Case Report

Polyostotic Fibrous Dysplasia Mimicking Metastatic Disease Radiographically: A Case Report and Literature Review

David Gay, MD;[1] Joey Philip, MD;[2] Shahida Ahmed, MD;[3] Jin Choe, MD;[3] Donghong Cai, MD, PhD[3]*

[1] *Department of Pathology, Rutgers New Jersey Medical School, Newark, NJ*
[2] *Department of Radiology, VA Medical Center, East Orange, NJ*
[3] *Department of Pathology and Lab Medicine Services, VA Medical Center, East Orange, NJ*

Fibrous dysplasia is a benign intramedullary lesion characterized by an excessive proliferation of cellular fibrous tissue intermixed with irregular trabeculae. It involves any of the bones presenting as monostotic, polyostotic, or panostotic lesion. It is caused by mutation in the GNAS1 gene (20q13.2, encoding a G-protein) resulting in inhibition of intrinsic GTPase activity of Gs alpha protein. The timing of mutation in the developmental course determines the extent of the disease, in which an earlier mutational event leads to a wider distribution of mutant cells, and consequently a more severe course of the disease.

We report a case of polyostotic fibrous dysplasia in a 58-year-old male with CT scan revealing multiple lucent and sclerotic areas in bilateral ribs and iliac bones. A metastatic process was suspected by radiologists. However, a bone marrow biopsy from left posterior iliac crest demonstrated a bland fibroblastic proliferation admixed with irregular metaplastic bone in a collagenized stroma. By pyrosequencing of alpha subunit of G-protein, a mutation in Arg201(p. R201H; c.602G>A) was detected. All the findings supported a diagnosis of polyostotic fibrous dysplasia. The present case highlights a rare clinical incidental disease with radiographic mimic of metastatic process.

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INTRODUCTION

Fibrous dysplasia (FD) is a benign intramedullary fibro-osseous lesion characterized by replacement of normal bone and marrow by an excessive proliferation of cellular fibrous tissue intermixed with irregular trabeculae.[1] It involves any of the bones presenting as single lesion (monostotic), multiple bone lesion (polyostotic), or all of the skeletal system (panostotic).[1,2] It is caused by mutation in the GNAS1 gene (20q13.2, encoding a G-protein), in which the 201^{Arg} position is replaced by either cysteine or histidine (R201C or R201H), resulting in inhibition of intrinsic GTPase activity of Gs alpha protein, leading to overproduction of intracellular cAMP and interleukin-6 secretion.[2-4] In bone, this upregulatory effect of cAMP/protein kinase A signaling precludes the maturation of osteoprogenitor cells into osteoblasts such that the skeletal lesions are composed largely of undifferentiated mesenchymal cells, which produce abnormal matrix, bone trabeculae, and collagen orientation. Interleukin-6 is responsible for increased numbers of osteoclasts and bone resorption seen in FD.[5] The timing of mutation in the developmental course determines the extent of the disease, in which an earlier mutational event leads to a wider distribution of mutant cells, and consequently a more severe course of the disease.[2]

Radiographically, FD's presentation varies depending on location.[2] In the appendicular skeleton, lesions appear radiolucent with cortical thinning and a characteristic "ground glass" feature. In craniofacial area, FD may appear sclerotic on X-ray film, while showing expansile homogeneous "ground glass" appearance on CT scan. In senior patients, FD may present more heterogeneous with focal cystic and sclerotic areas, which, sometimes is mistakenly interpreted as metastatic malignant process.

CASE REPORT

A 58-year-old male came to hospital clinic complaining lower back pain for 3 weeks. CT scan revealed multiple lucent and sclerotic areas in bilateral ribs and iliac bones. A bone scan showed extensive tracer uptake in the multiple bilateral ribs, right humerus, mid shaft of left humerus, left proximal femur, and skull (**Figure 1A**). Metastatic survey reveals several well corticated oval-shaped lucencies on the left frontal skull (**Figure 1B**), large intramedullary sclerosis in the proximal left femoral diaphysis and multiple lytic lesions in the pelvic bone (**Figure 1C**). A malignant metastatic process was suspected by radiologists.

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***Corresponding Author:** Pathology and Lab Medicine Services, VA Medical Center, East Orange, NJ 07018. (Email: dcai2@hotmail.com)

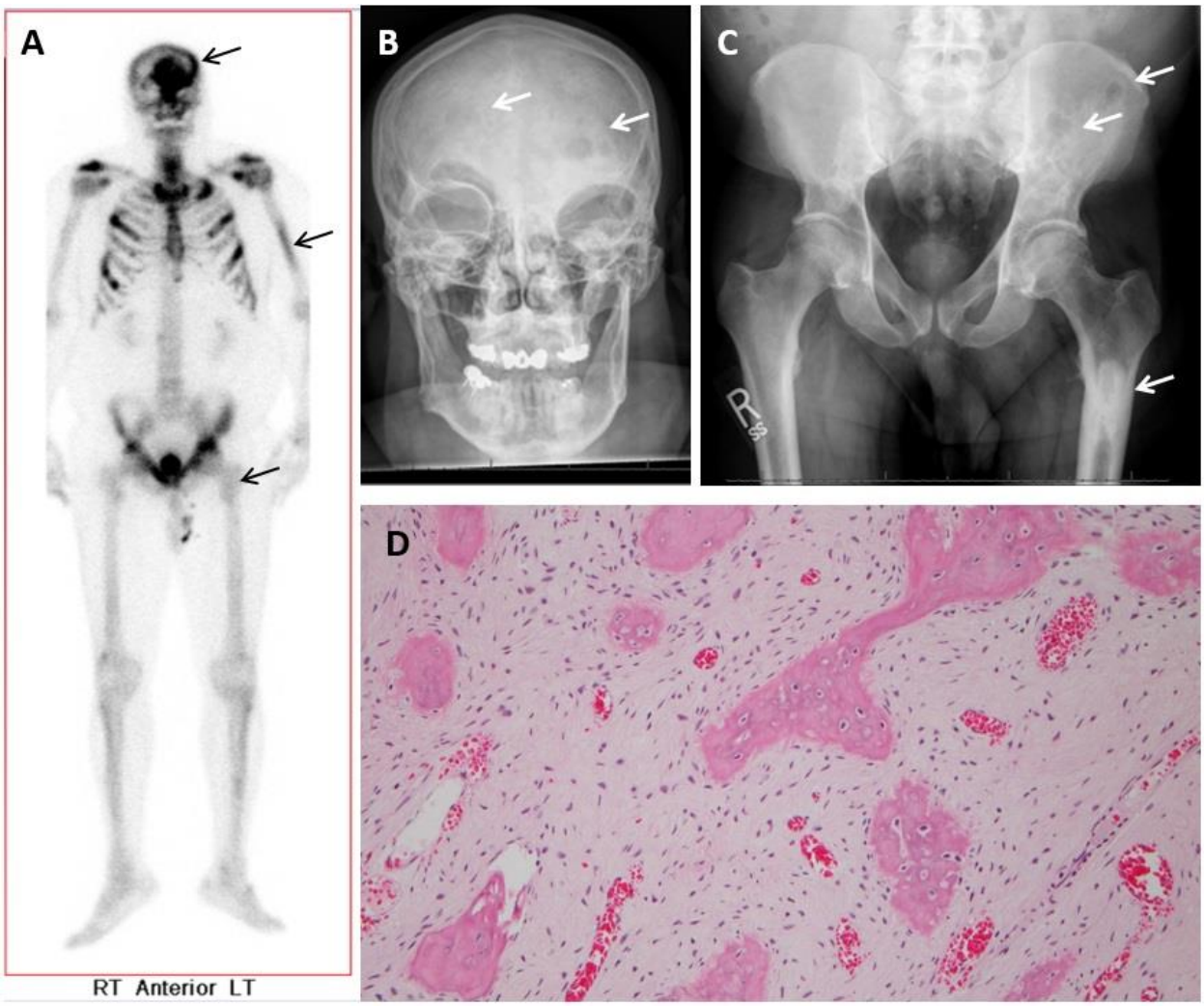

Figure 1. Radiology and microscopic features of polyostotic fibrous dysplasia. **A.** Bone scan, arrows pointing tracer overtake area; **B.** Skull with lytic lesions (arrows); **C.** Pelvic and left femur lesions (arrows). **D.** H&E section of bone marrow biopsy (400X). Bland spindle cells admixed with immature trabeculae without osteoblastic rimming.

A bone marrow biopsy from left posterior iliac crest was performed by oncologist. Surprisingly the biopsy showed that the bone marrow was replaced by a bland fibroblastic/stromal cell proliferation admixed with irregular metaplastic bone in a collagenized stroma (**Figure 1D**). FD was suspected, and was confirmed by pyrosequencing of alpha subunit of G-protein in that a mutation in Arg201 (p. R201H; c.602G>A) was detected. Consequently a diagnosis of polyostotic fibrous dysplasia was established. Besides back pain, the patient presents with no hematological disorder, neurological disorder, or bone fractures. He was given pain management and closely monitored since.

DISCUSSION

FD was first reported by Von Recklinghausen in 1891, followed by Lichtenstein in 1938 and Jaffe in 1942.[6-9] FD accounts for 2.5% to 7.0% of all benign bone tumors, with an equal predilection for men and women.[1,6] The most commonly seen monostotic form accounts for 70-85% of FDs and manifests later in life, usually 20-30 years of age. Majority of the monostotic patients are asymptomatic, identified by incidental radiology workup for other indications.[6] In contrast, the polyostotic form manifests earlier in life (usually younger than 10 years), frequently affects the maxilla or other craniofacial bones, ribs, femur, or tibia.[10] 3% of these polyostotic patients are associated with café-au-lait spots and a hyperfunctional endocrine disorder, which is named as McCune-Albright syndrome. This syndrome is more commonly seen in females than males (10:1).[11]

Clinically, a radiography finding is usually sufficient for a diagnosis, especially in children, a population rarely has concerns about metastatic diseases.[12] But in adults, the radiologic presentation of the lesions might include cystic change, sclerotic change, or irregular shape, etc., other than the "ground glass" feature seen in children.[12] These characteristics in adults inevitably trigger the differential diagnosis of metastatic malignancy, which covers a wide varieties of carcinomas, originated from prostate, lung, breast,

or GI organs. Etc. Therefore, a bone biopsy reflex to a molecular test for GNAS1 mutation is essential to establish a diagnosis.

Histologically, FD can be diagnosed by its typical characteristics: isolated trabeculae of woven bone generally without rimming of osteoblasts, a fibrous stroma with bland appearing spindle cells, and in some cases bundles of collagen fibers oriented perpendicular to the bone surface, compatible with Sharpey's fibers.

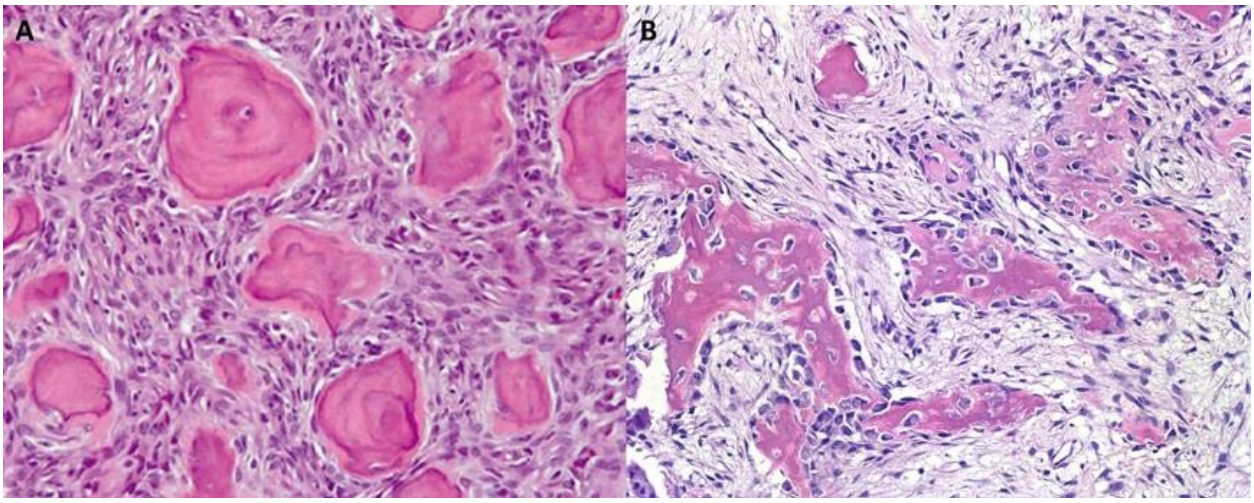

Figure 2. Histologic features of ossifying fibroma and osteofibrous dysplasia. **A.** Ossifying fibroma shows osteoid/calcified spherules similar to cementicles, lying in a moderately cellular, dense fibrous stroma (400X). **B.** Osteofibrous dysplasia is characterized by woven bone trabeculae with rimming of osteoblasts and a cellular proliferation of fibroblast-like cells (400X). The images are taken from world wide web.

It's worth to point out there is a category of "fibro-osseous" lesions presenting as mimics of FD. One of which is ossifying fibroma of the jaw (OFJ) (**Figure 2A**).[13] OFJ is a benign tumor arising from the periodontal ligament and can occur in any bone in the craniofacial region, predominantly in the jaws. It is usually slow growing and indolent, but in some instances can be destructive, resulting in facial deformity. Histologically, OFJ shows calcified spherules similar to cementicles, which lie in a moderately cellular, dense fibrous stroma. OFJ contains no woven bone/osteocyte, which is a key to differentiate from FD.

Another mimic is Osteofibrous dysplasia (OD) (**Figure 2B**).[14] OD is a rare, nonneoplastic condition of unknown etiology that affects almost exclusively in the tibia or fibula of children younger than 10 years of age and often presents as a painless enlargement of the tibia with anterior or anterolateral bowing. Histologically, osteofibrous dysplasia is characterized by woven bone trabeculae with a rimming of osteoblasts and a cellular proliferation of fibroblast-like cells, and has long been thought to be related to adamantinoma of long bones. Rimming of osteoblasts on the woven bone is the critical feature that differentiates OD from FD (FD has no osteoblast rimming on the woven bone).

The ultimate diagnostic evidence for FD lies in identifying the GNAS1 mutation, of which more than 95% cases harbor R201C or R201H, with the rest cases containing other rare mutation sites in GNAS1 gene. Of note, GNAS1 mutation has not been detected in OFJ or OD.

CONCLUSION

Overall, here we report a case of FD radiographically mimicking metastatic process. Definite diagnosis of FD relies on typical microscopic findings of delicate trabeculae without osteoblastic rimming enmeshed within a bland fibrous stroma of dysplastic spindle cells, and molecular evidence of GNAS1 mutation.

CONFLICT OF INTEREST

The authors have no conflict of interests.

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