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 indurated 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 hálucis. 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 hálucis. 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.
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 45º (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 heterotopic ossification was observed in two radiographic...
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 Sympsoon in a case report of a 7-year-old boy with classic features of FOP whose father had the same characteristic of this disorder8.

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 4q27-315. Lucotte et al. published in 2000 that the FOP gene was related to chromosome 17q21-229. Further studies, published by XU et al. and Kaplan et al. showed that there is no link between FOP and this gene10,11.

Abnormalities of the great toes are observed at birth in most cases of FOP (bilateral hallux valgus - microdactylyia with hypoplasia or synostosis of the phalanges or both). In our case, the parents reported that the patient had hallux valgus since birth12. 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 pelvis1.

Conductive hearing impairment is a common feature associated with this condition14 and it probably occurs due to the fusion of the ossicles of the ear15. 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 wheelchairs16. Cardiopulmonary problems may occur and are associated with severe restrictive disease of the chest wall17.

FOP diagnosis is clinical and it is usually made based on the presence of three major criteria15: Congenital malformation of the great toes, progressive heterotopic enchondral 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-syndrome15. 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 authors19. 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 edema18. Prednisone is given for four days, 2 mg/kg/day, and should be restricted to the early symptomatic “flare-ups” that affect major
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-inflammatory drugs 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 inflammatory prostaglandins, 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/m².

Leukotriene inhibitors may reduce the downstream effects of released mast cell mediators that are involved in the pathological process of heterotopic bone formation. 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**