Fibrous Dysplasia

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Abstract

*Fibrous dysplasia is a developmental disorder of bone that can present in a monostotic or polyostotic form. Primarily affecting adolescents and young adults, it accounts for 7% of benign bone tumors. Many of the asymptomatic lesions are found incidentally; the remainder present with symptoms of swelling, deformity, or pain. Fibrous dysplasia has been associated with multiple endocrine and nonendocrine disorders and with McCune-Albright and Mazabraud's syndromes. The etiology remains unclear, but molecular biology suggests a mutation in the $G_s\alpha$ subunit and activation of c-*fos *and other proto-oncogenes. Fibrous dysplasia has a characteristic radiographic appearance. Most cases do not require intervention, but those that do usually are managed surgically with curettage, bone grafting, and, in some cases, internal fixation. When some intervention is necessary but surgery is not practical, treatment is with bisphosphonates. The prognosis generally is good, although poor outcomes are more frequent in younger patients and in those with polyostotic forms of the disease. The risk of malignant transformation is low.*

J Am Acad Orthop Surg 2004;12:305-313

Initially identified by Lichtenstein[1] in 1938, then more fully described in a larger series by Lichtenstein and Jaffe[2] in 1942, fibrous dysplasia is a benign developmental disorder of the bone. Usually observed in adolescents and young adults, it accounts for 7% of benign bone tumors.[3] In fibrous dysplasia, normal lamellar cancellous bone of the medullary canal is replaced with immature fibro-osseous tissue, resulting in poorly formed trabeculae of immature woven bone.[4] Fibrous dysplasia may affect one (monostotic) or multiple (polyostotic) bones. The monostotic form is more common, occurring in 75% to 80% of cases.[5] The polyostotic form can affect one (monomelic) or multiple (polymelic) extremities.

Multiple endocrine disorders have been associated with fibrous dysplasia, typically with severe polyostotic fibrous dysplasia. These include hyperthyroidism, hypophosphatemia, acromegaly, hyperprolactinemia, and Cushing's disease.[4,6-12] Nonendocrine abnormalities of the brain, thymus, heart, bone marrow, liver, spleen, and gastrointestinal tract are occasionally associated as well. Fibrous dysplasia is characteristic of McCune-Albright syndrome (polyostotic fibrous dysplasia, café-au-lait spots, and endocrine dysfunction) and Mazabraud's syndrome (polyostotic fibrous dysplasia and soft-tissue myxomas).

Clinical Presentation

Although more than half of cases are recognized during the first three decades of life, fibrous dysplasia can present at any age. The polyostotic form usually presents before age 10 years, and the monostotic form between age 5 and 20 years.[4] Distribution between the sexes is equal.

Usually, bone lesions are distributed throughout the skeleton, including the ribs, craniofacial bones, and appendicular skeleton. Fibrous dysplasia is the most common bone tumor of the ribs (Fig. 1). The extent of involvement within a single long bone can vary. Common sites for monostotic fibrous dysplasia include the ribs (28%), proximal femur (23%), and craniofacial bones (20%)[13] (Fig. 2). The more extensive and aggressive lesions are commonly found in polyostotic fibrous dysplasia, which can affect as few as two bones to as much as 75% of the skeleton, predominant-

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None of the following authors or the departments with which they are affiliated has received anything of value from or owns stock in a commercial company or institution related directly or indirectly to the subject of this article: Dr. Parekh, Dr. Donthineni-Rao, and Dr. Ricchetti. Dr. Lackman or the department(s) with which he is affiliated has received research or institutional support from Stryker. Dr. Lackman or the department(s) with which he is affiliated serve(s) as a consultant to or is an employee of Stryker.

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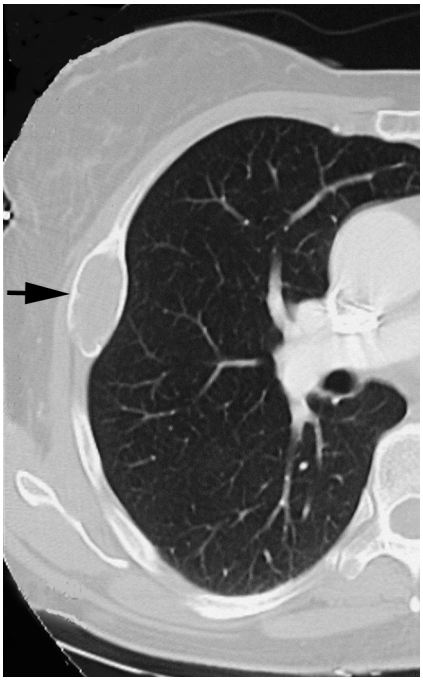

Figure 1 Axial CT scan of the chest showing fibrous dysplasia of the rib (arrow). (Copyright © Rakesh Donthineni-Rao, MD.)

ly involving the femur (91%), tibia (81%), pelvis (78%), and foot (73%)[13] (Fig. 3). Polyostotic lesions progress in number and size until skeletal maturity and then usually become quiescent. However, a small percentage may continue to enlarge.

Patients with polyostotic disease are more often symptomatic, whereas those with monostotic lesions commonly are asymptomatic and diagnosed only incidentally on radiographs.[14,15] The most common clinical symptoms of fibrous dysplasia are swelling and/or deformity of the affected site and pain. Female patients may have an increase in pain or even an increased tendency to fracture during and immediately after pregnancy. Deformity results from abnormal bone growth or microfractures and subsequent remodeling in the affected bone. Marked deformity, disability, and pathologic fractures may occur in the more severe presentations. Deformities of the proximal femur can be very painful and affect gait; these deformities also are at a risk of pathologic fracture.[16] Physical deformities include leg-length discrepancies, bossing of the skull, prominent jaw, tibial bowing, and rib/chest wall masses. Extraskeletal manifestations are more frequent in patients with the polyostotic form. The most common of these is skin hyperpigmentation, or café-au-lait spots, such as is seen in McCune-Albright syndrome.

First reported by Albright et al[17] in 1937, McCune-Albright syndrome consists of the triad of polyostotic fibrous dysplasia, cutaneous café-au-lait spots (typically ipsilateral to the bone lesions), and endocrine dysfunction. Unlike the smooth ("coast of California") borders of type 1 neurofibromatosis skin lesions, the hyperpigmented skin lesions of McCune-Albright syndrome have irregular ("coast of Maine") borders.[18] McCune-Albright syndrome occurs in 30% to 50% of cases of polyostotic fibrous dysplasia.[6,19] Although it affects both sexes, it has been reported more often in females. Girls with the syndrome may present with precocious puberty, vaginal bleeding, faster-than-normal growth, and advanced Tanner stages of development. The precocious puberty evident in these patients has been attributed to both central nervous system stimulation and autonomous ovarian activity.[12] Reports of cessation of vaginal bleeding after removal of unilateral follicular ovarian cysts[20] support these findings.

In Mazabraud's syndrome, soft-tissue myxomas develop in patients with polyostotic fibrous dysplasia. The myxomas usually seem to develop later than the fibrous dysplasia and arise adjacent to the affected long bones. Myxomas present as slowly growing masses. Occasionally they are symptomatic from pressure on the surrounding tissue (Fig. 4). Malignant transformation of these myxomas has not been reported.

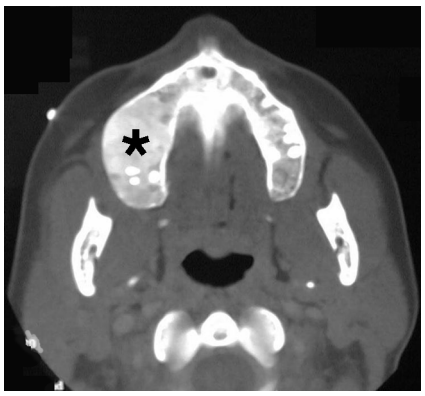

Figure 2 Axial CT scan of the jaw showing expansion caused by fibrous dysplasia (asterisk). (Copyright © Rakesh Donthineni-Rao, MD.)

Cherubism is a form of fibrous dysplasia with symmetric involvement of both the mandible and maxilla. The subsequent swelling of the cheeks can be severe enough to distort the orbit and deviate the eyes. Cherubism usually presents during the second decade of life with lesions that become static once skeletal maturity is reached. Unlike other forms of fibrous dysplasia, which display no inheritance pattern, cherubism has been shown to be an autosomal dominant disorder[21] with both familial and nonfamilial forms.

Malignant transformation has been reported in about 0.5% of patients with monostotic fibrous dysplasia but in nearly 4% of those with McCune-Albright syndrome.[22] Malignancy should be suspected in patients who report increasing pain that persists during inactivity or wakes them at night or who have an enlarging mass. Radiographic changes that suggest malignancy include lytic regions in previously mineralized zones, areas of periosteal reaction, cortical disruption, and a soft-tissue mass. Malignant degeneration is most common to osteosarcoma, although fibrosarcoma, chondrosarcoma, or malignant fibrous histiocytoma sometimes develops.[23] The craniofacial bones and the femur are the most common sites of

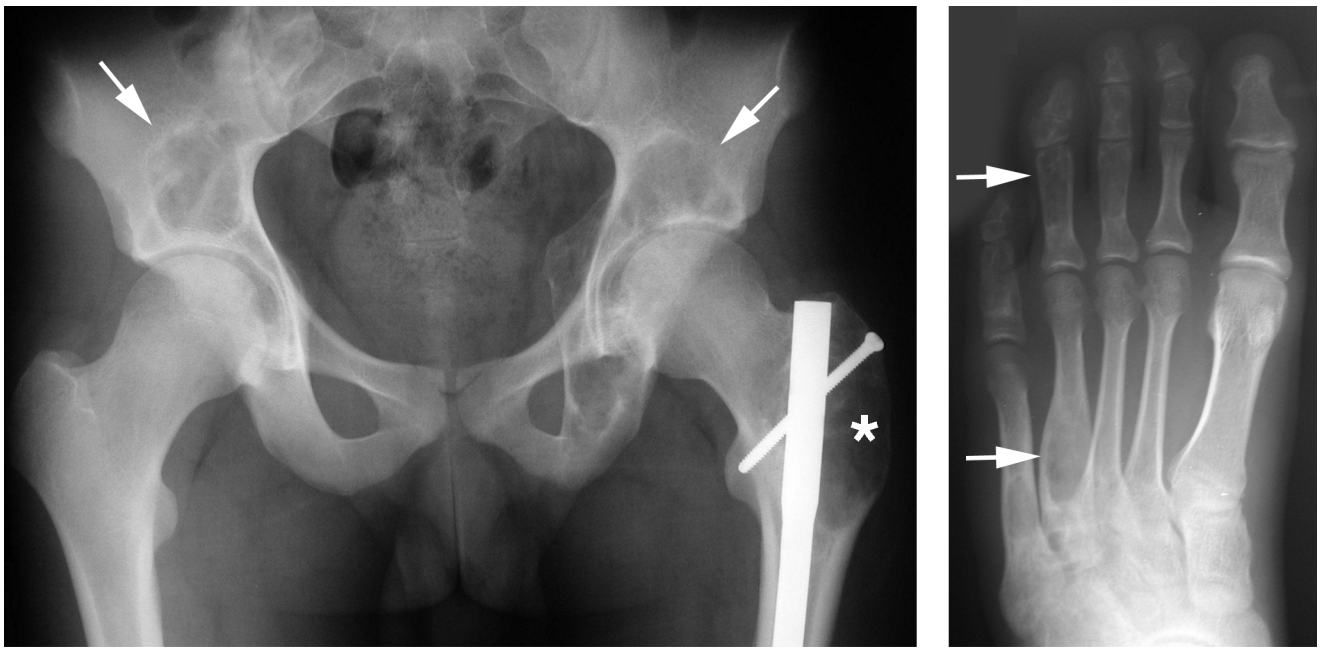

Figure 3 **A,** Anteroposterior radiograph showing polyostotic fibrous dysplasia affecting the pelvis (arrows) and the proximal femur (asterisk). **B,** Anteroposterior radiograph showing polyostotic disease of the foot (arrows). (Copyright © Rakesh Donthineni-Rao, MD.)

malignant transformation. Prognosis is generally poor, but early detection and treatment may improve outcomes.

Pathophysiology

The hallmark of fibrous dysplasia is a focal or generalized inability of bone-forming tissue to produce mature lamellar bone. Tissue is arrested at the stage of immature, woven bone, suggesting a defect in cell differentiation. It has therefore been postulated that genes involved in the modulation of cellular differentiation into mature osteocytes capable of producing lamellar bone are somehow altered in patients with fibrous dysplasia.[4]

The precise pathophysiology remains obscure, but recent studies suggest a mutation that affects the α subunit of the cell membrane–bound G protein. Analysis of the $G_s\alpha$ subunit in fibrous dysplastic lesions as well as in McCune-Albright syndrome reveals a missense point mutation at the arginine 201 codon. This results in an arginine-to-histidine or an arginine-to-cysteine substitution. This point mutation is thought to lead to sustained activation of adenylate cyclase. Within the cell, the signal-transducing function of adenylate cyclase elevates concentrations of intracellular cyclic adenosine monophosphate (cAMP).

Both monostotic and polyostotic fibrous dysplasia result from the abnormal proliferation of mesenchymal osteoblast progenitor cells with this $G_s\alpha$ mutation. It is plausible that the resulting elevation of cAMP concentrations may stimulate osteoblastic expression of proto-oncogenes, such as c-*fos*.[24,25] The products of the c-*fos* proto-oncogene have been implicated in control of bone cell proliferation and differentiation.[26] The expression of the c-*fos* proto-oncogene may lead to altered cellular differentiation and osteoblastic proliferation and therefore may play a role in the development of fibrous dysplasia.

Evidence suggests that the point mutation of the $G_s\alpha$ subunit is a somatic rather than a germline mutation. Occurring after fertilization in one of the cell lines, the mutation is localized to the lesional tissues.[27] Chromosome 12 has been implicated in the pathogenesis,[28] although no studies have shown a consistent association with any one chromosome. The pathophysiology of this disease is further confounded by findings of increased levels of interleukin-6 (IL-6) secretion in McCune-Albright syndrome.[29] IL-6 production may be responsible for the increased resorption of bone by increasing the numbers of osteoclasts in these lesions.

Pregnancy can exacerbate both forms of fibrous dysplasia. The increased hormone concentrations during pregnancy may lead to the enlargement of lesions with an exacerbation of symptoms. The osteoblasts in fibrous dysplastic lesions have been found to have an elevated number of hormone receptors.[30,31]

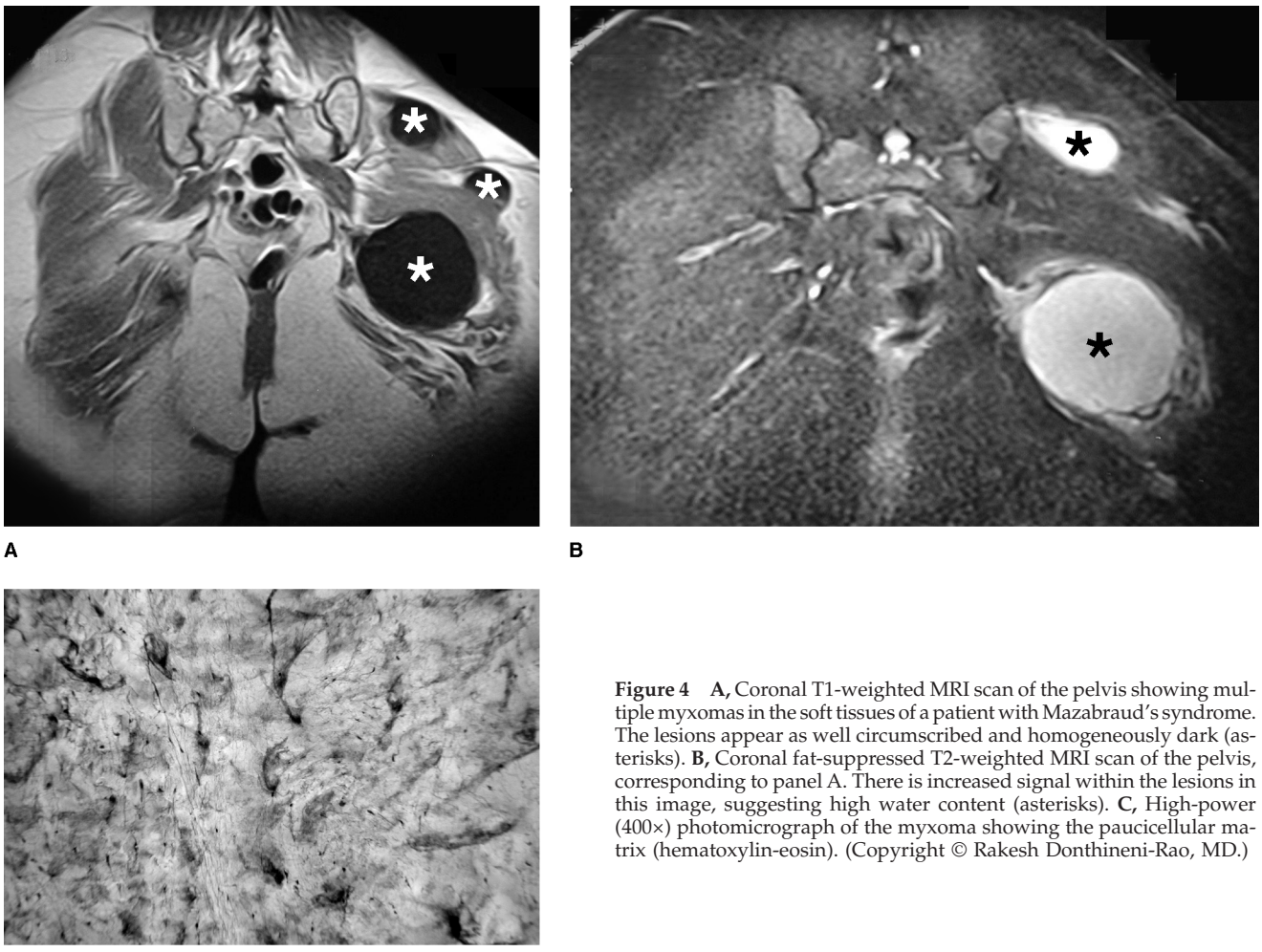

Figure 4 **A,** Coronal T1-weighted MRI scan of the pelvis showing multiple myxomas in the soft tissues of a patient with Mazabraud's syndrome. The lesions appear as well circumscribed and homogeneously dark (asterisks). **B,** Coronal fat-suppressed T2-weighted MRI scan of the pelvis, corresponding to panel A. There is increased signal within the lesions in this image, suggesting high water content (asterisks). **C,** High-power (400×) photomicrograph of the myxoma showing the paucicellular matrix (hematoxylin-eosin). (Copyright © Rakesh Donthineni-Rao, MD.)

The increased levels of circulating hormones during pregnancy may therefore further stimulate these osteoblasts.

Radiologic Evaluation

Although fibrous dysplasia can have a variety of radiographic appearances, certain findings are frequently present. The lesions are located within the medullary canal of the metaphysis or diaphysis (Fig. 5). The normal architecture of the bone is altered as the medullary canal is replaced with fibrous tissue characterized by delicate woven-bone spicules that give the tissue its "ground glass" appearance. Endosteal scalloping of the adjacent cortex may be noted. The affected bone may undergo an expansive remodeling process, eventually resulting in a border layer of thick, sclerotic, reactive bone, referred to as a rind. Typically the lesion is sharply marginated, even without the rind. Occasionally there are small islands of cartilage, which calcify and undergo endochondral bone formation. Foci of dense, punctate, "popcorn" calcifications are then evident on radiographs. The amount of such calcification is far lower than that seen in a cartilage lesion.

Characteristic distributions of lesions and subsequent bony deformities are seen in fibrous dysplasia. In the calvaria, hemicranial involvement is the norm. In the proximal femur, microfractures and remodeling over a long time result in a varus deformity ("shepherd's crook" deformity).

In the rare instance that a definitive diagnosis of fibrous dysplasia cannot be made from plain radiographs, then either further radiographic evaluation or a biopsy will be definitive. Although bone scans typically reveal increased uptake of radioisotope in the lesions, a cold bone scan does not exclude the diagnosis. Bone scans are most useful for identifying the distribution of lesions in patients with polyostotic disease (Fig. 6). Bone scans also may be useful

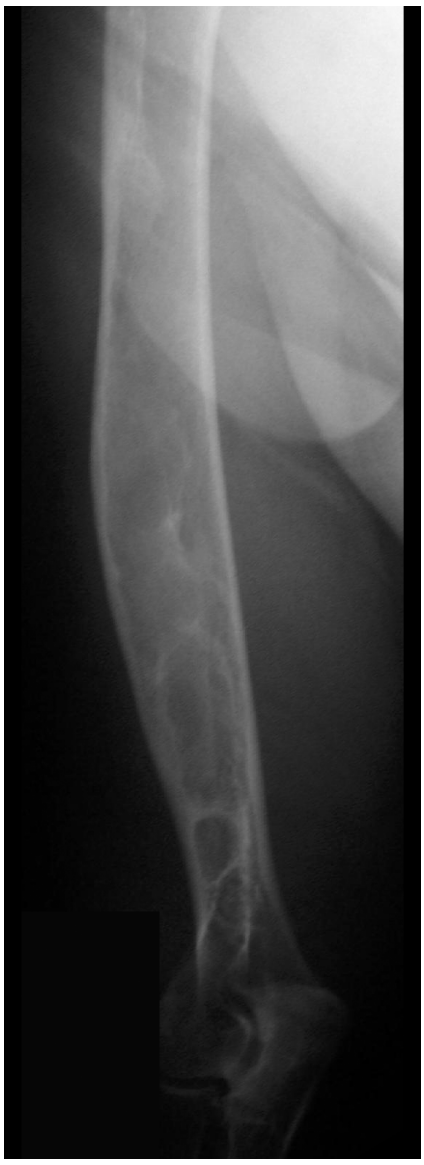

Figure 5 Anteroposterior radiograph showing fibrous dysplasia of the humerus demonstrating the deformity with expansion of the diaphysis and the "ground glass" appearance of the medullary cavity. (Copyright © Rakesh Donthineni-Rao, MD.)

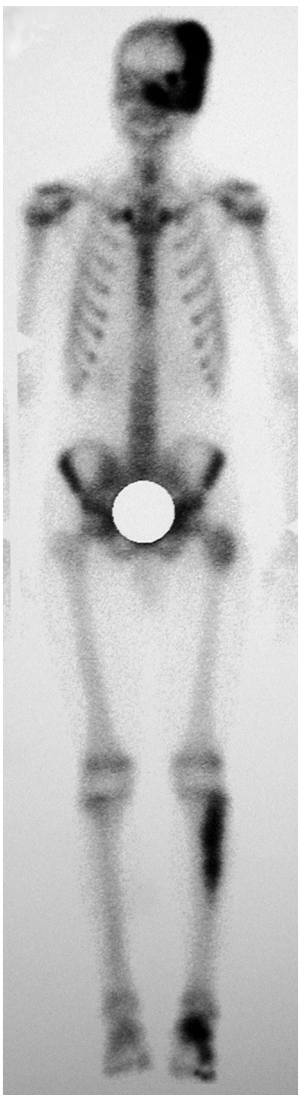

Figure 6 Bone scan of a patient with polyostotic disease affecting the left side of the cranium, acetabulum, proximal femur, tibia, and foot. (Copyright © Rakesh Donthineni-Rao, MD.)

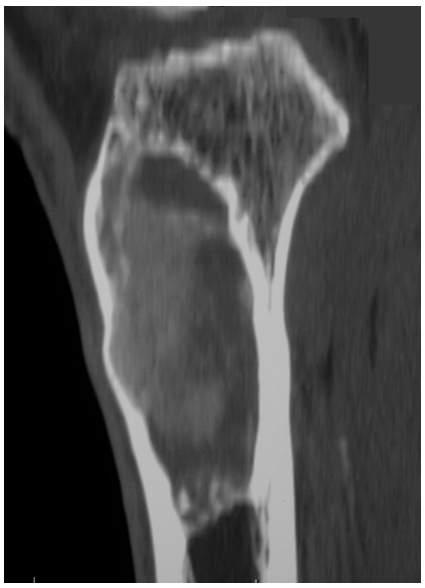

Figure 7 Sagittal CT scan of the proximal tibia affected by fibrous dysplasia. The matrix and the rind are well demonstrated. (Copyright © Rakesh Donthineni-Rao, MD.)

when stress fractures are suspected in symptomatic large lesions, although the scans need to be closely correlated with plain radiographs and possibly magnetic resonance imaging (MRI). Computed tomography (CT) accurately delineates the extent of lesions. Areas of ossification within the lesion may have high tissue attenuation, although the absence of such signals does not exclude the diagnosis of fibrous dysplasia. The appearance on CT varies in direct proportion to the extent of mineralization within the lesion but usually is similar to the density seen in normal cancellous bone (Fig. 7).

On MRI, the bone lesions have decreased signal on T1-weighted images and variable signal intensity on T2-weighted images.[32] The major benefit of MRI compared with other imaging modalities is that it allows for coronal and sagittal evaluation of the extent of bony involvement. Large lesions presenting over an extended period may undergo cystic degeneration. These cysts demonstrate high signal intensity on T2-weighted images, largely because of their high water content (Fig. 8). MRI is also very useful when malignant transformation is suspected, and these scans may show soft-tissue masses within or around the lesions of fibrous dysplasia or adjacent areas of aggressive bone destruction.

Histology

On gross examination, the lesions are centrally located and consist of fibrous, tan to gray gritty tissue. Hemorrhage and cystic change may be present. Microscopically, lesions are composed of a fibrous stroma that is usually avascular and of low cellularity. The predominant cells are fibroblasts that display a defect

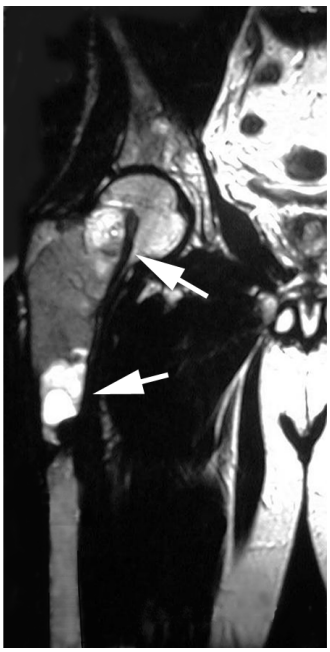

Figure 8 Coronal fat-suppressed T2-weighted MRI scan of the proximal femur. The fibrous component intermixed with bone trabeculae appear as similar or higher in signal intensity than muscle. Cystic degeneration is present in the proximal and distal parts of the fibrous dysplasia (arrows). (Copyright © Rakesh Donthineni-Rao, MD.)

in both proliferation and maturation. They lack atypia, and mitotic figures are infrequent. The stroma consists of fibroblastic spindle cells arranged in a pinwheel or storiform pattern, interspersed with irregularly shaped bony trabeculae. The trabeculae are composed of woven, immature bone that varies from round, solid islands to weaving, serpiginous, branching shapes (Fig. 9). The mixture of these shapes has been likened to Chinese characters or alphabet soup. Trabeculae vary in shape, size, and level of maturation, not only across different lesions but also in different areas of the same lesion.[4] The trabeculae are not lined with osteoblasts ("rimming"). Osteoclasts can be found on the concave side of the trabeculae. Older lesions may have secondary changes with a giant-cell fibrohistiocytic or cystic reaction and can confuse the histologic picture if not correlated with the radiographs.

Serologic Studies

Bone markers have been used to assess the activity of the disease and follow response to treatment. Total serum bone alkaline phosphatase and urine hydroxyproline are measures of bone remodeling. During the active phase of fibrous dysplasia, levels of both of these markers are elevated in approximately 75% of patients. Serum and urine concentrations of N-telopeptide (another marker of collagen breakdown) have been shown to decrease dramatically in response to bisphosphonate treatment.[33,34] Osteocalcin, urinary deoxypyridinoline, and the C-telopeptide of type I collagen breakdown products also are elevated in patients with fibrous dysplasia, although the role of these markers in assessing the activity of disease and response to treatment remains unclear.

Patients suspected of having McCune-Albright syndrome should have levels of testosterone, estradiol, and estrone measured because these may be elevated. Because the precocious puberty is independent of gonadotropin-releasing hormone, laboratory values of gonadotropin-releasing hormone, luteinizing hormone, and follicle-stimulating hormone may be lower than normal prepubertal concentrations.

Management

Management of fibrous dysplasia ranges from observation to surgical intervention. Asymptomatic lesions can be observed for progression. Surgery is indicated when the patient has progressive deformity, large lesions with pain, nonunion, failure of nonsurgical therapy, or malignancy. Pain and deformity are signs that microfractures are developing in a lesion and should be addressed. The healing callus also seems to make further dysplastic bone.

Many different surgical therapies have been used, with less success in younger patients, in those with larger or proximal femoral lesions, and in those with polyostotic disease, especially with McCune-Albright syndrome.[15,16,35] Curettage and bone grafting may work in smaller monostotic lesions, but success is limited in younger patients and in those with polyostotic disease.[15,16,35] Cancellous and occasionally cortical bone grafts may be rapidly incorporated and subsequently replaced with dysplastic bone. The success of grafting depends on the local healing response for remodeling the graft. Instead of creeping substitution with healthy normal bone, the cancellous bone grafts in fibrous dysplasia are completely replaced with the same poorly formed, immature woven bone.

Cortical strut grafts have a slower rate of incorporation and are beneficial as a structural support.[16] However, cancellous and strut grafts with and without implants are not always successful (Fig. 10). For example, a recent study by Guille et al[15] examining curettage and grafting in fibrous dysplasia of the proximal femur found that the disease was not eradicated in any femur, no lesion decreased in size after curettage and bone grafting, and all grafts, either cortical or cancellous, were resorbed. Although autografts are resorbed earlier than allografts, most bone grafts, regardless of type, are resorbed.

In their review of various treatments and outcomes of symptomatic lesions, Stephenson et al[36] noted that closed treatment or even curettage and bone grafting for upper extremity lesions led to a high number of satisfactory results. With closed methods or with curettage and bone grafting in the lower extremity, the outcome was more likely to be unsatisfactory in skeletally

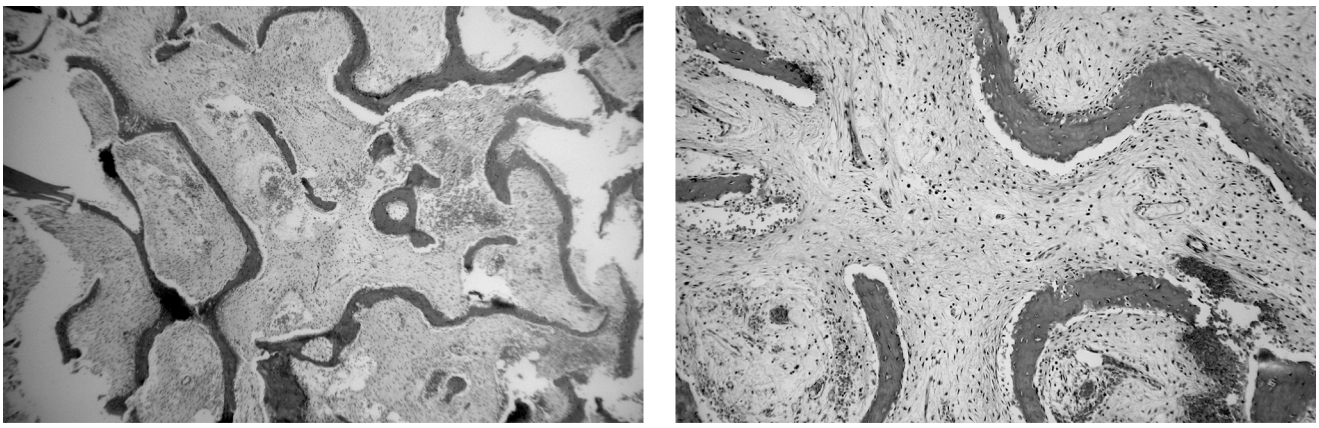

Figure 9 **A,** Low-power (40×) photomicrograph of a lesion in fibrous dysplasia shows the fine trabeculae of woven bone with the interspersed fibrous tissue (hematoxylin-eosin). **B,** High-power (100×) photomicrograph of a lesion (hematoxylin-eosin). (Copyright © Rakesh Donthineni-Rao, MD.)

immature patients (<18 years) than in mature patients. This was usually because of recurrent pathologic fractures. Open reduction and internal fixation improved the outcome in the immature patients.

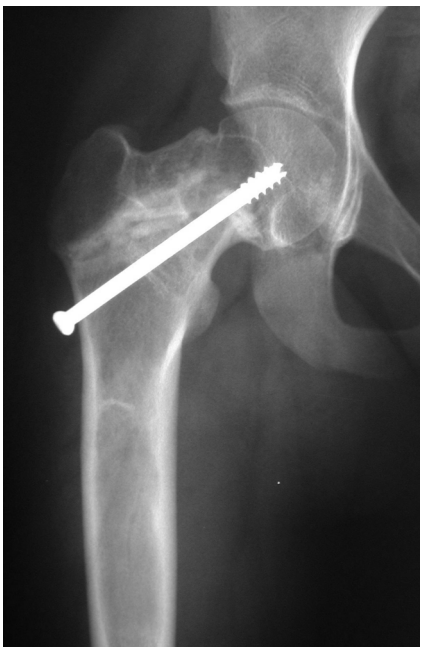

Figure 10 Anteroposterior radiograph of a pathologic fracture of the proximal femur treated with bone grafting and internal fixation. Only part of the graft seems to remain. (Copyright © Rakesh Donthineni-Rao, MD.)

Compression plates, intramedullary rods, dynamic hip screws, or any method of internal fixation can be used as needed to suit the anatomy of affected bones. Intramedullary rods are very useful for the long bones, and cephalomedullary fixation may be chosen for the proximal femur. Curetting the lesion and allograft bone grafting may be considered if the lesion is accessible.

Disease of the proximal femur in a young patient must be followed for progression because it may lead to microfractures and further deformity. Cases of microfracture or complete nondisplaced fracture may be managed by immobilization with a cast until healing occurs. Early detection and osteotomy with valgus realignment have been reported to have good outcomes.[15] Medial displacement osteotomy can be considered for patients with a shepherd's crook deformity, whereas valgus osteotomy can be considered in coxa vara. Internal fixation after osteotomy is necessary to achieve satisfactory results.

Large lesions or extensive disease that cannot be managed surgically can be managed with pharmacologic therapies that target osteoclasts. Because they successfully treat other conditions with excessive osteoclastic activity, such as Paget's disease, second-generation bisphosphonates may have a similar effect in fibrous dysplasia. Combined intravenous and oral bisphosphonates have improved cortical thickness, allowed progressive ossification of the lesion, decreased N-telopeptide levels and lesional diameters, improved function, minimized pain, and prevented pathologic fractures in fibrous dysplasia.[34] In several studies, bone pain and all markers of bone remodeling were reduced at a mean of 3 years of follow-up.[37-39] On plain radiographs, some lesions also have been noted to shrink.[34] A case report by Weinstein[40] showed that treatment with alendronate resulted in major improvements in bone quality, with filling of the lytic lesions and improved cortical thickness. Based on these reports, some have concluded that second- and third-generation bisphosphonates (alendronate, pamidronate, etidronate, risedronate, tiludronate), administered either intravenously or orally, can lead to partial resolution of fibrous dysplasia (especially in patients with generalized skeletal involvement).[35] Patients usually receive a course of intravenous pamidronate 180 mg over 3 days every 6 months.

Zoledronic acid can be administered over a shorter period intravenously. Zacharin and O'Sullivan[41] recommended that this treatment be continued for at least 2 years. In addition, patients should receive a daily dose of calcium and vitamin D to avoid secondary hyperparathyroidism.

Because of the severity of the disease and frequency of pathologic fractures, patients with McCune-Albright syndrome should be managed aggressively. Proximal femoral fractures are especially common in this group and lead to increasing varus deformity. A combination of internal fixation and intravenous bisphosphonate infusions has shown success.[42]

Summary

Fibrous dysplasia is a benign bone disease that primarily affects adolescents and young adults. The disease presents in either a monostotic or polyostotic form. Most patients are asymptomatic, and the lesions typically are found incidentally. Large lesions or the polyostotic form of fibrous dysplasia tend to be more symptomatic and present with pain, deformity, or fractures. The polyostotic form may be found in association with café-au-lait spots and endocrinopathies (McCune-Albright syndrome) or multiple soft-tissue myxomas (Mazabraud's syndrome). The etiology of fibrous dysplasia remains unclear, but recent molecular biology studies suggest that a mutation in the $G_s\alpha$ subunit leads to elevated intracellular cAMP levels and activation of c-*fos* and other proto-oncogenes within the lesions.

Fibrous dysplasia usually can be managed by observation. Large symptomatic lesions at risk of fracture may require a surgical procedure, such as curettage and bone grafting, with or without implants. Bisphosphonates are used for nonsurgical management when the disease cannot be managed surgically. The prognosis for fibrous dysplasia is generally good, although outcomes are poorer in young patients and those with the polyostotic forms.

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