

Dedifferentiated chondrosarcoma arising in fibrous dysplasia: A case report and review of the current literature

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Background: Fibrous dysplasia is an uncommon bone disease that has rare but clear potential for malignant transformation. The frequency is increased in polyostotic forms, McCune–Albright syndrome, Mazabraud’s syndrome, and previously irradiated sites. Rapidly progressing pain unrelated to trauma is the most concerning symptom. The early radiological features of sarcomatous transformation are moth-eaten or cystic areas of osteolysis, cortical destruction, and gradual formation of a soft tissue mass. The prognosis is unfavorable as most of the cases are in an advanced stage at the time of diagnosis.

Methods: This case was diagnosed at a large cancer center in Florida. Pertinent clinical findings were obtained from chart review and inter-departmental consultation.

Results: Histopathological examination revealed dysplastic lamellar bone with no osteoblastic rimming and “Chinese letter” shapes, areas composed of lobulated hyaline cartilage with mild to severe nuclear atypia, and areas of poorly differentiated cells with a spindled appearance, consistent with chondrosarcoma arising within fibrous dysplasia.

Conclusions: Sarcomatous transformation of fibrous dysplasia is an uncommon occurrence, yet has significant importance for those with the disease. There may be difficulty with diagnosis given the symptoms and radiologic findings of benign fibrous dysplasia. We report a case of chondrosarcoma arising in fibrous dysplasia and review the current literature. This case is of interest due to the fact that the diagnosis of monostotic fibrous dysplasia was first made at the age of 59 and malignant transformation occurred within a decade with no history of trauma or radiation. This is an excellent example of how a change in symptoms without a history of trauma should be alarming to the clinician and warrants a thorough work-up for malignancy. To the best of our knowledge, this represents the second case of dedifferentiated chondrosarcoma within the English literature.

Keywords: dedifferentiated chondrosarcoma, fibrous dysplasia, malignant transformation, McCune–Albright syndrome, Mazabraud’s syndrome

Case report

A 66-year-old Caucasian male with a seven-year history of fibrous dysplasia (FD) of the right tibia treated with curettage in 1999 was asymptomatic for 4½ years at which point he represented in December 2005 with complaints of increased pain in the area. He denied any history of radiation therapy or trauma. Radiographs of right tibia and fibula demonstrated a variegated, ill-defined lesion in the proximal tibial diaphysis with mixed areas of sclerosis and osteolysis, anterior cortical endosteal scalloping, and irregular posterior cortical thickening (Figure 1). No areas suggestive of bone formation were identified in the radiographs. Delayed phase bone scan demonstrated markedly

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increased radiotracer localization within the proximal tibial diaphysis and along the posterior cortex highly suspicious for neoplasm (not shown here); however, FD will typically show increased response. Magnetic resonance imaging revealed a heterogeneous, T1-hypointense, T2-hyperintense, enhancing mass involving the proximal tibial diaphysis with extension along the posterior tibial cortex and into the adjacent soft tissues consistent with aggressive neoplasm (Figure 2). The patient's symptoms were also concerning for malignant transformation and a short interval clinical follow-up was scheduled in three months. At this time, the patient reported increasingly severe pain, which now restricted his activity. Follow-up imaging demonstrated some progression of disease. An incisional biopsy revealed dysplastic lamellar bone with no osteoblastic rimming and "Chinese letter" shapes, areas composed of lobulated hyaline cartilage with mild to severe nuclear atypia. Figure 3 shows malignant cartilage in association with poorly differentiated cells with a spindled appearance. The histopathological findings were consistent with dedifferentiated chondrosarcoma of grade 3/3 seen in



Figure 1 Lateral radiograph demonstrates a variegated, ill-defined lesion in the proximal tibial diaphysis with mixed areas of sclerosis and osteolysis, anterior cortical endosteal scalloping, and irregular posterior cortical thickening.

a background of FD. After confirming the final pathological diagnosis, radical resection was performed with right tibia replacement, total knee arthroplasty, and gastrocnemius flap. No residual tumor was identified. Postoperatively, the patient recovered well without complication and had no evidence of metastatic disease. Two years after the diagnosis of chondrosarcoma, he was assessed and was without any suspicious findings for tumor recurrence. This case appears to be the second case of dedifferentiated chondrosarcoma in the English literature.

Discussion

Fibrous dysplasia (FD) is a benign medullary fibro-osseous lesion, which may present in either monostotic or polyostotic forms.^{1,2} In 2005, Enneking and DiCaprio wrote a concise but thorough paper on FD and more recently Chapurlat and Orcel wrote an updated version with in-depth clinical and molecular information.^{1,3} The monostotic form (MFD) represents approximately 70%–80% of FD cases. This form most frequently occurs, in decreasing order of frequency, in the craniofacial bones, rib, femur, tibia, and humerus. This form may present with pain or a pathologic fracture in patients aged 10–70 years, but most frequently occurs in those aged 10–30 years. The degree of bone deformity is relatively less severe compared with that of the polyostotic type. No clearly documented evidence supports the conversion from MFD to the polyostotic form (PFD).^{1,4} Approximately 20%–30% of FD cases are PFD. The common sites of involvement are, in decreasing order of frequency, the femur, tibia, skull and facial bones, pelvis, ribs, upper extremities, lumbar spine, clavicle, and cervical spine. The dysplasia may be unilateral or, less commonly, bilateral. Two thirds of patients are symptomatic before 10 years of age. The initial symptom is pain in the involved limb associated with a limp, spontaneous fracture, or both. Leg-length discrepancy of varying degrees occurs in about 70% of patients with limb involvement due to the weakened structural integrity of the bone leading to significant bowing.^{1,2,5} FD often presents with a shepherd's crook deformity, curvature of the femoral neck and proximal shaft resulting in a coxa vara deformity, which can be severe. Pregnancy can also activate dormant lesions, much more commonly in PFD than MFD. An infrequent, but important subset of FD occurs along with endocrine abnormalities and café-au-lait spots, a triad called McCune–Albright syndrome (MAS). Named for two physicians who separately described the syndrome in 1937, Donovan McCune and Fuller Albright, symptoms matching their descriptions can be found in cases years before.^{6,7} Precocious puberty is the most common of

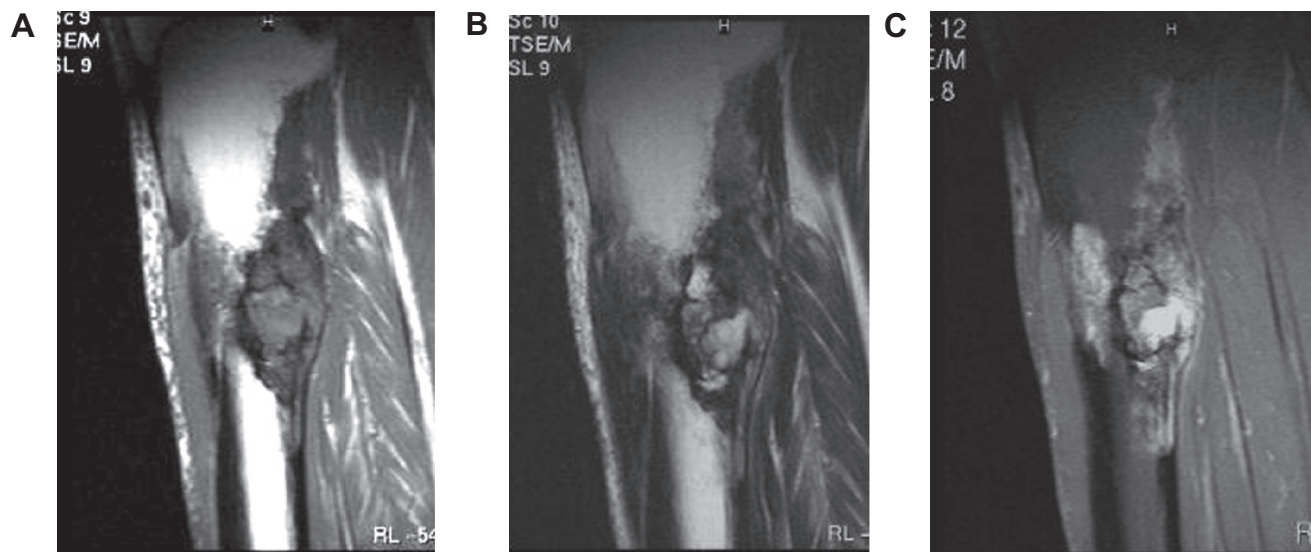


Figure 2 Sagittal T1-weighted (a), T2-weighted (b), and gadolinium-enhanced (c) magnetic resonance images demonstrate a heterogeneous, T1-hypointense, T2-hyperintense, enhancing mass involving the proximal tibial diaphysis with extension along the posterior tibial cortex and into the adjacent soft tissues consistent with aggressive neoplasm.

the endocrine abnormalities. Patients may have only two of the three characteristics, and may not have one or more of the numerous endocrine symptoms.⁸ MAS accounts for approximately 3% of FD cases. The list of possible endocrine problems is extensive, including hyperthyroidism, adrenal disorders, diabetes, hyperpituitarism, and hypercalcemia.⁸⁻¹¹ The disease is more common among females, 3:1, and holds no racial predilection. Separate from MAS, and comprising an even smaller percentage (~1%) of FD patients, are those with associated intramuscular myxomas typically around the sites of the lesions – an entity called Mazabraud's syndrome.¹² This disorder is also more common in women.

Generally thought of as a pediatric disease with dormancy reached by early adulthood, patients with FD should be aware of the possible ramifications. Though the prognosis of FD is normally very good, malignant transformation may occur rarely (1% average, 4% in MAS), with almost all cases being of sarcomatous origin. One series of literature review experienced 28 cases of sarcoma among 1122 FD cases (2.5%).¹³ A new diagnosis should bring with it the information and understanding of the possible implications to the patient and their family. Usually years or decades will pass from the time of diagnosis until malignancy develops. Findings may be hard to identify on plain radiographs, but are suggested by a rapid increase in the size of the lesion and an alteration in the mineralization pattern from a previously mineralized bony segment to a lytic lesion.¹⁴⁻¹⁹ Computed tomography (CT) scans can be helpful in recognizing malignancy as well as their extent. In MFD the skull and facial bones are

most common sites to develop malignancy. In PFD the sites are the facial bones, femur, and tibia. However, any site of FD may undergo malignant transformation. The most common tumor is osteosarcoma (~70%), with fibrosarcoma (~20%), chondrosarcoma (~10%), and malignant fibrous histiocytoma (~4%) occurring less commonly.^{13,20-23} Our case represents dedifferentiated chondrosarcoma based on the presence of malignant cartilage from low-grade to high-grade, a dedifferentiated high-grade spindle cell component, and no osteoid or bone formation. The major differential diagnosis of this histology is chondroblastic osteosarcoma, however, that would have high-grade cartilage of predominately hyaline type and an associated osteosarcoma component defined as osteoid or bone produced by a sarcoma.²⁴ We found no evidence of osteoid or bone grossly, microscopically or radiologically. The frequency of malignant change is increased in PFD, especially in patients with MAS, Mazabraud's, or prior radiation exposure.^{14,25,26} The incidence is approximately 0.5% in MFD and eight times greater (4% in MAS). Unfortunately, most of these cases are identified at an advanced stage and do not respond to conventional chemotherapy treatment. However, with early diagnosis, there are cases that suggest the prognosis of secondary sarcoma is comparable with *de novo* cases.²⁷ Identifying malignant transformation in FD may be extremely difficult due to the nature of the benign disorder (the pain, fractures, and radiologic findings). Rapidly increasing pain without trauma or significant change in radiological appearance should alert the clinician to investigate further.

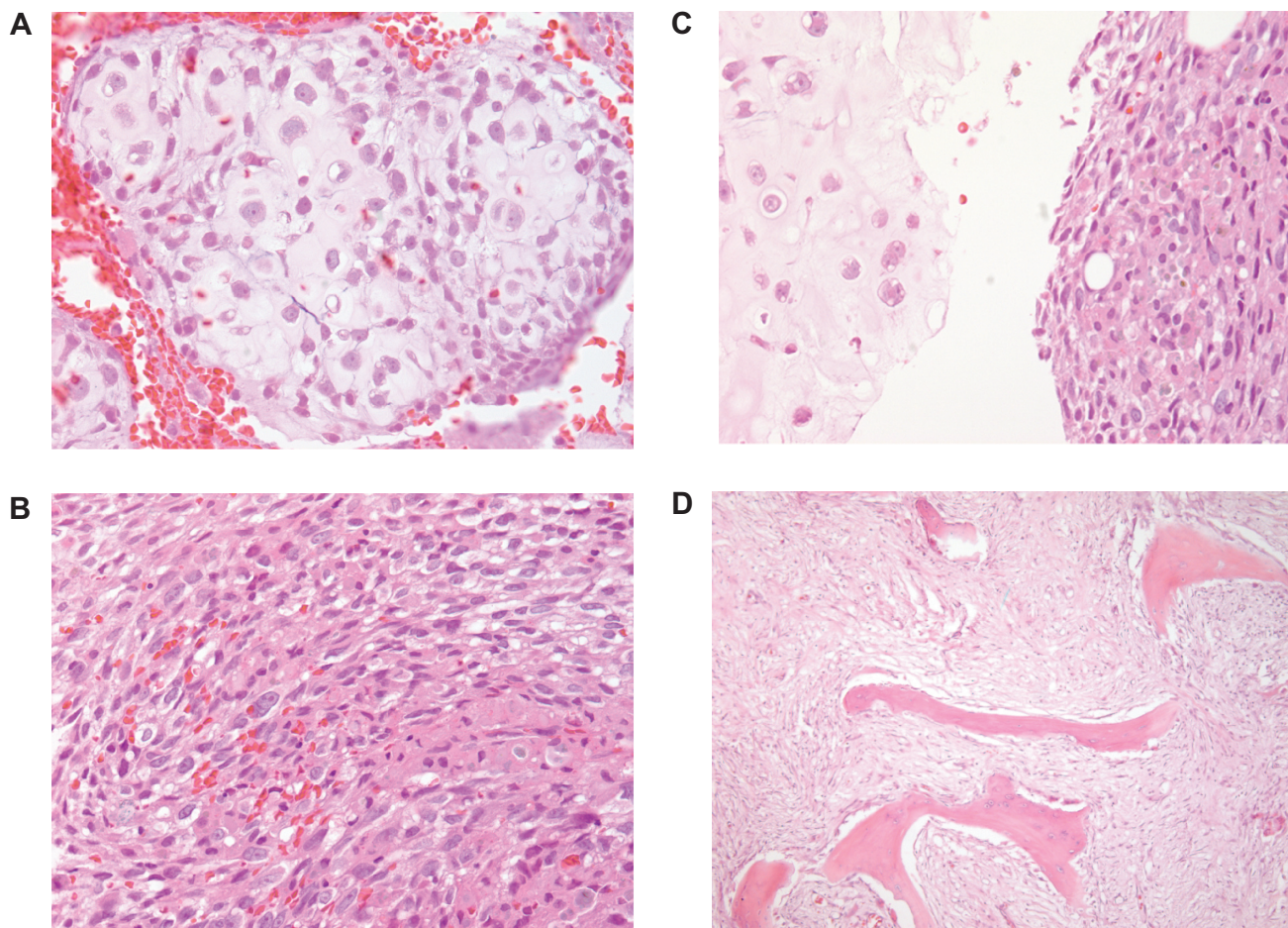


Figure 3 (a) Lobulated hyaline cartilage with moderate to severe nuclear atypia; H&E, x400. (b) Dedifferentiated area with spindle and small cells; H&E, x400. (c) Chondroblastic and dedifferentiated areas of this chondrosarcoma; H&E, x400. (d) Background of typical fibrous dysplasia with lack of osteoblastic rimming and atypical bony trabeculae; H&E, x100. **Abbreviation:** H&E, hematoxylin & eosin.

And once a diagnosis of FD is made follow-up should occur on a yearly basis with X-ray examination and the patient should be aware that any symptomology (increased pain, weakness, deformity) should be addressed immediately. At the present time a long-term clinical follow-up of a large series of cases is lacking in the literature which would be helpful as many cases do not burn out in adulthood, but rather are reactivated.²⁸

The latest molecular findings in FD, and especially in MAS, suggests it is caused by a somatic mutation early in embryonic life which results in a gene mosaicism. The earlier the mutation occurs the more widespread the effects will be. Research has found that the gene is located on chromosome 20; q13, an area that codes for the alpha subunit on G-protein receptors.^{1,29-35} This mutation is also present in various endocrine tumors as well as FD. G-proteins begin a cascade that ultimately leads to activation of the enzyme adenylyl cyclase that produces cAMP. In MAS there is a

missense mutation that causes the substitution of arginine in position 201 of the Gs-alpha gene. Normally, there is an almost immediate deactivation of adenylyl cyclase and break down of cAMP. In MAS this does not occur. Overproduction of cAMP leads to increased amounts of activity that affect each tissue differently based on its designated function. Café-au-lait spots are from overproduction of the enzyme tyrosinase which is the rate-limiting step in melanin production. In FD this mutation results in the hyperproliferation and incomplete differentiation of marrow stromal cells to abnormal osteoblasts. cAMP also activates Fos, which inhibits osteoblastic-specific genes as well as stimulates cytokines that promote bone resorption by osteoclasts. Hypophosphatemia/phosphaturia sometimes found in FD and MAS results from excess secretion of a phosphatonin fibroblast growth factor. Similarly, most of the endocrine problems associated with MAS can be related to Gs-alpha activation.

We recently investigated the potential of novel targeted therapy for FD with HER-2/*neu*, epidermal growth factor receptor (EGFR) and CD 117 (c-kit) antagonists that have shown therapeutic promise in many neoplasms. Disappointedly they are uniformly negative in FD specimens. In our experiment we confirmed that the negative immunoreactivity of the above markers was not due to the decalcification process. This suggests that therapies targeted against these biomarkers should have no utility in the treatment of FD. We strongly encourage further investigations to search optimal therapy for FD. This disease not only causes bone deformity, but also potential malignant transformation.

Conclusion

Fibrous dysplasia is usually thought of as a benign disease, though severe and devastating cases have been described. Malignant transformation is a rare complication of which all patients with this diagnosis should be aware. Here we describe a case of a 66-year-old male with monostotic FD of the tibia with secondary transformation to chondrosarcoma. This case is of specific importance due to the late age of original FD diagnosis and the short time lapse before malignancy occurred, as well being the second case in the literature of dedifferentiated chondrosarcoma. The take away message of this case is that FD is an important risk factor for malignant transformation, which should keep all clinicians alert to changing symptoms such as increased pain without a history of trauma or changing radiologic studies in the FD patient. Preliminary study indicates that HER2-2/*neu*, EGFR, and CD117 (C-KIT) are not expressed in FD.

Disclosure

The authors report no conflicts of interest in this work.

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