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CURRENT CONCEPTS REVIEW

FIBROUS DYSPLASIA

PATHOPHYSIOLOGY, EVALUATION, AND TREATMENT

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- ▶ Fibrous dysplasia is a common benign skeletal lesion that may involve one bone (monostotic) or multiple bones (polyostotic) and occurs throughout the skeleton with a predilection for the long bones, ribs, and craniofacial bones.
- ▶ The etiology of fibrous dysplasia has been linked to an activating mutation in the gene that encodes the α subunit of stimulatory G protein ($G_s\alpha$) located at 20q13.2-13.3.
- ▶ Most lesions are monostotic, asymptomatic, and identified incidentally and can be treated with clinical observation and patient education.
- ▶ Bisphosphonate therapy may help to improve function, decrease pain, and lower fracture risk in appropriately selected patients with fibrous dysplasia.
- ▶ Surgery is indicated for confirmatory biopsy, correction of deformity, prevention of pathologic fracture, and/or eradication of symptomatic lesions. The use of cortical grafts is preferred over cancellous grafts or bone-graft substitutes because of the superior physical qualities of remodeled cortical bone.

Fibrous dysplasia is a benign intramedullary fibro-osseous lesion originally described by Lichtenstein¹ in 1938 and by Lichtenstein and Jaffe in 1942². The true incidence and prevalence of fibrous dysplasia are difficult to estimate, but the lesions are not rare; they are reported to represent approximately 5% to 7% of benign bone tumors^{3,4}. Fibrous dysplasia can present in one bone (monostotic) or multiple bones (polyostotic) and can be associated with other conditions (Table I). The lesions of fibrous dysplasia develop during skeletal formation and growth and have a variable natural evolution. Clinical presentation may occur at any age, with the majority of lesions being detected by the age of thirty years. The disease has no gender predilection. Common sites of skeletal involvement are long bones, ribs, craniofacial bones, and the pelvis.

Etiology and Pathophysiology

Fibrous dysplasia is postulated to occur as a result of a 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 process⁵. 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.

The etiology has been linked with a mutation in the $G_s\alpha$ gene that occurs after fertilization in somatic cells^{6,7} and is located at chromosome 20q13.2-13.3. All cells that derive from the mutated cells manifest the dysplastic features. The clinical presentation varies depending on where in the cell mass the mutation is located and the size of the cell mass during embryogenesis when the mutation occurs^{7,8}. 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 $G_s\alpha$ mutation was first identified in patients with McCune-Albright syndrome, a rare disorder that combines polyostotic fibrous dysplasia, skin pigmentation, and one of several endocrinopathies. The $G_s\alpha$ gene has also been linked to other endocrine tumors and human diseases⁷.

Weinstein et al.⁶ analyzed DNA from four patients with McCune-Albright syndrome and found that all four had mutations of the gene that rendered it active for the α subunit of the guanine-nucleotide binding protein ($G_s\alpha$) that inhibit GTPase activity and lead to constitutive activation of adenylate cyclase and increased cyclic adenosine monophosphate (cAMP) forma-

TABLE I Forms of Presentation of Fibrous Dysplasia

	Bone Involvement		Café au Lait Spots	Endocrine Disorders	Soft-Tissue Masses
	Single	Multiple			
Monostotic	X				
Polyostotic		X			
McCune-Albright disease		X	X	X	
Mazabraud disease		X			X

tion. Mutations were found within coding region 8 of the $G_s\alpha$ gene when polymerase chain reaction analysis was used to amplify the patients' genomic DNA. Other molecular studies were also used to screen for mutations. The specific location of the mutation is position 201, which usually is occupied by an arginine (R201) and is replaced by either a cysteine (R201C) or a histidine (R201H). In a multi-institution study in which similar techniques were used, Shenker et al.⁹ identified the mutation of residue Arg²⁰¹ of $G_s\alpha$ in three additional patients with McCune-Albright syndrome. The strongest evidence to support a genetic link to the etiology of fibrous dysplasia was found in an experimental study by Bianco et al.¹⁰, who isolated the $G_s\alpha$ genes from patients with McCune-Albright syndrome, transplanted them into immunocompromised mice, and induced dysplastic bone production. This in vivo cellular model of fibrous dysplasia illustrated the importance of both normal and mutant cells in the development of fibrous dysplasia. Marie et al.¹¹ showed that an activating mutation of $G_s\alpha$ in osteoblastic cells of patients with McCune-Albright syndrome and monostotic disease leads 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.

The increase in cAMP as a result of the genetic mutation has several so-called downstream effects. Yamamoto et al.¹² found increased levels of interleukin-6 (IL-6) in two patients with McCune-Albright syndrome. The $G_s\alpha$ mutation, which leads to increased intracellular cAMP content and increased IL-6 secretion, was identified in the genomic DNA of cultured fibroblastic cells from both patients. IL-6 may be responsible for the increased numbers of osteoclasts and the bone resorption seen in fibrous dysplasia. The increased expression of c-fos proto-oncogene seen in fibroblastic cells obtained from these lesions may be yet another downstream effector of cAMP and may be important in the pathogenesis of fibrous dysplasia.

Through genetic amplification techniques such as polymerase chain reaction, it is now possible to test for the genetic mutation in peripheral blood samples. In a recent study¹³, genomic DNA from peripheral blood cells of ten patients with McCune-Albright syndrome and three with isolated fibrous dysplasia were analyzed with a novel polymerase chain reaction-based method described by Bianco et al.¹⁰. All thirteen patients were found to have activating mutations in their genomic DNA. This novel technique may have application in the diagnostic and therapeutic monitoring of patients with fibrous dysplasia.



Fig. 1

Clinical photograph demonstrating the irregular "coast-of-Maine" café-au-lait spots on the thorax of a fourteen-year-old girl with McCune-Albright syndrome.

Natural History

The natural history of fibrous dysplasia depends on the form in which the lesion(s) presents. Monostotic presentation is more frequent, and lesions enlarge in proportion to skeletal growth¹⁴. The polyostotic form is less common. 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. Precocious development of secondary sexual characteristics is the most common endocrine presentation in patients with McCune-Albright syndrome¹⁴. Compared with bone lesions in patients without McCune-Albright syndrome, the skeletal lesions in patients with the syndrome tend to be larger, more persistent, and associated with more complications. Café au lait areas of skin pigmentation frequently are found about the trunk or the proximal parts of the extremities of these patients (Fig. 1). These areas have a variegated border that resembles the coast of Maine as opposed to the smooth-bordered (coast-of-California) café au lait areas characteristic of diffuse neurofibromatosis or von Recklinghausen disease. Another rare disorder seen with fibrous dysplasia is Mazabraud syndrome^{15,16}, in which skeletal lesions of fibrous dysplasia are combined with intramuscular myxomas.

In 1962, Harris et al.¹⁷ studied the natural history of fibrous dysplasia by retrospectively reviewing the records of ninety patients who had been treated over a thirty-year period at the Massachusetts General Hospital. Fifty-one patients, thirty-seven with polyostotic disease and fourteen with monostotic disease, met the inclusion criteria of the study. Seventy-one percent (thirty-six) of the patients had presented with a limp, pain, or a fracture, at a median age of ten years. The most common skeletal deformity was limb-length discrepancy, which was seen in twenty-two patients, thirteen of whom had a so-called shepherd's crook deformity of the proximal part of the femur. Two sarcomas (one osteosarcoma and one myxofibrosarcoma) developed in association with the fibrous lesions.

The European Paediatric Orthopaedic Society recently performed a multicenter clinicopathologic study to gain insight into the natural history of fibrous dysplasia¹⁸. Fifty-three patients from eleven centers were included. Twenty-three patients, with a mean age of fifteen years, had monostotic involvement; ten, with a mean age of eleven years, had polyostotic involvement; and twenty, 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. The other common areas of involvement were the tibia, humerus, rib, clavicle, and craniofacial skeleton. Fractures occurred in 50% of the patients with monostotic disease. A majority of the monostotic cases did not progress, and the long-term outcome was usually satisfactory in those cases regardless of treatment. Of the ten 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 ten patients

had limb-length discrepancy, ranging from 1 to 4.5 cm. All twenty patients with McCune-Albright syndrome had poly-melic skeletal disease. Six patients had an ipsilateral distribution and fourteen, a bilateral distribution. Moderate-to-severe scoliosis was identified with radiographic and bone-scan imaging in ten of the twenty patients. However, the scoliosis was attributed to multilevel vertebral fibrous dysplasia lesions in only three of the ten patients. Seventeen of the twenty patients had at least one fracture, and twelve had multiple fractures. Mutation analysis was performed in ten patients, nine of whom showed the G_{α} mutation. The authors recommended that the initial evaluation include genomic testing for activating G-protein mutations if there is any uncertainty about the diagnosis.

Patient Evaluation

Clinical Presentation

Incidental Finding

The majority of monostotic lesions are asymptomatic and are discovered when radiographs of the involved region are made for other indications^{14,17,18}.

Bone Pain

Localized pain may be the presenting symptom in patients with fatigue fractures in high-stress areas in dysplastic bone. This is particularly true with lesions in the femoral neck. In a clinicopathologic study, Nakashima et al.¹⁹ described the features of eight patients with monostotic fibrous dysplasia in the femoral neck. The age at presentation ranged from six to fifty-six years. Seven patients had pain, five had a limp, and one had a pathologic fracture.

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 dysplasia²⁰.

Deformity

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. The classic deformity of polyostotic fibrous dysplasia is the so-called shepherd's crook deformity of the proximal part of the femur (Fig. 2-A). The curve of the crook is reproduced radiographically and is reflected clinically by lateral bowing of the proximal part of the thigh, widening of the hip region, and shortening of the limb (Fig. 2-B). Structural deformation, with both expansion and weakness of the bone, can be caused by fibrous dysplasia. Deformation is postulated to be a result of intermittent fatigue fractures through the dysplastic bone, which deforms from normal mechanical forces.

Similarly, fibrous dysplastic lesions of the spine may cause scoliosis. Leet et al.²¹ reported that, in a study of sixty-two patients with polyostotic fibrous dysplasia, pain was an

uncommon symptom but 40% (twenty-five) of the patients had scoliosis. Frodel et al.²² reported that local expansion of fibrous dysplasia in the maxilla, zygomatic, or ethmoid bones of the face can produce substantial functional and cosmetic deformity.

Fatigue Fracture

Fractures through dysplastic bone heal promptly but do so with dysplastic bone; thus, after healing is complete, the lesion has virtually resumed its prefracture status. Undisplaced stress or fatigue fractures are common in areas of stress concentration within dysplastic lesions, with the most common site being the medial aspect of the femoral neck²³.

Pathologic Fracture

In some patients, fibrous dysplasia is first diagnosed at the time of a pathologic fracture through a previously unknown lesion. There are no strict criteria for determining which patients are at increased risk for pathologic fracture, and the decision to provide prophylactic intervention is multifactorial, as it is for patients with metastatic bone disease. One major difference between patients with fibrous dysplasia and those with bone metastasis is that, in the former group, the fixation needs to remain stable over a longer period of time because fibrous dysplasia is a benign disease and most individuals re-

quiring intervention are younger than thirty years old. 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; type, size, extent, and anatomical site of the lesion; and associated metabolic abnormalities. In a study of thirty-five patients with polyostotic fibrous dysplasia or McCune-Albright syndrome, Leet et al.²⁴ reported that 172 fractures (103 femoral, twenty-five tibial, thirty-three humeral, and eleven forearm) had occurred by the time of follow-up, at an average of 14.2 years (range, two to thirty-nine years). Twenty-seven patients had polyostotic fibrous dysplasia with one or more endocrinopathies (nineteen had precocious puberty; nine, hyperthyroidism; six, excess growth hormone; one, Cushing syndrome; and one, primary hyperparathyroidism) and/or phosphaturia, and eight patients had isolated polyostotic fibrous dysplasia. A patient was considered to have phosphaturia, or renal phosphate wasting, when the tubular maximum of phosphate reabsorption relative to the glomerular filtration rate was below the age and gender-specific normal range. Twelve patients were diagnosed with this condition. The peak fracture rate occurred between the ages of six and ten years and decreased thereafter. Patients



Fig. 2-A

Fig. 2-A Anteroposterior radiograph of the pelvis of a twenty-three-year-old woman with polyostotic fibrous dysplasia and classic shepherd's crook deformity. **Fig. 2-B** Clinical photograph of another patient with a shepherd's crook deformity on the left.



Fig. 2-B



Fig. 3-A

Fig. 3-A Lateral radiograph of the elbow of a skeletally mature individual with a radiolucent lesion in the proximal part of the radius. There has been expansile remodeling of the cortex, and the typical “ground-glass” appearance is present. **Fig. 3-B** Photograph of a glass bottle stopper, illustrating the hazy appearance of ground glass.



Fig. 3-B

with metabolic abnormalities sustained a pathologic fracture at an earlier age (6.9 compared with 16.6 years for those without metabolic abnormalities, $p < 0.005$) and had a higher lifetime risk of fracture (0.2 compared with 0.08 fractures per year). Phosphaturia was the metabolic dysfunction associated with the earliest age at the time of the first fracture and with the greatest lifetime fracture risk.

Wai et al. performed a review of eleven pathologic fractures of the proximal part of the femur secondary to benign bone lesions, seven of which were fibrous dysplasia lesions²⁵. They did not discuss the criteria to be used to determine which patients were at risk for fracture. Treatment was uniform and consisted of biopsy, intralesional curettage, high-speed burring, and reconstruction with use of morselized allograft, autograft, and a fixed-angle implant. The average duration of follow-up was longer than four years. All fractures healed, and there were no recurrences or cases of osteonecrosis. The authors advocated the use of a fixed-angled implant to provide a mechanical bypass for the structural lesions. They compared their 0% rate of recurrence with the 13.3% rate reported by Enneking and Gearen²⁶ in patients in whom an autogenous fibular cortical graft had been used to provide structural support. Guille et al.²⁷ reported a 66.6% rate of recurrence or microfracture in patients treated primarily with curettage and bone-grafting. Few patients in their series had adequate bone to support internal fixation, and most had pathologic fractures or microfractures at the time of the original operative treatment.

Radiographic Features

Plain Radiographs

The radiographic features of fibrous dysplasia vary widely²⁸. The normal bone is replaced by tissue that is more radiolucent, with a grayish “ground-glass” pattern that is similar to

the density of cancellous bone but is homogeneous, with no visible trabecular pattern (Figs. 3-A and 3-B). The radiolucent region is composed histologically of a solid fibro-osseous mass of tissue, which occasionally contains a cystic component with a fluid-filled cavity. The lesion characteristically is bounded by a distinct rim or shell of reactive bone that is defined more sharply on its inner border than on its outer border, where it may fade gradually into normal cancellous bone. The lesions arise within the medullary canal but consistently replace both cancellous and cortical bone, so that the usual sharp distinction between the cortex and the medullary canal is obscured. Often, the diameter of the bone is increased by growth of the lesion, but the lesion continues to be bounded by the shell of reactive bone. Variations in the cortical thickness are caused by slow resorption of the endosteal surface, commonly referred to as “endosteal scalloping.” The periosteal surface is smooth and without reaction.

Monostotic lesions mature after skeletal growth ceases. Their radiographic features reflect this maturation, with an increase in the thickness of the reactive rim about the lesion and in the density of the lesion itself. Individual polyostotic fibrous dysplasia lesions have the same radiographic characteristics as monostotic lesions. Because polyostotic lesions are larger, as a rule, they more commonly are accompanied by deformation. Frequently identified deformities include coxa vara, the shepherd’s crook deformity, bowing of the tibia, the Harrison groove (a horizontal depression along the lower border of the thorax, corresponding to the costal insertion of the diaphragm), and protrusio acetabuli¹⁷. When a patient is being evaluated for the first time, a radiograph of the pelvis and the proximal parts of the femora is the most valuable single survey radiograph for diagnosing polyostotic disease. Radiographs of lesions of a femoral neck in which a fatigue fracture is present often show two humps of reactive

bone on the medial cortex separated by a thin radiolucent line resembling a parrot's beak (Fig. 4).

Scintigraphy

At the initial presentation, radionuclide bone scintigraphy is useful to demonstrate the extent of the disease²⁹. Actively forming lesions in adolescents have greatly increased isotope uptake that corresponds closely to the radiographic extent of the lesion (Fig. 5-A). The isotope scan shows increased uptake throughout life, but the uptake becomes less intense as the lesions mature. Bone scintigraphy is sensitive for detecting lesions, but the tracer uptake is nonspecific. Some characteristic findings within lesions of fibrous dysplasia are a bar-shaped pattern, whole-bone involvement, and a close match between the size of the lesion on radiographs and the size of the area of uptake.

Computed Tomography

Computed tomography scanning is the best technique for demonstrating the radiographic characteristics of fibrous dysplasia (Fig. 5-B). The extent of the lesion is clearly visible on computed tomography, and the cortical boundary is depicted



Fig. 4
Anteroposterior radiograph of the hip of a twenty-two-year-old man who presented with a two-year history of hip pain. The radiograph demonstrates a fatigue fracture of the femoral neck with the characteristic "parrot's beak" deformity.

with more detail than is seen on radiographs or magnetic resonance images. The thickness of the native cortex, amount of endosteal scalloping and periosteal new bone reaction, and homogeneity of the poorly mineralized lesional tissue are demonstrated best with computed tomography imaging. As a result of its vascularity, the lesional tissue is enhanced with contrast medium.

Magnetic Resonance Imaging

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 computed tomography 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 a low water content, T1-weighted images have a low-intensity signal (Fig. 5-C). T2-weighted images have a higher-intensity signal that is not as bright as the signal of malignant tissue, fat, or fluid. Some heterogeneity may be seen secondary to islands of cartilaginous differentiation, areas of degenerative cysts, and areas of hemorrhage. In a study correlating characteristics on magnetic resonance imaging with radiopathologic findings, cystic regions were seen in two of thirteen lesions³⁰. These cysts demonstrate high signal intensity on T2-weighted images secondary to a high water content. The hypointense fibrous areas show moderate-to-marked enhancement following intravenous administration of gadolinium as a result of the multiple small vessels within this component of the lesion.

Gross 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. The lesion can be easily peeled away from the encircling shell of reactive bone by blunt dissection, and lesions rarely, if ever, penetrate the reactive shell and extend into soft tissue. The tissue can be cut with a scalpel and may bleed briskly when cut, as a result of its concentration of small vessels. If bleeding is a problem during a procedure, it can be controlled by rapid and complete curettage back to normal bone.

Histologic Features

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 (Fig. 6-A). The ratio of fibrous tissue to bone ranges from fields that are totally fibrous to those filled with dysplastic trabeculae. Examination of macrosections of intact lesions reveals the margins of the lesion to be separated from 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 trabeculae has been likened to “alphabet soup.” 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. 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 (Figs. 6-B and 6-C). These trabeculae, which fail to undergo remodeling, seldom contain cement lines. Multiple delicate capillaries are found throughout the lesion and, when injured, incite a giant-cell reactive process. Lobules of cartilage are infrequently seen and, when present, are composed of mature hyaline cartilage (Fig. 6-D).

Malignant Transformation

Malignant transformation of fibrous dysplasia occurs very infrequently, with reported prevalences ranging from 0.4% to 4%^{17,31-33}. Determining the incidence of this transformation is difficult. Many of the reports in the literature involve a single case or only a few cases^{34,35}. Reports from cancer clinics, while including more cases, may overestimate the true incidence of malignant transformation because the most difficult and complicated cases usually are referred to those centers. Also, many patients included in studies of malignant transformation have received radiation therapy, which increases the risk of malignant transformation.

In 1988, Yabut et al.³³ reported one new case of malignant transformation of fibrous dysplasia and reviewed a total of eighty-three cases reported in fifty-three papers in the literature.

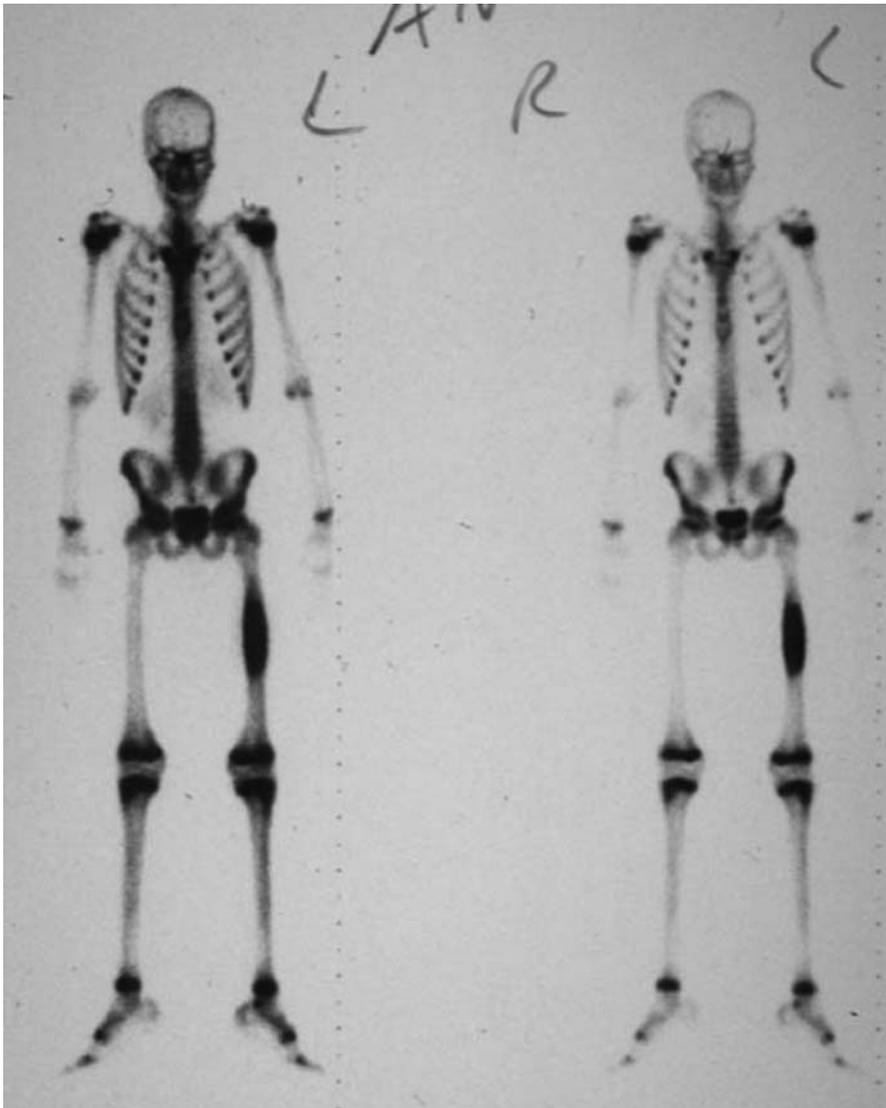


Fig. 5-A

Figs. 5-A, 5-B, and 5-C Radiographic features of fibrous dysplasia. **Fig. 5-A** Bone scan of a patient with an isolated increase in radiotracer uptake within the femoral lesion.

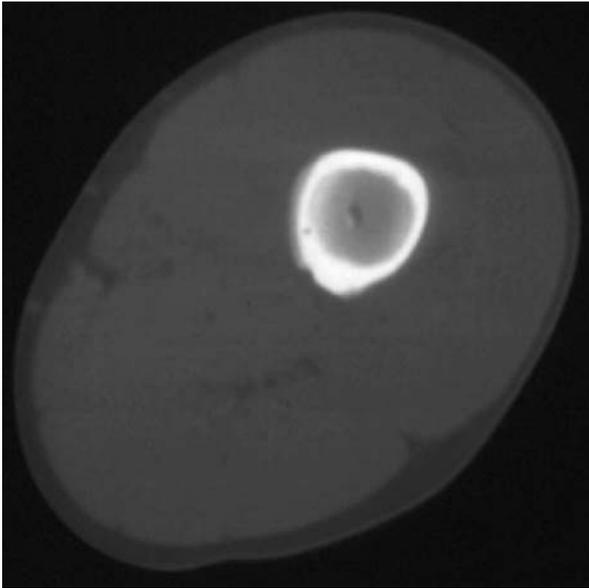


Fig. 5-B
Axial computed tomography scan demonstrating the "ground-glass" appearance of the lesion within the femoral diaphysis.

Forty-one patients had monostotic disease, thirty-one had polyostotic disease, and the type of disease was not specified for eleven patients. Forty-six patients had had no radiation exposure, twenty-three had received radiation therapy, and radiation therapy or the lack thereof had not been recorded for fourteen patients. The most common malignant tumors were osteosarcoma, fibrosarcoma, and chondrosarcoma. The majority of patients were older than thirty years of age when the sarcoma was diagnosed³¹⁻³³. The craniofacial region was the most common site of involvement, followed by the femur, tibia, and pelvis. Ruggieri et al.³¹ retrospectively reviewed the Mayo Clinic files and identified sarcoma in twenty-eight (2.5%) of 1122 patients with fibrous dysplasia. Of the 1122 patients, 12% (135) had polyostotic disease and the remainder (987 patients) had monostotic disease. Nineteen of the twenty-eight 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% (nineteen of 987 patients), whereas the rate for polyostotic lesions was 6.7% (nine of 135 patients). The histologic subtypes included nineteen osteosarcomas, five fibrosarcomas, three chondrosarcomas, and one malignant fibrous histiocytoma. Forty-six percent (thirteen) of the twenty-eight patients with a sarcoma had had previous radiation exposure. The interval between the radiation therapy and the diagnosis of the sarcoma ranged from three to fifty-two years (mean, nineteen years). In most cases, the dose of radiation was unknown. The second largest reported series of patients treated at one institution was seen at Memorial Sloan-Kettering Cancer Center, where Huvos et al.³² identified fifteen patients with fibrous dysplasia who had a secondary sarcoma. In contrast to the other reports, only one of these fifteen patients had documented exposure to radiation therapy.

Patients with Mazabraud syndrome may have a higher risk of malignant transformation. Recently, a case of sarcomatous degeneration in a patient with Mazabraud syndrome was reported³⁶. This was the third sarcoma to be documented in the thirty-six cases of Mazabraud syndrome described in the literature, so the rate of malignant transformation in such patients is 8.3%. None of the three patients had had radiation exposure.

Treatment is based on the histologic subtype of the sarcoma, but the prognosis tends to be worse for patients with malignant transformation than it is for those with a similar primary sarcoma not associated with fibrous dysplasia. The mean survival period is 3.4 years from the time of diagnosis³³.

Differential Diagnosis

Lesions that may suggest fibrous dysplasia include simple bone cysts, nonossifying fibromas, osteofibrous dysplasia, adamantinoma, low-grade intramedullary osteosarcoma, and Paget disease.

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. The greater density of fibrous dysplasia and its homo-

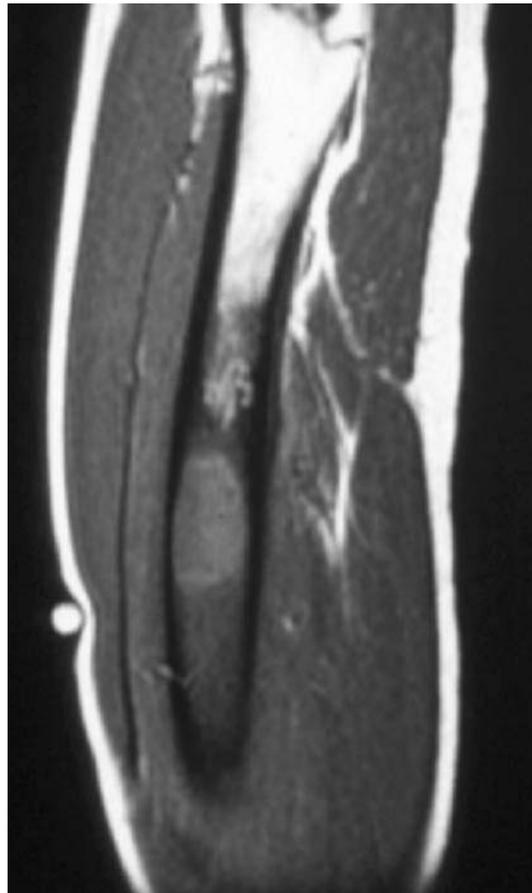


Fig. 5-C
Sagittal T1-weighted magnetic resonance image of the same lesion, showing primarily a low signal intensity.

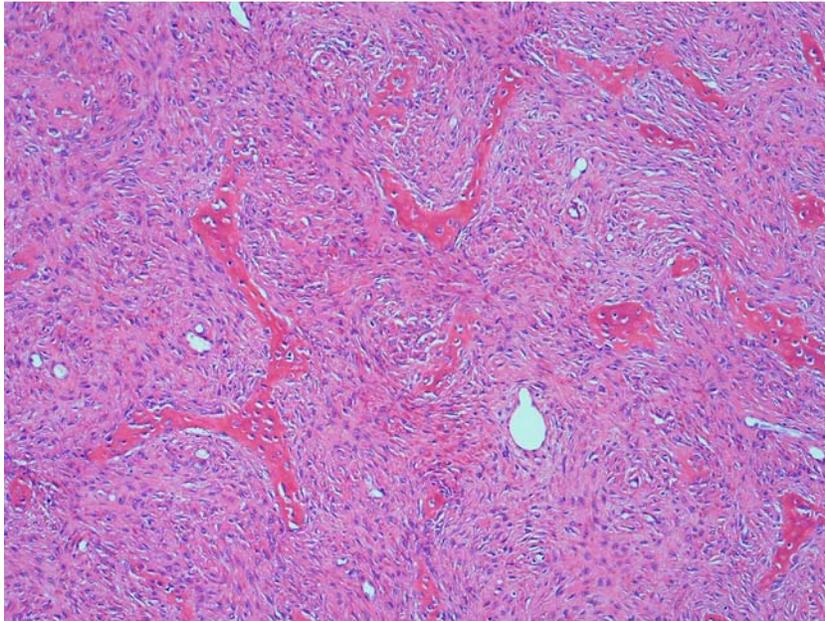


Fig. 6-A

Figs. 6-A through 6-D Histologic features of fibrous dysplasia. **Fig. 6-A** A panoramic photomicrograph of a specimen from a fibrous dysplasia lesion, showing the characteristic pattern of disconnected, bizarrely contoured dysplastic trabeculae enmeshed in primitive mesenchymal cells (hematoxylin and eosin, $\times 100$).

geneous “ground-glass” texture can often be revealed by computed tomography. 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.

Nonossifying fibromas are common benign fibrous lesions of bone⁴. They originate eccentrically in the growing

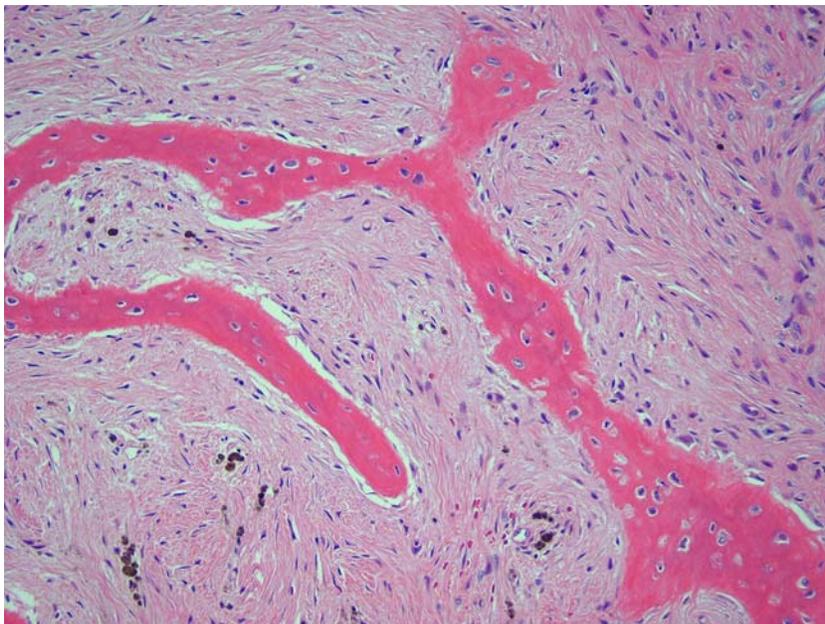


Fig. 6-B

The mesenchymal stroma surrounding the dysplastic trabeculae is relatively hypocellular. There is a lack of osteoblastic rimming surrounding the dysplastic trabeculae. Both features are characteristic of fibrous dysplasia (hematoxylin and eosin, $\times 200$).

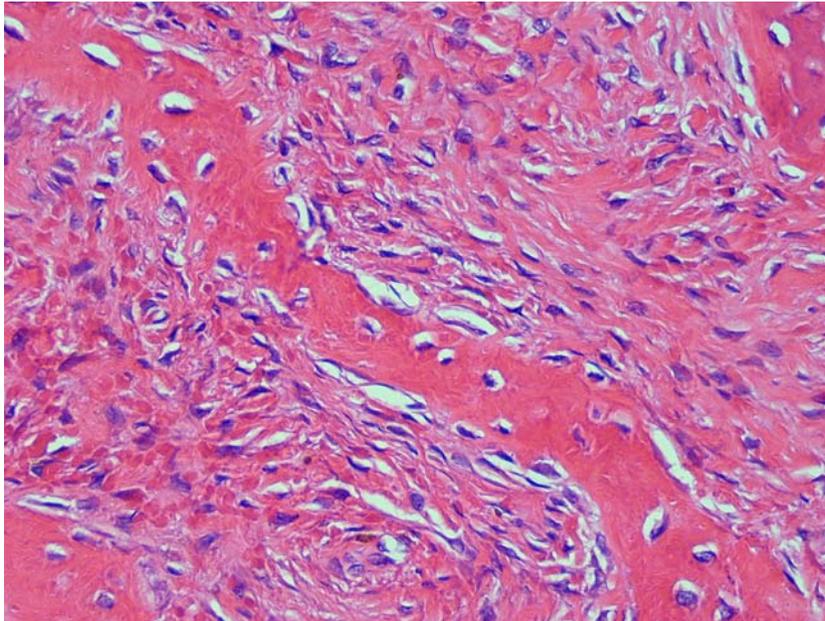


Fig. 6-C

Higher magnification emphasizes the lack of osteoblast rimming and wide osteoid seams (hematoxylin and eosin, $\times 400$).

metaphysis, are usually asymptomatic, and spontaneously regress with age. Large lesions in weight-bearing long bones occasionally present with a pathologic fracture that readily heals with immobilization³⁷. The radiographic picture is usually diagnostic, without a need for a biopsy. Nonossifying lesions start as small, osteolytic, frequently intracortical lesions in the metaphyseal region of bone. With skeletal growth, they become elon-

gated with the long axis oriented parallel to the length of the bone, and they generally have a scalloped appearance. After skeletal maturity, the lesion ceases to enlarge and gradually ossifies. Nonossifying fibromas can be distinguished from fibrous dysplasia by their intracortical origin, smaller size, lack of intralesional ossification, and spontaneous regression.

Osteofibrous dysplasia, or ossifying fibroma, first identi-

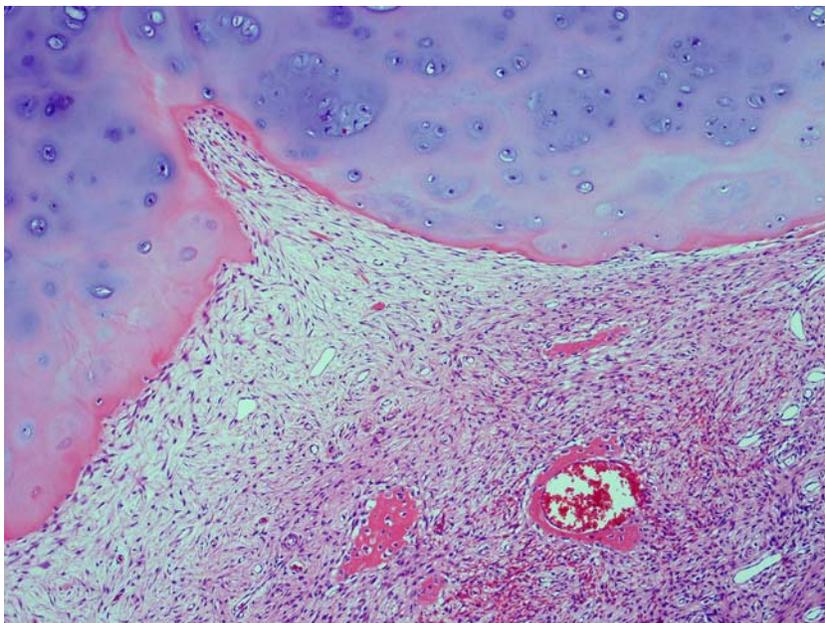


Fig. 6-D

A field of mature hyaline cartilage is shown adjacent to a bland fibrous stroma (hematoxylin and eosin, $\times 100$).

fied as a distinct entity in 1976 by Campanacci³⁸, is a rare lesion localized almost exclusively to the distal third of the tibia or fibula. It usually is identified in children younger than ten years of age, and it has a remarkable radiographic resemblance to fibrous dysplasia. One key radiographic difference is that osteofibrous dysplasia usually has an intracortical location as opposed to the more central distribution of fibrous dysplasia³⁹. 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. Sakamoto et al.⁴⁰ utilized polymerase chain reaction-restriction fragment length polymorphism analysis of paraffin-embedded tissues to compare fibrous dysplasia and osteofibrous dysplasia with regard to $G_s\alpha$ mutation at the Arg²⁰¹ codon. All seven patients with fibrous dysplasia in that study showed missense point mutations in the $G_s\alpha$ at the Arg²⁰¹ codon that resulted in Arg-to-His substitution in three cases and Arg-to-Cys substitution in four. None of the seven patients with osteofibrous dysplasia or normal bone showed the mutation. The 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.⁴¹ demonstrated that bone-lining cells in fibrous dysplasia are negative for proliferating cell nuclear antigen expression, whereas osteoblasts in osteofibrous dysplasia are positive.

Adamantinoma is a low-grade sarcoma found almost exclusively in the anterior aspect of the tibia⁴². Its two distinct histiogenic components include an epithelioid component of epithelial histogenesis and a fibro-osseous component of mes-

enchymal 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 dysplasia⁴². A biopsy is often needed to differentiate between the two lesions. Maki and Athanasou⁴³ recently investigated the relationship between adamantinoma and osteofibrous dysplasia by using histochemistry to analyze the expression of several proto-oncogene products and extracellular matrix proteins in specimens from twenty-five tumors (eighteen osteofibrous dysplasias, three differentiated adamantinomas, and four classic adamantinomas). Results were correlated with histologic and ultrastructural findings. 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 intramedullary (central) osteosarcoma is a rare variant, accounting for only 1% of all osteosarcomas^{44,45}. A retrospective review of the cases of ten patients at the Rizzoli Institute demonstrated the complexity of diagnosing these lesions; radiographic analysis suggested a benign lesion in three of the ten patients, with two of the three appearing to have fibrous dysplasia⁴⁴. Despite the marked similarities between low-grade central osteosarcoma and fibrous dysplasia, distinction may be made on the basis of lack of a reactive shell, permeative borders, denser mineralization, and more aggressive changes over time in low-grade central osteosarcoma.



Fig. 7-A

Figs. 7-A and 7-B Examples of fibrous dysplasia of the femoral neck treated with fibular grafting. **Fig. 7-A** Preoperative and postoperative radiographs of a patient treated with dual fibular autografts.

TABLE II Commonly Used Bisphosphonates and Dosages

Drug Name	Form of Administration	Dosage (mg)	Frequency of Treatment
Alendronate (Fosamax)	Oral	10	Daily
		70	Weekly
Pamidronate (Aredia)	Intravenous	180	Every 6 mo
Etidronate (Didronel)	Oral or intravenous	Weight-based	Daily (not for >6 mo)

Paget 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 with a Northern European ancestry. Radiographic features can vary, but on occasion the resorptive phase of Paget disease may resemble fibrous dysplasia. Juvenile Paget disease, or hereditary hyperphosphatasia, is a rare form of Paget disease that usually appears in infancy or early childhood, and it can even be present at birth⁴⁶. This disorder affects virtually every bone in the body, and its effects are seen easily on radiographs. The disorder is characterized by a generalized widening and often bowing of the long bones and thickening of the skull⁴⁷. It is readily distinguishable from fibrous dysplasia by the accompanying marked elevation in the serum alkaline phosphatase level.



Fig. 7-B
Fifteen-year follow-up radiograph of the proximal part of the femur in a patient treated with a fibular allograft for monostotic fibrous dysplasia. (See Fig. 4 for the preoperative radiograph.) Persistence of the graft and substantial ossification of the lesion are well visualized.

Treatment

Observation and Patient Education

Many lesions are discovered incidentally on radiographs and are asymptomatic. If the radiographic findings are characteristic of fibrous dysplasia, a biopsy is not indicated. Such lesions ordinarily pose no risk for pathologic fracture or deformity, and only clinical observation is warranted. Follow-up radiographs should be made every six months to verify that there has been no progression. In newly identified cases, a bone scan is needed to exclude a diagnosis of polyostotic disease. When polyostotic disease is found, a referral to an endocrinologist for endocrine and metabolic testing is paramount so that associated endocrine abnormalities can be diagnosed and treated early.

Bisphosphonates

As a result of the radiolucency of fibrous dysplasia and despite the absence of histologic evidence of abnormal osteoclastic activity, bisphosphonate therapy has been utilized for patients with symptomatic polyostotic disease, as it has been used for metabolic bone disorders such as Paget disease and high-turnover osteoporosis (Table II). Bisphosphonates, primarily pamidronate, have been used most extensively for patients with polyostotic disease. Many authors can be credited with reporting the initial European experience with bisphosphonate therapy for patients with fibrous dysplasia⁴⁸⁻⁵⁰. Pamidronate is a second-generation bisphosphonate that has had documented success in selected patients with the disease. It is a potent inhibitor of bone resorption and has a lasting effect on bone turnover. Liens et al.⁴⁹ reported the short-term effects of pamidronate in nine patients, eight with polyostotic and one with monostotic disease. All patients were treated with intravenous infusions of pamidronate over three days, with a total dose of 180 mg (60 mg/day), repeated every six months, supplemented with calcium (500 to 1500 mg/day) and vitamin D (800 to 1200 IU/day). Each infusion was administered over a four-hour period. The mean duration of follow-up was twenty-six months. The major effect was decreased bone pain, with the pain intensity at each painful site classified as none, moderate, or severe. Before treatment, the nine patients had a total of fourteen painful sites, eight of which were severely painful and six, moderately painful. Pamidronate decreased the pain intensity in all patients, with the pain completely resolving at twelve sites and decreasing from severe to moderate at the other two. Radiographic changes, consisting of thickening of cortices and/or ossification of radiolucent areas, were seen in four patients. Side effects were transient fever in three patients, symptomatic hypocalcemia in two, and transient diffuse bone pain in two.

A follow-up, open-label, phase-III study of the long-term effects of intravenous pamidronate in twenty patients with fibrous dysplasia (two with monostotic disease) was performed in 1997⁴⁸. All patients received 180 mg of intravenous pamidronate every six months. At the time of follow-up, at an average of thirty-nine months, there was a significant reduction in the severity of bone pain ($p = 0.007$ to 0.04) and the number of painful sites ($p = 0.006$ to 0.02). All biochemical markers of bone-remodeling (levels of serum alkaline phosphatase, fasting urinary hydroxyproline, and urinary type-I collagen C-telopeptide) were lowered substantially. Radiographs showed filling of radiolucent lesions in nine patients. One patient had a transient mineralization defect, defined as increased osteoid volume or widened osteoid seams similar to those seen in rickets. Twenty-four months after cessation of treatment, these lesions were seen to be healed radiographically. Young patients receiving pamidronate should be monitored with serial radiographs to check for a transient mineralization defect, which presents as increased growth plate thickness.

A potentially more serious reaction has been identified recently. In December 2004, the FDA (Food and Drug Administration) and Novartis issued a warning concerning reports of osteonecrosis of the jaw, mainly in patients with cancer, related to intravenous zoledronic acid⁵¹. A dental examination with appropriate preventative dentistry is recommended prior to treatment with bisphosphonates in patients with concomitant risk factors such as cancer, chemotherapy, corticosteroids, and/or poor oral hygiene.

Lane et al.⁵² evaluated six patients in whom fibrous dysplasia had been treated with oral bisphosphonates, with four patients receiving a loading dose of pamidronate followed by 10 mg of alendronate orally each day and the other two receiving only the alendronate therapy. The mean age of the patients was forty-five years. After a minimum of two years of follow-up, all six patients had clinical improvement, with an average decrease in the pain scores of 74%. There was no difference between the patients treated with oral therapy alone and those treated with oral therapy and a loading dose. No new pathologic fractures developed during the follow-up period, and all patients had improved function. Four of the six patients had improvement in the radiographic findings, with cortical thickening (>2 -mm increase), progressive ossification of the lesion, and a $>20\%$ decrease in the diameter of the lesion. The authors concluded that second and third-generation bisphosphonates already in use for diverse bone diseases offer promise for the treatment of fibrous dysplasia.

Several other studies have shown clinical improvement in both children and adults treated with bisphosphonate therapy⁵³⁻⁵⁶. A few studies have demonstrated improved bone density with pamidronate therapy in patients with fibrous dysplasia^{55,57-59}. Monitoring markers of bone turnover (N-telopeptide and alkaline phosphatase) at six-month intervals and bone mineral density yearly during treatment is a means of assessing the efficacy of bisphosphonate therapy.

Surgical Indications

Writing about fibrous dysplasia more than sixty years ago, Lichtenstein and Jaffe stated: "No hard and fast rule can be laid down for treatment of the lesions in bone . . . a solitary lesion uncovered only incidentally in the course of a routine physical examination can in many instances safely be left entirely alone after the diagnosis has once been established, perhaps with the aid of a biopsy. In a case of polyostotic involvement, it is again only such lesions as are causing difficulty that really require attention."² The age of the patient and the location, size, and biological behavior of the lesion all influence the selection of the therapeutic intervention^{28,29,60}. Open biopsy is seldom necessary, but it may be indicated to confirm the diagnosis when there is a nonclassic presentation. Surgical procedures may be required for correction of a deformity, prevention of pathologic fracture, and/or eradication of symptomatic lesions. Patient age is important because monostotic lesions remain active only until skeletal maturity, whereas polyostotic lesions may progress during adulthood. Patients with upper-extremity lesions often can manage well, with little functional or symptomatic disability, if they are treated with observation only, but surgical intervention is required for many comparable lower-extremity lesions to relieve symptoms and/or restore function.

In 1973, Funk and Wells²³ noted that, in children, a polyostotic lesion involving the proximal part of the femur was usually more complex than a comparable monostotic lesion. They also observed that, when polyostotic disease was severe, it was difficult to correct deformity, even with an osteotomy or repeated autogenous cancellous bone-grafting, and complete excision of the intertrochanteric area was therefore necessary.

Stephenson et al.⁶⁰ performed a retrospective review of sixty-five symptomatic lesions in forty-three patients treated between 1954 and 1984. Twenty-four patients had a monostotic lesion, and nineteen had polyostotic lesions. The average duration of follow-up was 10.4 years (range, two to fifty-five years). Most patients presented with pain or pathologic fracture, and the average age at presentation was fifteen years for the patients with monostotic disease and thirteen years for those with polyostotic disease. Patients were treated with one of four methods: observation, curettage and bone-grafting, internal fixation, or excision or amputation. The sixty-five symptomatic lesions required a total of 130 separate operative procedures. Twenty-one lesions in the upper extremities were treated a total of twenty-four times. Fifteen of them were treated with observation, and fourteen of the fifteen had a satisfactory result, regardless of their age or whether the disease was monostotic or polyostotic. Eight lesions underwent curettage and bone-grafting, and one was treated with internal fixation. Of the ten lesions involving the upper extremity in skeletally mature patients (eighteen years of age or older), nine had a satisfactory result. Of the fourteen upper-extremity lesions in skeletally immature patients (younger than eighteen years old), twelve had a satisfactory outcome. The outcomes were not as good in the skeletally immature patients with a lower-extremity lesion, with only four (13%) of thirty-two treated with closed fracture management

and six (19%) of thirty-one treated with curettage and bone-grafting having a satisfactory result. Internal fixation resulted in a satisfactory outcome in eighteen (86%) of the twenty-one skeletally immature patients with a lower-extremity lesion.

A majority of the orthopaedic literature on fibrous dysplasia focuses on its treatment in the proximal part of the femur, a common site of involvement in a region of high mechanical forces prone to fracture or deformity when weakened by dysplastic bone. Simple curettage and nonstructural cancellous bone-grafting in active lesions are not likely to correct deformity or relieve symptoms. These goals and the restoration of function are more likely to be achieved by osteotomies and procedures utilizing fixed-angled internal-fixation devices and/or cortical allografts to add mechanical strength to the affected bone(s).

Several authors who have evaluated small numbers of patients have reported exclusively on the treatment of fibrous dysplasia of the femoral neck^{17,19,23}. Nakashima et al.¹⁹ reviewed the cases of eight patients with monostotic disease of the femoral neck treated with curettage and autogenous bone-grafting. Although the lesion resolved in six patients, the authors did not report the sizes of the lesions or the type of graft, and the patients' ages ranged from six to fifty-six years. Harris et al.¹⁷ reported on ten patients with a femoral neck lesion, all of whom were treated with curettage and autogenous bone-grafting. Four had a good result; one, a fair result; and five, a poor result. Both patients who were treated prior to puberty had recurrence of the lesion and progressive deformity.

Guille et al. reported on a larger series of lesions treated with curettage and autogenous cancellous bone-grafting²⁷. Their series of twenty-two patients (twenty-seven femora) is, to our knowledge, the largest published series in which the long-term outcomes of treatment of biopsy-proven fibrous dysplasia of the proximal part of the femur were studied. Nine patients with monostotic disease had an average age of 8.1 years (range, 4.3 to 14.2 years) at diagnosis and were followed for an average of 13.6 years (range, 2.5 to 28.5 years). The presenting symptoms in all of those patients consisted of pain and/or an antalgic limp, presumably due to a fatigue fracture of the femoral neck. Thirteen patients with polyostotic disease had an average age of

7.8 years (range, 1.5 to 13.9 years) at diagnosis. All patients presented with pain and/or a limp, and eleven had evidence of a fatigue fracture on radiographs. The average duration of follow-up for this group was fifteen years (range, two to 41.3 years). At the time of the last follow-up, complete resorption of all autogenous cancellous bone grafts was observed radiographically. None of the lesions had been eradicated or were decreased in size. However, twenty patients (twenty-four femora) had no fracture or incapacitating pain. Two patients (three femora) had an unsatisfactory clinical result. One of those patients had bilateral disease as well as involvement of most of the skeleton, and the other had a 12-cm limb length discrepancy and a recurrent shepherd's crook deformity.

The high prevalence of resorption of autogenous cancellous bone grafts and persistence of the dysplastic lesions led to treatment with cortical grafts. In 1986, Enneking and Gearen²⁶ reported their experience with fifteen patients who had a symptomatic lesion of the femoral neck, twelve of whom had a radiographically evident fatigue fracture treated with autogenous cortical bone-grafting. The study group consisted of six male and nine female patients with an age range of nine to thirty-two years at the time of the grafting. Ten patients had only one lesion, and five patients had more than one lesion; one of the five had an endocrinopathy. The duration of follow-up averaged six years (range, two to fourteen years). A cortical graft was used only in patients who had sufficient normal bone in both the proximal (femoral head) and distal lateral cortex of the proximal part of the femur to anchor the graft at both ends in normal bone. The continuity and integrity of the grafts were visible on the final follow-up radiographs made of all fifteen patients (Figs. 7-A and 7-B). However, two patients had had slow resorption of the initial graft, with the development of pain and a fatigue fracture, and had required a second cortical graft. Both of these patients remained asymptomatic five years after the second operation. Ten of the fifteen patients had a decrease in the size of and substantial reossification within the lesion.

Choice of Bone Grafts (Table III)

Simple curettage is associated with a high risk of recurrence,

TABLE III Characteristics of Bone Grafts and Common Bone-Graft Substitutes

Type of Bone Graft	Mechanical Support	Osteoconductive	Osteoinductive	Potential for Graft Material to be Replaced by Dysplastic Bone*
Autograft cancellous		X	X	XXX
Allograft cancellous		X	X	XXX
Autograft cortical	X	X	X	XX
Allograft cortical	X	X		X
Demineralized bone matrix		X	X	XXXX
Calcium sulfate		X		XXXX
Coral		X		?

*X = lowest potential, and XXXX = highest potential.

as is curettage with use of autogenous cancellous bone graft. As internal repair and remodeling begin, the graft of normal bone is replaced gradually by dysplastic bone and, in many instances, the cavity eventually reverts to its preoperative status. Recurrence of fibrous dysplasia following curettage is more common in children than in adults.

Cortical autogenous grafts, used to replace curetted cavities or inserted through dysplastic lesions to strengthen them against fracture, persist much longer than do cancellous grafts. In the normal repair of a cortical bone graft, only the osteonal portion (approximately 50% of the graft) is replaced by dysplastic host bone, whereas the interstitial lamellae (the remaining 50%) are not replaced and persist. Because cortical allogeneic grafts have the least and slowest internal replacement by host bone, more of the graft persists for longer. This makes fibrous dysplasia one of the few diseases for which allogeneic grafts are biologically preferable to autogenous grafts.

Vascularized bone grafts also provide a safe and reliable means of ensuring good continuity of bone with little risk of recurrence or failure. There is a limited role for such grafts in the benign lesions of fibrous dysplasia because of the surgical morbidity of harvesting the graft and the surgical expertise and time required. Nonetheless, they remain an important option in a surgeon's armamentarium for the treatment of fibrous dysplasia⁶¹.

Correction of Deformity

Anterior bowing of the tibia (saber shin) and lateral bowing of the proximal part of the femur (shepherd's crook deformity) are common deformities, are often symptomatic, and may require correction. It is better to postpone treatment until skeletal maturity, if this is practical, because of the risk of recurrence with subsequent growth. Osteotomy sites heal with dysplastic bone, as do fractures, making recurrence of the deformity a serious risk. In addition, the poor physical qualities of dysplastic bone make conventional internal fixation devices less effective. For this reason, intramedullary fixation extending into uninvolved bone is the most effective means of maintaining corrective osteotomy sites and preventing recurrence of deformity.

In the study by Guille et al.²⁷, a valgus osteotomy was performed when the proximal part of the femur had a progressive varus deformity that reached $\geq 10^\circ$. When the lesion was more extensive and involved the calcar or when bone quality prohibited use of internal fixation, a medial displacement valgus osteotomy was performed. These later features were seen only in patients with polyostotic bone involvement. Osteotomy was performed in four of nine patients with monostotic disease and nine of thirteen patients with polyostotic disease. Twenty of the twenty-two patients had a satisfactory clinical result. Two patients with endocrinopathy had an unsatisfactory result and a femoral neck-to-shaft angle of $< 90^\circ$ at the time of the most recent follow-up evaluation. The authors advocated correction of varus deformity of the proximal part of the femur with a valgus osteotomy (with a desired

neck-shaft angle of $> 130^\circ$ for overcorrection) and internal fixation early in the course of disease.

Connolly⁶² and Freeman et al.⁶³ reported on five patients with extensive polyostotic fibrous dysplasia in whom a proximal femoral deformity extending well distal to the femoral neck had been treated with multiple osteotomies and intramedullary Zickel nail fixation. The Zickel nail allowed stabilization of the entire femur and femoral neck, with fewer failures of fixation or progressive deformities. Recently, Ippolito et al.⁶⁴ reported on patients with polyostotic fibrous dysplasia who had been operated on for correction of long-bone deformity or fixation of a shaft fracture. Ten femora, three tibiae, and one humerus in seven patients were stabilized with intramedullary nailing. The average age was seventeen years (range, eight to thirty years) at the time of surgery. Prior to nailing, the patients had sustained an average of six fractures (range, three to twelve fractures). The mean duration of follow-up was two years (range, 0.67 to four years), and no patient had an additional fracture after the intramedullary fixation.

Combined Treatment

O'Sullivan and Zacharin⁵⁹ reported on five patients with McCune-Albright syndrome who had been treated with bisphosphonates and surgical correction with elongating intramedullary devices to manage femoral and tibial lesions. The mean duration of follow-up was eighteen months. The quality of life improved for all patients, with decreased pain scores, a decreased fracture rate, and improved walking ability. Two patients who had been wheelchair-dependent before treatment gained the ability to walk about the community.

An instrument for measuring the skeletal burden of fibrous dysplasia and predicting the functional outcome was tested and validated recently by Collins et al.⁶⁵. Weighted scores based on the amount of fibrous dysplasia measured on bone scintigraphs in anatomical segments are combined with results from questionnaires that assess function. To validate the interpretations of the scintigrams, six observers scored twenty scans twice. The interobserver and intraobserver agreements were $r = 0.96$ and 0.98 , respectively. Seventy-nine patients were enrolled in the study, and childhood and adult scans were available for six patients. Pamidronate treatment had no effect on the scores. Skeletal burden scores correlated with bone markers, quality of life, and walking status. Childhood scores of > 30 predicted a need for assistance with walking in adulthood.

This instrument may be useful for determining the most appropriate operative procedure for a patient. Patients with a low score might be spared procedures that are not strictly necessary as they are unlikely to change long-term results. Conversely, when the score is high, early excision of the lesion and fixation of the bone might prevent the more severe deformity that could result from a series of operative procedures. In other cases, a realistic prediction of impairment in adulthood might prevent the patient from experiencing repeated emotional and physical setbacks and allow realistic planning for the future.

Overview

Fibrous dysplasia is a benign skeletal lesion that can involve one or more bones. Its etiology has been linked to an activating mutation of G_{α} and the downstream effects of the resultant increase in cAMP. Polyostotic lesions tend to be larger than monostotic lesions and result in more skeletal complications, including pain, deformity, and fractures. Some patients with polyostotic bone involvement also have skin lesions and endocrinopathies (McCune-Albright disease) or multiple myxomas (Mazabraud syndrome). Monostotic lesions frequently are discovered incidentally and require only clinical observation. Confirmatory biopsy is indicated if the radiographic findings are not characteristic of fibrous dysplasia. Bisphosphonates have been shown to offer pain relief and improve skeletal strength in appropriately selected patients with either polyostotic or monostotic fibrous dysplasia. Occasionally, operative treatment is needed to correct deformity or to prevent or stabilize a pathologic or fatigue fracture. Cortical allograft or intramedullary fixation of the entire long bone provides the best material properties for patients who require operative intervention.

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