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FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

Case report

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ABSTRACT - Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disorder characterized by postnatal progressive heterotopic ossification of the connective tissue and congenital malformation of the big toes. We report on a nine-year-old girl with clinical and radiological features of FOP. She was born with bilateral hallux valgus and at the age of nine presented an indurate mass in the left cervical region that was painful. A significant decreased range of motion in all levels of the spine and shoulder girdle was found. The radiographs showed heterotopic ossification in the thoracic region. The patient had two outbreaks of the disease ("flare-ups") that were treated with prednisone 2 mg/kg/day for four days. After the "flare-ups", she had a continuous therapy with a Cox-2 inhibitor (25 mg/day) and a leukotriene inhibitor, montelukast (10 mg/day).

KEY WORDS: fibrodysplasia ossificans progressiva, myositis ossificans progressiva, myositis ossificans, heterotopic ossification.

Fibrodisplasia ossificante progressiva: relato de caso

RESUMO - A fibrodisplasia ossificante progressiva (FOP) é doença rara, autossômica dominante, caracterizada por ossificação heterotópica progressiva pós-natal do tecido conjuntivo e malformação congênita dos háluces. Relatamos o caso de menina de nove anos com o quadro clínico-radiológico típico de FOP, nascida com hálux valgo bilateral e que aos 9 anos de idade apresentou massa dolorosa, de consistência endurecida, sem sinais inflamatórios, situada na região cervical. Adicionalmente, era possível observar diminuição importante da movimentação em todos os níveis da coluna vertebral e da cintura escapular. A avaliação radiológica revelou a presença de ossificações heterotópicas na região torácica e malformação bilateral dos háluces. A paciente teve outros dois surtos da doença, que foram tratados com corticosteróide oral por quatro dias, (2 mg/kg/dia) seguido por tratamento prolongado com inibidores da Cox-2 (25 mg/dia) e com inibidor de leucotrienos (10 mg/dia).

PALAVRAS-CHAVE: fibrodisplasia ossificante progressiva, miosite ossificante progressiva, miosite ossificante, ossificação heterotópica.

Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disorder in which congenital abnormalities of the big toes are associated with progressive heterotopic ossification of the connective tissue structures including those related to the striated muscles, leading to permanent disability. Studies from Europe and United States concluded that the estimate incidence of FOP is one in two million births[1]. In Brazil there are some cases related in literature like publish by Tonholo et al. in 1994[2], Nucci et al. in 2000[3], and Araujo et al. in 2005[4]. Currently, the Brazilian FOP Association (FOP BRASIL) has 49 registered cases of FOP.

Most cases of FOP are due to new gene mutations, but genetic studies confirm the autosomal dominant nature and variable expression of the presumed defective gene. Genetic analysis revealed that the FOP phenotype is linked to markers located in chromosome 4[5]. It is believed that a gene mutation causes an overexpression of a bone morphogenetic protein (BMP4)[6].

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CASE

A nine-year-old girl presented the initial symptoms of FOP with tender and painful masses on the anterior abdominal wall accompanied by warm overlying skin and erythema. These masses progressively appeared on the thoracic and dorsal regions with the same clinical features. At that time she was admitted to hospital for two weeks. Her blood and urinary tests were normal and no abnormal sign was seen on the magnetic resonance imaging of the abdomen. No history of local trauma was reported. Later the patient had two "flare-ups" of the disease in the right and left cervical regions that disappeared after two weeks. Physical examination showed a hard mass on the left side of the cervical region. The mass was tender and painful, but no warmth or inflammation was noted (Fig 1A). Palpation revealed stiffness of all abdominal and paraspinal muscles. Abduction of the shoulders was restricted to a 45° (Fig 1B). The patient had bilateral hallux valgus but no other abnormality of any other toes (Fig 2). Her parents didn't show any similar abnormalities on the physical examination. No heteropic ossification was observed in two radiographic

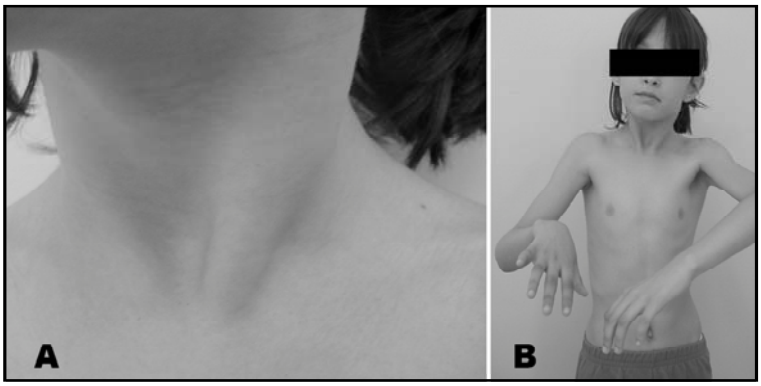

Fig 1. (A) Presence of cervical mass on the left side without inflammatory signs. (B) Restricted shouders abdction with a 45º angle.

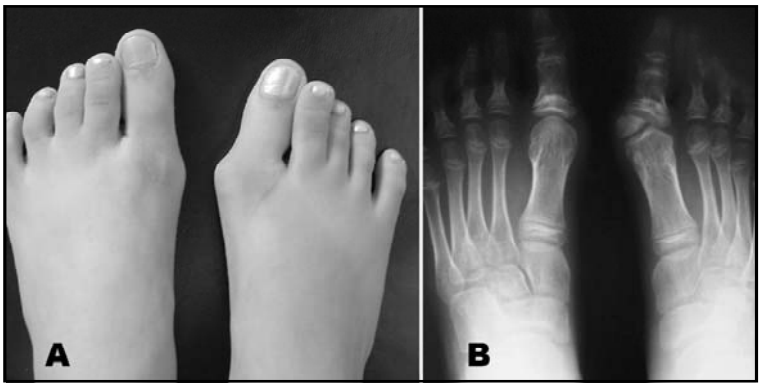

Fig 2. Halux valgus bilateral - clinical and radiological view.

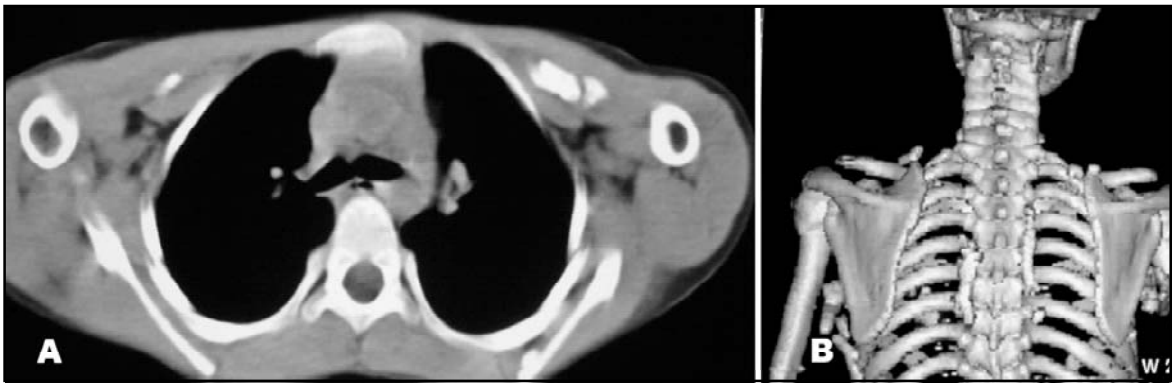

Fig 3. (A) Axial CT scan of the thoracic region and (B) a three dimensional reconstruction of the trunk showed heterotopic ossifications.

series at one- and two-month of follow-up. Axial trunk computerized tomography (CT) showed points of ossification (Fig 3A). The three-dimensional (3D) surface shaded display of the trunk CT showed multiple heterotopic ossifications in the spine and scapulas (Fig 3B). The patient took Vioxx® for 6 months without any side effects and now is taking Montelukast (10 mg/daily) and corticosteroids (2 mg/Kg/4 days) for "flare-ups".

This case report was approved by the hospital ethic commission and the parents gave informed consent for publication.

DISCUSSION

Guy Patin first described FOP in 1692 in a young patient who "turned to wood"[7]. The autosomal dominant inheritance of FOP was first described by Sympson in a case report of a 7-year-old boy with classic features of FOP whose father had the same congenital deformity of the great toes but no other characteristics of this disorder[8].

Genetic linkage analysis has shown that the FOP phenotype is heterogeneous linked to markers located in the long arm of chromosome 4. In 2000, Feldman et al. described four affected families with markers located in the 4q27-31[5]. Lucotte et al. published in 2000 that the FOP gene was related to chromosome 17q21-22[9]. Further studies, published by XU et al. and Kaplan et al. showed that there is no link between FOP and this gene[10,11].

Abnormalities of the great toes are observed at birth in most cases of FOP (bilateral hallux valgus - microdactylia with hypoplasia or synostosis of the phalanges or both). In our case, the parents reported that the patient had hallux valgus since birth[12]. The initial symptoms of FOP are painful and hard soft tissue swellings over the affected muscles that lead to ossification. It usually occurs from birth up to the age of 16 years (mean age 4.6 years), following spontaneous or trauma-induced "flare-ups"[1,13]. Heterotopic ossification usually begins in the cervical paraspinal muscles and later spreads from axial to appendicular, cranial to caudal and proximal to distal sites. Scoliosis is a common finding and is often the result of asymmetric heterotopic bones connecting the trunk and pelvis[1].

Conductive hearing impairment is a common feature associated with this condition[14] and it probably occurs due to the fusion of the ossicles of the ear[15]. Progressive episodes of heterotopic ossification lead to ankylosis of all major joints of the axial and appendicular skeleton, rendering movement impossible. Generally, in the second decade of life, FOP patients are confined to bed or wheelchairs[16]. Cardiopulmonary problems may occur and are associated with severe restrictive disease of the chest wall[17].

FOP diagnosis is clinical and it is usually made based on the presence of three major criteria[15]: Congenital malformation of the great toes, progressive heterotopic endochondral ossification (heterotopic bones that gradually form from cartilage) and progression of the disease in well-defined anatomical and temporal patterns. Laboratory tests may show a discrete increase of ESR during the "flare-ups". Imaging exams like radiographs and tomographies shows the heterotopic bones and are useful to confirm the diagnosis.

Differential diagnosis includes other genetic illnesses that also cause the development of heterotopic ossifications, such as progressive osseous heteroplasia (POH), Albright hereditary osteodystrophy (AHO), osteoma cutis, ankylosing spondylitis, Still's disease and Klippel-Feil-syndrome[15]. The "flare-ups" of FOP must be differentiated from the inflammatory processes of osseous tumors, and aggressive juvenile fibromatosis.

Treatment of FOP is multifactorial and is based on injury prevention and clinical therapy. Prevention of soft tissue injury and muscle damage, as well as the prevention of falls, is extremely important. Intramuscular injections, including vaccines, must be avoided. Moreover, in routine dental care, overstretching of the jaw and intramuscular local anesthetic injections should also be avoided.

Patients with FOP may have an additional risk of "flare-ups" after influenza-like illness. Thus, a subcutaneous influenza vaccine could help these patients, particularly those who have severe restrictive disease of the chest wall and are at a greater high risk of presenting complications of respiratory infections that are a frequent cause of death.

Drug treatment of our patient was based initially on the guidelines published by Kaplan et al.[18] and currently on the new guidelines published by the same authors[19]. The patient received corticosteroids in the acute phases of the disease and a long-term treatment using a combination of a leukotriene inhibitor and a Cox-2 inhibitor.

Corticosteroids given within the first 24 hours of flare-up may reduce the intense lymphocytic infiltration and tissue edema[18]. Prednisone is given for four days, 2 mg/kg/day, and should be restricted to the early symptomatic "flare-ups" that affect major

joints[18]. When prednisone is discontinued, a non-steroidal anti-inflammatory drug or a Cox-2 inhibitor may be used symptomatically for the duration of the "flare-up". None of these drugs avoided the progression of the disease in our patient. Non-steroidal anti-inflammatorydrugs like ibuprofen and indomethacin can be used the doses of 4-10 mg/kg (every 6 hours) and 2-4 mg/kg/day, respectively.

The Cox-2 inhibitors restrain the activity of inflammatoryprostaglandins, which are potent co-stimulatory molecules along with BMPs in the induction of the heterotopic bone. Recently, after the Vioxx® recall, the use of Cox-2 inhibitors in the pediatric population change to Celebrex® (although it has been used compassionately in children, it is not approved for pediatric use). The dose range is from 100 to 200 mg per day and can not exceed a maximum total daily dose of 600 mg for more than 16 months or maximum anti-angiogenic dose of 6 mg/kg or 250 mg/m^2.

Leukotriene inhibitors may reduce the downstream effects of released mast cell mediators that are involved in the pathological process of heterotopic bone formation[18]. Montelukast, a leukotriene inhibitor may be prescribed in a dose of 5 or 10 mg/day.

Fibrodysplasia ossificans progressiva is a rare and disabling disease that still does not have an effective treatment that can cure it or stop its progression. Physicians, health care professionals, patients and their families must be educated about the disease. Although drugs can be used to decrease some symptoms, the best approach is still the early diagnosis and prevention of trauma that can provide a better quality of life.

REFERENCES

1. Smith R. Fibrodysplasia (myosistis) ossificans progressiva: clinical lessons from a rare disease. Clin Orthop 1998;346:7-14.
2. Tonholo-Silva ER, Adachi EA, Tafner MS, Yoshinaga L. Fibrodysplasia ossificans progressiva. Arq Neuropsiquiatr 1994;52:100-102.
3. Nucci A, Queiroz LS, Santos AO, Camargo EE, Moura-Ribeiro MVL. Fibrodisplasia ossificante progressiva: relato de caso. Arq Neuropsiquiatr 2000;58:342-347.
4. Araújo CR Jr, Carvalho TN, Costa MAB, Lobo LV, Fonseca RC, Teixeira KS. Fibrodysplasia ossificans progressiva: a case report and radiographic findings. Radiol Bras 2005;38:69-73.
5. Feldman G, Li M, Martin S, et al. Fibrodisplasia ossificans progressiva a heritable disorder of severe heterotopic ossification, maps to human chromosome 4q27-31. Am J Hum Genet 2000;66:128-135.
6. Lanchoney TF, Olmsted EA, Shore EM, et al. Characterization of bone morphogenetic protein 4 receptor in fibrodysplasia ossificans progressiva. Clin Orthop 1998;346:38-45.
7. Goldman AB. Heritable diseases of connective tissue, epiphyseal dysplasias, and related conditions. In Resnick D, (ed) Diagnosis of bone and joint disorders. Philadelphia: W.B. Saunders; 2002:4409-4415.
8. Delatycki M, Rogers JG. The genetics of fybrodisplasia ossificans progressiva. Clin Orthop 1998;346:15-18.
9. Lucotte G, Bathelier C, Mercier G, et al. Localization of the gene for fibrodysplasia ossificans progressiva (FOP) to chromosome 17q21-22. Genet Couns 2000;11:329-334.
10. Xu MQ, Feldman G, LeMerrer M, et al. Linkage exclusion and mutational analysis of the noggin gene in patients with fibrodysplasia ossificans progressiva (FOP). Clin Genetics 2000;58:291-298.
11. Xu MQ, Shore EM, Kaplan FS. Reported noggin mutations are PCR errors. Am J Med Genet 2002;109:161.
12. Falliner A, Drescher W, Brossmann J. The spine in fibrodysplasia ossificans progressiva: a case report. Spine 2003;28:519-522.
13. Mahboubi S, Glaser DL, Shore EM, Kalpan FS. Fibrodysplasia ossificans progressiva. Pediatr Radiol 2001;31:307-314.
14. Levy CE, Lash AT, Janoff HB, Kaplan FS. Conductive hearing loss in individuals with fibrodysplasia ossificans progressive. Am J Audiol 1999;8:29-33.
15. Delai PLR, Kantanie S, Santili C, et al. Fibrodysplasia ossificans progressiva: a hereditary illness of multidisciplinary interest. Rev Bras Ortop 2004;39:205-213.
16. Cohen RB, Hahn GV, Tabas J, et al. The natural history of heterotopic ossification in patients who have fibrodysplasia ossificans progressiva. J Bone Joint Surg Am 1993;75:215-219.
17. Kussmaul WG, Esmail NA, Sagar Y, et al. Pulmonary and cardiac function in advanced fibrodysplasia ossificans progressiva. Clin Orthop 1998;346:104-109.
18. Kaplan FS, Shore EM, Glaser DL, et al. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. Clin Proc Intl Consort FOP 2003;1:1-81.
19. Kaplan FS, Shore EM, Glaser DL, et al. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. Clin Proc Intl Clin Consort FOP 2005;1:1-71.