

Polyostotic form of fibrous dysplasia in a 13 years old Colombian girl showing clinical and biochemical response to neridronate intravenous therapy

Edwin Jobany Parra Prada, MD^a
 Khodr Haidar Hassan, MD^a
 Maria Luisa Brandi, MD, PhD^b
 Alberto Falchetti, PhD^a

^a Unit of Bone Metabolic Diseases, AOUC, Florence, Italy

^b Department of Internal Medicine
 University of Florence, Florence, Italy

Address for correspondence:
 Edwin Jobany Parra Prada
 Via Kennedy 4, 52100 Arezzo, Italy
 Ph. +39 05751788660
 E-mail: edwinjpp@hotmail.it

Summary

Fibrous dysplasia affects principally the bone, it might also comprise extra skeletal anomalies; whereby the bone is replaced by a dysplastic fibrous tissue. It is classified according to the number of affected bones, and its association to endocrine alterations in: monostotic, polyostotic forms and Albright's disease. A congenital etiology is suggested. Pathologic fractures are the most frequently associated complications. We present a case with a polyostotic form of fibrous dysplasia in a 13 years old Colombian girl, wherein a differential diagnosis and treatment decision was made.

KEY WORDS: fibrous dysplasia, McCune Albright syndrome, neridronate.

Introduction

Fibrous dysplasia (FD), a rare skeletal disorder owing to activating mutations of the *GNAS1* gene, is characterized by an impaired proliferation of the medullary fibrous tissue, an abnormal bone matrix, focal areas of woven bone and osteolytic areas. The clinical consequences are represented by bone deformities and an increased skeletal fragility. FD rarely occurs as an isolated monostotic or polyostotic form, and more frequently it is part of the McCune-Albright Syndrome (MAS), in which bone deformities are associated with precocious puberty, endocrinopathy, 'milky-coffee' skin marks. As with Paget's bone disease, FD exhibits an increase of the bone alkaline phosphatase (BAP) and other bone turnover markers (BTMs). Symptoms consist of bone pain, long or facial bones deformities and pathological fractures.

Case report

We describe the case of a 13 years old Colombian girl resident in Italy since 2006. Familial history for bone metabolic disorders is negative. In 2003, due to strong facial pain and a tumefaction on the right side, a diagnosis of FD by CT was made. Moreover, the patient had 'milky-coffee' skin marks on the limbs and at gluteus level. Clinical examination evidenced pain

at the level of the right humer, ulna, left femur, right tibia and a moderate impaired deambulation. BAP and Deoxypyridinoline (DPD), were increased. A biopsy of the affected maxillary bone showed characteristics of a dysplasia. A skeletal scintigraphy evidenced a polyostotic form: skull, left humer distal epiphysis, left ulnar diaphysis, medial arch of the sixth left rib, right femur proximal epiphysis, and right tibia distal diaphysis. Clinical and biochemical assessments did not suggest MAS. In order to differentially diagnose FD with Paget-like syndromes and MAS a mutational analysis of exon 1 of the *TNFRSF11A* gene and an analysis of the *GNAS1* gene were made with negative results. On October 2007, we decided to treat the patient with an intravenous infusion of Neridronate, an amino-bisphosphonate (a-BP) already used in children affected by Osteogenesis Imperfecta; 2 mg/kg of body weight every three months. A daily supplementation of calcium carbonate, 1 g/day, and cholecalciferol, 800 UI/day, has been also associated. After the third month of therapy, bone pain had disappeared, BAP and DPD resulted within the normal ranges and at X-ray control an improvement of bone mineralization was observed. Up to date no side effects have been reported.

Discussion

Fibrous dysplasia is a benign, slowly growing bone disorder in which the normal cancellous bone is replaced by immature woven bone and fibrous tissue.

Fibrous dysplasia results from a defect in the osteoblastic differentiation affecting the final maturation of the bone. Although described as a non-familial, congenital bone disorder, it usually manifests before the 3rd decade of life. Our case fell within the age group described. The disease has a tendency to develop in the pre-adolescence years.

Approximately 20-30% of fibrous dysplasias are polyostotic. Polyostotic Fibrous Dysplasia (PFD) more frequently involves the skull and facial bones, pelvis, spine, and shoulder girdle. PFD may occur alone or as part of the McCune-Albright Syndrome (MAS).

The sites of involvement are the femur (91%), tibia (81%), pelvis (78%), ribs, skull and facial bones (50%), upper extremities, lumbar spine, clavicle, and cervical spine, in decreasing order of frequency. The dysplasia may be unilateral or bilateral, and it may affect several bones in a single limb or both limbs with or without axial skeleton involvement. Although the polyostotic variety tends to occur in a unilateral distribution, involvement is asymmetric and generalized when the disease is bilateral.

Two thirds of patients are symptomatic before they reach 10 years of age. Often, the initial symptom is pain in the involved limb usually associated with a limp, a spontaneous fracture, or both. In one series, a pathologic fracture was present in 85% of polyostotic fibrous dysplasias. Leg-length discrepancy of varying degrees occurs in about 70% of patients with limb involvement. The structural integrity of the bone is weakened, and the weight-bearing bones become bowed. The curvature of the femoral neck and proximal shaft of the femur is markedly increased because a femoral lesion commonly causes a severe

coxa vara abnormality, 'shepherd's-crook deformity', which is a characteristic sign of the disease. Overgrowth of adjacent soft tissues may also be present.

Establishing the diagnosis of fibrous dysplasia requires close cooperation between clinician, radiologist, pathologist and a genetic mutational analysis which was demonstrated very well in the case reported.

Currently there are no clearly-defined systemic therapies for this bone disease. Small, uncontrolled trials using the second generation bisphosphonate (Pamidronate), suggest that bisphosphonates may be effective.

We suggest that Neridronate is able to improve both clinical and biochemical features to prevent fractures and improve the bone quality of FD and it could also be added to a therapeutical armamentarium.

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