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Chapter 89. Fibrous Dysplasia

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INTRODUCTION

Fibrous dysplasia of bone (FD; OMIM 174800) is an uncommon skeletal disorder with a broad spectrum of clinical expressions, ranging from an incidentally discovered asymptomatic

radiographic finding, involving a single skeletal site, to a severe disabling disease. The disease may involve one bone (monostotic), multiple bones (polyostotic FD), or even the entire skeleton (panostotic FD). In polyostotic disease, lesions of dif-

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ferent limb bones are often (but not necessarily) ipsilateral.^(1,2) FD may be associated with extraskeletal lesions or dysfunction, most commonly cutaneous hyperpigmentation (Figs. 1A and 1B), and hyperfunctioning endocrinopathies, including precocious puberty, hyperthyroidism, growth hormone (GH) excess, and Cushing syndrome. FD in combination with one or more of the extraskeletal manifestations is known as McCune-Albright syndrome (MAS).⁽³⁾ A renal tubulopathy, which includes renal phosphate wasting, is one of the most common extraskeletal dysfunctions associated with polyostotic disease.⁽⁴⁾ More rarely, FD may be associated with myxomas of skeletal muscle (Mazabraud's syndrome)⁽⁵⁾ or dysfunction of heart, liver, pancreas, or other organs within the context of the MAS.⁽⁶⁾

ETIOLOGY AND PATHOGENESIS

All forms of FD are caused by dominant, gain-of-function (activating), missense mutations of the *GNAS* gene, encoding the α subunit of the stimulatory G protein, $G_s\alpha$.^(7,8) Mutations occur postzygotically, are never inherited, and result in a somatic mosaic state. Single base transitions lead to replacement of arginine at position 201 with histidine or cysteine (most commonly), or rarely with other amino acids,⁽⁹⁾ and recently, substitutions at Q227 have been reported.⁽¹⁰⁾ The two most common mutations arise in early development as a consequence of methylation and deamination of cytosines within the CpG dinucleotide in the Arg 201 codon, presumably during de novo methylation of cells in the inner cell mass. The multipotency of inner cell mass cells may explain how the original mutation is transmitted to derivatives of all three germ layers, accounting for the broad organ distribution of severe forms of the disease.⁽¹¹⁾ Size and viability of the mutated clone arising from the single, original mutated cell may determine the variable distribution and frequency of the mutated cells in the postnatal organism, and the extent and severity of disease.⁽¹⁾ As a consequence of the mutation, the catalysis of GTP to GDP by $G_s\alpha$ is significantly decreased. Constitutive activation of adenylyl cyclase by the mutated $G_s\alpha$ ensues, and the resulting excess cAMP is thought to mediate a number of pathological effects in mutated cells.⁽¹⁾ In bone, mutations impact on

cells of the osteogenic lineage, with adverse effects both on osteoprogenitor cells and differentiated osteoblasts.^(12,13) Whereas the $G_s\alpha$ gene is not imprinted and is biallelically expressed in bone, asymmetric expression of the $G_s\alpha$ alleles in osteoprogenitors may account for the extent and severity of lesions.⁽¹⁴⁾ Expansion of the osteoprogenitor cell pool leads to their accumulation in marrow spaces, resulting in local loss of hematopoietic tissue and marrow fibrosis. Osteogenic cells derived from mutated skeletal progenitors are functionally and morphologically abnormal and deposit abnormal matrix. Bone trabeculae are abnormal in shape (so-called Chinese writing, alphabet soup patterns), collagen orientation, and biochemical composition,⁽¹²⁾ and in many cases, are severely undermineralized and abnormally compliant (Fig. 2D).^(15,16) Elevated serum levels of fibroblast growth factor 23 (FGF23), a recently identified phosphate-regulating hormone produced by highly activated osteoblastic cells in FD tissue (Fig. 2E), have been shown to be the etiology of the renal phosphate wasting commonly seen in association with FD.^(17,18) The histological pattern may be significantly different at different skeletal sites, and peculiar patterns are seen in craniofacial bones (Figs. 2A and 2B).⁽¹⁹⁾ Specific microscopic features, such as Sharpey fibers (Fig. 3C) and retracted osteoblasts, may, however, be recognized at all skeletal sites as recurrent histological hallmarks of the disease.⁽¹³⁾ The hormonal climate influences FD lesions⁽²⁰⁾ and may significantly alter the local rate of bone remodeling.⁽²¹⁾ FD tissue is highly vascularized and therefore prone to bleeding, leading to posthemorrhagic cysts.⁽²²⁾

CLINICAL FEATURES

The sites of skeletal involvement (the "map" of affected tissues) are established early in patients with FD. Ninety percent of the craniofacial lesions are established before 5 yr of age, and 75% of all sites of FD are evident by 15 yr of age.⁽²³⁾ Pathological effects of $G_s\alpha$ mutations in osteogenic cells are most pronounced and evident during the phase of rapid bone growth and account for that fact that childhood and adolescence are the periods during which the disease most commonly presents and the period of peak rate of fractures.^(24,25) Presentation in infancy is rare and usually heralds severe, widespread

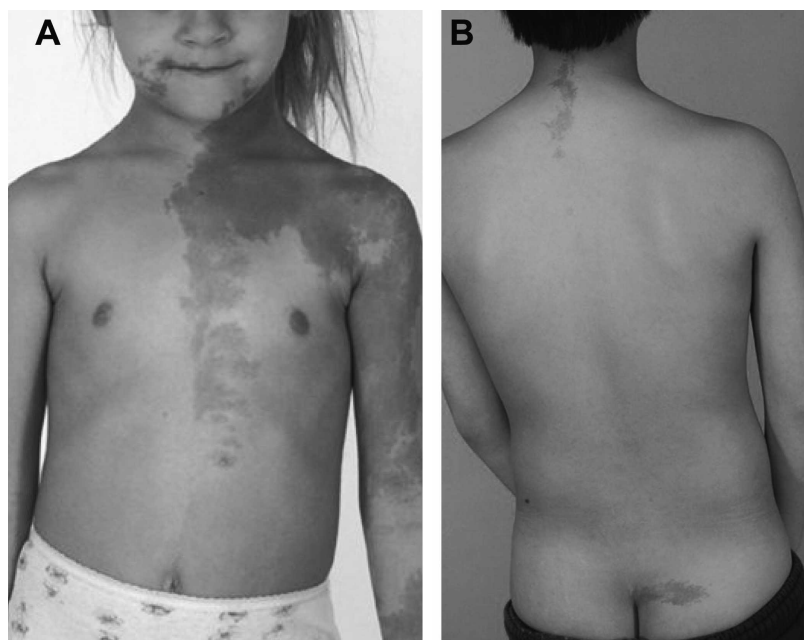


FIG. 1. Café-au-lait skin pigmentation. (A) A typical lesion on the face, chest, and arm of a 5-yr-old girl with MAS that shows jagged "coast of Maine" borders and the tendency for the lesions to both respect the midline and follow the developmental lines of Blaschko. (B) Typical lesions that are often found on the nape of the neck and crease of the buttocks are shown.

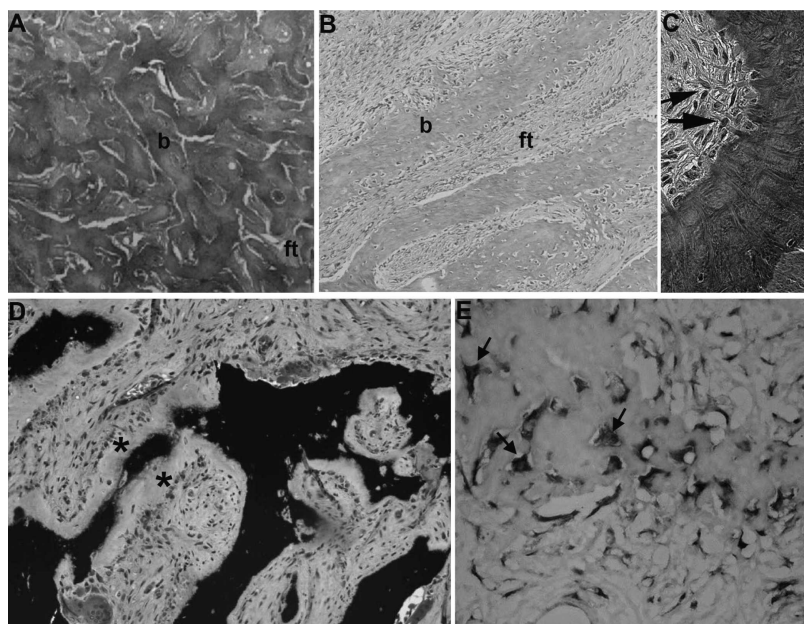


FIG. 2. Representative histological images of craniofacial FD. (A) Calvarial FD lesions are characterized by uninterrupted networks of bone trabeculae (b) embedded in the fibrous tissue (ft). (B) In FD lesions from gnathic bones, newly formed bone trabeculae (b) are deposited within the fibrous tissue (ft) in a typical discontinuous and parallel pattern. (C) Collagen fibers perpendicularly oriented to forming bone surfaces (Sharpey fibers, arrows) represent a recurrent histological feature of FD at all skeletal sites. (D and E) Osteomalacic changes and FGF23 production in FD. (D) In many cases of FD, processing for undecalcified embedding reveals excess osteoid (asterisks) and severe undermineralization of the fibrous dysplastic bone. (E) The mineralization defect of the FD tissue is related to elevated levels of FGF23 produced by activated FD osteogenic cells (arrows), as shown by in situ hybridization.

disease with multiorgan involvement. Pain, fracture, and deformity are the most common presenting features. In general, children are less likely to have pain and/or complain of pain, per se, and may instead report stiffness or tiredness.⁽²⁶⁾ In adults the complaint of pain is common, especially in the ribs, long bones, and craniofacial bones. It is often severe and may require narcotic analgesics.⁽²⁶⁾ Lesions in the spine and pelvis are usually less painful. Pathological fractures or stress fracture of weight-bearing limb bones is a prime cause of morbidity. Deformity of limb bones is caused by expansion and abnormal compliance of lesional FD, fracture treatment failure, and local complications such as cyst formation.⁽¹⁾ Deformity of craniofacial bone is solely the result of the overgrowth of lesional bone.

Although any bone may be affected, the proximal metaphysis of the femora and the skull base are the two sites most commonly involved.⁽²⁶⁾ Femoral disease usually presents in childhood with limp, fracture, pain, and deformity, ranging from coxa vara to the classical shepherd's crook deformity (Fig. 3A). Radiographically, the lesion may be limited to the metaphysis or extend along the diaphysis for variable length.⁽²²⁾ The picture most commonly observed in children and adolescents consists of an expansile, deforming, medullary lesion, with cortical thinning and an overall "ground glass" density (Fig. 3A). The radiographic picture is significantly affected by the evolution of the lesion over time and by the appearance of superimposed changes, such as aneurysmal bone cysts. Hence, lesions observed in adults tend to appear more sclerotic and less homogeneous (Fig. 3B). Sclerosis in FD lesions of the femur and other limb bones may signify less active disease.

In the skull, FD mostly involves the skull base and facial bones. The typical presentation is in childhood with facial asymmetry or a "bump" that persists, but symmetric expansion of the malar prominences and/or frontal bosses may also be seen. The disease can progress into adulthood and disfiguration may be marked when FD is accompanied by GH excess.⁽²⁰⁾ Abnormal growth and deformity of craniofacial bones may result in encroachment on cranial nerves. However, severe adverse consequences are rare, but much more common in patients with associated growth hormone excess.^(20,27,28) FD

tissue in craniofacial bones is especially prone to bleeding, herniation through cranial foramina and vascular passages, as well as formation of posthemorrhagic cysts. These events may precipitate blindness when they occur in the vicinity of the optic nerves.⁽²⁹⁾ Radiographically, craniofacial FD typically has a homogenous "ground glass" appearance in children (Fig. 3C), but in adults, lesions with a more sclerotic, "pagetoid" appearance are typical (Fig. 3D), which correlate with site-specific osteosclerotic histological changes.⁽¹⁹⁾ Lesions in the spine, ribs, and pelvis are common, may be elusive on plain radiographs, but are easily detected by bone scintigraphy, the most sensitive imaging technique for the detection of FD lesions (Figs. 3E–3G). Disease in the spine is common and is frequently associated with scoliosis, may require surgery, and can be progressive into adulthood.⁽³⁰⁾

Malignancy in FD is rare (<1%).⁽³¹⁾ Whereas there is an association with the development of cancer with prior treatment with high-dose external beam radiation,^(32,33) it may also occur independent of prior exposure to ionizing radiation. Rapid lesion expansion and disruption of the cortex on radiographs should alert the clinician to the possibility of sarcomatous change. Osteogenic sarcoma is the most common, but not the only type of bone tumor that may complicate FD. The clinical course is usually aggressive, surgery is the primary treatment, and chemotherapeutic regimens do not seem to improve prognosis significantly.

MANAGEMENT AND TREATMENT

Diagnosis of FD must be established based on expert assessment of clinical, radiographic, and histopathological features. Markers of bone turnover are usually elevated.⁽⁴⁾ The extent of the skeletal disease is best determined with total body bone scintigraphy, which can be used to assess the skeletal disease burden and predict functional outcome.⁽³⁴⁾ The metabolic derangements associated with FD, especially hypophosphatemia and growth hormone excess, are associated with a significantly worse clinical outcome and therefore must be screened for and treated.^(16,20,25,28)

Mutation analysis may be helpful in distinguishing FD from unrelated fibro-osseous lesions of the skeleton, which may

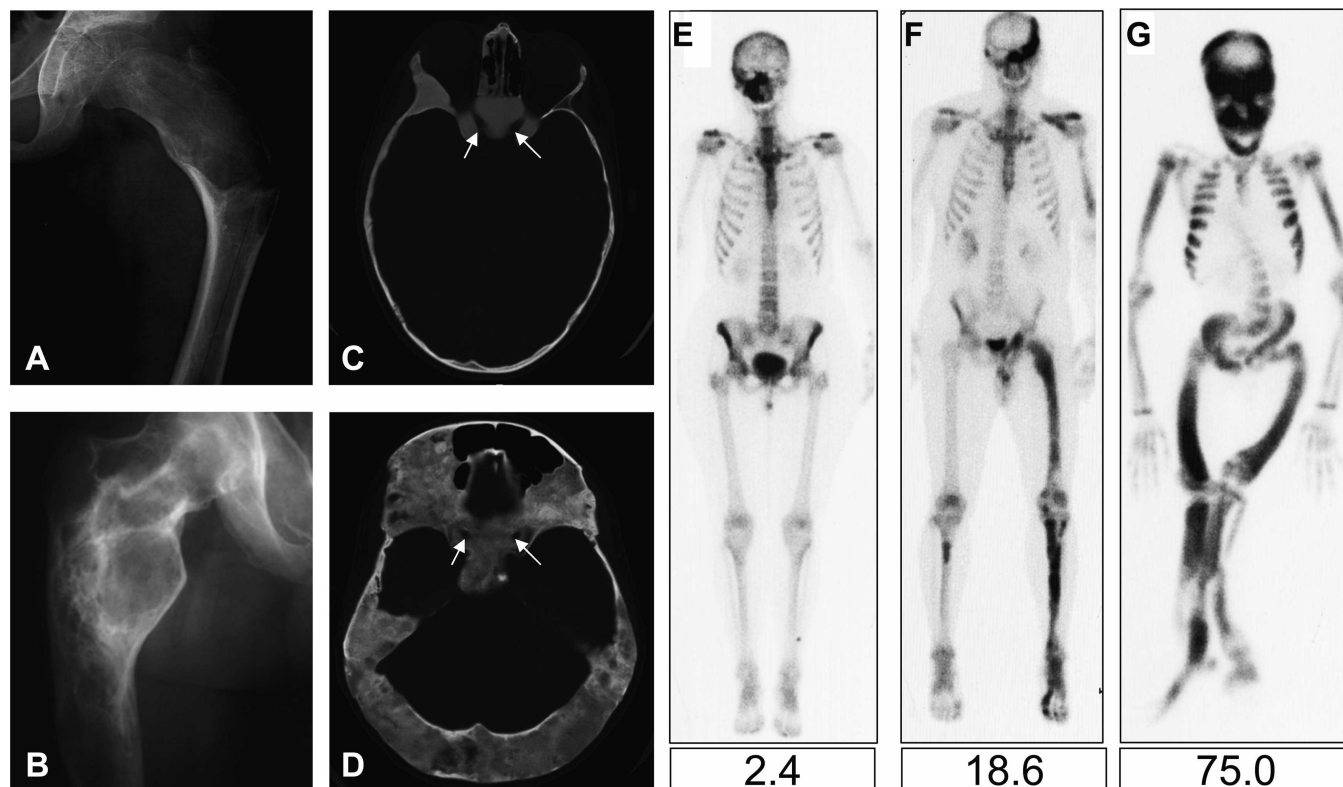


FIG. 3. Radiographic appearance of fibrous dysplasia. (A) A proximal femur with typical ground glass appearance and shepherd's crook deformity in a 10-yr-old child is shown. (B) The appearance of FD in the femur of an untreated 40-yr-old man shows the tendency for FD to appear more sclerotic with time. (C) The typical ground glass appearance of FD in the craniofacial region on a CT image of a 10-yr-old child is shown. The white arrows indicate the optic nerves, which are typically encased with FD. (D) A CT image in a 40-yr-old woman shows the typical appearance of craniofacial FD in an older person, with mixed solid and "cystic" lesions. The Hounsfield unit measurements of "cystic" lesions are quite useful in distinguishing soft tissue "cystic" lesions from true fluid-filled cysts, which are much more uncommon and tend to behave aggressively with rapid expansion and compression of vital structures. (E–G) Bone scintigraphy in FD. Representative $^{99}\text{Tc-MDP}$ bone scans that show tracer uptake at affected skeletal sites and the associated skeletal disease burden score⁽³¹⁾ are shown. (E) A 50-yr-old woman with monostotic FD confined to a single focus involving contiguous bones in the craniofacial region. (F) A 42-yr-old man with polyostotic FD shows the tendency for FD to be predominantly (but not exclusively) unilateral and to involve the skull base and proximal femur. (G) A 16-yr-old boy with MAS and involvement of virtually all skeletal sites (panostotic) is shown.

mimic FD both clinically and radiographically (osteofibrous dysplasia, ossifying fibromas of jawbones⁽¹⁾). Isolated lesions of the proximal femur in adults may be improperly diagnosed and classified as distinct fibro-osseous lesions. For example, all cases of so-called "liposclerosing myxofibrous tumor" in which GNAS mutations were sought were found to represent monostotic fibrous dysplasia.⁽³⁵⁾ Multiple nonossifying fibromas, skeletal angiomatosis, and Ollier's disease may sometimes enter the differential diagnosis, which again relies on histology and mutation analysis.

Disease of the proximal femur, in which there is fracture or impending fracture, is often best treated by insertion of intramedullary nails, in an effort to prevent serious deformity and limb length discrepancy.^(22,36,37) Design of specific types of nails is felt to be necessary, and development of such devices is underway.⁽¹⁴⁾ Surgery is not advocated for craniofacial disease unless hearing or vision loss are documented, and prophylactic optic nerve decompression seems to be contraindicated.⁽²⁸⁾ Treatment with bisphosphonates (pamidronate, etc.) has been advocated based on observational studies with claims of reduced pain, decreased serum and urine markers of bone metabolism, and improvement in the radiographic appearance of the disease.^(38,39) However, a recently completed open label, prospective study with appropriate histological, radiographic, and clinical endpoints showed pain relief but showed no ben-

efit radiographically or histologically.⁽⁴⁰⁾ Ongoing placebo-controlled studies in the United States and Europe may help to better define the role of bisphosphonates in treating FD.

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