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FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

CASE REPORT

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ABSTRACT - Fibrodysplasia ossificans progressiva is a rare genetic disease characterized by widespread soft tissue ossification and congenital stigmata of the extremities. We report on a male child followed for ten years since the age of 3 years and 9 months, when the diagnosis was made. He was born with bilateral hypoplasic hallux valgus and ventricular septal defect, corrected by transsternal approach when 32 months old. Restriction of neck mobility followed and foci of ectopic ossification appeared. Four crises of disease exacerbation were treated with oral prednisone and/or other antiinflammatory drugs. Sodium etidronate 5 to 10 mg/kg/day was prescribed intermittently during about six years but was discontinued due to osteopenia. The disease course has been relentless, with severe movement restriction including the chest wall. A review showed few similar case reports in the Brazilian literature. We revisit the criteria for diagnosis and the essentials of management and treatment.

KEY WORDS: fibrodysplasia ossificans progressiva, myositis ossificans, muscle biopsy, rigid spine, ^{99m}Tc-MDP scan, etidronate treatment.

Fibrodisplasia ossificante progressiva: relato de caso

RESUMO - Fibrodisplasia ossificante progressiva é uma doença genética rara, caracterizada por ossificação disseminada em tecidos moles e estigmas congênitos nas extremidades. Relatamos sobre uma criança do sexo masculino, branca, que vem sendo acompanhada desde seus 3 anos e 9 meses quando diagnosticamos a doença. Nascida com halux valgo hipoplásico bilateral e defeito do septo interventricular, submeteu-se a correção cirúrgica através de esternotomia, aos 32 meses de vida. Seguiram-se progressiva restrição de movimentos cervicais e aparecimento de nódulos duros e dolorosos em regiões paravertebrais cérvico-torácicas. Em dez anos, assistimos a quatro episódios bem definidos de exacerbação da doença, com acréscimos de ossificação ectópica. Nessas ocasiões, prescrevíamos prednisona oral e/ou antiinflamatórios não hormonais. Etidronato de sódio, 5 a 10 mg/kg/dia, foi utilizado em períodos de dois ou três meses, com intervalos de dois meses, durante seis anos. Osteopenia obrigou-nos a interromper o uso do quelante. A evolução tem sido inexorável, com limitação intensa de movimentos torácicos e corpóreos. A revisão da literatura brasileira revelou poucos casos semelhantes. Enfatizamos os critérios para diagnóstico e princípios básicos de tratamento.

PALAVRAS-CHAVE: fibrodisplasia ossificante progressiva, miosite ossificante, biópsia muscular, espinha rígida, cintilografia com MDP-^{99m}Tc, tratamento com etidronato.

Fibrodysplasia ossificans progressiva (FOP) is a rare, autosomal dominant disease[1-3] affecting all ethnic backgrounds[4]. It is particularly disabling in children and is characterized by two cardinal

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features: heterotopic progressive osteogenesis and congenital abnormalities of the great toes[5,6]. The disease should be familiar to neonatologists, pediatricians, neurologists, orthopedic clinicians and surgeons, rheumatologists and ancillary personnel engaged in the diagnosis and management of neuromuscular conditions.

The term *fibrodysplasia ossificans progressiva* is preferred to *myositis ossificans*[5] because ectopic osteogenesis occurs in the connective tissue within muscles, fasciae, ligaments, tendons and joint capsules, rather than in the muscle fibers themselves. These may show nonspecific, possibly secondary pathological changes[6].

Recently, FOP has been considered a connective tissue disorder due to overexpression of a bone morphogenetic protein, BMP 4 [7,8]. Since curative therapy is not available, management is based on the principle of *primum non nocere*, particularly at preventing abnormal ossification[5]. Therefore, an increased awareness of the disease among clinicians is of great importance.

We report on a patient with FOP followed up for ten years who used sodium etidronate on an intermittent schedule. We revisit the criteria for diagnosis, treatment and main rules for management. Emphasis is placed on the adverse effects of simple surgical procedures, such as muscle biopsy, which may propitiate ectopic ossification and is not contributory for the diagnosis.

CASE

A caucasian boy, the first child of young, healthy, non-consanguineous parents (father, 23; mother, 20 years old), was born in September 1985 by caesarean section after an uneventful full-term gestation. The parents do not have any obvious clinical skeletal malformation and a younger sister of the patient is reported as normal.

The neonate was considered in good condition, with 53 cm and 3,800 g. An orthopedic consultation was requested because of malformation of the great toes. A plain roentgenogram of the feet was done and the child discharged. Routine pediatric follow up elsewhere revealed cardiac murmur and delayed somatic development. Although cyanosis was not a complaint, a congenital interventricular septal defect was corrected by transsternal approach in May 1988 (at the age of 2 years and 8 months). Psychomotor development was always within normal limits. He was first seen at the Neuromuscular Clinic, UNICAMP in June, 1989. The parents observed progressive difficulty in the child's neck extension and, in the last six months, appearance of several hard nodules in the cervical and dorsal regions. Some were painful and the overlying skin was erythematous. Examination revealed a cooperative, intelligent boy with restricted mobility during walking, sitting and standing caused by a rigid kyphoscoliotic spine. All paraspinal muscles were hard on palpation. There were several nodular masses fixed to deep planes and scattered over the back (Fig 1). Abduction of the shoulders and mobility of the hips were severely restricted. Clinodactyly of both fifth fingers (Fig 1) and bilateral short hallux valgus (Fig 1) were also observed.

Hemogram, erythrocyte sedimentation rate, serum calcium, phosphorus, alkaline phosphatase, creatine phosphokinase, alanine and aspartate transaminases, routine urinalysis, urine calcium and phosphorus, and creatinine clearence were within normal limits. Alkaline phosphatase ranged from normal to mildly elevated during evolution. A recent ^{99m}Tc-MDP scan (Fig 2) showed areas of abnormal uptake in the soft tissue of the left lumbar paravertebral region, right posterior chest wall and posterior aspect of the right arm, consistent with soft tissue calcifications with variable degrees of uptake. Several foci of increased uptake were also demonstrated adjacent to the ribs and lateral aspects of the thoracic spine, corresponding to the palpable nodules of heterotopic calcification. The intense tracer uptake in the proximal third of the right femur was in agreement with the patient's right hip ankylosis. A focal area of mild uptake in the distal third of the left fibula was reported as the site of possible trauma or microfracture due to osteomalacia. The other sites of heterotopic bone formation were not observed probably because of complete maturity of the process of ossification in those regions.

Follow up from 1989 to 1999 documented four periods of exacerbation, heterotopic ossification appearing in the dorsal thoracic region, inferior right abdomen, biceps and medial left arm and forehead, the latter two after local trauma. All episodes were accompanied by local inflammatory signs, restriction of movement and pain and were treated by oral prednisone and/or nonsteroidal antiinflammatory drugs. For about six years since August 1989 sodium etidronate (ethane-1-hydroxy-1,1-diphosphonate) was prescribed in oral doses of 5 to 10 mg/kg/day for

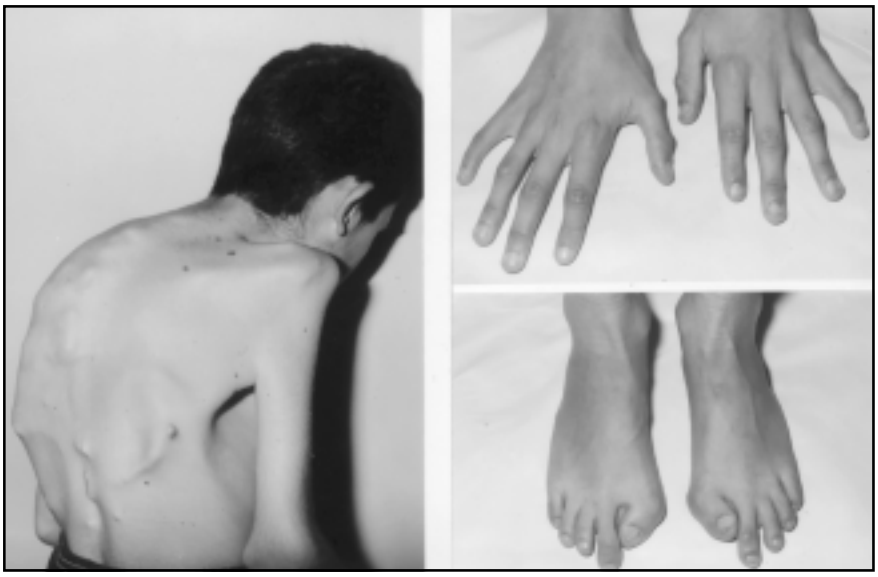

*Fig. 1 (*left*) Dorsal view of patient at age 13. (*above*) Hands to show bilateral clinodactyly of the fifth finger. (*below*) Typical deformity of the feet (bilateral short hallux valgus).*

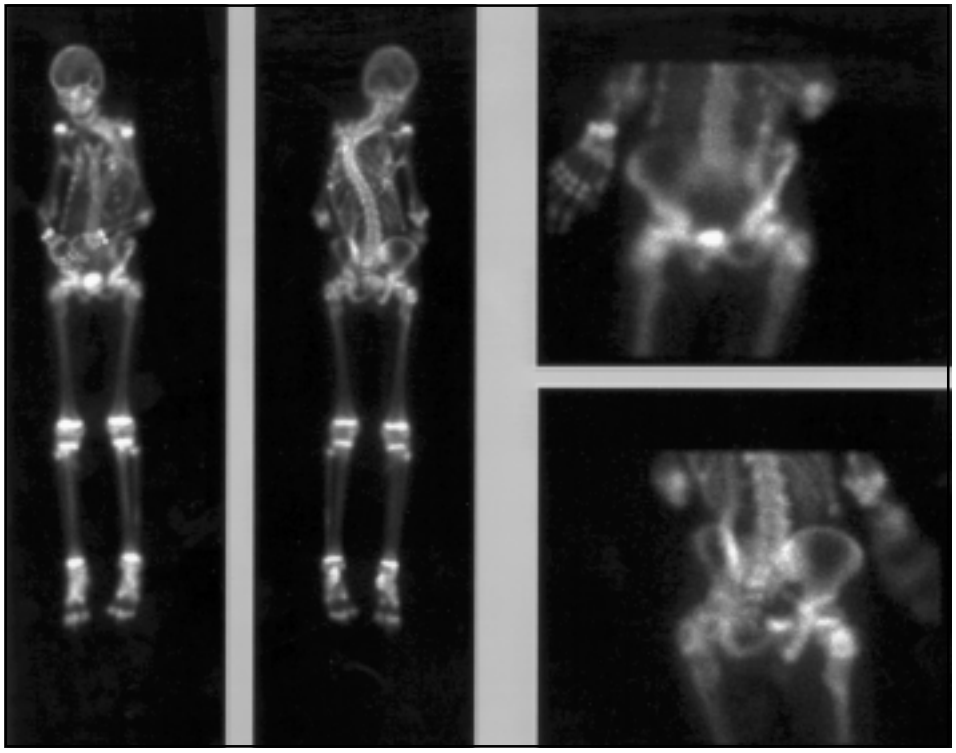

Fig 2. Whole body and spot images of the bone scan, with mild abnormal tracer uptake in the soft tissues of the left lumbar paravertebral region, posterior chest wall, right arm and right hip (soft tissue calcification).

periods of two or three months intercalated by two month drug free intervals. Diphosphonate was definitely withdrawn in 1995 because osteopenia was detected by bone densitometry.

Presently the patient is ambulatory, but with severe limitations in axial movements due to rigidity of the whole spine. Shoulders and hips show bilateral ankylosis. Chest expansion is greatly restricted as documented by pulmonary function tests. Cardiac function is normal.

DISCUSSION

FOP should be diagnosed as early as possible and non-invasively, based upon history, clinical and radiological findings[5]. The mainstay of diagnosis is bilateral great toe anomaly present from birth, reported in 79 to 100% of patients in representative series[9-12]. The most characteristic deformity is microdactyly of both halluces due to a single phalanx in valgus position[9,10] (type I deformity according to Connor and Evans[11]). Three other subtypes of malformed big toes can be diagnosed up to the second decade[11], and this is where radiologic examination is especially important. Isolated congenital hallux valgus (i.e. not as part of FOP) is much rarer than FOP itself[5]. Therefore, the finding of congenital hallux valgus must raise the possibility of FOP so that management should be early and adequate.

Hand malformation is generally associated with, and proportional to the severity of hallux dysmorphism, and indeed is not seen in its absence[10]. The most frequent anomalies are short first metacarpal and brachymesophalangy of the fifth finger with clinodactyly[10].

Ectopic ossification, another hallmark of disease, occurs lifelong, with records of its initial appearance at the mean age of three[11] or five years[13]. In almost all patients, onset of the lesions was noted under 15[9-13]. Ectopic ossification follows a well defined pattern, the axial body being compromised first and most. Shoulder and hip regions are affected more than distal segments of the limbs[9]. Deafness and baldness have been reported in up to one fourth of the cases, while mental retardation is rare[11].

Exacerbation of FOP may occur spontaneously or be precipitated by trauma, such as intramuscular injections including vaccines[14], local anesthesia, specially troncular block near the temporomandibular joint[11], muscle biopsy[6] and careless venepuncture[11]. Biopsy of calcified nodules is to be avoided if the diagnosis of FOP is clear on clinical and radiological grounds (foot and hand stigmata). Biopsy may result in recurrent ossification of the site, sometimes worse than the original lesion[11]. Another clinical expression of FOP is acute or chronic limb swelling, defined as an enlargement of the limb circumference at one or more locations with increased tissue turgor, the pathogenesis of which is multifactorial[15].

In the present case, cardiac surgery was followed on a short term by increased limitation of neck flexion. This is to the best of our knowledge the first patient with FOP reported who was submitted to this procedure. Patients undergoing other types of surgical intervention such as abdominal hysterectomy, appendicectomy, herniorrhaphy and excision of fibroadenomas of the breast did not present ossification[11].

Routine laboratory tests including calcemia and phosphatemia are usually normal or non contributory in FOP. Roentgenograms may aid in documenting minor osseous dysmorphism. Bone scintigraphy with ^{99m}Tc-MDP may demonstrate early the heterotopic ossification and aid in the assessment of the extent and progression of the disease[16,17].

So far no effective treatment for FOP is known. All management is conservative and based on the principle of *primum non nocere*, that is, of avoiding conditions potentially provocative of abnormal ossification[5]. Several types of treatment have been tried[18]. Administration of calcium chelants such as sodium etidronate have been proposed since 1969 with variable results[19]. In our

patient the drug was given over some five years on an intermittent schedule in order to delay osteopenia. However, during treatment the nodules did not stop appearing and bone demineralization did become a significant side effect, although in the literature it has been described only with higher doses[19]. Inflammatory signs preceding ossification were generally less severe when corticosteroid was used and indeed the drug is recommended *per os* on these occasions. In acute flareups, oral corticosteroids and intravenous etidronate were used simultaneously in an open trial with promising results. Controlled trials are thus encouraged[20].

The phenotype and natural history of FOP are by now so well defined that differential diagnosis is limited. Other disorders of ectopic ossification may be considered, such as Albright hereditary osteodystrophy, pseudomalignant heterotopic ossification, progressive osseous heteroplasia and even osteosarcoma[21-23].

In the recent Brazilian literature, three cases fulfill clinical and radiologic criteria for FOP[24,25]. In the case of Tonholo-Silva et al.[26], although there were ectopic ossifications they did not appear to be axial, and the characteristic skeletal stigmata of FOP were not mentioned. Garcia Filho et al.[27] studied 25 cases of 'heterotopic ossification' including one of 'progressive myositis ossificans' which may represent an instance of FOP.

It is hoped that the recent surge of knowledge on molecular genetics will lead to better understanding of the pathogenesis and to effective treatment for FOP.

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