Monostotic Fibrous Dysplasia of the Lumbar Spine With Secondary Features of Solid Variant Aneurysmal Bone Cyst

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ABSTRACT: Fibrous dysplasia is a benign, mass-forming disease of bone composed of abnormal fibrous and osseous elements that can be accompanied by endocrine dysfunction, skin pigmentation, and intramuscular myxomas. It is usually encountered as a solitary lesion in the tibia or femur but can develop in any bone and can be unifocal or multifocal. Difficulty arises when a solitary lesion is identified in an uncommon site or when there are prominent secondary changes, such as aneurysmal bone cyst (ABC). Molecular studies are available as an adjunct to histomorphology to aid distinction from other entities. *GNAS* mutations, present in greater than 70% of fibrous dysplasia cases, help in the distinction from primary ABC and low-grade osteosarcoma, which exhibit different molecular abnormalities. We report a case of monostotic fibrous dysplasia in a lumbar vertebral body with secondary change consisting of the solid variant of ABC.

KEYWORDS: Fibrous dysplasia, *GNAS*, aneurysmal bone cyst, ABC, McCune-Albright, Mazabraud, CDH11

Introduction

Fibrous dysplasia is a benign, mass-forming lesion of bone composed of abnormal fibrous and osseous elements. It has a propensity to develop in the femur, tibia, ribs, craniofacial bones, and the pelvis but can be seen in any bone. Lesions are discovered as a result of pain, physical deformity, pathologic fracture, or as an incidental finding on radiographic imaging. Most are identified within the first few decades of life, although they can be seen at any age, particularly if small and asymptomatic. The majority of cases are monostotic, in which a single bone is involved. The polyostotic variant affects multiple bones and is subclassified into monomelic and polymelic forms. Monomelic fibrous dysplasia is restricted to unilateral or regional involvement, whereas widespread involvement defines the polymelic form.

Radiography often reveals an expansile mass within the bone that has a ground glass appearance and a sclerotic rim. Opacity to X-ray radiation is variable, depending on the amount of bone within the lesion and the degree of mineralization. Radiologic appearance can also vary with location. In the axial skeleton, fibrous dysplasia is more likely to demonstrate the classic radiologic imaging, but in sites such as craniofacial skeleton, it is often more dense in appearance.[1] Atypical imaging characteristics can make definitive radiologic diagnosis difficult, especially when the lesion is in an uncommon location. Microscopic examination usually reveals a well-delineated mass comprising irregular branches, arcs, and bends of woven bone found within a background of whorled to storiform fibrous stroma that lacks atypia and mitotic activity. Normal marrow elements of bone and rimming osteoblasts and osteoclasts are not typically seen within the lesion. Depending on the location of the fibrous dysplasia lesion, treatment can be observation, curettage, or local resection. We report the pathologic and molecular findings in a case of monostotic fibrous dysplasia of the lumbar spine with areas that demonstrate the solid variant of aneurysmal bone cyst (ABC).

Methods and Case Presentation

A 21-year-old male presented with low back pain that had begun after a fall 2 years prior to his presentation and had steadily worsened since onset. He also complained of mild left leg numbness, but no weakness or bowel/bladder dysfunction. On examination, deep tendon reflexes were normal, he had a normal gait, and he had no spinal tenderness to palpation. A magnetic resonance imaging (MRI) of the lumbar spine demonstrated a 2.0 cm discrete L3 vertebral body lesion, which was T1 hypointense (Figure 1C) and focally T2 hyperintense with a T1 and T2 hypointense rim. There was mild diffuse enhancement with gadolinium (Figure 1D), which increased slightly at the periphery. The lesion was lucent on computed tomography (CT; Figure 1B), with a ground glass central component and peripheral sclerotic rim. Review of an abdominal CT from 6 years prior (originally performed for abdominal trauma) revealed that the mass was present at that time and was only 1.3 cm in greatest dimension (Figure 1A). Repeat imaging demonstrated a slight increase in size over the subsequent 3 months. A CT guided core needle biopsy was performed, which showed a bland spindle cell proliferation but was inadequate for diagnosis. As a result, curettage of the lesion was performed with a reconstruction consisting of a rib autograft and a metallic structural support.
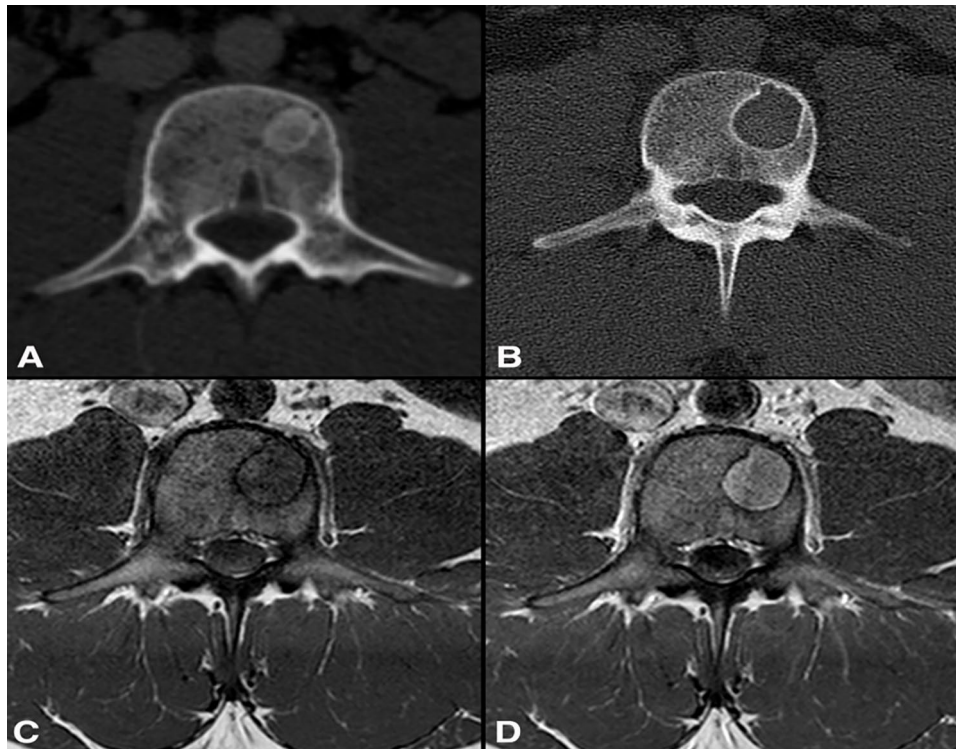
Figure 1. Monostotic fibrous dysplasia of the third lumbar vertebral body with secondary ABC changes. (A and B) axial CT cross-section in the same patient at (A) age 15 and (B) age 21 showing growth of the lesion over time. The lesion is lucent and has a thin sclerotic rim but is not expansile. (C and D) T1-weighted MRI of the same lesion at age 21 (C) before and (D) after gadolinium administration. ABC indicates aneurysmal bone cyst; CT, computed tomography; MRI, magnetic resonance imaging.

Histologic examination of the resected specimen demonstrated areas with a fibro-osseous appearance reminiscent of fibrous dysplasia with irregular trabeculae of woven bone that were without lining osteoblasts and without atypia or mitotic activity in the intervening spindle cells (Figure 2A and B). However, there were large areas dominated by a solid spindle cell component without woven bone; instead, there were foci of hemorrhage and dilated pseudovascular spaces with associated multinucleated giant cells (Figure 2C and D).

Mutational analysis by next generation sequencing was performed using a targeted 50-gene panel (Cancer Hotspot Panel v2, AmpliSeq, Ion Torrent), which includes the *GNAS* gene. This revealed a point mutation in exon 8 of the *GNAS* gene (c.601C>T). Fluorescence in-situ hybridization (FISH) for rearrangement of the *USP6* gene (17p13) using break-apart probes was negative. Cytogenetic analysis was not performed.

Discussion

Fibrous dysplasia was first described separately in 1937 by Fuller Albright et al and Donovan James McCune as a syndrome that includes skin pigmentation and endocrine hyperfunction.[2,3] In the McCune-Albright syndrome, café au lait skin pigmentations have jagged borders, often likened to the "coast of Maine." The hormone dysfunction can take many different forms, with the most frequent presentation being precocious puberty. It was later recognized that the bone lesions of

this syndrome could occur in isolation and was given the name "fibrous dysplasia of bone" by Lichtenstein and Jaffe in 1942.[4] A more detailed characterization of the disease course in 90 patients was documented by Harris et al[5] in *The Journal of Bone and Joint Surgery* in 1962. Mazabraud[6] subsequently described the rare association of single or multiple intramuscular myxomas (previously soft tissue fibromyxomas) with fibrous dysplasia, now known as the Mazabraud syndrome.

While fibrous dysplasia can be seen in any bone, involvement of the spine is rare. When present, it is almost always due to the polyostotic form and usually involves the lumbar spine.[7] In 1 series of 418 patients with monostotic fibrous dysplasia, spinal involvement was reported in only 1.4% of cases.[8] Fibrous dysplasia, like many bone lesions, can undergo secondary changes, including ABC formation, aggregation of foamy macrophages, and myxoid change.[9] These changes may obscure the diagnosis and raise other possible diagnoses such as xanthoma, fibroxanthoma, primary ABC, or giant cell tumor of bone. The combination of an unusual location and secondary changes can be diagnostically challenging, especially if the material received is scanty or not representative of the whole lesion. Recent molecular developments have provided some additional tools to aid in the diagnosis.

While it was recognized that overactive cyclic AMP (cAMP) played a role in the fibrous dysplasia, it was not identified until 1991 that this was driven by mutations in the
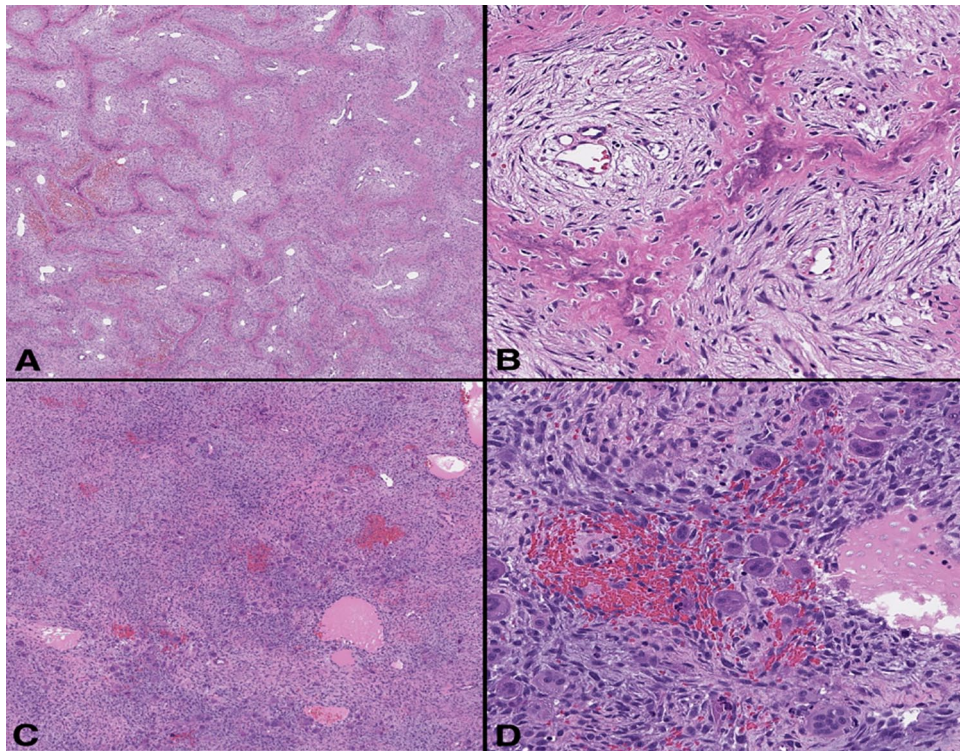
Figure 2. (A and B) Fibro-osseous appearance reminiscent of fibrous dysplasia. (C and D) Solid variant of aneurysmal bone cyst with hemorrhage, blood-filled cystic spaces, and aggregation of multinucleated giant cells: hematoxylin-eosin, original magnifications ×2.5 (A, D), ×20 (B), and ×4 (C).

alpha subunit of the activating G protein (encoded by the *GNAS* gene located at 22q13.2-3).[10] In more than 70% of cases of fibrous dysplasia, point mutations are found in *GNAS*, predominantly missense mutations at codon 201 in exon 8.[11] Transmembrane receptors, specific to individual ligands, associate with a G protein (G-protein-coupled receptors), and upon activation by a ligand, the alpha subunit of the G protein dissociates and activates the familiar cAMP-dependent pathway. Activating point mutations in the *GNAS* gene lead to increased alpha-subunit-mediated production of cAMP and alteration of other downstream signaling molecules. These molecular changes result in the abnormal proliferation and differentiation observed in fibrous dysplasia. The hyperfunctioning endocrinopathies and skin pigmentation of the McCune-Albright syndrome and the intramuscular myxomas of the Mazabraud syndrome are again related to overactivation of G protein signaling from *GNAS* mutations. In fact, *GNAS* mutations have been found in both fibrous-dysplasia-related intramuscular myxomas and sporadic cases.[12] Postzygotic acquisition of this mutation has been theorized to explain the focal to mosaic presentation of fibrous dysplasia, the skin pigmentation, and endocrine hyperfunction of the McCune-Albright syndrome.[13] The stage of development/differentiation at which the mutation occurs determines the anatomic and physiologic presentation.

In 1942, the same year that they first described isolated fibrous dysplasia, Jaffe and Lichtenstein were also the first to describe what later became known as ABC.[14] Aneurysmal bone cysts are lytic lesions of bone that most commonly occur in the vertebra and long bones of the upper and lower extremities. They can be either primary or can develop as a result of the influence of a nearby bone lesion, such as fibrous dysplasia. Secondary ABC changes in fibrous dysplasia can look identical to primary ABC. Radiology often shows a lytic and expansile mass; the rim may be partially sclerotic but may also have an infiltrative appearance with destruction of the cortex.[15] The major components of ABCs are blood-filled cystic spaces bordered and septated by connective tissue containing spindle cells with admixed multinucleated giant cells and a mixture of inflammatory cells. The multinucleated giant cells are preferentially distributed near the cystic spaces. Whether it is primary or secondary, the wide spectrum of this lesion should be appreciated. Approximately 5% to 8% of lesions have a more substantial solid component or are completely solid.[15,16] This solid variant is dominated by the spindled fibroblastic stroma and may contain microscopic foci hemorrhage or blood-filled cystic spaces with multinucleated giant cells in close proximity to the hemorrhage. The combination of this spindled stroma and the potential for surrounding reactive woven bone can mimic fibrous dysplasia. Extensive sampling of the lesion is imperative to evaluate what components are present; a specimen comprised entirely of either the classic or solid variant ABC still raises the question of a nearby primary lesion. It is also worth noting that the vertebral column is a common site of involvement for primary ABCs. Primary ABCs will contain a translocation involving

the *USP6* (17p13) and/or *CDH11* (16q22) genes in approximately 70% of cases.[16] Most of these translocations are a fusion between *USP6* and *CDH11*, but fusions between *USP6* and numerous other genes have been identified.[17–19] Also, of note, a translocation has been reported in a solid variant ABC arising from the T6 vertebra of a 10-year-old girl, 46,XX, t(11;16)(q13;q22-23)[10]/46,XX[10].[20] However, these genetic alterations are not seen in secondary ABCs. Unlike fibrous dysplasia, primary ABCs frequently recur after surgical resection.

Another critical entity that needs to be distinguished from fibrous dysplasia in any location is a low-grade osteosarcoma. Radiologic imaging can help lead to a diagnosis of osteosarcoma if the lesion demonstrates a more infiltrative border and lacks a sclerotic rim. While the bone trabeculae in osteosarcoma can display complex shapes and branching as in fibrous dysplasia, the architecture tends to be simpler. Osteosarcoma may entrap preexisting lamellar bone, while fibrous dysplasia comprised woven bone. Most notably, the spindle cell component of osteosarcomas is more cellular and mitotically active, and exhibits cytologic atypia. Osteoblastic rimming may or may not be present in osteosarcoma. *MDM2, CDK4*, and *FRS2* amplifications have been detected in the vast majority of low-grade osteosarcomas; detection of amplifications can be detected by immunohistochemistry or FISH for the *MDM2* and *CDK4* genes.[21,22] While there are reports of *GNAS* mutations in low-grade osteosarcomas, there has been a lack of reproducibility in subsequent studies and *GNAS* mutations are thought to be relatively reliable in distinguishing the 2 entities.[23-26] Taking into account these histologic and molecular features, the appropriate diagnosis can be reached in most cases.

In summary, fibrous dysplasia is an uncommonly encountered lesion of bone that can have unexpected presentations. Monostotic fibrous dysplasia of the spine with secondary ABC formation is rare. This presentation brings up important additional differential diagnoses that are not always considered with fibrous dysplasia, notably primary ABC. We have reviewed the histologic and molecular features that are most helpful in distinguishing these entities. Fibrous dysplasia is an important diagnosis to consider in a radiolucent bone lesion with a sclerotic margin of any site, keeping in mind the morphologic overlap with entities seen there.

Author Contributions

Both authors have contributed to and approve the content of this manuscript.

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