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Fibrodysplasia Ossificans Progressiva (FOP): A Case Report with Oral and Maxillofacial Manifestations and new radiographic feature

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Abstract

Fibrodysplasia ossificans progressiva (FOP) is a rare form of genetic disorder categorized by progressive heterotopic ossification and congenital deformity of the big toes. Heterotopic ossification follows gradual inflammation of the soft tissues (flare-up) and results in limited movements in joints such as the Temporomandibular joint (TMJ). No effective medical treatment has been recognized for the treatment of FOP. FOP is commonly misdiagnosed, especially in the maxillofacial region. Patients with FOP often experience temporomandibular joint ankylosis. Therefore, dental professionals should be careful in planning treatment, including avoiding anesthesia injections, especially in the mandible.

This study presents a case of FOP with temporomandibular joint ankylosis. An eight-year-old boy with the chief complaint of reduced mouth opening and clinical and radiological features of FOP. The patient was referred to Mashhad Dental School in January 2016. He had not previously been diagnosed with FOP.

Key Words: Dental treatment, Fibrodysplasia ossificans progressiva (FOP), Temporomandibular joint (TMJ).

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1- INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP), is a genetic disorder with a global prevalence of one case per two million population (1, 2). Since FOP is a rare genetic disorder, most FOP cases are misdiagnosed and led to unnecessary diagnostic procedures (3).

This genetic disorder is caused by a mutation in the Activin A receptor type 1 (ACVR1) gene. The ACVR1 gene promotes the development of bone morphogenetic protein receptors and is involved in the growth and development of bone and muscle tissues (4, 5). FOP is characterized by extraskeletal ossification of connective tissue, including tendons, ligaments, and skeletal muscle tissue (1). Children with FOP appear normal at birth, except for the great toe(s) deformity, known as congenital hallux valgus. FOP chiefly starts in infancy as painful nodules (as bone replaces the tissues) which progressively spreads to the neck, trunk, and shoulders (1). Ectopic ossification occurs spontaneously in the FOP, but may be associated with physical trauma and surgery (6).

Within a few weeks of the onset of heterotopic ossification (early phase), the patient experiences pain, redness, swelling, fever, and moderate sensitivity called flare-up (3, 7). After a few weeks (mild phase), the swelling begins to subside, and the patient experiences a decrease in pain, tenderness, and erythema. After about 12 weeks (late phase) the edema disappears and hardens, forming a new area of heterotopic ossification that can be diagnosed on radiographs (7).

Temporomandibular joint involvement is probably a late manifestation of the FOP disease. Still, approximately 70% of patients with FOP develop jaw movement limitation by the 18, resulting in incurable malnutrition and severe weight loss (8, 9).

The International Clinical Council on FOP was officially established in 2017 to share valuable clinical experiences and provide best practices for clinical care and research for people who suffer from FOP. The FOP treatment guidelines were proposed in 2011 for the management of FOP and updated in 2021 (10).

Currently, there is no definitive or standard treatment for FOP, and the medical intervention is supportive. The most effective medication for management of the early flare-ups is high-dose Glucocorticoids which affect the joints of the appendicular skeleton and jaw, mainly if prescribed immediately at the onset of a flare-up. Other medicaments including cyclo-oxygenase-2 inhibitors, leukotriene inhibitors, occasional intravenous amino bisphosphonates, mast cell stabilizers, oral and topical non-steroidal anti-inflammatory medications can be used to manage the chronic pain, arthritic symptoms, and constant disease progression (5, 10).

This study presents a case of FOP with Temporomandibular joint (TMJ) ankylosis. An eight-year-old boy with the chief complaint of reduced mouth opening and clinical and radiological features of FOP. The patient was referred to Mashhad Dental School and then to a Rheumatologist. He had not previously been diagnosed with FOP.

2- CASE REPORT

The patient was an 8-year-old boy referred to Mashhad Dental School in January 2016 with a complaint of difficulty in opening his mouth. He had no history of any disease. In October 2016, the patient had a swelling on the left side of the face due to a dental problem, which subsided by abscess drainage and medication, and no other intervention was made for him. In November 2016, with the recurrence of the abscess, the patient underwent an inferior alveolar nerve block,

and the abscess was drained. The child then had difficulty opening his mouth. After several sessions of physiotherapy, he was referred to the Department of Oral Diseases & Diagnosis of Mashhad Dental School for further management. On physical examination, mandibular trismus was observed as mouth opening less than 2 mm deviation to the left (**Fig. 1**).

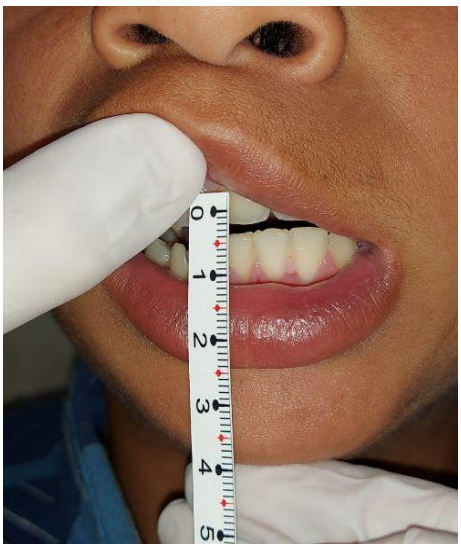


Fig. 1: Mandibular truisms with 2 mm mouth opening limit and mandibular deviation to the left

Clinical records revealed that a stone hit a child in the neck six years ago, followed by a hard mass in the trauma area. In the affected regions, bone masses replaced the connective tissue from the same age. CBCT imaging was prescribed to the patient. The CBCT axial and coronal sections analysis revealed calcified masses in the left masseter muscle (**Fig. 2**). This calcification was chronic inflammation caused by caries distribution in the mandibular left D and E teeth. The temporomandibular joint evaluation showed flattening and erosion of condyle on both sides, which was more severe on the right side (**Fig. 3**).

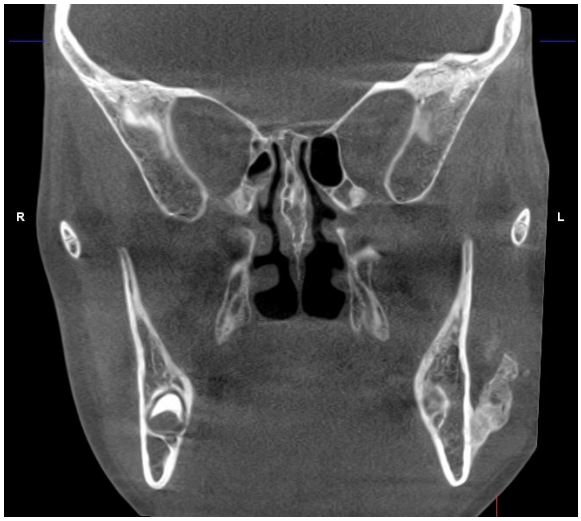
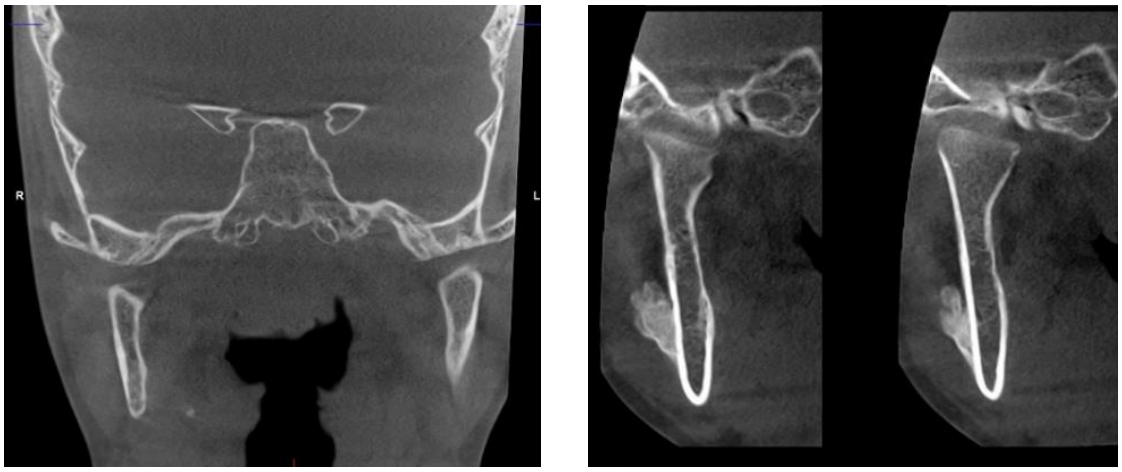


Fig. 2: Calcification of masseter muscle from coronal plane



(A) (B)

Fig. 3: (A): CBCT flattening and erosion in the condyles on both sides, which is more intense on the left (Coronal plane), (B): Left condyle flattening and erosion with reduced joint (Coronal plane)

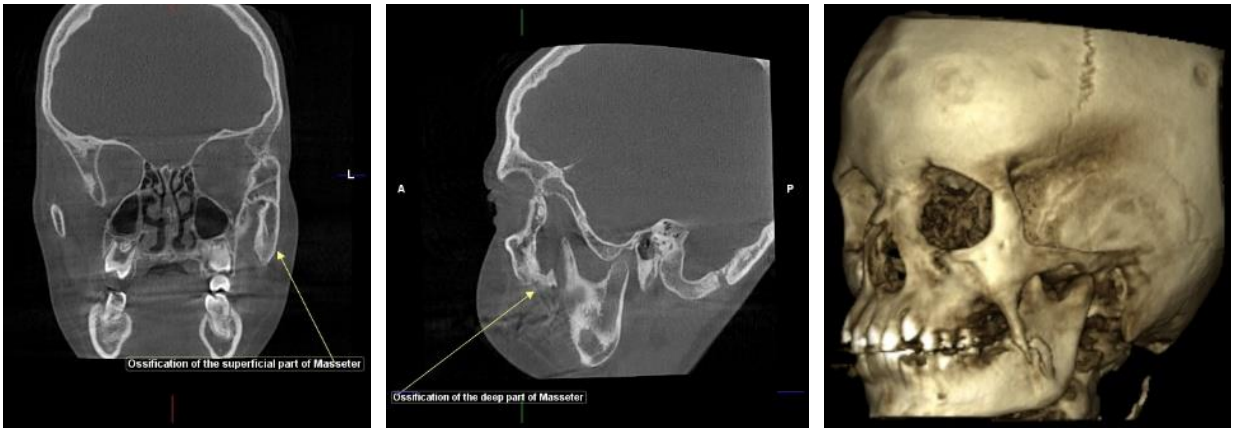
The patient was referred to a pediatric rheumatologist with a diagnosis of FOP. The diagnosis of FOP was established by diagnostic criteria including short thumb, hallux valgus, and progressive heterotopic ossification.

The patient was treated with intravenous pamidronate every three months for two years (guidelines for the symptomatic relief of FOP) (15). Since low calcium level in the blood serum (hypocalcemia) is harmful to intravenous pamidronate or any amino bisphosphonates, serum calcium level was monitored to be normal. The patient received adequate daily supplemental dietary calcium and vitamin D during and following pamidronate treatment. All necessary blood factors) were analyzed before the treatment including serum calcium, albumin, phosphate, alkaline phosphatase, BUN, 25-Hydroxy vitamin D, creatinine, and complete blood count (CBC). In each injection, a dosage of 1 mg/kg intravenous pamidronate was given over a 4-hour period every three months. The patient received 5 mg Montelukast sodium chewable tablets USP and 700 Mg Shark Cartilage capsule per day on the subsequent visit. The patient received the same dose of pamidronate every six months for the next two years. Following any traumatic injury, the patient received prednisolone (2 mg/kg/d).

In September 2020, the patient received the ninth dose of pamidronate. A traumatic femur fracture was reported in his medical history. Radiographic images were obtained, and heterotopic ossification within skeletal muscles, ligaments, and tendons was observed in 2020.

After receiving the 11th dose of pamidronate, CBCT was prepared again from the patient's maxillofacial region. The examination of CBCT images on axial, coronal, and sagittal planes revealed calcification within the superficial masseter muscle, from the posterior zygomatic arch to the external surface of the masseter and mandibular bodies which were interconnected (**Fig 4**).

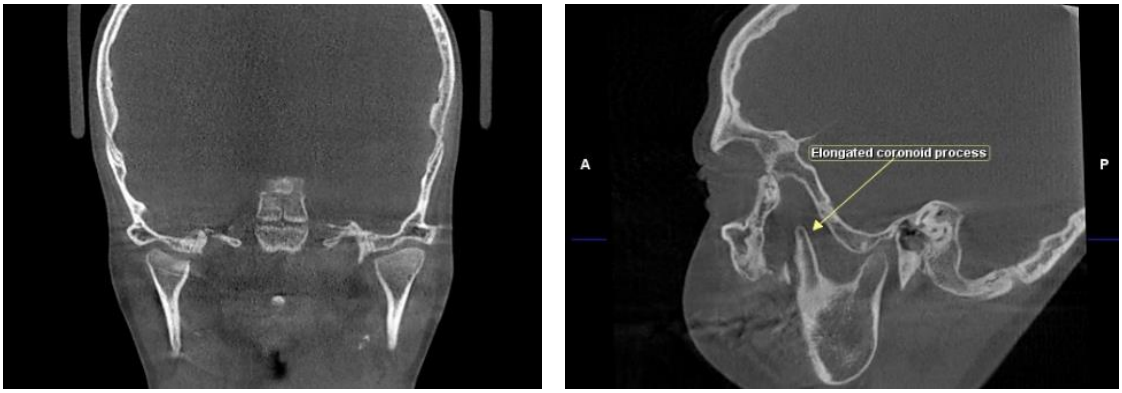
The CBCT images also showed progressive ossification in the masseter muscle compared to previous CBCT images.



(A) (B) (C)

Fig. 4: (A) calcification in the superficial masseter muscle below the zygomatic arch region up to the border of the mandible (coronal and sagittal plane), (B) ossification in the deep portion of the masseter muscle, from the zygomatic arch region up to the coronoid appendage, (C) calcification in the superficial masseter muscle below the zygomatic arch region up to the external surface of the masseter and mandibular body.

The condyles on both sides were flattened similar to the last view. The coronoid appendage on the affected side (left) was elongated, which could be a secondary cause of TMJ immobilization. The radiological examination of the head and neck also showed ossification of the trapezius muscle (**Fig. 5**).

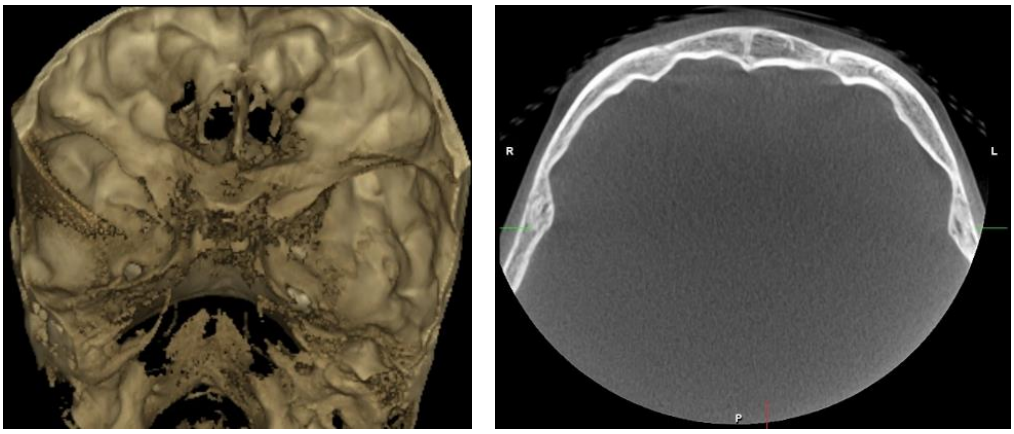


(A) (B)

Fig. 5: (A) Condylar bony changes (flattened on the both sides) in coronal and sagittal sections, (B) Elongation of the left coronoid appendage

The lateral view of the skull revealed the copper-beaten skull appearance. In the patient's last visit in February 2021, varnish fluoride was applied at buccal and occlusal levels and to the extent that accessibility was available at lingual levels of teeth (**Fig 6**).

At the moment, the patient has a severely restricted range of motion with limitations to walk and sit and cannot eat solid foods, and only receives liquids such as soups, juices, and smoothies. Currently, the patient undergoes pulmonary function testing every six months and receives routine medical care and clinical follow-up every six months.



(A) (B)

Fig. 6: Copper beaten skull appearance in axial plane

3- DISCUSSION

An accurate and timely diagnosis of FOP is essential for appropriate treatment. There is currently no treatment for FOP; however, early detection through clinical signs and radiography may reduce the disease and avoid unnecessary invasive procedures. Radiographic imaging is a powerful technique for early and confident diagnosis of FOP. Panoramic radiography, lateral cephalometric radiograph, and mandibular oblique lateral (Ramus, Body) are the initial steps in the radiographic examination; however, plain radiographs may provide supplementary information, at the onset of FOP. In the FOP radiological analysis, soft-tissue calcification becomes apparent within a few weeks. Calcification appears more often in the vicinity of the affected muscle and increases until the mass of soft tissue becomes fully bony (11).

FOP was formerly called myositis ossificans progressive, since ossification was associated with periods of myositis in which the affected area initially becomes swollen and tender. Then the muscular inflammation (myositis) gradually turns to bone (3).

FOP is commonly misdiagnosed as aggressive juvenile fibromatosis, lymphedema, or soft tissue sarcoma. The reason might be explained due to the fact that the health care professionals often fail to differentiate the progressive soft tissue swellings on the head, neck, and upper back with the malformed great toes (7).

Since most patients with FOP experience restricted mouth opening and subsequent dietary difficulties by the age of 18, dental treatment becomes more complicated in these cases. Spontaneous or Post-traumatic TMJ ankylosis is common among FOP patients, which results in poor oral hygiene and eating disorders. Preventive oral health measures are necessary for patients with FOP, particularly during childhood years. Furthermore, periodic and preventive oral care is crucial to prevent long-term dental and oral complications in FOP patients (10).

Intramuscular injections are contraindicated in FOP patients due to the risk of heterotopic ossification at the injection site. Since dental treatments are associated with injections, dental treatment of FOP patients is very complicated. Block injection during dental procedures leads to ossification of the pterygoid muscles and TMJ ankylosis. Another dental treatment method without local injections is general anesthesia, which is also best used in the shortest possible way due to the subsequent trauma of intubation and bone-building. General anesthesia can be

administered safely instead of local injections. However, this method may not always be the best choice due to the subsequent trauma of intubation and bone formation. Therefore, the best method for FOP patients is to prevent oral and dental diseases. The effect of anesthesia drugs or local anesthesia injection on the regression of heterotopic ossification is not apparent. Local anesthesia through anesthetic penetration into interligamentaries areas has been recommended in the previous studies. Other anesthesia methods including dental electronic anesthesia have been suggested for the dental treatment of patients with FOP (7, 10, 12, 13).

All people with FOP should have early, regular, and periodic dental examinations along with oral health education and nutritional instruction. High-dose fluoride toothpaste, dental sealants, fluoride supplements, and plaque removal are also recommended to prevent tooth decay and the need for dental treatment (10, 12, 13).

Patients with FOP may also experience thoracic insufficiency syndrome (restrictive chest wall disease), which is life-threatening and causes cardiopulmonary complications such as right-sided heart failure and pneumonia. Careful attention like prophylactic measures can maximize pulmonary function and minimize rapid progression to respiratory failure and mortality from thoracic insufficiency syndrome (14).

Abnormal skull deformity is commonly associated with initial deformity of the brain. Copper beaten skull appearance was first reported in a patient with FOP. The copper beaten skull is seen throughout the cranial vault due to intense intracranial pressure on the internal surface of the skull. In the radiological analysis, the copper beaten skull can be detected in some diseases, including Hypophosphatasia, Crouzon syndrome, Obstructive hydrocephalus, and Craniosynostosis.

The copper beaten skull is more prominent during brain development between 2-3 and 5-7 years and is less noticeable after 8. The copper-beaten pattern on skull radiography has poor sensitivity in detecting the increased intracranial pressure because such an appearance can also emit errors in normal patients. The origin of the copper-beaten pattern was assumed to result from increased intracranial pressure. However, recent studies have overlooked the pathological significance of the copper-beaten pattern and considered it as a reflection of normal brain growth (15, 16).

Several studies examined the role of physical therapy in the treatment of FOP, but the results were controversial. A patient in good health may postpone the subsequent treatment, or even such treatment may be unnecessary.

In addition, physical therapy is helpful because it strengthens muscles that are not affected by FOP and increase lung capacity. In the advanced stages of the disease, death occurs due to decreased respiratory capacity and/or respiratory infection, which is characterized by chest stiffness intensified by ossification of the abdominal wall (7).

At present, management of FOP is problematic since there is no active targeted therapy.

This patient has been under medical and dental follow-up from January 2017 to February 2022.

4- CONCLUSION

FOP can be diagnosed during the dental exam. A dentist should be vigilant about facial morphology and occlusion changes during a dental examination. A dentist may be the first person to diagnose a rare disease such as FOP.

5- CONFLICTS OF INTEREST

None.

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