva (MOP)[3]. With extensive progressive heterotopic ossification of the tissues the affected individual becomes progressively rigid and apparently 'turns to stone'. Children with fibrodysplasia ossificans progressiva characteristically have short great toes with halux valgus deformity. Lumps of ectopic bone formation usually start before 10 years of age, initially involving the muscles at back or neck and then spreading to limbs. Trauma can trigger off the heterotopic calcification cascade. Lumps of new bone formation and joint fusion can occur even without trauma. Early FOP flare ups are associated with intense mast cell, macrophage and lymphocytic infiltration into skeletal muscles and are often accompanied by intense inflammatory changes. Because the disease is so rare so the lumps are often misdiagnosed as cancer and biopsies are taken from the lumps which can actually exacerbate bone growth.

FOP with primary amenorrhea is a very rare condition.[4] The differential diagnosis of primary amenorrhoea is broad and can range from genetic abnormalities to endocrine disorders, psychological, environmental, and structural abnormalities of ovaries, uterus, or vagina. Regular menses is a sign that normal amounts of estrogen, androgens and progesterone are being produced by ovaries. These sex hormones play an important role in building and maintaining bone mass. Late menarche was associated with a three fold rise in the risk of wrist fracture[5]. It has been reported that mutations in BMP4 cause eye, brain, and digit abnormalities. BMP4 signaling through ACVR1 has been speculated to lead to some of the atypical features in FOP patients[6]. However, it is not known if atypical FOP features are intercurrent findings coincidentally associated with FOP or whether they are casually related to the underlying mutations in ACVR1 and unmasked by polymorphisms in the BMP or other signaling pathways in the affected individuals[4]. We present the first case report of fibrodysplasia ossificans progressiva with primary amenorrhoea from Pakistan.

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CASE REPORT

A 28 years old female was admitted in Neurology Unit, Lady Reading Hospital, Peshawar with a history of progressive generalized rigidity involving muscles and tendons of the back, limbs and jaws for the last 8 years. There was also a history of appearance of hard, rounded (1-2 cm), mildly tender lumps along tendons and muscles at various places especially on her back, legs and arms for the same duration. She was initially diagnosed as having myositis and/or arthritis and was treated accordingly though she had no radiographic record of her initial condition. During the initial 2 to 3 years, the lumps appeared at places of trauma only and then resolved gradually over a period of 3-12 months. For the past 5 years they were appearing de novo and were not resolving. Due to her extremely rigid state she was bedbound for 3 years with generalized wasting, and fixed flexion deformities of upper limbs and extension of lower limbs. Her head was turned to the left side with limited range of movement. Her body mass index was very low at 15.

There was limited opening of her mouth due to reduced movement at temporo-mandibular joints, thus making it difficult for her to speak and eat. One noticeable feature during her general physical examination was her short toes which were laterally deviated bilaterally. There was no family member suffering from the same condition. She did not consent for her photographs. On further enquiry, she denied any menstrual bleeding. There was poor breast tissue development. Her scalp hairs were adequate and although she did not allow genital examination, she gave a history of normal growth and female pattern of hair distribution.

Her baseline investigations revealed normal complete blood picture and erythrocyte sedimentation rate. Serum levels of calcium (9.6 mg/dl), phosphorus (3.3 mg/dl), alkaline phoshatase (184 u/l), follicle stimulating hormone (44 mU/ml), leutinizing hormone (30 mU/ml), were all within normal limits. Ultrasound scan of abdomen and pelvis was unremarkable with no evidence of ovarian or uterine pathology. X-rays of temporomandibular joint and cervical spine revealed gross sclerosis at temporomandibular joints and hypoplasia and rarefaction of vertebral bodies with fusion at facet joints of cervical vertebrae, and extensive calcification of paravertebral muscles respectively (Figure 1).

X-ray of left knee joint revealed extensive ossification of patellar tendon (Figure 2). X-ray of left foot showed short, laterally deviated 1st metatarsal as well as rarefied and sclerosed bones (Figure 3). On the basis of history, clinical presentation, laboratory and radiological workup a diagnosis of fibrodysplasia ossificans progressiva with primary amenorrhoea was made.

SCLEROSED TEMPOROMANDIBULAR JOINT, HYPOPLASIA OF VERTEBRAL BODIES AND FUSION OF FACET JOINTS OF CERVICAL VERTEBRAE WITH CALCIFICATION OF PARAVERTEBRAL MUSCLES.

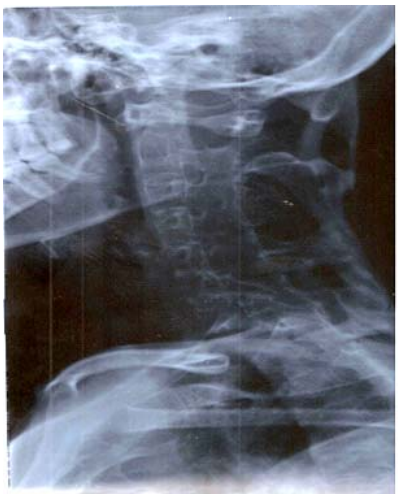

Fig. I

OSSIFIED PATELLAR TENDON

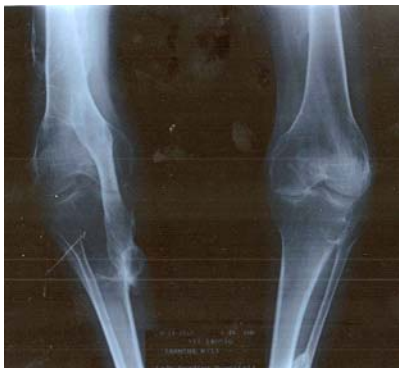

Fig. II

LEFT FOOT SHOWING SHORT, LATERALLY DEVIATED HALUX AND SCLEROSED BONES.

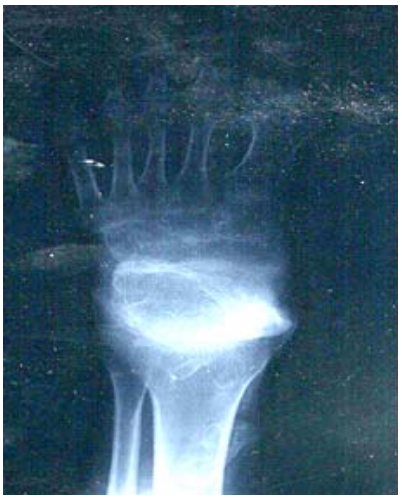

Fig. III

DISCUSSION

This is the first confirmed case of fibrodysplasia ossificans progressiva presenting with primary amenorrhoea, to our knowledge. This lady remained undiagnosed for many years, receiving treatment for muscular disorder and/or arthritis until it was realized that she was gradually turning into a bone. Several atypical FOP features e.g., aplastic anemia, primary amenorrhoea, blindness, glaucoma, polyostotic fibrous dysplasia, deafness, baldness, mental retardation, craniopharyngioma, etc. have been mentioned in previous case reports[3,5,7] but primary amenorrhoea has never been mentioned as a case report like this case.

Our patient presented at an advanced stage of the disease with extensive tissue involvement. Our investigations revealed neither a hormonal cause nor a structural adnexal abnormality to account for her primary amenorrhoea. We believe that her primary amenorrhoea was secondary to her very poor nutritional status. Her body mass index at presentation was only 15. We speculate that she had been running a low body mass index since her childhood. The other potential explanation for primary amenorrhea in FOP could be hypopituitarism caused by extensive ossification of the base of the brain. However, this was not confirmed in our patient.

Malformed great toes may raise the clinical suspicion of FOP in earlier stage of life leading to timely selection of the appropriate, confirmatory genetic testing. This earlier clinical diagnosis of FOP will prevent the patient from unnecessary and harmful diagnostic and therapeutic procedures.[7] The shortened big toes, each possessing only a single phalanx which may be deviated laterally (type 1) are highly indicative of FOP.[8]

There is no definite treatment of FOP. Avoidable factors which can precipitate ectopic ossification include local trauma, careless venepuncture, intramuscular injections, biopsy of the lumps and operations to excise the ectopic bone[9]. During flare ups corticosteroids along with non-steroidal anti-inflammatory drugs (NSAIDS) are used. The use of bisphosphonates has been found to produce some degree of improvement in mobility, normalization of deranged calcium/phosphate metabolism and a decrease in alkaline phosphatase levels with slower rate of new bone formation. Rosiglitazone with small doses of prednisolone was found to be effective in a patient with FOP.[10] Our patient was also treated on similar lines with the use of non-steroidal anti-inflammatory drugs and bisphosphonates. In future, effective treatment for FOP and other common conditions of heterotopic ossification, may be based on therapeutic options that block activin A type 1 receptor/activin-like kinase 2 (ACVR1/ALK 2) signaling.[11]

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CONFLICT OF INTEREST

Authors declare no conflict of interest