Clinical Quiz

Fibrous dysplasia; confirmation of clinical diagnosis by DNA tests instead of biopsy

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Case report

A 33-year-old woman (1.85 m, 110 kg) presented to our out-patient clinic complaining about pain localized at the distal half of the left tibia, which did not respond to analgesics. Symptoms had begun eight years ago with mild pain and swelling in the area (with no history of trauma) that appeared occasionally thereafter. Two months before her visit, the pain became severe and constant leading to ambulatory discomfort. Inspection of the left limb revealed swelling of the tibia and wasting of the calf (Figure 1A). On palpation, there was a painful area matching the area the patient was complaining about. Knee movements were free and painless, while movements of the ankle joint were restricted and painful.

Initial X-ray examination showed large expanded intramedullary lesions in the distal tibia shaft with homogeneous "ground glass" appearance, endosteal scalloping, but no periosteal new bone formation (Figure 1B). Further evaluation with computed tomography (CT) demonstrated widening of the tibia shaft, thinned cortices and sharply defined homogeneous high-density lesions of amorphous texture with uninterrupted sclerotic margins at the medullary cavity (Figure 1C). Assessment of bone metabolism with biochemical markers was indicative of high bone turnover [serum bone alkaline phosphatase: 61.5 μg/L (reference range-r.r. <14.3 μg/L),

serum osteocalcin: 116.2 ng/ml (r.r. 12-41 ng/ml), serum Cross Laps: 0.623 ng/ml (r.r. <0.54 ng/ml), serum PINP: 317.8 ng/ml (r.r. 16.3- 73.9 ng/ml)]. The patient underwent a Tc-99m bone scan which revealed homogeneous enhancement in the left tibia, the left femur, the 7th right rib (anterior and posterior part) and the left ankle joint (Figure 1D). Further assessment with blood and urinary tests did not reveal other medical problems.

Based on the clinical and imaging findings the predominant diagnosis was that of polyostotic fibrous dysplasia (FD). The patient denied a confirmatory bone biopsy, so genomic analysis offered an alternative approach, since FD has a demonstrated association with somatic mutations at codon 201 of the α subunit of G protein (Gsα), encoded by the GNAS gene. Genomic DNA was extracted from peripheral blood and Sanger sequencing analysis was performed in triplicates using one pair of primers designed to cover the known mutations of the GNAS gene that had been linked to FD. The R201C mutation was detected using Chromas software (Chromas Lite 2.01) and BLAST in the patient (Figure 2).

We opted to start treatment with intravenous bisphosphonates (5 mg zoledronic acid every six months). After approximately five months since the first infusion, the patient reports a significant improvement in the level of pain.

Commentary

Fibrous dysplasia of bone is a benign, non-inheritable disease characterized by bone pain, bone deformities and fractures. It was first described by Lichtenstein in 1938. Its prevalence is approximately 1 in 30,000 individuals; sex distribution is equal and it is thought to account for 5 to 7% of benign bone tumors. FD affects either one bone (monoostotic form - around 60% of patients) or multiple bones (polyostotic form - around 40% of patients). Less than 5% of the patients also have endocrine abnormalities (most often precocious pu-

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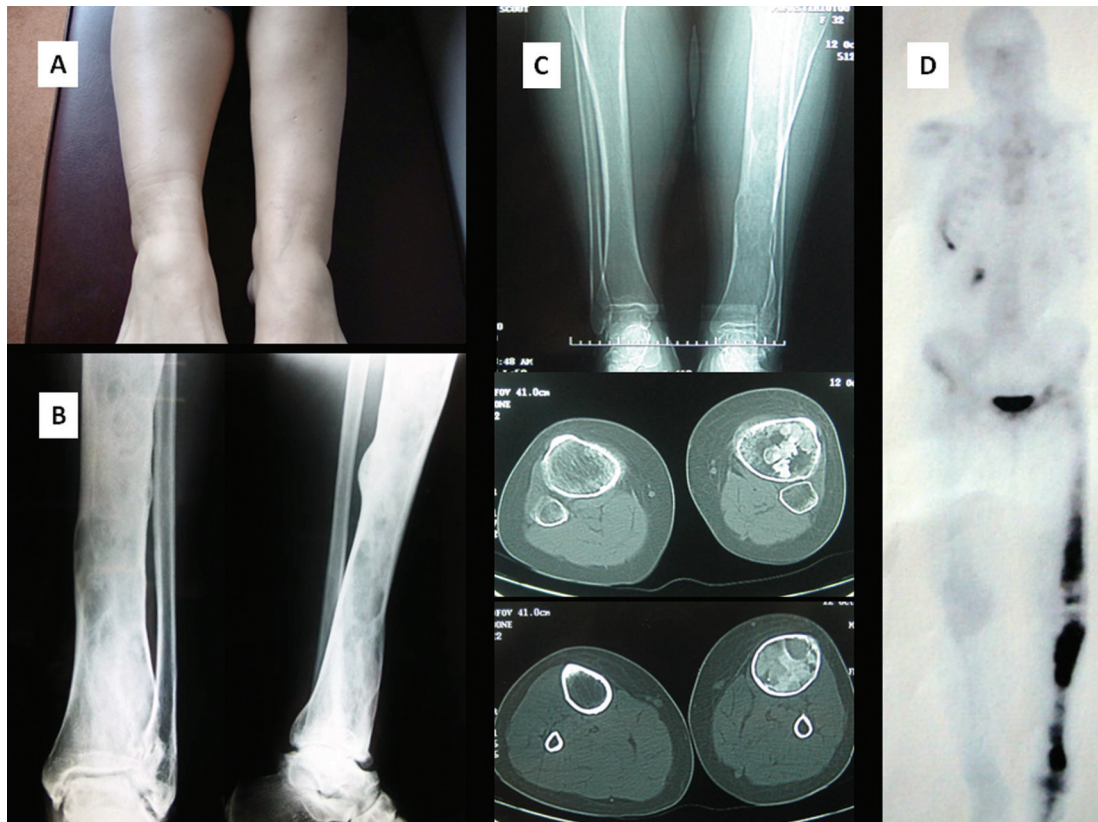The authors have no conflict of interest.

Figure 1. A) Photograph of the patient's legs. There is obvious deformity of the left tibia with wasting of the calf. **B)** Anteroposterior and lateral X-rays of the left tibia. Large expanded intramedullary lesions in the distal tibia shaft with homogeneous "ground glass" appearance, endosteal scalloping, but no periosteal new bone formation. **C)** Computed tomography of tibias. Widening of the left tibia shaft, thinned cortices and sharply defined homogeneous high-density lesions of amorphous texture with uninterrupted sclerotic margins at the medullary cavity. **D)** Tc-99m bone scan. Homogeneous uptake in the left tibia, the left femur, the 7th right rib and the left ankle joint.
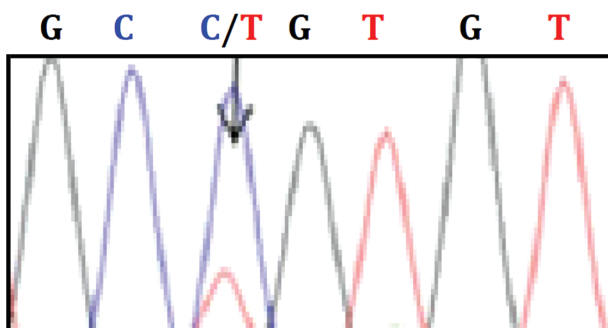

Figure 2. Sequence chromatogram covering the R201C (CGT>TGT) mutation, identified in the patient. The arrow indicates the mutation's site.

berty) and FD is part of McCune-Albright syndrome's triad (FD, endocrine anomalies and café-au-lait cutaneous spots). Common sites of skeletal involvement are long bones, ribs, the skull and the pelvis, with the proximal part of the femur and craniofacial bones being most commonly affected[1-3].

Clinical presentation may occur at any age with localized pain, deformity, fracture or neurological symptoms and signs due to nerve compression, though first symptoms appear before the age of 15 years in 80% of patients[2]. Most of monoostotic lesions are asymptomatic and discovered incidentally in radiographs performed for other reason[1]. Pain is due a complete or incomplete fracture or without any apparent cause. Long bones' shape and length can be altered, leading to a plethora of deformities such as shepherd's crook deformity of the femur. When craniofacial bones are involved asymmetry of the face is the commonest finding. Fractures occur even with minor trauma because of the impaired mechanical properties of the involved bones[3].

FD's is caused by dominant activating mutations in the coding gene for the α subunit of the stimulatory G-protein, in the GNAS complex locus in chromosome 20q13[4]. The mutations occur postzygotically resulting in somatic mosaicism. It is believed that the earlier the mutation presents during the development process, the more widespread the organ involvement, with the severity of the disease being proportional to the number of mutated cells[2]. The mutations replace the arginine

residue in codon 201 with either cysteine or histidine or more rarely other amino acids, leading to the production of proteins with reduced GTPase activity[4]. The net result is increased adenylyl cyclase activation and over-production of cAMP that induces c-fos over-expression and down-regulation of the osteoblastic transcription factor Runx2. The aforementioned factors are thought to be responsible for the abnormal high proliferation rate and poor differentiation of bone marrow stromal cells in FD. These abnormal pre-osteoblastic cells secrete high levels of IL-6 (with consequent activation of surrounding osteoclasts, causing osteolytic lesions) and produce great amounts of fibrous tissue within bone marrow[2].

Diagnosis is based on the clinical and radiologic findings and is confirmed by biopsy. In plain radiographs FD appears as an eccentric expansible lesion with a narrow transitional zone and a "ground glass" appearance of the matrix, with no periosteal reaction or soft tissue mass. The lesions can be cystic, pagetoid, or dense and sclerotic, are normally located in the metaphysis or diaphysis of a long bone and are sometimes associated with an endosteal scalloping called "scalloping from within". The affected area can vary in size from a focal abnormality to a large lesion involving most of a long bone. Calcifications and secondary aneurysmal bone cysts are not uncommon findings and should be considered as part of the spectrum of the disease. The surrounding cortical bone is generally thinned and a dense calcification can be observed around the lesion ('rind sign')[2].

Computed tomography is the best technique for demonstrating the radiographic characteristics of FD. The extent of the lesion is clearly visible and the cortical boundary is depicted with more detail than is seen on radiographs or magnetic resonance images. The thickness of the native cortex, amount of endosteal scalloping and periosteal new bone reaction, and homogeneity of the poorly mineralized defective tissue are demonstrated best with computed tomography imaging. Bone scans are not routinely used as a diagnostic tool; however, there are useful to diagnose the extent of the disease and to identify asymptomatic lesions. A bar-shaped pattern on bone scanning with total bone involvement and a close match to the radiographic size of the lesion are helpful to differentiate FD from other diseases[1].

Histologically, FD is characterised by the "alphabet soup" pattern, e.g. trabeculae of immature bone, with no osteoblastic rimming, embedded in an abundant fibrous stroma of dysplastic spindle-shaped fibroblast-like cells (corresponding to the mutated cells). Islands of hyaline cartilage can also be observed within the fibrous tissue[1]. When biopsy is not available, detection of the underlying mutation may verify the diagnosis. Liang et al. confirmed that a mutant rate of approximately 20% could be determined by direct sequencing method[5]. However, a negative result of Arg201 mutation does not rule out the diagnosis of FD. This is particularly true in older patients, as mutated cells are increasingly less detectable as a function of age[5].

Differential diagnosis of FD includes simple bone cysts, multiple enchondromatosis (Olier's disease), primary hyperparathyroidism, neurofibromatosis, multiple bone hemangiomas, eosinophilic granuloma, fractures, Paget's disease and osteoblastic metastases[1].

Treatment is most of the times symptomatic. Bisphosphonates have proved to offer pain relief and improve skeletal strength, while surgery is needed occasionally to correct deformity or to prevent or stabilize a pathologic or fatigue fracture[2].

References

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Questions

1. FD is not part of
A. McCune – Albright syndrome
B. Jaffe – Lichtenstein syndrome
C. Mazabraud syndrome
D. Singleton – Merten syndrome

Critique

Jaffe – Lichtenstein syndrome consists of polyostotic FD and café-au-lait cutaneous spots. McCune – Albright syndrome has the additional feature of endocrine disorders such as precocious puberty. In Mazabraud syndrome polyostotic FD is combined with intramuscular myxomas. In contrast, in Singleton-Merten syndrome FD is absent (main features are dental dysplasia, progressive calcification of the thoracic aorta, osteoporosis, and expansion of the marrow cavities in hand bones).
The correct answer is D.

2. Malignant transformation in FD
A. is observed only in the monoostotic form
B. is observed only in the polyostotic form
C. is not observed
D. is observed in both types

Critique

Malignant transformation is rare in FD but may be observed in both types. Reported prevalences range from 0.4% to 4%. The most common malignant tumors are osteosarcoma, fibrosarcoma, and chondrosarcoma.
The correct answer is D.

3. Half of the patients with polyostotic FD have renal phosphate wasting, which is mainly attributed to
A. primary hyperparathyroidism
B. over-production of FGF-23
C. none of the above

Critique

In these patients FGF-23 is over-produced by both normal and mutated cells leading to hyperphosphatouria. The levels of FGF-23 correlate with disease activity.
The correct answer is B.