



## Early Recognition of Fibrodysplasia Ossificans Progressiva-Important For the Clinician

Ankur Singh,<sup>1</sup> Gaurav Pradhan,<sup>1</sup> Chandravati Kumari,<sup>1</sup> Seema Kapoor<sup>1</sup>

<sup>1</sup>Maulana Azad Medical College, New Delhi, India.

### ABSTRACT

Fibrodysplasia ossificans progressiva is a rare disorder of heterotopic ossification. Procedures like biopsy and surgery are known to be aggravating factors in promoting heterotopic ossification. Clues to clinical diagnosis may therefore be a great advantage to treating orthopedician. Valgus deformity of great toe is an important diagnostic clue for treating physicians and thus aids in preventing the clinicians from subjecting the patients to unnecessary invasive and traumatic procedures. Hence clinical clues to early diagnosis are important in establishing the correct diagnosis and directing future management.

**Keywords:** *fibrodysplasia ossificans progressiva; valgus deformity of greater toe.*

### INTRODUCTION

Fibrodysplasia ossificans progressiva is a genetic disorder of ectopic ossification and congenital valgus deformity of big toes. The prevalence of the condition is 1 in 20,00,000.<sup>1</sup> Sites of ectopic ossification are muscles, tendons and joint capsule. The disease follows a course of exacerbations separated by variable intervals. Consecutive spells can be spontaneous or triggered by intramuscular injections and surgical operations. Most cases are sporadic, but familial ones are inherited in autosomal dominant pattern. Thus establishing the correct diagnosis is important in deciding management, prognosis and to avoid iatrogenic harm. Clinical clues which would alert the treating surgeon are therefore of paramount importance.

### CASE-REPORT

A 6 year old boy presented with swelling in paraspinal muscles of the thoracic region for duration of 3 months. He had torticollis of neck on right side for same

duration. Development of torticollis was preceded by similar episode of swelling. Another painful swelling had appeared near left infraspinal area in last 5 days. There was inability to move the right hand away from body axis for last 1 month. There was no history of fever, trauma and similar swellings in other parts of the body. No history of contact with tuberculosis was forthcoming. There was no family history of similar complaints. There was history of on and off appearance of scalp nodules since the age of 1 year which were not painful and the parents had not sought any medical attention for them.

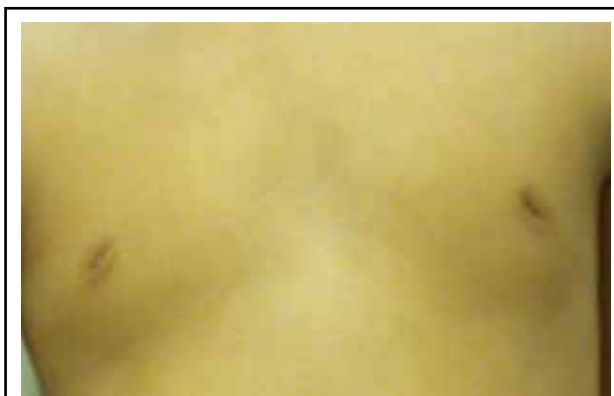
Examination showed swellings were hard, tender, (4.0 x 2.5, 3.0 x 1.5 cm) in size. Area around swelling was also hardened. There was no local rise of temperature

**Correspondence:** Dr. Seema Kapoor, Department of Paediatrics, Maulana Azad Medical College, New Delhi. Email: [drseemakapoor@gmail.com](mailto:drseemakapoor@gmail.com), Phone: 01123221927.

anytime in preceding last 3 months. Torticollis of neck was present on right side. Movements around right shoulder joint were painful and restricted. The only dysmorphic features present were bilateral hallux valgus (Figure 1) and bilateral inverted nipples (Figure 2). His neurological examination was normal. He was average in studies with normal intelligence. Rest of systemic examination was within normal limits.



**Figure 1. Bilateral hallux valgus, a clue to diagnosis.**



**Figure 2. Bilateral inverted nipples, a new finding.**

Needle aspiration of swelling performed prior to our consultation showed inflammatory infiltrates with no malignant cells. Zeihl-Nelson staining of smear was negative. Clinical radiographs showed sheets of ossification in soft tissues of pelvis (lateral to and above right innominate bone), along, along right lower ribs, right lateral chest wall extending in to soft tissues of right arm (Figure 3). All other laboratory investigations including Hemogram, peripheral smear, liver and kidney function tests were normal. Mutation analysis demonstrated ACVR1:c.617G>A, p.R206H in our case (Figure 4).

## DISCUSSION

Fibrodysplasia ossificans is a condition of heterotopic

bone ossification with congenital valgus deformity of big toe. Majority of cases present before 15 years of age. Our case presented to us at 7 years of age with paraspinal muscles ossification, torticollis of right neck, restriction of movement around right shoulder joint, and, valgus deformity of big toe. This abnormal toe was present from birth and has been reported in 79-100% of patients which is considered as a pathognomic sign.<sup>2</sup> Other mentioned features in literature are alopecia areata, deafness (conductive/sensorineural), wide spaced teeth, clinodactyly, short phalanx, absent or hypoplastic thumb, mental retardation and metaphyseal dysplasia. In our case the unusual finding is presence of bilateral inverted nipple. This could be an incidental finding in our case as prevalence of this condition in female population is 3.26%.<sup>3</sup> Although we report this finding in a boy, it needs to be further validated by carefully observing it in cases of FOP. The bilateral inverted nipple could not be explained by pulling effect of ossification in muscles around right shoulder joint as the muscles around left shoulder joint were without ossification; even then nipples on left side were inverted.



**Figure 3. Sheets of ossification in soft tissues of pelvis (lateral to and above right innominate bone), along right lower ribs, right lateral chest wall extending in to soft tissues of right arm.**

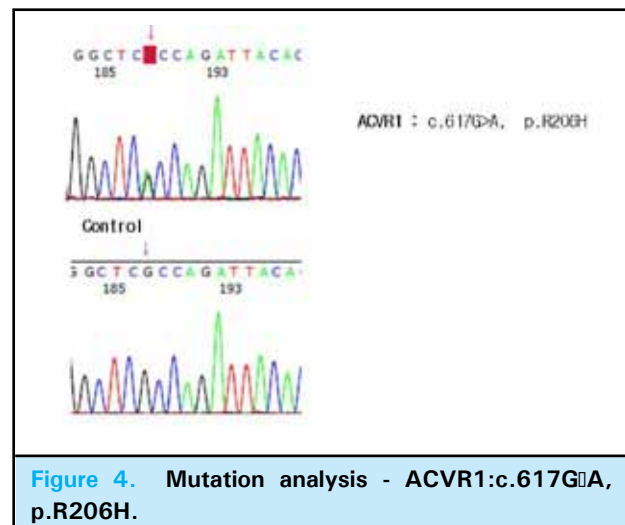
Scoliosis is a common finding and is often result of asymmetric heterotopic bones connecting trunk and pelvic bones.<sup>4</sup> Progressive episodes of heterotopic ossification leads to ankylosis of all major joints of axial and appendicular skeleton, rendering movement impossible. Generally in second decade of life, patients with FOP are confined to bed or wheel chairs.<sup>5</sup> Cardiopulmonary problems may occur and are associated with severe restrictive disease of chest wall.<sup>6</sup> Our case had classical progression of disease with involvement of right sternocleidomastoid muscles leading to torticollis, painful hard swelling on back in thoracic paraspinal area, restrictive movement deformity of right shoulder joint, scoliosis and valgoid deformity of bilateral big toes.

The diagnosis of FOP is basically clinical and it is usually made based on the presence of three major criteria as outlined by Delai et al.<sup>7</sup> Congenital malformation of great toes, progressive heterotopic enchondral ossification (heterotopic bones that gradually form the cartilage) and progression of disease in well defined anatomical and temporal patterns offer diagnosis. Imaging exams like radiographs and tomographs shows the heterotopic bones and are useful to confirm the diagnosis. Biopsy is contraindicated and harmful.

Shore et al<sup>8</sup> mapped FOP to chromosome 2q23-24 by linkage analysis and identified an identical heterozygous mutation (617G>A;R206H) in the glycine-serine (GS) activation domain of ACVR1, a BMP type 1 receptor, in all affected individuals examined. Protein modeling predicts destabilization of the GS domain, consistent with constitutive activation of ACVR1 as the underlying cause of the ectopic chondrogenesis, osteogenesis and joint fusions seen in FOP. Nakajima et al identified the R206H mutation in three unrelated sporadic Japanese patients with FOP, indicating that this mutation is

common and recurrent in global population.<sup>9</sup> We also found this common mutation ACVR1:c.617G>A, p.R206H in our case (Figure 4). This finding further strengthens the view that R206H is commonest mutation reported worldwide irrespective of ethnicity, race and geographical location.

Our case is a prototype presentation of FOP, but presence of bilateral inverted nipple has not been reported so far. This extra skeletal deformity may be an incidental finding and it needs to be further validated. An early identification clue, like bilateral hallux valgus, even exists at birth. Knowledge of this simple clue can fetch an early diagnosis and timely management of case. This identification will prevent patients from subjected to irrelevant blood investigations, needle aspirations and surgical procedures. These unnecessary invasive procedures are known precipitating factors for disease exacerbations.



**Figure 4. Mutation analysis - ACVR1:c.617G>A, p.R206H.**

## REFERENCES

- Connor JM, Evans DA. Genetics aspects of fibrodysplasia ossificans progressive. *J Med Genet.* 1982;19(1):35-9.
- Rogers JG, Geho WB. Fibrodysplasia ossificans progressive. A survey of forty cases. *J Bone Joint Surg.* 1979; 61(6A):909-14.
- Park HS, Yoon CH, Kim HJ. The prevalence of congenital inverted nipple. *Aesthetic Plast Surg.* 1999;23(2):144-6.
- Andre Leite Gonclaves, Marcelo R. Masruha, et al. Fibrodysplasia ossificans progressiva. *Arq Neuropsiquiatr.* 2005;63(4):1090-3.
- Cohen RB, Hahn GV, Tabas J, et al. The natural history of heterotopic ossification in patients who have fibrodysplasia ossificans progressiva. *J Bone Joint Surg Am.* 1993;75(2):215-9.
- Kussmaul WG, Esmail NA, Sagar Y, et al. Pulmonary and cardiac functions in advanced fibrodysplasia ossificans progressive. *Clin Orthop.* 1998;346:104-9.
- Delai PLR, Kantanie S, Santili C, et al. Fibrodysplasia ossificans progressive: a hereditary illness of multidisciplinary interest. *Rev Bras Ortop.* 2004;39: 205-13.
- Shore EM, Xu M, Feldman GJ et al. A Recurrent mutation in BMP type 1 receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressive. *Nat Genet.* 2006;38(5):525-7.
- Nakajima M, Haga N, Takikawa K, Manabe N, Nishimura, G, Ikegawa S. The ACVR1 617G-A mutation is also recurrent in three Japanese patients with fibrodysplasia ossificans progressiva. *J Hum Genet.* 2007; 52(5): 473-5.