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Case Report

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

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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.[1,2] 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.[1,2] 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,

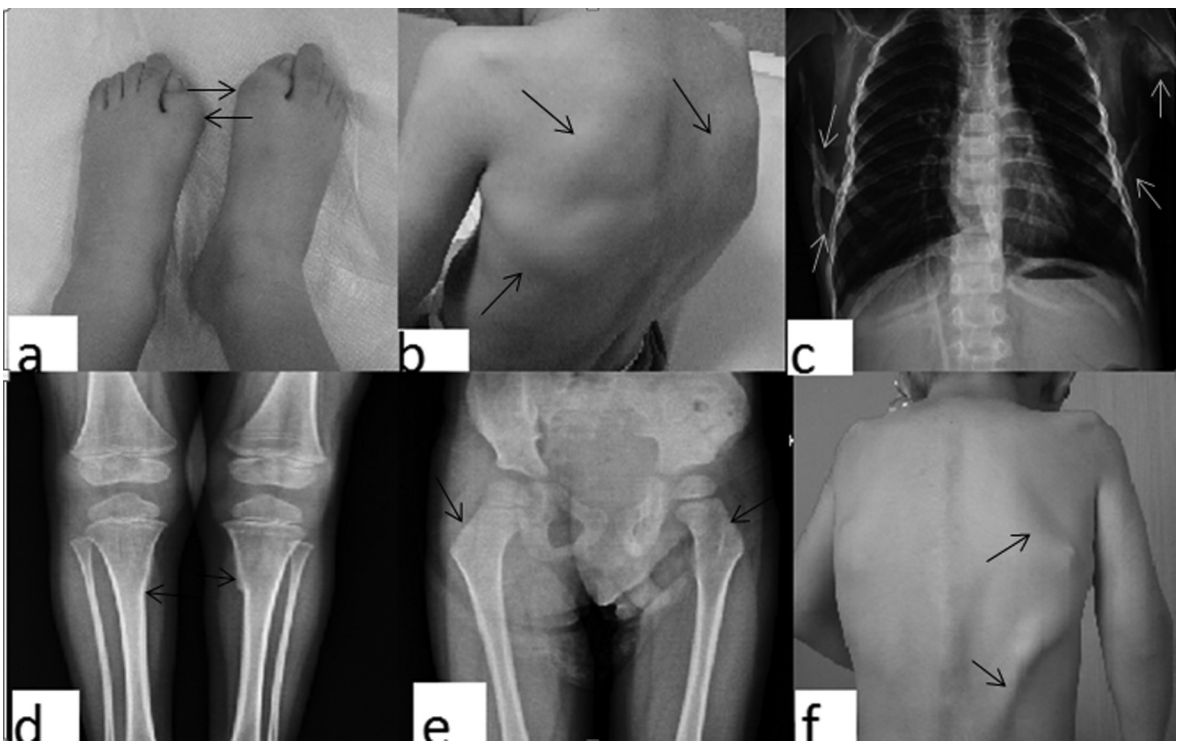

Fig. 1. a) bilateral hallux valgus deformity of the great toes **b)** swellings on the back at the time of diagnosis **c)** heterotrophic ossifications around bilateral axillary regions and head of the right humerus **d)** bilateral proximal medial tibial osteochondromas **e)** broad femoral necks **f)** view of the back 2 years after diagnosis showing severe calcifications on the right side of the back

pathophysiology and treatment of FOP and also to collect the demographics of Turkish FOP patients.

Fibrodysplasia ossificans progresiva is an extremely disabling disease that causes endochondral bone formation at extraskeletal sites and immobilizing the patient in a second skeleton of heterotopic bone.[1] There are approximately 800 known FOP patients and estimated to be just more than 3,500 patients with FOP in the world.[5,6] Genetic transmission is autosomal dominant but since reproductive fitness is very low, most cases arise as a result of spontaneous de novo mutation.[7] The diagnosis is made on the basis of clinical findings and all patients with classic FOP have two typical clinical features: 1) characteristic malformation of the great toes and 2) onset of episodic soft tissue flare-ups leading to progressive ossification in characteristic anatomic pattern.[5] Our case had congenital hallux valgus deformity of the great toes and soft tissue swellings first starting on the back around 3 years of age.

Swellings and ossifications occur in specific anatomic and temporal patterns that mimic the patterns of normal embryonic skeletal formation and are seen first in the dorsal, axial, cranial and proximal regions of the body. Later the ventral, appendicular, caudal and distal regions are affected.[7] The tongue, diaphragm, extra-ocular, cardiac and smooth muscles are not involved in FOP.[1]

Differential diagnosis of FOP is broad and includes desmoid tumors, aggressive juvenile fibromatosis, progressive osseous heteroplasia, osteosarcoma, lymphedema, and soft tissue sarcoma.[1,7] Most of the pediatricians suspect a malignant disease after seeing these tumor-like lesions on the back and refer these children to the pediatric oncologists, pediatric surgeons or orthopedic surgeons for the biopsy. Rarely, these children may be referred to a rheumatologist because of the restriction of the joint movements, initially of the shoulder and cervical joints. The child was referred to us due to restriction of the shoulder and neck movements.

There are some common, but not specific, radiographic features of FOP. These are: hallux valgus deformity, short first metatarsals, orthotopic fusion of posterior elements of cervical vertebrae, short and broad femoral necks and proximal medial tibial osteochondromas.[1] Our case had all previously described radiologic features of the disease. The disease is characterized by episodic painful swellings (flare-ups) which may be spontaneous or triggered by influenza-like viral illness, muscle fatigue, blunt muscle trauma from bumps, falls, stretching of a muscle group, intramuscular injections including immunizations.[1,8] Some flare-ups spontaneously regress but most of the time, these swellings transform skeletal muscles, ligaments, fascia, tendons and aponeuroses into ribbons, sheets, and plates of heterotopic bone.[7,8] Most of the flare-ups resolve within 8 weeks of onset but flare-ups around back and hip region tend to last more than 2 months.[8] The mother stated that the first swelling on the back was observed after a severe influenza-like viral illness.

In 2006, genetic mutation causing FOP was found to be 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, causing hyperactivitity of bone morphogenic protein pathway.[9] Classical FOP patients comprise around 98% of FOP cases. A small number of patients have unusual clinical features of FOP and are termed atypical FOP.[10] Atypical FOP patients are categorized as FOP – plus (classic defining features of FOP plus one or more atypical features) and FOP variants (major variations in one or both of the two classic defining features of FOP, such as normal great toes or severe reduction deficits of digits).[10] All classical and atypical FOP patients have missense mutations in the ACVR1/ALK2 gene.[5,7,10]

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 in any other inflammatory myopathy. After rapid and destructive inflammatory stage comes intense fibroproliferative phase associated with angiogenesis and neovascularization. Fibroproliferative tissues undergo an avascular condensation into cartilage followed by revascularization stage with heterotopic bone formation that appear histologically normal

and often contain marrow elements.[1]

Currently there is no proven treatment modality to prevent FOP flare-ups or to slow or regress the heterotopic bone formation.[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.[11] Non-steroidal anti-inflammatory agents, cyclo-oxygenase-2 inhibitors, leukotriene inhibitors, mast cell stabilizers, and aminobisphosphonates are useful anecdotally in managing chronic discomfort and ongoing flare-ups.[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.[1,7,11,12] 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.[11] Subcutaneous injections are thought to be safe and influenza and pneumococcal vaccinations are recommended to decrease the rate of respiratory tract infections.[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.[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.[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 '*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

1. Pignolo RJ, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva: Diagnosis, management, and therapeutic horizons. Pediatr Endocrinol Rev 2013; 10 (Suppl 2): 437-448.
2. Kaplan FS, Xu M, Glaser DL, et al. Early diagnosis of fibrodysplasia ossificans progressiva. Pediatrics 2008; 121: e1295-e1300.
3. Rider LG, Lindsey CB, Miller FW. Juvenile Dermatomyositis. In: Petty RE, Laxer RM, Lindsey CB, Wedderburn LR (eds). Textbook of Pediatric Rheumatology (7th ed). Philadelphia: Elsevier, 2016: 351-383.
4. Kitterman JA, Kantanie S, Rocke DM, Kaplan FS. Iatrogenic harm caused by diagnostic errors in fibrodysplasia ossificans progressiva. Pediatrics 2005; 116: e654-e661.
5. Kaplan FS, Kobori JA, Orellana C, et al. Multi-system involvement in a severe variant of fibrodysplasia ossificans progressiva (ACVR1 c.772G>A; R258G): A report of two patients. Am J Med Genet A 2015; 167A: 2265-2271.
6. Kaplan FS. The skeleton in the closet. Gene 2013; 528:7-11.
7. Pignolo RJ, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva: Clinical and genetic aspects. Orphanet J Rare Dis 2011; 6: 80.
8. Pignolo RJ, Bedford-Gay C, Liljesthröm M, et al. The natural history of flare-ups in fibrodysplasia ossificans progressiva (FOP): A comprehensive global assessment. J Bone Miner Res 2016; 31: 650-656.
9. Shore EM, Xu M, Feldman GJ, et al. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. Nat Genet 2006; 38: 525-527.

10. Kaplan FS, Xu M, Seemann P, et al. Classic and atypical fibrodysplasia ossificans progressiva (FOP) phenotypes are caused by mutations in the bone morphogenetic protein (BMP) type I receptor ACVR1. Hum Mutat 2009; 30: 379-390.
11. Kaplan FS, Shore EM, Pignolo RJ; The International Clinical Consortium on Fibrodysplasia Ossificans Progressiva. The medical management of fibrodysplasia ossificans progressiva: Current treatment considerations. Clin Proc Intl Clin Consort FOP 2011; 4: 1-100.
12. Kaplan FS, Pignolo RJ, Shore EM. From mysteries to medicines: Drug development for fibrodysplasia ossificans progressive. Expert Opin Orphan Drugs 2013; 1: 637-649.
13. Kaplan FS, Zasloff MA, Kitterman JA, Shore EM, Hong CC, Rocke DM. Early mortality and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva. J Bone Joint Surg Am 2010; 92: 686-691.
14. Önal M, Bajin MD, Yılmaz T. Fibrodysplasia ossificans progressiva: A case report. Turk J Pediatr 2014; 56: 561-564.
15. Topçu HO, Özgü B, Turgut O. Normogonadotropik primary amenorrhea; fibrodysplasia ossificans progressiva. Endokrinolojide Diyalog 2013; 10: 124-126.
16. Toprak U, Erhuner Z, Selvi AN, Paşaoğlu E, Karademir MA. Progresif ossifikan fibrodisplazi: Olgu sunumu. Ankara Üniversitesi Tıp Fakültesi Mecmuası 2007; 60: 173-175.
17. Özbudak Demir S, Karahan G, Aydın G, Köseoğlu F. Fibrodisplazi (miyozitis) ossifikans progresiva: İki olgu sunumu. Romatizma 2001; 16: 164-168.
18. Baysal T, Elmali N, Kutlu R, Baysal O. The stone man: Myositis (fibrodysplasia) ossificans progressiva. Eur Radiol 1998; 8: 479-481.
19. Kocyigit, H, Hizli, N, Memis A, Sabah D, Memis A. A severely disabling disorder: Fibrodysplasia ossificans progressiva. Clin Rheumatol 2001; 20: 273-275.
20. Eresen Yazıcıoğlu C, Karatosun V, Kızıldağ S, Ozsoylu D, Kavukçu S. ACVR1 gene mutations in four Turkish patients diagnosed as fibrodysplasia ossificans progressiva. Gene 2013; 515: 444-446.
21. Aslan G, Celik F, Görgü M. Unusual ankylosis of the jaw due to fibrodysplasia ossificans progressiva. Ann Plast Surg 1999; 43: 576-578.
22. Gülaldi NC, Elahi N, Sasani J, Erbengi G. Tc-99m MDP scanning in a patient with extensive fibrodysplasia ossificans progressiva. Clin Nucl Med 1995; 20: 188-190.
23. Orhan K, Uyanik LO, Erkmen E, Kilinc Y. Unusually severe limitation of the jaw attributable to fibrodysplasia ossificans progressiva: A case report with cone-beam computed tomography findings. Oral Surg Oral Med Oral Pathol Oral Radiol 2012; 113: 404-409.
24. Atik T, Işık E, Onay H, Tekin İM, Günay H, Özkınay F. Fibrodisplazi ossifikans progresiva: Klinik ve moleküler bulgularıyla klasik bir olgu. Turkiye Klinikleri J Pediatr 2015; 24: 164-168.
25. Şimşek E, Binay Ç, Göbüt N. Fibrodisplazi ossifikans progressiva: Olgu sunumu. Güncel Pediatri 2015; 13: 222-226.
26. Tüysüz B, Kırcı F, Erginel A, et al. Corpus callosum agenezisi olan bir fibrodysplasia ossificans olgusu. Turk Pediatri Ars 1993; 28.