

Fibrodysplasia ossificans progressiva: a case report

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Fibrodysplasia ossificans progressiva (FOP) is a rare, severely disabling, autosomal dominant disease characterized by recurrent painful episodes of soft tissue swelling and the development of heterotopic ossification. The main target is the axial musculature, but eventually ectopic bone formation occurs in the ligaments, the fascia, the tendons and the joint capsules. Small soft tissue traumas and intramuscular injections exacerbate this extraskeletal bone formation. We present a 16-year-old male patient who has osseous lesions beginning from the left ramus mandible and extending along the sternocleidomastoid muscle, vertebral region and deltoid, with visible restriction in temporomandibular joint movement. Surgery was not performed due to parental concerns.

Unfortunately, no effective medical therapy for FOP is known. These patients may require extra care during some oral surgery and anesthetic procedures. In this report, the importance of the decision to perform surgery has been stressed.

Key words: fibrodysplasia ossificans progressiva, autosomal dominant, ossification.

Fibrodysplasia ossificans progressiva (FOP) is an extremely rare connective tissue disease, which manifests with congenital malformation of the big toe and heterotopic ossification of the soft tissues¹. The disease has a prevalence of 1/2,000,000 and is not specific to any ethnic group, geographic region or gender². Besides the autosomal dominant transition, this disease is seen sporadically in many patients as a result of new mutations. FOP progresses with ossification episodes. Small soft tissue traumas, myotonia, fatigue, intramuscular injections and influenza-like infections exacerbate this extraskeletal bone formation³. So far, no effective preventive or treatment method has been developed for FOP. Although surgical treatment has proven successful in some rare cases, new bone formation is observed postoperatively due to surgical trauma⁴. In this case, we present a 16-year-old patient who was diagnosed at birth.

Case Report

A 16-year-old male patient was admitted to our department due to swelling in the neck. On physical examination there was swelling

of the neck on the left side and movement restriction in the arms. He had no problem in lower extremity movement. His ability to open his mouth was restricted, and the left vocal cord was paralytic. Nodular ossified lesions were detected in the left auricle. There was a stiff, osseous lesion beginning from the left ramus mandible, extending downwardly along the side of sternocleidomastoid muscle, extending to the vertebral region and deltoid muscle on the left side and also running to the supraclavicular region (Fig. 1). Computed tomography revealed diffuse calcification in the subcutaneous tissue, progressing from the left posterolateral area of the neck toward the left shoulder joint, to the left chest wall and the posterior paravertebral area (Fig. 2 and Fig. 3). Furthermore, there was ossification in the adjacent bony structures (hypertrophic dysplastic appearance at the proximal and distal end of the clavicle), the left auricle and on the left side of the laryngeal cartilage, and a hypertrophic dysplastic bone extending inferiorly from the left styloid process so as to form a pseudoarticulation in the native mandible. Findings consistent with fatty

atrophy in the left half of the tongue and left vocal cord paralysis (involvement of the left 9th and 10th nerves) were also evident. Surgery was recommended for easing the restriction in opening the mouth, but the patient's family rejected this.

Discussion

Fibrodysplasia ossificans progressiva is a disease characterized by the replacement of connective tissues, such as the tendons, ligaments and fascia, and muscular tissue with bony tissue over time. Heterotopic bone formation leads to locking in the joints and makes movement impossible. Attacks of ossification emerge in a specific anatomical structure; these typically begin from the dorsal, axial, cranial and proximal regions of the body. They then proceed to involve the ventral, appendicular, caudal and distal regions⁵. Immobilization gradually increases, and most patients become dependent on a wheelchair by the end of the second or third decade. The mean duration of survival is 40 years³. These patients seem normal at birth other than malformations (hallux valgus, malformed first metatarsal, monofalangism) in their big toes. Painful soft tissue swellings that will turn to bone occur in the first decade⁶. The diaphragm, tongue, extraocular, cardiac and smooth muscles are not involved. A stiff neck and abnormalities of the cervical spine are seen, and these patients develop ankylosis at an early age³.

Severe weight loss, pneumonia and cardiac failure due to thoracic insufficiency are other

life-threatening conditions. Malnutrition is seen because of ankylosis of the mandible. Thoracic insufficiency syndrome, which is the major cause of most deaths, is developed as a result of ankylosis of the costovertebral joints and ossification of the intercostal and paravertebral muscles⁷.

Hearing loss is usually seen in the form of conductive hearing loss due to ossification of the tympanum, but sensorineural hearing loss may also develop when the cochlea and acoustic nerve are affected⁸.

Fibrodysplasia ossificans progressiva develops from a heterozygous activating mutation in the activin receptor A type I/activin-like kinase 2 (ACVR1/ALK2) gene, which encodes a bone morphogenetic protein (BMP)⁽⁹⁾. This mutation is present in all FOP patients, both familial and sporadic; in addition, it is considered one of the most disease-specific mutations in the human genome. Many cases are misdiagnosed as sarcoma or aggressive fibromatosis due to the soft tissue swellings that occur during childhood before ossification. Worldwide, 67% of patients are exposed to hazardous and unnecessary diagnostic methods and 90% are misdiagnosed¹⁰. Findings of heterotopic bony tissue are detected earlier with radiologic bone scan testing as compared to conventional radiographs. The diagnosis is clinically established by the progressive, ossified soft tissue lesions and malformations of the big toe, and confirmed through a DNA test performed for ACVR1 gene¹¹.



Fig. 1. Vertebral deviation, neck lesion and auricular involvement.

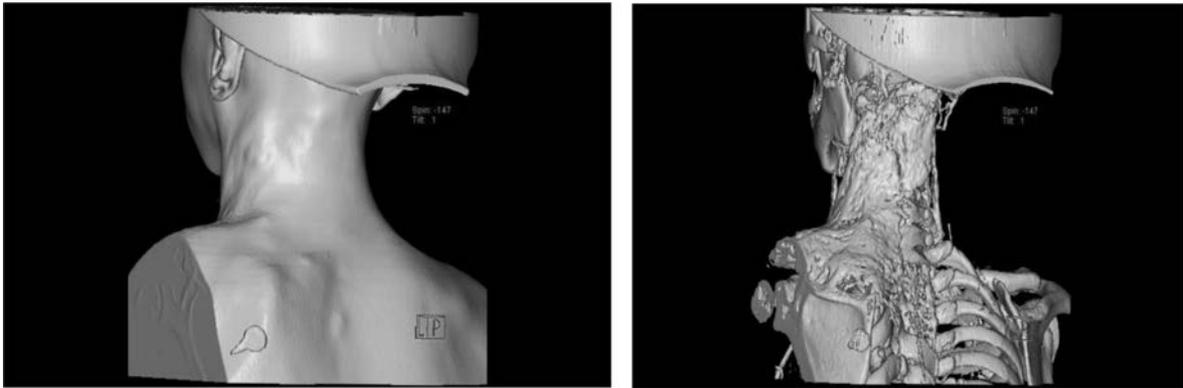


Fig. 2. Three-dimensional reconstruction of the neck lesion.

So far, there is no effective treatment for FOP. It is essential to decrease trauma; modify daily activities to an acceptable level; use apparatus that will decrease falls and injuries; and avoid sports that might cause tissue damage and muscle fatigue. Furthermore, excessive stretching of the jaw during intramuscular injections and dental procedures are among the situations that need to be paid attention to, since they might cause new bone formation³. Protective therapy has been tried with various medications such as non-steroidal anti-inflammatories, cyclooxygenase-2 inhibitors, leukotriene inhibitors and mast cell stabilizer, but a markedly positive outcome has not been achieved⁴. Corticosteroids can be used during attacks in the regions of the extremities and thorax. Surgical excision of heterotopic bone is not recommended, because new bone formation usually occurs by around 4 months following the operation. However, positive responses have been achieved in some cases using a combination of surgical and medical therapies¹. In our case, the patient had a problem with feeding because of his temporomandibular joint.

He was unable to open his mouth sufficiently, a condition that will worsen to the point that it is intractable. We suggested a surgical procedure combined with medical therapy of the joint in the early period, a multidisciplinary approach involving the fields of rheumatology, otorhinolaryngology and dentistry.

The pathophysiology of this disease will be better understood as issues such as the mechanism triggering the inflammatory system and the interaction between the immune system, progenitor cells and microenvironmental formations are clarified; in the future, new developments will take place in antenatal diagnosis and therapy.

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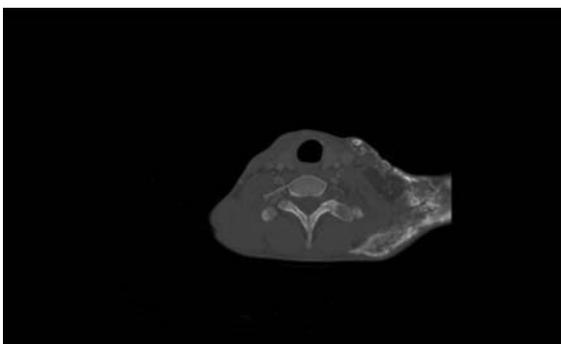


Fig.3. Axial computed tomography of the neck lesion.

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