An extreme entity in differential diagnosis of musculoskeletal involvement-fibrodysplasia ossificans progressiva: a case based review

Mustafa Çakan¹, Nuray Aktay-Ayaz¹, Şerife Gül Karadağ¹, Gonca Keskindemirci²
Clinics of ¹Pediatric Rheumatology, and ²Pediatrics, Kanuni Sultan Süleyman Research and Training Hospital, Istanbul, Turkey. E-mail: mustafacakan@hotmail.com
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Fibrodysplasia ossificans progressiva is one of the most devastating disorder of mankind characterized by progressive heterotopic ossification. Apart from hallux valgus, other symptoms start to develop in the first decade of life. The initial symptoms are tumefactive lesions on the back that gives an impression of benign or malignant tumoral lesion. It may cause restricted motion of the neck and shoulders and magnetic resonance imaging of the lesions may be reported as myositis or myofasciitis and these children may be referred to rheumatologists. Currently there is no definitive treatment of the disease but the most important issue in these patients is “primum non nocere”, because any invasive procedure could potentially trigger a flare and heterotopic calcification. Herein, we present a young case of fibrodysplasia ossificans progressiva to remind the typical signs and symptoms of the disease to all clinicians caring for children.

Key words: fibrodysplasia ossificans progressiva, hallux valgus, heterotopic calcification.

Fibrodysplasia ossificans progressiva (FOP) (OMIM135100), also formerly known as myositis ossificans progressiva, is a rare and disabling genetic condition characterized by congenital malformations of the great toes and progressive heterotopic ossification.¹ There is no ethnic, gender or geographic predisposition and worldwide prevalence is estimated to be one in two million individuals.² Although it is an autosomal dominant disorder most of the cases are sporadic. The disease is caused by mutations in the ACVR1/ALK2 gene.¹² Classic FOP is characterized by congenital malformations of the great toes, most commonly hallux valgus deformity, and by progressive heterotopic endochondral ossifications that usually begin in the first decade of life and follow a specific anatomic spread pattern.¹² The first symptoms are episodic, painful inflammatory swellings (flare-ups) that usually begin on the back of the neck and posterior trunk.³ The sudden appearance of these tumor-like lesions makes physicians consider malignancy such as sarcoma and aggressive fibromatosis. Around 90% of the FOP cases are misdiagnosed and may undergo invasive diagnostic procedures that would trigger a flare-up and lead to permanent harm.⁴ To the present day, there is no cure for FOP but early recognition of great toe deformities and soft tissue swellings and timely diagnosis of a FOP case are essential to prevent iatrogenic harms and to take precautions to minimize trauma.

Case Report
A 3-year-old boy was admitted to the hospital with the complaints of swellings on the back and inability to raise the arms fully for 2 months. He was the second child of healthy, non-consanguineous parents; and had a healthy 5-year-old brother. Prenatal and postnatal history was unremarkable and parents stated that the child was normal until 2 months ago and all started after an upper respiratory tract infection. The family observed first a lump on the back of the neck. In 2-3 weeks the lump started to get wider with diffuse swelling and
discrete lumps on the upper and lower back with limited range of motion of the neck and shoulders. He was investigated for a month focusing on soft tissue infection and aggressive infantile fibromatosis.

On physical examination, there was bilateral hallux valgus deformity (Fig. 1a) and diffuse hardening of the skin of the back with swellings on the neck, scapular and lumbar regions (Fig. 1b). He had limited rotation of the neck with limited abduction of the shoulders. All laboratory tests, including acute phase reactants, bone markers and muscle enzymes were normal. Magnetic resonance imaging (MRI) findings of the lesions were suggestive of aggressive fibromatosis and myofasciitis but on the chest X-ray, ossifications around the axillary region were observed (Fig. 1c). After combining the history, clinical findings and heterotopic ossifications, we have suspected FOP in our case. Roentgenograms of the skeleton showed typical findings of FOP (Fig. 1d-e). Genetic analysis showed single nucleotide substitution causing a missense mutation in codon 206 (c.617G>A; R206H) in the glycine-serine activation domain of the gene encoding activin receptor IA (ACVR1).

The case is being followed for two years. We have used prednisolone two times for four days because of the flare-ups around the proximal parts of the upper extremities. Montelukast (4 mg/day, per oral) is being used for 2 years. Bisphosphonate (1 mg/kg/day; intravenous, 3 consecutive days, every 3 month) is being used for 1.5 years. Unfortunately, none of the medications showed stabilization of the symptoms. Axial architecture was deteriorating rapidly with new ossifications on the back (Fig. 1f). On the last visit, the disease seemed to be quiescent and we have not observed new swellings in the last 6 months.

Informed consent was received from the family.

Discussion

We made a review of the literature via PubMed, Google Scholar, and ULAKBİM (1993-2016; terms: fibrodysplasia ossificans progressiva, myositis ossificans progressiva) to retrieve the most recent developments about genetics,
Fibrodysplasia ossificans progressiva (FOP) is an extremely disabling disease characterized by the formation of heterotopic bone at extraskeletal sites, leading to immobility of the patient due to the development of a second skeleton. Approximately 800 known FOP patients exist worldwide, with an estimated population of over 3,500. The genetic transmission is autosomal dominant, yet reproductive fitness is low, resulting in most cases arising from de novo mutations.

The disease is diagnosed based on clinical findings, with hallmark features including characteristic malformation of the great toes and episodic soft tissue swellings leading to progressive ossification. Our case presented with congenital hallux valgus deformity and soft tissue swellings starting on the back around 3 years of age. The tongue, diaphragm, extraocular, cardiac, and smooth muscles are not involved in FOP.

Differential diagnosis includes desmoid tumors, aggressive juvenile fibromatosis, progressive osseous heteroplasia, osteosarcoma, lymphedema, and soft tissue sarcoma. Most of the pediatricians suspect a malignant disease and refer these children to pediatric oncologists, pediatric surgeons, or orthopedic surgeons. Some flare-ups may regress, but most transform skeletal muscles, ligaments, fascia, tendons, and aponeuroses into heterotopic bone.

In 2006, genetic mutation causing FOP was identified as a recurrent single nucleotide substitution causing a missense mutation in codon 206 (c.617G>A; R206H) in the glycine-serine activation domain of the gene activin receptor IA/activin-like kinase 2 (ACVR1/ALK2), a bone morphogenic protein type 1 receptor. This mutation causes hyperactivity of bone morphogenic protein pathway.

Early FOP lesions contain an intense infiltration of macrophages, mast cells, and lymphocytes leading to widespread death of skeletal muscles. Mast cells are found at a density much higher than any other inflammatory myopathy. After rapid and destructive inflammatory stage comes an avascular condensation into cartilage followed by revascularization stage with heterotopic bone formation that appear histologically normal.
and often contain marrow elements.\textsuperscript{1}

Currently there is no proven treatment modality to prevent FOP flare-ups or to slow or regress the heterotopic bone formation.\textsuperscript{1,11} As flare-ups of FOP are episodic and unpredictable, and there is great individual variability in the rate of disease progression, all reported treatment successes seem to be coincidental.\textsuperscript{11} Non-steroidal anti-inflammatory agents, cyclooxygenase-2 inhibitors, leukotriene inhibitors, mast cell stabilizers, and aminobisphosphonates are useful anecdotally in managing chronic discomfort and ongoing flare-ups.\textsuperscript{1,11} A brief 4 day course of corticosteroids (prednisone 2 mg/kg/d), started within the first 24 hours of a flare-up involving the major joints, jaw or submandibular area, may be used. Use of corticosteroids for the flare-ups of the back, neck and trunk is not recommended.\textsuperscript{1,11,12}

We were using montelukast and bisphosphonates since the diagnosis and have used corticosteroids two times. We have observed that he had constant flare-ups on the back without benefit of any medication for more than one and a half years. Finally, for the last 6 months, the disease seems to be calmed.

The hallmark of FOP management is prevention of trauma induced flare-ups and iatrogenic harms. Preventive measures include, but not limited to: avoidance of intramuscular injections, overstretching of muscles, falls, any kind of invasive procedures except for emergency surgeries that should be performed in centers familiar with FOP patient care.\textsuperscript{11} Subcutaneous injections are thought to be safe and influenza and pneumococcal vaccinations are recommended to decrease the rate of respiratory tract infections.\textsuperscript{1,11} The flare-ups are episodic but the damage is cumulative and most of the patients become immobile and wheelchair-bound towards the end of the second decade and die around 40 years of age because of thoracic insufficiency syndrome.\textsuperscript{13}

We have also conducted a search to find Turkish FOP patients reported both in English and Turkish literature. We have seen that 17 cases (8 female; 9 male) from Turkey were reported between 1993 and 2017.\textsuperscript{14-26} Unfortunately, even though all cases had typical signs and symptoms, the mean age of the reported cases at the time of diagnosis was 16.1 years (range: 5-26 years). Half of the cases were reported from the departments of orthopedics and physical therapy and only 3 cases were reported from pediatrics.

In conclusion, the aim of this case based review was to increase the awareness of this easily diagnosed disease between all clinicians taking care of the children. Although currently none of the medications seem to make any difference in the progression of the disease, we think that the first rule of medicine ‘\textit{primum non nocere}’ may be most applicable for FOP patients. Early diagnosis and avoidance of any iatrogenic harm can make big differences in that individual’s life.

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REFERENCES


