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REVIEW

Fibrous dysplasia of bone: a clinicopathologic review

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Abstract: Fibrous dysplasia of the bones is an uncommon congenital skeletal disorder that is found equally in both genders and is not inherited. Its etiology has been linked to an activating mutation of Gsα and the downstream effects of the resultant increase in cAMP. Fibrous dysplasia is categorized as either monostotic or polyostotic, and may occur as a component of McCune-Albright syndrome or the rare Mazabraud syndrome. Long bones, skull bones, and ribs are the most commonly affected bones. The radiological picture is somewhat variable, including a ground-glass appearance, expansion of the bone, and sclerosis surrounding the lesion. Histologically, fibrous dysplasia shows irregularly-shaped trabeculae of immature, woven bone in a background of variably cellular, loosely arranged fibrous stroma. It may be complicated by pathologic fracture, and rarely by malignant transformation. This review examines interesting issues surrounding the etiology of fibrous dysplasia, its clinical and laboratory manifestations, radiological picture, utility of bone biopsy, gross and microscopic pathology, complications, and its differential diagnostic considerations.

Keywords: fibrous dysplasia, McCune-Albright syndrome, monostotic form, polyostotic form

Introduction

Fibrous dysplasia is a rare benign intramedullary fibro-osseous lesion, which may present in either monostotic or polyostotic forms.[1,2] It is a genetic noninherited condition caused by missense mutation in the *GNAS1* gene on chromosome 20. Fibrous dysplasia is characterized by abnormal proliferation of fibrous tissue interspersed with normal or immature bone, and may be associated with endocrine dysfunction, abnormal pigmentation, and precocious puberty in girls.[3] It occurs in equal proportions in males and females, most often during the first two decades of life.[4] The abnormal skin pigmentation also tends to be present on the same side.[5] The initial clinical sign is usually a painless enlargement of the affected bone. Other signs and symptoms include bone pain, pathologic fractures, and bone deformities.[6,7] Malignant transformation is rare, and is usually precipitated by radiation therapy.[6,8]

The diagnosis of fibrous dysplasia can be made by radiologic imaging and confirmed by bone biopsies. Computed tomography (CT) and magnetic resonance imaging are useful for evaluating the soft tissue components and the entire extent of a lesion.[9]

Fibrous dysplasia is not a new entity. Although von Recklinghausen, a student of Virchow, is credited with the first accurate pathologic description of the disorder in 1891, characteristic lesions have been identified in prehistoric specimens and in

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a seventh century Anglo-Saxon.[3] In 1934, Freund named it as "osteitis fibrosa localizata/disseminata". Jacobson in 1937 in his extensive review of jaw bone diseases, described it as "fibrous dystrophy".[10] The terms fibrous dysplasia and polyostotic fibrous dysplasia were first suggested by Lichtenstein in 1938.[11] McCune and Bruch[12] and Albright et al[13] recognized in separate publications in 1937 the entity of "osteodystrophia fibrosa disseminata", characterized by endocrinopathies, cutaneous hyperpigmentation, and precocious puberty in females. This severe form of fibrous dysplasia subsequently became known as the Albright triad or McCune-Albright syndrome.[3]

Epidemiology

Determining the true incidence of fibrous dysplasia, particularly for the more prevalent monostotic form, is difficult because many patients are asymptomatic and are often diagnosed incidentally after radiographic evaluation for other reasons. If considered with bone tumors, fibrous dysplasia comprises nearly 1% of primary bone tumors and 5%–7% of all benign bone tumors.[5,14] Onset is typically in adolescence or late childhood, although more severe forms can arise in infancy.[3] Average age at presentation in a study by Lawrence et al[3] was 22 years, and the median age was 17 years. Polyostotic fibrous dysplasia has its onset mainly in children younger than 10 years of age, and the lesions grow with the child and stabilize after puberty.[6,15] The ratio of occurrence of polyostotic to monostotic fibrous dysplasia is 3:7.[16,17] Gender prevalence of monostotic and polyostotic fibrous dysplasia is equal.[6] However, McCune-Albright syndrome has a clear female predilection.[3]

Any bone may be affected by fibrous dysplasia. The common sites of involvement, in decreasing order of frequency, are 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. In patients with polyostotic disease, the most commonly involved bones are the craniofacial bones, ribs, and metaphysis or diaphysis of the proximal femur or tibia, and the lesions are often found on one side of the body.[6,15] The abnormal skin pigmentation also tends to be present on the same side. The craniofacial bones are affected in about 10% of cases of monostotic fibrous dysplasia and in 50%–100% of cases of polyostotic fibrous dysplasia.[16,18,19] When only the cranial and facial bones are affected, the term craniofacial fibrous dysplasia is used. Van Tillburg analyzed skull lesions from 144 patients identified in the literature and noted that the frontal bones were most commonly involved, followed by the sphenoid, ethmoid, parietal, temporal, and occipital bones.[3]

Etiology, genetics, and molecular biology

Fibrous dysplasia is postulated to occur as a result of developmental failure in the remodeling of primitive bone to mature lamellar bone and a failure of the bone to realign in response to mechanical stress. Failure of maturation leaves a mass of immature isolated trabeculae enmeshed in dysplastic fibrous tissue that are turning over constantly but never (or very, very slowly) completing the remodeling process. In addition, the immature matrix does not mineralize normally. The combination of a lack of stress alignment and insufficient mineralization results in substantial loss of mechanical strength, leading to the development of pain, deformity, and pathologic fractures.[14]

The etiology of fibrous dysplasia has been linked with a mutation in the *GNAS1* gene that encodes the alpha subunit of the stimulatory G protein-coupled receptor, Gsα, and is located at chromosome 20q13.2–13.3.[6,14,20] The activating mutations occur post-zygotically, replacing the arginine residue amino acid with either a cysteine or a histidine amino acid.[6] All cells that derive from the mutated cells manifest the dysplastic features. The clinical presentation varies, depending on the location of the mutation in the cell mass and the size of the cell mass during embryogenesis when the mutation occurs.[21] Severe disease may be associated with an earlier mutational event that leads to a larger number or a more widespread distribution of mutant cells. The sporadic occurrence of these diseases and the characteristic lateralized pattern of skin and bone involvement in the polyostotic forms of fibrous dysplasia suggest this mosaic distribution of abnormal cells. The Gsα mutation was first identified in patients with McCune-Albright syndrome, and the Gsα gene has also been linked to other endocrine tumors and human diseases.[21] The strongest evidence to support a genetic link to the etiology of fibrous dysplasia was found in an experimental study by Bianco et al[22] who isolated Gsα genes from patients with McCune-Albright syndrome, transplanted them into immunocompromised mice, and induced dysplastic bone production.

The mutation selectively inhibits GTPase activity, leading to constitutive activation of adenylate cyclase, increased cell proliferation, and inappropriate cell differentiation, resulting in overproduction of a disorganized fibrotic bone matrix in polyostotic and monostotic fibrous dysplasia.[7,14,23,24] It is now apparent that the constitutive elevation in cAMP

level induced by Gsα mutations leads to alterations in the expression of several target genes, the promoters of which contain cAMP-responsive elements, such as c-fos, c-jun, interleukin-6, and interleukin-11. This, in turn, affects the transcription and expression of downstream genes and results in alterations of osteoblast recruitment and function in dysplastic bone lesions.[25,26] Interleukin-6 may be responsible for the increased numbers of osteoclasts and the bone resorption seen in fibrous dysplasia.[14]

The systemic manifestations of the mutated Gsα protein-coupled receptor complex include autonomous function in bone through the parathyroid hormone receptor, in skin through the melanocyte-stimulating hormone receptor, in ovaries through the follicle-stimulating hormone receptor; and in the thyroid and the pituitary gland, through the thyroid and growth hormone receptors, respectively.[15]

With the help of genetic amplification techniques, such as polymerase chain reaction, it is now possible to test for the genetic mutation in peripheral blood samples. This novel technique may have application in the diagnostic and therapeutic monitoring of patients with fibrous dysplasia.[14]

Natural history and clinical presentation

The natural history of fibrous dysplasia is highly variable and is determined by the form of fibrous dysplasia with which the lesions present. The monostotic presentation is more frequent, and lesions enlarge in proportion to skeletal growth. The polyostotic form is less common.[14] By early adolescence, patients with widespread polyostotic fibrous dysplasia may have severe deformities. Polyostotic lesions often continue to enlarge after skeletal maturity, with progressive deformity and an increase in pathologic fractures. Skeletal lesions in patients with McCune-Albright syndrome tend to be larger, more persistent, and associated with more complications. Café au lait areas of skin pigmentation are frequently found about the trunk or the proximal parts of the extremities in these patients. Precocious development of secondary sexual characteristics is the most common endocrine presentation in patients with McCune-Albright syndrome.[14,27]

The European Paediatric Orthopaedic Society performed a multicenter clinicopathologic study to gain insight into the natural history of fibrous dysplasia.[28] Fifty-three patients from 11 centers were included. Twenty-three patients with a mean age of 15 years had monostotic involvement, 10 cases with a mean age of 11 years had polyostotic involvement, and 20 with a mean age of 4.5 years had McCune-Albright syndrome. In the cohort with monostotic disease, the most common site of involvement was the femur. Lesions in that group presented as an incidental finding or with pain, swelling, or fracture. Fractures occurred in 50% of the patients with monostotic disease. The majority of the monostotic cases did not progress, and the long-term outcome was usually satisfactory in those cases, regardless of treatment. Of the 10 patients with polyostotic disease, four had a bilateral distribution of lesions and six had an ipsilateral distribution. The femur was involved in nine patients, the tibia in eight, the pelvis in four, the humerus in two, and the radius and fibula in one patient each. Six of the 10 patients had limb-length discrepancy, in the range of 1–4.5 cm. All 20 patients with McCune-Albright syndrome had polymelic skeletal disease. Moderate-to-severe scoliosis was identified in 10 of the 20 patients. Seventeen of the 20 patients had at least one fracture, and 12 had multiple fractures. Mutation analysis was performed in 10 patients, nine of whom showed the Gsα mutation.

In patients with fibrous dysplasia, the initial symptom is pain in the involved limb associated with a limp, spontaneous fracture, or both.[1] Localized pain along with fatigue fractures in high-stress areas is particularly common with lesions in the femoral neck. Female patients can experience an increase in the pain level during pregnancy and at particular times during their menstrual cycle because of estrogen receptors found in fibrous dysplasia.[14] 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.[29] The degree of deformation depends on the extent and site of the lesion, the age of the patient, and whether the disease is monostotic or polyostotic. Diffuse polyostotic lesions in large weight-bearing bones are prone to lead to bowing deformities that increase with age and skeletal growth. Unlike deformities in patients with monostotic disease, deformities in patients with polyostotic disease may continue to progress after skeletal maturity.[14] The classic deformity of polyostotic fibrous dysplasia is the so-called "shepherd's crook" deformity, ie, curvature of the femoral neck and proximal shaft resulting in a coxa vara deformity which can be severe.[1] Similarly, fibrous dysplastic lesions of the spine may cause scoliosis.[14] Leet et al[30] reported in their study of 62 patients with polyostotic fibrous dysplasia that pain was an uncommon symptom, but 40% (25) of the patients had scoliosis.

In some patients, fibrous dysplasia is first diagnosed at the time of a pathologic fracture through a previously unknown lesion. Patients with polyostotic disease and large, painful lesions in weight-bearing long bones are at the greatest risk

for pathologic fracture and should be evaluated to determine the appropriateness of biopsy and prophylactic fixation of the involved bone. Other factors related to an increased risk of fracture are the number of lesions, the type, size, extent, and anatomic site of the lesion, and associated metabolic abnormalities.[14] Leet et al[31] reported that patients with metabolic abnormalities sustained a pathologic fracture at an earlier age (6.9 years compared with 16.6 years for those without metabolic abnormalities, $P < 0.005$) and had a higher lifetime risk of fracture (0.2 versus 0.08 fractures per year). Wai et al[32] performed a review of 11 pathologic fractures of the proximal part of the femur secondary to benign bone lesions, seven of which were fibrous dysplasia lesions.

In McCune-Albright syndrome, a triad of fibrous dysplasia, ie, bony lesions, endocrine abnormalities, and café au lait spots, are seen.[1] The incidence of sarcomas in fibrous dysplasia appears to be increased. As in the case of Paget's disease, the tumors always originate in abnormal bone, and not in the normal regions of the skeleton.[5] Another neoplastic complication reported in fibrous dysplasia is the development of benign intramuscular myxomas. The great majority of patients were reported to have multiple tumors in polyostotic disease.[5]

Syndromes and malignant transformations

McCune-Albright syndrome is an endocrinopathy occurring mainly in girls, consisting of the triad of precocious puberty, polyostotic fibrous dysplasia, and characteristic cutaneous pigmentation. Lesions of fibrous dysplasia associated with McCune-Albright syndrome tend to be more disabling than those of pure polyostotic disease.[9] The abnormal pigmentation often found in the skin overlying the lesions of fibrous dysplasia is a consequence of the development of melanotic macules.[5] These cutaneous lesions are flat pigmented macules, often referred to as café au lait spots and likened to the coast of Maine because of their irregular contour.[9] This feature sometimes distinguishes them from the lesions associated with neurofibromatosis which often have a smooth outline.[5]

Little is known of the pathology of the endocrine organs in the McCune-Albright syndrome. The findings in an autopsy of a 10-year-old girl revealed enlargement and hyperplasia of the adrenals, anterior lobe of the pituitary gland, thyroid, parathyroid, and pancreas.[33] The ovaries were enlarged and revealed numerous developing and regressing follicles without evidence of ovulation or corpus luteum formation. Clinically, the patient had the sexual characteristics of an adult, elevated blood sugar, hypertension, and increased basal metabolic rate, in addition to polyostotic bone lesions and extensive pigmentation of the skin.[33]

Serum calcium and phosphorus levels are normal in the great majority of patients with fibrous dysplasia. Serum alkaline phosphatase levels may be elevated, roughly corresponding to the extent of the bone lesions. In patients with McCune-Albright syndrome, various endocrinopathies are associated with elevations of circulating hormones depending on which glands are affected. Approximately 20% of female children with polyostotic fibrous dysplasia manifest signs of estrogen excess, whereas a much smaller percentage of male children exhibit enlarged genitalia and advanced secondary sex characteristics.[5] A great variety of other associated endocrinopathies have also been described. These include acromegaly, gigantism, hyperprolactinemia, hyperthyroidism, hyperparathyroidism, Cushing's syndrome, hypothalamic hypogonadism, and hypophosphatemic rickets.[34,35]

Mazabraud syndrome is the rare combination of fibrous dysplasia and soft tissue myxomas.[9] This disorder is also more common in women.[1] The benign, generally asymptomatic, myxomatous tumors usually develop in muscle near the most extensively involved bones years after the initial diagnosis of fibrous dysplasia.[9] Mazabraud syndrome is associated with a higher incidence of transformation to osteosarcoma.[36]

Although the prognosis of fibrous dysplasia is normally very good, malignant transformation may occur rarely (1% average, 4% in McCune-Albright), with almost all cases being of sarcomatous origin.[1] Ruggieri et al[36] retrospectively reviewed the Mayo Clinic files and identified sarcoma in 28 (2.5%) of 1122 patients with fibrous dysplasia. Of these 1122 patients, 12% (n = 135) had polyostotic disease and the remainder (n = 987 patients) had monostotic disease. Nineteen of the 28 sarcomas were in patients with monostotic fibrous dysplasia and nine were in patients with polyostotic disease. The rate of malignant transformation of monostotic lesions was only 1.9% (19 of 987 patients), whereas the rate for polyostotic lesions was 6.7% (nine of 135 patients). The histologic subtypes included 19 osteosarcomas, five fibrosarcomas, three chondrosarcomas, and one malignant fibrous histiocytoma. Thirteen (46%) of the 28 patients with a sarcoma had had previous radiation exposure. The interval between radiation therapy and diagnosis of the sarcoma was 3–52 years (mean, 19 years).

Usually years or decades elapse between the time of diagnosis and development of malignancy. 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.[37–40] CT scans can be helpful in recognizing malignancy as well as its extent. In monostotic fibrous dysplasia, the skull and facial bones are the most common sites to develop malignancy. In polyostotic fibrous dysplasia, the sites are the facial bones, femur, and tibia.[1] However, any site of fibrous dysplasia may undergo malignant transformation. The most common tumor is osteosarcoma (about 70%), with fibrosarcoma (about 20%), chondrosarcoma (about 10%), and malignant fibrous histiocytoma (about 4%) occurring less commonly.[41] The frequency of malignant change is increased in polyostotic fibrous dysplasia, especially in patients with McCune-Albright syndrome, Mazabraud syndrome, or prior radiation exposure.[37,42] The incidence is approximately 0.5% in monostotic fibrous dysplasia and eight times greater (4% in McCune-Albright syndrome). Patients with Mazabraud syndrome also have a higher risk of malignant transformation. Three cases of sarcoma have been documented in the 36 cases of Mazabraud syndrome described in the literature, so the rate of malignant transformation in such patients is 8.3%.[14]

Unfortunately, most of these cases are identified at an advanced stage and do not respond to conventional chemotherapy. Prognosis tends to be worse in patients with malignant transformation than in those with a similar primary sarcoma not associated with fibrous dysplasia.[14] However, with early diagnosis, there are cases that suggest the prognosis of secondary sarcoma is comparable with de novo cases. So once a diagnosis of fibrous dysplasia is made, follow-up should occur on a yearly basis with X-ray examination and the patient should be aware that any symptomatology (increased pain, weakness, deformity) should be addressed immediately.[1]

Diagnostic procedures

The diagnosis of fibrous dysplasia is made by X-ray, although it is not unusual for bone biopsies to be required because of uncertainty based on X-rays alone.[5]

Laboratory chemistry

The changes in bone metabolism parameters in a case of fibrous dysplasia as assessed by laboratory chemistry are not necessarily pathognomonic. Nevertheless, in the case of the polyostotic form, increases in alkaline phosphatase and osteocalcin mostly appear.[43] However, levels of alkaline phosphatase do not usually increase to the same extent as in patients with Paget's disease who have an equivalent extent of skeletal involvement. Urinary hydroxyproline, an older marker of bone resorption, can be elevated.[5] Likewise, increased collagen metabolites may be demonstrated (N-telopeptide). In McCune-Albright syndrome, high levels of growth hormone, prolactin, thyroid hormones and, less commonly, testosterone, adrenocorticosteroids, and parathyroid hormone have been reported.[5,43]

Imaging findings

The radiologic features of fibrous dysplasia[44] are diverse and are dependent upon the proportion of mineralized bone to fibrous tissue in the lesion (Figure 1). Early fibrous dysplasia is radiolucent with either ill-defined or well-defined borders, and may be unilocular or multilocular. As the lesions mature, the bony defects acquire a mixed

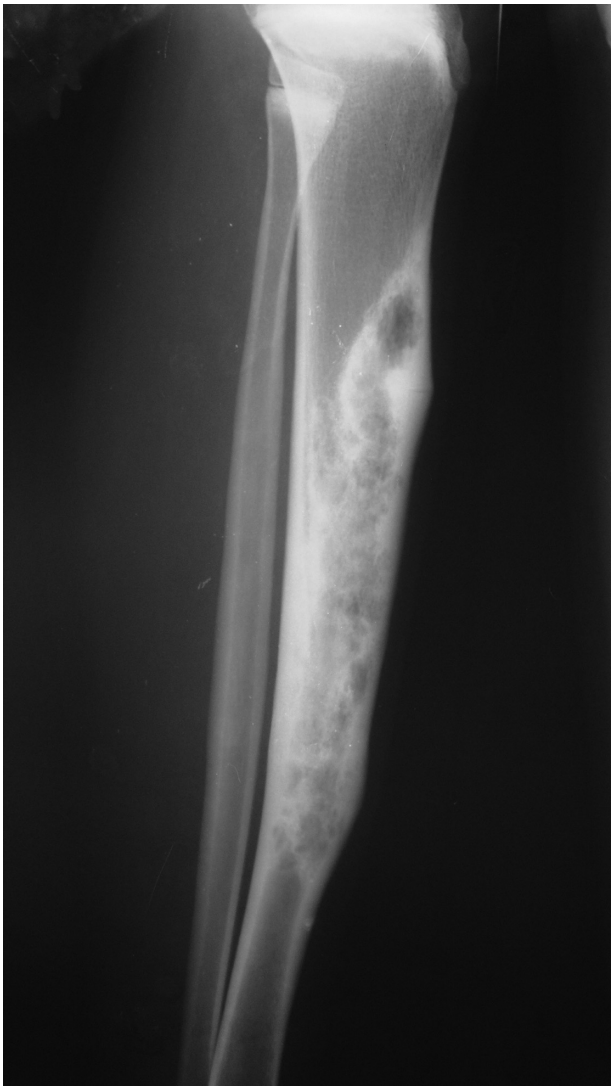

Figure 1 Radiographic picture demonstrating a well-defined geographic expansile lesion (with mixed areas of radiolucency as well as sclerosis) involving the metadiaphyseal region in the shaft of the tibia.

radiolucent/radiopaque appearance, and established fibrous dysplasia exhibits mottled radiopaque patterns, often described as resembling ground glass, orange peel, or fingerprints, with ill-defined borders blending into the normal adjacent bone.[19,45]

CT is the study of choice for diagnosis and follow-up of fibrous dysplasia because of its superior bony detail and accurate assessment of the extent of the lesion. Furthermore, CT can often assist with differentiating fibrous dysplasia from other osteodystrophies of the skull base, including otosclerosis, osteogenesis imperfecta, Paget's disease, and osteopetrosis. Aneurysmal bone cyst formation is also readily apparent on CT.[3] Magnetic resonance imaging is a sensitive means of establishing the lesion's shape and content, and the size of the affected region. It provides complementary information when performed in conjunction with CT imaging. Signal intensity on T1- and T2-weighted images and the degree of contrast enhancement on T1-weighted images depend on the amount and degree of fibrous tissue, bone trabeculae, cellularity, collagen, and cystic and hemorrhagic changes. Because the lesion is composed mainly of fibrous tissue and osteoid with low water content, T1-weighted images have a low-intensity signal. T2-weighted images have a higher intensity signal that is not as bright as the signal of malignant tissue, fat, or fluid (Figure 2). Heterogeneity may be seen secondary to islands of cartilaginous differentiation, areas of degenerative cysts, and areas of hemorrhage.[14] Bone scans with radiolabeled bisphosphonates usually but not always produce increased uptake in radiologically-defined lesions.[5]

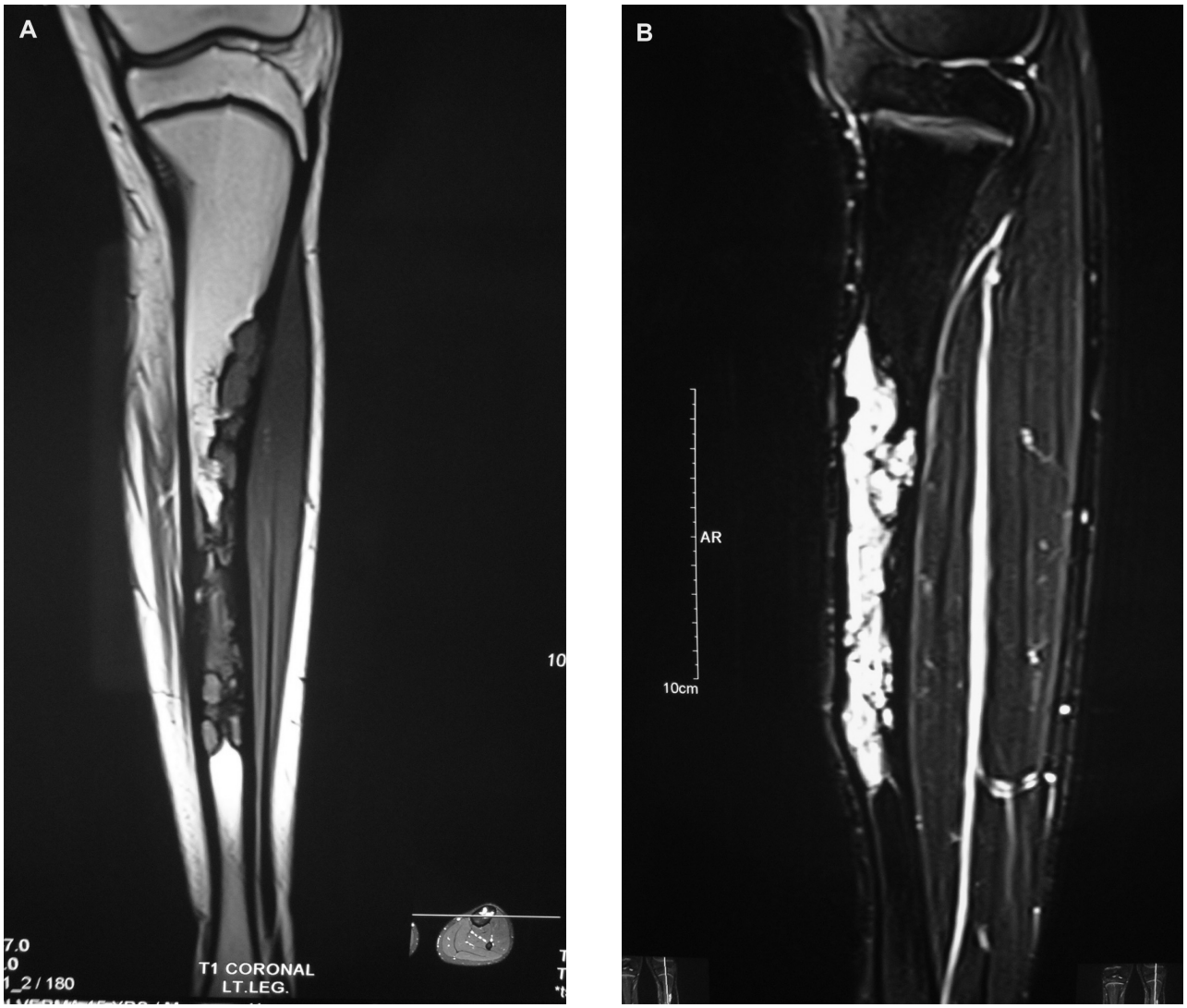

Figure 2 Magnetic resonance findings of the same lesion in a T1-weighted image showing an elongated hypointense mass lesion (**A**) while a T2-weighted image shows a hyperintense mass lesion involving the tibial diaphysis (**B**). Both images show a thin rim of low signal at the periphery.

Gross and microscopic pathology

Surgical exposure of fibrous dysplasia reveals a yellowish-white tissue with a distinctive gritty feel, imparted by the small trabeculae of bone scattered throughout the lesion (Figure 3). Fibrous dysplasia is medullary in location and this distinguishes it from osteofibrous dysplasia which is cortical. The lesion can be easily peeled away from the encircling shell of reactive bone by blunt dissection, and rarely, if ever, penetrates the reactive shell and extends into soft tissue. The tissue can be cut with a scalpel and may bleed briskly when cut owing to its concentration of small vessels.[14] Lesions within the skull tend to have a firmer consistency than their counterparts in the long bones of the body due to a greater amount of bony spicules. Cystic lesions can often be filled with an amber fluid and can occasionally be vascular.[3]

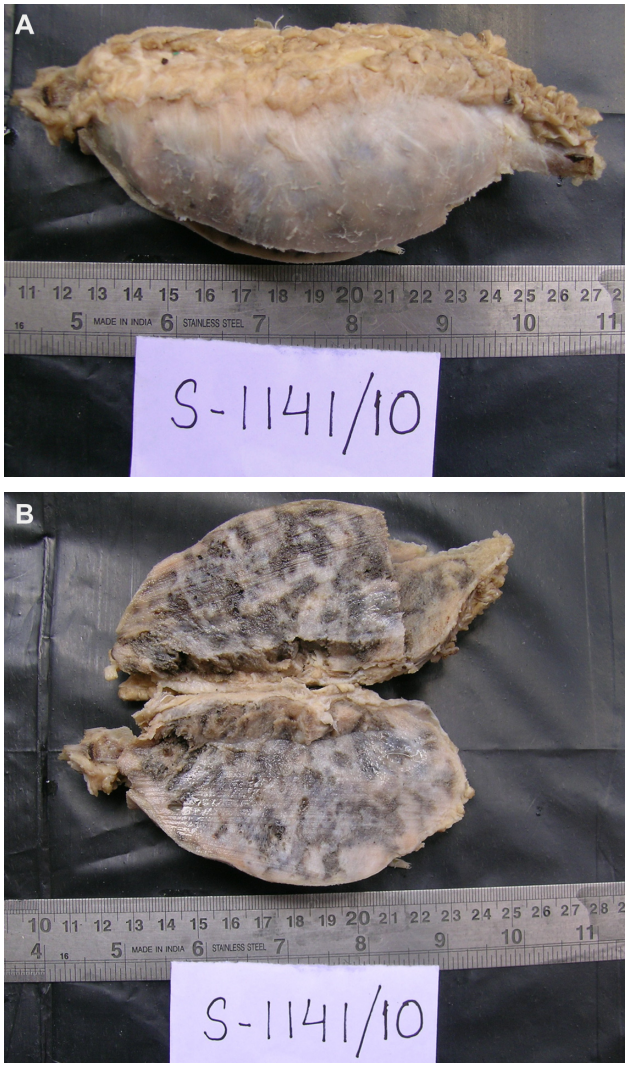

Figure 3 Gross appearance of fibrous dysplasia of rib showing a gray white expansile swelling (**A**). Cut surface of the lesion is gritty with focal gray tan areas (**B**).

The key histologic features of fibrous dysplasia are delicate trabeculae of immature bone, with no osteoblastic rimming, enmeshed within a bland fibrous stroma of dysplastic spindle shaped cells without any cellular features of malignancy (Figure 4). The ratio of fibrous tissue to bone ranges from fields that are totally fibrous to fields filled with dysplastic trabeculae. The degree of haziness shown radiographically by a given fibrous dysplasia lesion directly correlates with its underlying histopathology.[14] More radiolucent lesions are composed of predominantly fibrous elements, whereas more radiopaque lesions contain a greater proportion of woven bone.[9] Examination of macrosections of intact lesions reveals the margins of the lesion to be separated from the surrounding bone by a thin shell of mature lamellar reactive bone. The overall impression is of a variable number of immature, non-stress-oriented, disconnected dysplastic trabeculae floating in a sea of immature mesenchymal cells that have little or no collagen about them. The pattern of the bizarrely shaped curvilinear trabeculae has been likened to "alphabet soup" or a "Chinese letter" appearance.[4,14] The mesenchymal stroma surrounding the dysplastic trabeculae is relatively hypocellular and is composed of spindle-shaped primitive mesenchymal cells that produce little or no collagenous fibrils (Figure 5). In some lesions there is greater cellularity consisting of immature-appearing, small, slender spindle cells in a loose and whorled arrangement.[5]

There is a characteristic absence of plump osteoblasts rimming the isolated immature trabeculae, which often have abnormally thick seams of osteoid, similar to those seen in osteomalacia.[14] Because it has been difficult to identify osteoblasts on the surface of the woven bone, the apparent

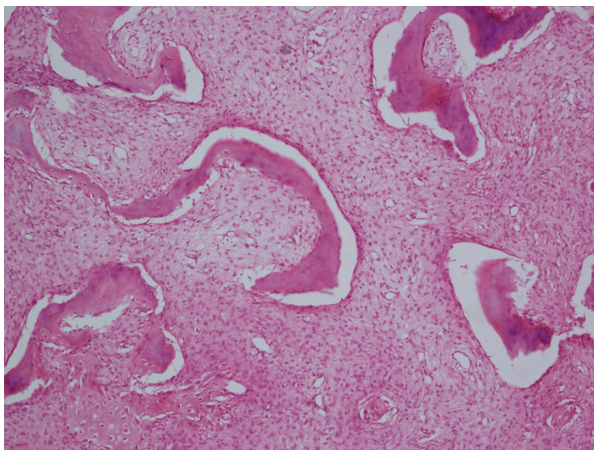

Figure 4 Photomicrograph shows characteristic delicate curvilinear bony trabeculae not associated with osteoblastic rimming and surrounded by bland mesenchymal stroma (hematoxylin and eosin, 100×).

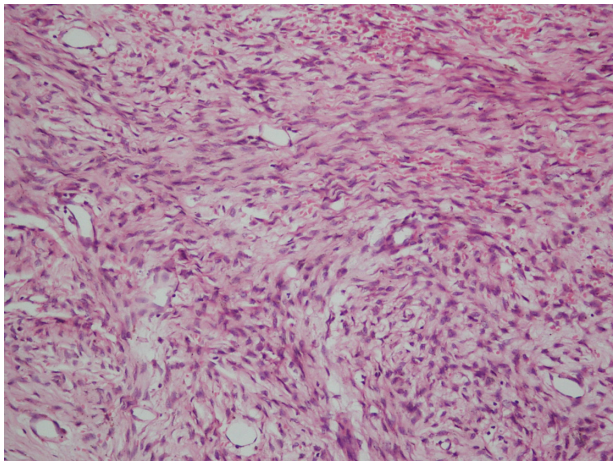

Figure 5 Fibrous stroma composed of spindle-shaped cells without any cellular atypia (hematoxylin and eosin, 200×).

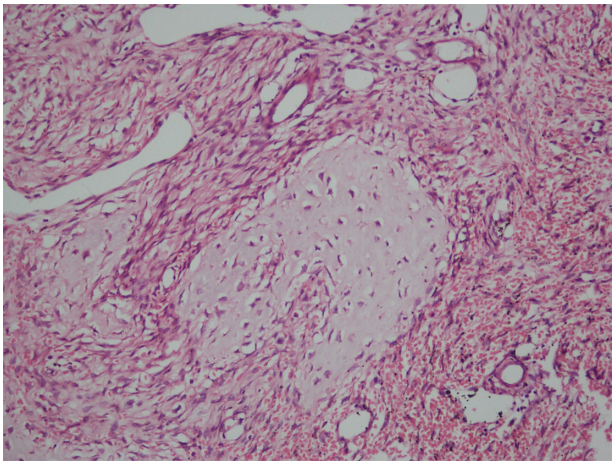

Figure 6 Photomicrograph showing lobules of mature cartilage in fibrous dysplasia (hematoxylin and eosin, 400×).

conversion of fibrous tissue to bone has been termed fibro-osseous metaplasia.[5] Ultrastructurally, immature woven bone trabeculae are lined by abnormal osteoblasts with a fibroblast-like appearance.[46] Early craniofacial fibrous dysplasia is characterized by minimally mineralized deposits of woven bone with progressive lamellation of the woven bone trabeculae as fibrous dysplasia becomes more mature. This is in contrast with fibrous dysplasia lesions in long bones where mature lamellar bone is not found.[47]

Multiple delicate capillaries with extravasation of blood and hemosiderin pigment are found throughout the lesion and, when injured, incite a giant-cell reactive process.[5,14] Osteoclasts are usually not found in great numbers in the lesions of fibrous dysplasia, but can be seen adjacent to engorged blood vessels or to areas of blood extravasation. Presumably, osteoclasts are responsible for the spread of the lesion through normal adjacent bone, but this has not been reported in detail. Small areas of cystic degeneration can occur, but appear to be of minor significance.[5] Lobules of cartilage are infrequently seen and, when present, are composed of mature hyaline cartilage (Figure 6). Both cystic areas and foci of hyaline cartilage are more common in polyostotic fibrous dysplasia.[14] Gozalez et al[48] reported a case of fibrous dysplasia of the femoral neck in a 6-year-old girl in which there was extensive cartilaginous differentiation (60% of the tumor mass). A fibro-osseous component formed the rest of the 40%. The cartilage in fibrous dysplasia may show moderate atypism. The important thing is to recognize the benign nature of chondroid elements in fibrous dysplasia. Even if cartilage dominates the histologic picture, it is important to identify the fibro-osseous elements and thereby avoid the misdiagnosis of chondrosarcoma.[49]

Occasionally, calcified spherules similar to those in cementifying fibromas are seen in fibrous dysplasia.[50] As with many bone abnormalities, fibrous dysplasia can be superimposed by the formation of aneurysmal bone cysts (Figure 7). An aneurysmal bone cyst is a benign cystic lesion of bone, composed of blood-filled spaces separated by connective tissue septa with fibroblasts, osteoclast-like giant cells, and reactive woven bone.[51,52] The woven bone in this lesion is rimmed with osteoblasts and usually follows contours of the septa.[53] An aneurysmal bone cyst is frequently seen in association with fibrous dysplasia of the skull base. In a study by Lawrence et al,[3] five (24%) of 22 patients with fibrous dysplasia of the skull base had secondary aneurysmal bone cysts. The authors reported that, in contrast with its formation in the long bones throughout the body, because of the confined space within the base of the skull, their expansion can

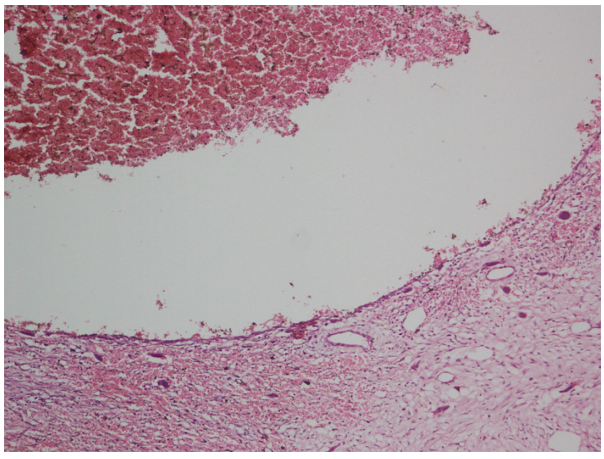

Figure 7 Photomicrograph showing secondary aneurysmal bone cyst-like area in fibrous dysplasia. Osteoclastic giant cells are seen at the periphery (hematoxylin and eosin, 100×).

lead quickly to clinical symptoms, with increased morbidity. All five patients in this series with aneurysmal bone cyst formation required surgery because of the expansile nature of the lesion. Fibrous dysplasia is thought to be particularly susceptible to bone cyst formation because of the vascularity of the lesion.[54]

Cytologic atypia is generally not considered a feature of the proliferating tissue of fibrous dysplasia. Bertoni et al[55] described the case of a 42-year-old man who presented with an osteolytic lesion of the right iliac bone. Histologic study demonstrated a fibro-osseous lesion with woven bone trabeculae and bland-looking fibrous tissue. Several areas showed atypical cells with enlarged pleomorphic nuclei and bizarre features. There was no change in the nuclear-cytoplasmic ratio, nor were mitotic figures identified. A histopathologic diagnosis of fibrous dysplasia with degenerative or regressive nuclear changes was made. Also, when there is a history of trauma, atypia may be seen in fibrous dysplasia. Hence, when radiographic and other histologic findings suggest fibrous dysplasia, the atypical nuclear changes should not, by themselves, alter the diagnosis.

The microscopic features of the pigmented macules in McCune-Albright syndrome include excessive deposition of melanin, despite a normal number of melanocytes, and the near-absence of giant pigment granules, which are typical of the melanotic macules of neurofibromatosis.[5]

Differential diagnosis

Entities that come into the differential diagnosis of fibrous dysplasia include nonossifying fibromas, osteofibrous dysplasia, cemento-osseous dysplasia, simple bone cysts, adamantinoma, low-grade intramedullary osteosarcoma, and Paget's disease, sarcoma, and cartilaginous tumors.[14,56,57]

Nonossifying fibromas are common benign fibrous lesions of bone. They originate eccentrically in the growing metaphysis, are usually asymptomatic, and spontaneously regress with age. Nonossifying fibromas can be distinguished from fibrous dysplasia by their intracortical origin, smaller size, lack of intralesional ossification, and spontaneous regression.[14] Osteofibrous dysplasia, or ossifying fibroma, first identified as a distinct entity in 1976 by Campanacci, is a rare lesion localized almost exclusively to the distal third of the tibia or fibula. It is usually identified in children younger than 10 years of age, and has a remarkable radiographic resemblance to fibrous dysplasia.[58] Histologically, osteofibrous dysplasia can be distinguished from fibrous dysplasia by the presence of lamellar bone and osteoblastic rimming of bone trabeculae. Immunohistochemically, in contrast with fibrous dysplasia, it is commonly reactive for keratin, neurofibromin, S-100 protein, and Leu 7.[59] When a differential diagnosis is not possible on the basis of clinical and radiographic features, a molecular analysis can be helpful. Tissue from an area of osteofibrous dysplasia does not have the characteristic genetic mutation seen with fibrous dysplasia.[14] These two lesions can also be distinguished by testing for proliferating cell nuclear antigen expression on osteoblasts within the lesion. In a retrospective clinicopathologic analysis, Maki et al[60] demonstrated that bone-lining cells in fibrous dysplasia are negative for proliferating cell nuclear antigen expression, whereas osteoblasts in osteofibrous dysplasia are positive.

Cemento-osseous dysplasia is a fairly common fibro-osseous lesion of the jaw, which can be described as a benign, self-limiting fibro-osseous condition, occurring possibly as a reaction to local injury. It can have a similar radiologic appearance to that of fibrous dysplasia. However, biopsy can help in differentiating the two. Cemento-ossifying dysplasia in histopathologic section shows a fibrous connective tissue stroma with numerous areas of hemorrhage. Within this connective tissue background is seen a mixture of woven bone and numerous irregularly shaped cementum-like particles.[56]

Simple bone cysts tend to be more radiolucent than lesions of fibrous dysplasia, produce greater enlargement of the affected area, be surrounded by a thinner amount of lamellar bone, and move away from the growth plate with skeletal growth. If clinically indicated, aspiration may be helpful for differentiating between the two lesions. Straw-colored fluid aspirated from the cyst and complete filling of the radiolucent lesion with contrast material strongly favor the diagnosis of a unicameral bone cyst.[14]

Adamantinoma is a low-grade malignant tumor found almost exclusively in the anterior aspect of the tibia. Its two distinct histiogenic components include an epithelioid component of epithelial histogenesis and a fibro-osseous component of mesenchymal histogenesis. Because the anatomic site and radiographic features may resemble those of osteofibrous dysplasia and because of the histologic resemblance of the mesenchymal component, some believe that adamantinoma is a malignant variant of osteofibrous dysplasia.[61] Biopsy is often needed to differentiate between the two lesions. Maki and Athanasou[62] recently investigated the relationship between adamantinoma and osteofibrous dysplasia using histochemistry to analyze the expression of several proto-oncogene products and extracellular matrix proteins in specimens from 25 tumors (18 osteofibrous

dysplasias, three differentiated adamantinomas, and four classic adamantinomas). The investigators found common expression of a number of oncoproteins and bone matrix proteins, including ones associated with mesenchymal-to-epithelial cell transformation. Because of this, they concluded that osteofibrous dysplasia may represent a precursor lesion of adamantinoma.

Low-grade intraosseous-type osteosarcoma is a rare variant, accounting for only 1% of all osteosarcomas. Fibrous dysplasia with degenerative atypical changes needs to be distinguished from low-grade intraosseous-type osteosarcoma.[55] Histologically, there may be focal areas showing an overlapping of morphologic features. However, low-grade intraosseous-type osteosarcoma, even if similar to fibrous dysplasia, has a consistent infiltrating pattern. Permeation, extensive or minimal, among the peripheral host bony trabeculae, or entrapment of the host trabeculae at the edge of the tumor, is always present. Occasionally, bone marrow infiltration may be present. Spindle cells in low-grade intraosseous-type osteosarcoma are arranged in an interlacing pattern and have nuclear pleomorphism with few mitotic figures.[55]

Paget's disease has a distribution that is similar to that of fibrous dysplasia, with a monostotic occurrence (skull or flat bones) or polyostotic occurrence (long bones), but it is seen in the middle, rather than the early, decades of life. It also occurs more frequently in males and in those of Northern European ancestry. Radiographic features can vary, but on occasion the resorptive phase of Paget's disease may resemble fibrous dysplasia. The disorder is characterized by a generalized widening and often bowing of the long bones and thickening of the skull.[63] It is readily distinguishable from fibrous dysplasia by the accompanying marked elevation in serum alkaline phosphatase levels.[14]

Sometimes highly cellular areas of fibrous dysplasia may be diagnosed incorrectly as sarcoma. Focal areas of hyaline cartilage can dominate the microscopic picture, resulting in misdiagnosis of cartilaginous tumor.[57]

Overview of management

There is no cure for fibrous dysplasia, and the existing guidelines for treatment are not universally accepted. Spontaneous resolution of fibrous dysplasia does not occur.[44] Fibrous dysplastic lesions that are not symptomatic, do not progress, and do not cause deformities or functional impairment, should simply be monitored.[18] Surgical intervention is required when important structures are in danger of compression.[19] As an alternative treatment, when surgery is not indicated, relief of bone pain and reduction of osteoclastic activity with partial filling of osteolytic lesions can be achieved with intravenous bisphosphonate therapy.[15,44] It is hopeful that fuller understanding of the pathogenesis of fibrous dysplasia can lead to improved treatment of the disease. Gene therapy targeted to the abnormal cell populations would likely be the ideal treatment for the skeletal as well as extraskeletal lesions.[5]

In conclusion, fibrous dysplasia is an uncommon benign bone disease, although severe and devastating cases have been described. It is found to exist in monostotic and polyostotic forms and is a component of McCune-Albright and Mazabraud syndromes. Biopsy is indicated for confirmation if the radiographic findings are not characteristic of fibrous dysplasia. The histopathology of fibrous dysplasia is characterized by a fibrous tissue stroma in which spicules of woven bone may be found, which are present as curled disconnected trabeculae resembling letters of the alphabet. Characteristic absence of osteoblastic rimming of the bony trabeculae is seen. Complications include occasional pathologic fracture, secondary aneurysmal bone cyst formation, and rare malignant change. Awareness of the varied histopathology, complications, and extra-osseous manifestations of fibrous dysplasia is important to ensure early accurate diagnosis and appropriate management of this disease.

Disclosure

The authors report no conflicts of interest in this work.

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