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Case report

Early stage fibrodysplasia ossificans progressiva: A case report

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ABSTRACT

Fibrodysplasia ossificans progressiva is a very rare autosomal dominant genetic connective tissue disease with a progressive ectopic ossification of muscle (intramuscular) or perimuscular connective tissue such as tendons or joint capsules. The osseous masses produced will form bridges that abnormally connect sections of the skeleton, causing disfiguration and normal motor function inhibition. We reported a 5-year-old girl with multiple hard nodules on the back region which initially present as a painful soft mass on the posterior neck region. As the pain subsided, the mass hardened and also appeared in other parts of her back. We decided not to do a biopsy or excisional surgery to prevent flaring up of the disease. Early diagnosis prevents catastrophic diagnostic and treatment procedures. The progressive nature of this disease is difficult to stop but we should delay it as much as possible by preventing muscle trauma, giving disease modifying agent and long-term physiotherapy to counter further disabilities which will eventually develop.

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Introduction

Fibrodysplasia ossificans progressiva (FOP) is a very rare autosomal dominant genetic connective tissue disease with a progressive ectopic ossification of muscle (intramuscular) or perimuscular connective tissue such as tendons or joint capsules [1–3]. The osseous masses produced will form bridges that abnormally connect sections of the skeleton, causing disfiguration and normal motor function inhibition [1–3]. Mutations in the cytoplasmic GS domain of the cell surface

receptor Activin A receptortype I (ACVR1) were recently identified as the genetic cause of the rare human disease FOP [4]. The inheritance is autosomal dominant, but that most cases are sporadic. The mutation in ACVR1 leads to overactivation of the bone morphogenetic protein signaling pathway [4].

This condition usually begins in childhood, which clinically present as painful swelling of the muscles and connective tissue. As the swelling subsides, after approximately 6 months or more, ossification starts at some sites at the mean age of 4–5 years. Congenital malformations which are characteristically observed in the great toes at birth in almost all cases of

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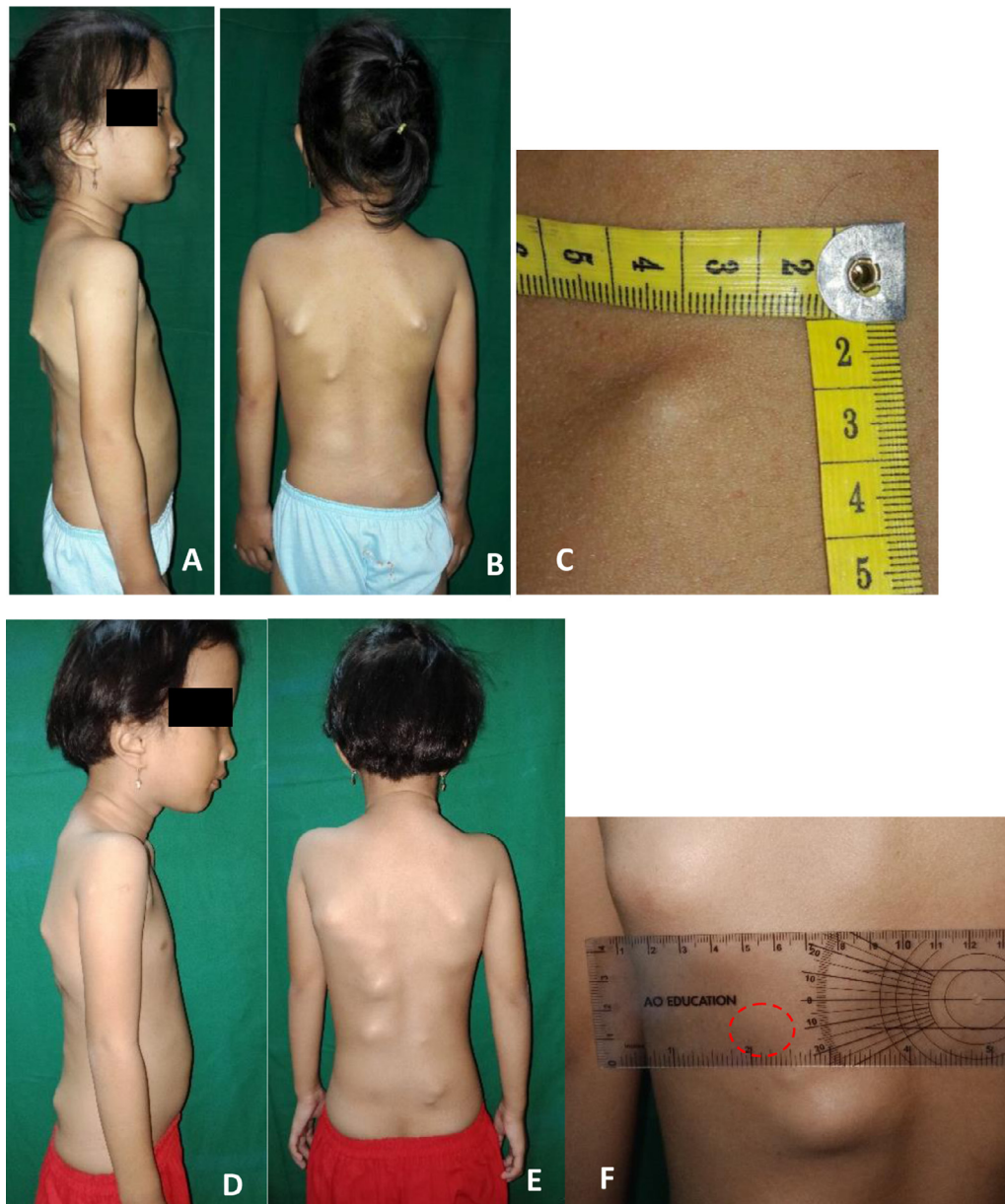


Fig. 1 – Para spinal lesions, note the increase in size and number. 1A-1C 10-month onset paraspinal lesions (1A/B) with largest diameter of 2 cm (1C). 1D-1F 16-month onset paraspinal lesions (1D/E) with largest diameter of 4.5 cm (1F)

FOP are the diagnostic hallmark. A child with FOP will eventually develop disabilities starting from abnormal gait and joint movement until they are confined to a wheel chair at the third decade of life. Mortality is usually caused by the restricted chest expansion which leads to respiratory failure [2,5].

We are reporting a 5-year-old girl presented with multiple hard nodules on the back region which initially present as a painful soft mass on the posterior neck region. As the pain subsided, the mass hardened and also appeared in other parts of her back. Based on the clinical and radiological examination, FOP was the most possible diagnosis. We decided not to do a biopsy or excisional surgery to prevent flaring up of the disease.

Case report

A 5-year-old girl was referred to our hospital with bilateral periscapular and multiple paravertebral nontender masses. The mass was first noticed after the patient fell from bed October 2017 (10 months before being referred to our hospital) with an initial mass on the occipitocervical region. The patient was brought to the masseuse and got massages at the mass 3 times but there was no improvement. She was brought to the pediatrician in a public hospital because there another mass appeared on the left paracervical region. A Mantoux test, blood, and radiological examinations were performed to rule out tuberculosis infection. The patient was referred

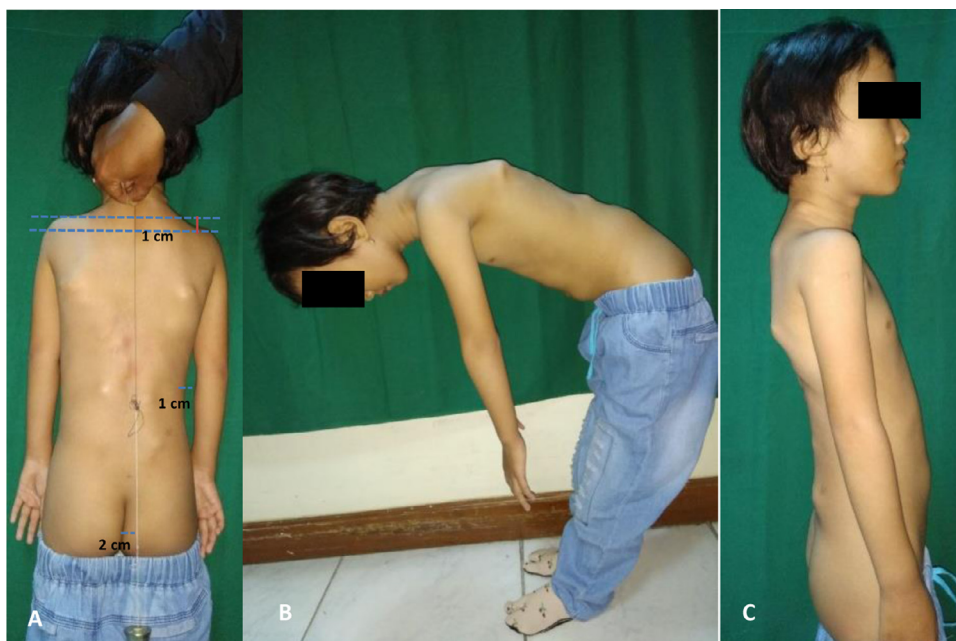


Fig. 2 – Spinal deformity. a. Increased in body-arm distance on the right side (1.5 cm), plumb line shift 2 cm to the right side, and 1 cm shoulder tilt; b and c. Straight lumbar

to the orthopedic surgeon in the same hospital. A cervical radiograph was performed which revealed no bony changes so the patient was initially observed for further progression. Three months after the first mass, other masses appeared in the scapular region. Masses were initially small in size and soft, then they grew slightly bigger and consistently became hardened. She was referred to a city public hospital and was diagnosed there as back tumor and referred to our center. On physical examination, we found that the general condition was good and no abnormality of organs was found in the other organ. There were multiple lumps varying from 5 mm to 2 cm in diameter at the paravertebral region from cervical to lumbar and scapular region (Figs. 1 and 2).

The consistency of each lump varied from soft until as hard as a bony prominence. Bilateral hallux valgus was also observed (Fig. 3) There was no pain, and all masses were immobile. There was a limitation to do all neck motions such as forward flexion, extension, and lateral bending (Fig. 4).

The shoulder girdle and all other joints had normal ranges of motion. We had observed progressiveness of clinical heterotopic ossification (HO) in approximately 6 months after initial diagnosis of FOP was established. There were increases in mass' number and size and in a region other than the paraspinal region (Figs. 1 and 5).

We performed radiographic examination in several regions related to the mass and Computed Tomography (CT) Scan. The radiograph revealed ossifications of soft tissue on lateral margin of both scapular bones and on the left supraclavicular region. The CT scan indicated ossification of subcutaneous soft tissue masses on both sides of T11-L4 paravertebral region, extensive dystrophic ossification of fascia and intramuscular of bilateral back muscles extending from semispinalis capitis muscle and fascia until to the level of sacral bone. The dystrophic ossification partly formed abony bridge from fascia



Fig. 3 – Bilateral hallux valgus

and intramuscular part of bilateral levator scapular muscle (particularly on the right side), spinaliscervicis muscle, splenius capitis muscle, trapezius muscle, rhomboid muscle, until erector spinae muscle (on the level of the sacrum). There was no bone destruction and the alignment and curvature of the spine were within the normal limit (Figs. 6 and 7).

Based on the typical clinical and imaging findings for the early stage of FOP such as the congenital malformation of bilateral hallux valgus as a hallmark was enough for us to diagnose the patient as FOP without an unnecessary biopsy. We had informed the patient regarding the nature of this disease

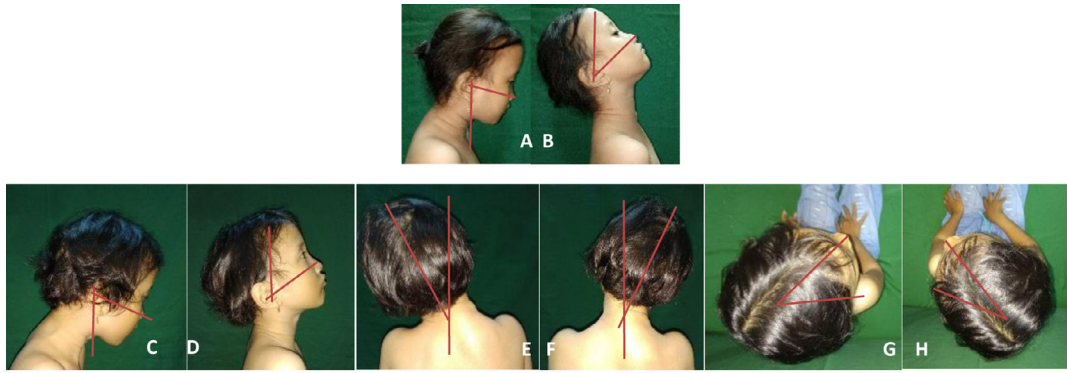


Fig. 4 – Limited neck range of motion (normal neck forward flexion and extension is 0-45°, lateral flexion 45°, rotation 80°). A and B 10 months onset: Neck flexion 60° (A), extension 45° (B). 4C-H 16 months onset: Neck flexion 60° (C), extension 60° (D), lateral flexion 35° left (F), and 30° right (G), rotation 45° left (G) and 35° right (H)



Fig. 5 – New masses on 16 months onset. a. on cervical region; b. on axillary region

which may lead to disability and even death. We closely observed the development of the disease in this patient and prescribed the patient nonsteroid anti-inflammatory drugs. We carefully prevented flare-up by not doing any iatrogenic triggers such as biopsy, excisional surgery, or any intramuscular injection. We also educated the parents to be more careful and not to accept intramuscular injection (such as for immunization) and prevent injury since these might also trigger a flare-up.

Discussion

FOP is an entity for progressive muscle ossification which will eventually lead to significant disability. This very rare genetic connective tissue disease was first described by Gay Patin in 1648 as a case who “turned to wood”. The prevalence

is approximately 1/2,000,000 and over 700 cases have been reported [2,5,6].

FOP is the most catastrophic disorder of heterotopic endochondral ossification in humans. The diagnosis is clinical and it is usually made based on the presence of 3 major criteria that are namely; congenital malformation of the great toes, progressive heterotopic endochondral ossification and progression of the disease in well-defined anatomic and temporal patterns. The FOP is initially developed as soft tissue swelling which spontaneously subsides. In time, there are episodic flare-ups which end up in immobility and confines the patient in a wheelchair by the third decade [2,5-8].

Our case also started with the above described pattern. The first noticed mass was on the occipitocervical region when the patient was 5 years old (mean age of symptom onset 4-5 years). It was actually an incidental finding after the patient fell from the bed. Patient complained of mild pain and then the mass was noticed as she got a mass age in that area.

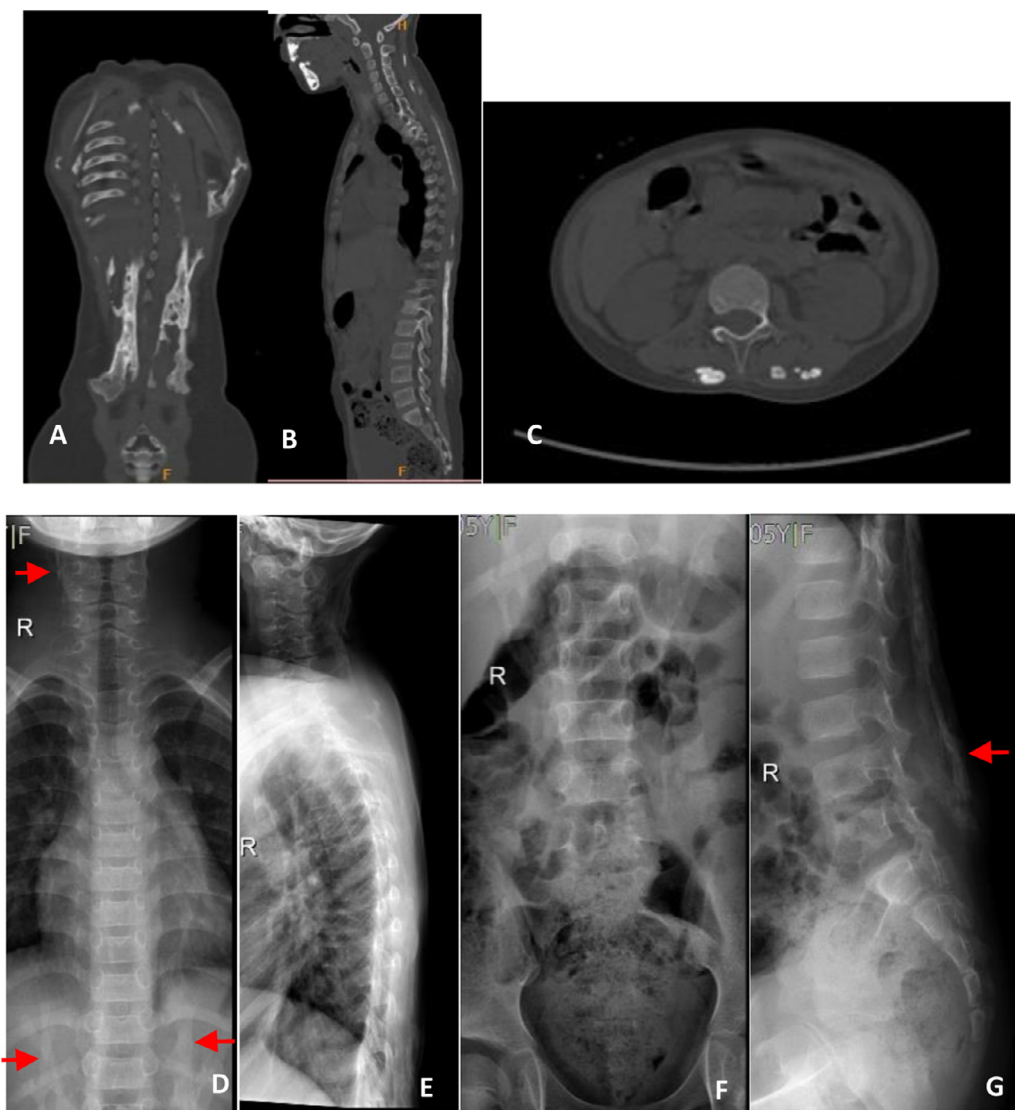


Fig. 6 – Radiological examination at 10 month-onset. HOs were seen on lateral margin of bilateral scapula, left supraclavicular and subscapular region, paravertebral region on the level of T11-L4. 6A-6C paraspinal heterotopic ossification (HO) observed in spine CT scan in coronal view (A), sagittal view (B), axial view (C). 6D-6G paraspinal HO in plain radiograph (arrows): cervical region (6D-E), thoracolumbar region (6F-G)

Other masses were noticed 3 months after on the periscapular region until the most recent on the paravertebral region. The patient started to develop limitation on neck movement and shoulder girdle movement. However, other joint were still within normal functional limit [8–10].

Other disabling features such as rapidly developing scoliosis associated with a unilateral osseous bridge along the spine prior to skeletal maturity which causes asymmetrical growth of vertebra and cardiopulmonary disability associated with thoracic insufficiency syndrome were not identified in the initial assessment [8–10]. In 6 months follow-up, there was a slight increase in the body to arm distance which is one sign of scoliosis. The cardiothoracic index (CTI) also slightly increased in the chest radiograph (CTI 0.55, normal CTI 0.4–0.5) compared to initial radiograph. However, this could have been

caused either by an actual thoracic insufficiency syndrome or simply due to inadequate inspiration during the examination.

Routine evaluations of the bone mineral metabolism were usually normal, although the serum alkaline phosphatase activity and the erythrocyte sedimentation rate may increase, particularly during flare-ups. C-reactive protein elevations are a more specific test than erythrocyte sedimentation rate for monitoring the acute inflammatory phase of heterotopic ossification after spinal cord injuries but have not been studied in FOP. In this patient, which present in our outpatient clinic, not at the stage of flaring will be more likely to have normal values of laboratory measurement so we have to carry out any laboratory examination [6,8].

Currently, there are no effective treatment for FOP. Present management focuses on early diagnosis, assiduous avoidance

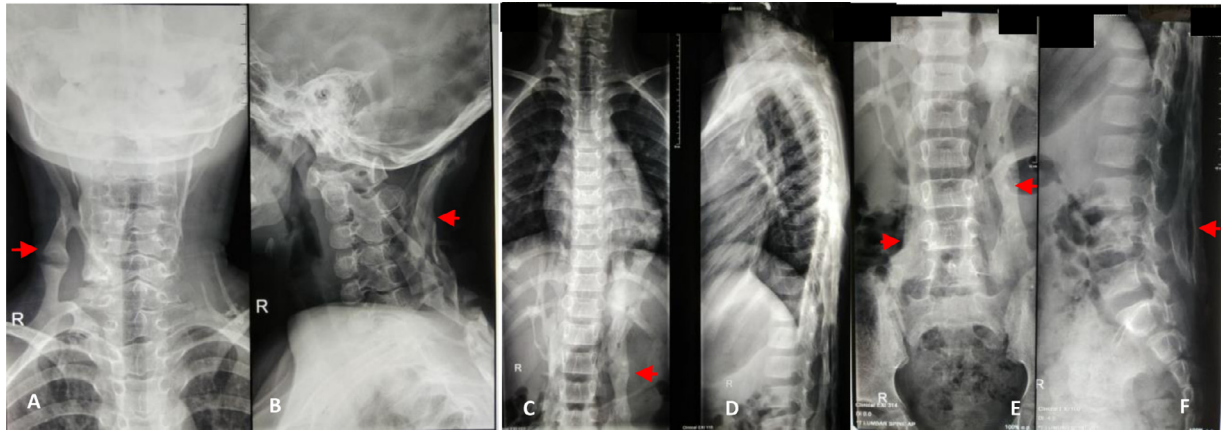


Fig. 7 – Radiological examination at 16 month-onset. Increased size of HO over the lateral margin of bilateral scapula, superior margin of right scapula, left supraclavicular, right paravertebral cervical, bilateral paravertebral thoracolumbar. 7A-B Cervical radiograph AP and lateral view; 7C-D Thoraco-lumbar radiograph AP and lateral view; 7E-F Lumbo-sacral radiograph AP and lateral view

of injury or iatrogenic harm, symptomatic amelioration of painful flare-ups, and optimization of residual function [2,3,8].

In the early stage, FOP is most commonly misdiagnosed as sarcoma and other cancers, aggressive fibromatosis or vascular masses. The definitive diagnosis of FOP can be made by a simple clinical evaluation that associates rapidly appearing soft tissue lesions with malformations of the great toes. Our patient presented after clinical manifestation occurred so we preferred to proceed with conventional radiograph and CT scan. Biopsy of FOP lesions is never indicated and may cause additional HO. Thus, we decided not carrying out a biopsy in this patient since the clinical and radiological findings in our patient were pathognomonic [1,8].

Prevention of soft-tissue injury and muscle damage remain the hallmark of FOP management. These include intramuscular injections as in immunization. Routine childhood diphtheria-tetanus-pertussis immunizations administered by intramuscular injection pose a substantial risk of permanent heterotopic ossification at the site of injection, whereas measles-mumps-rubella immunizations administered by subcutaneous injection pose no significant risk. For most individuals with FOP, the series of immunizations at infancy will have been completed before the diagnosis of FOP has been made. However, in those in whom FOP is diagnosed in infancy, there is a conflict regarding intramuscular immunizations. The patient had both injections at early childhood and no HO was observed on site of injections [8,11].

There are many proposed potential treatments for FOP, however, the unpredictable nature of this disease has made controlled trials difficult to perform. According to International Clinical Consortium on FOP (2011), medications are divided into 3 classes based on the known mechanism of action as it relates to the proposed FOP pathogenesis, experimental or anecdotal experience with the drug and also the knowledge of the drug's safety profile [8].

The first class is medication to control acute flare up such as inflammatory-related symptoms (pain and swelling). Drugs included in this class have generally good results and

Table 1 – Classes of medications [7].

Class	Description	Drugs
I	Have been widely used to control symptoms of the acute flare-up in FOP, with anecdotal reports of favorable clinical results and generally minimal side effects	Short-term use of high-dose corticosteroids, and use of nonsteroidal anti-inflammatory drugs including the new anti-inflammatory and anti-angiogenic cox-2 inhibitors
II	Have a theoretical application to FOP, are approved for the treatment of other disorders, and have limited and well-described effects.	Leukotriene inhibitors, mast cell stabilizers, and aminobisphosphonates (Pamidronate; Zoledronate)
III	Investigational new drugs	Signal transduction inhibitors, monoclonal antibodies targeting ACVR1, and retinoic acid receptor gamma agonists (presently under development)

minimal side effects (ie, short-term corticosteroids, nonsteroidal anti-inflammatory drugs, or the newer generation such as anti-angiogenic cox-2 inhibitors). The second class includes medications that are theoretically will give positive effect for FOP that also have been used safely for other diseases with limited and well-described effects (ie, leukotriene, amino-bisphosphonates, mast cell stabilizer). The third class includes drugs which are still under investigation such as signal transduction inhibitors, monoclonal antibodies targeting ACVR1, and retinoic acid receptor gamma agonists [8].

We had prescribed class I medication for an acute flare up and planned to prescribe bisphosphonates as class II medication based on its availability in our country. This pa-

tient was closely observed and our treatment focused on preventing new lesions by family education while seeking the most effective medication to delay the progress of this disease. (Table 1)

Conclusion

FOP is an extremely rare disease and often misdiagnosed thus the correct diagnosis sometimes happens late. General practitioners, pediatricians, orthopedics as well as radiologists should be aware of the early feature of FOP. Early diagnosis prevents catastrophic harmful diagnostic and treatment procedures. The progressive nature of this disease is difficult to stop but we should delay it as much as possible by preventing muscle trauma, giving disease modifying agent and long-term physiotherapy to counter further disabilities which will eventually develop.

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