

Fibrous Dysplasia

Bone pathology: molecular basis, morphology, clinical phenotypes

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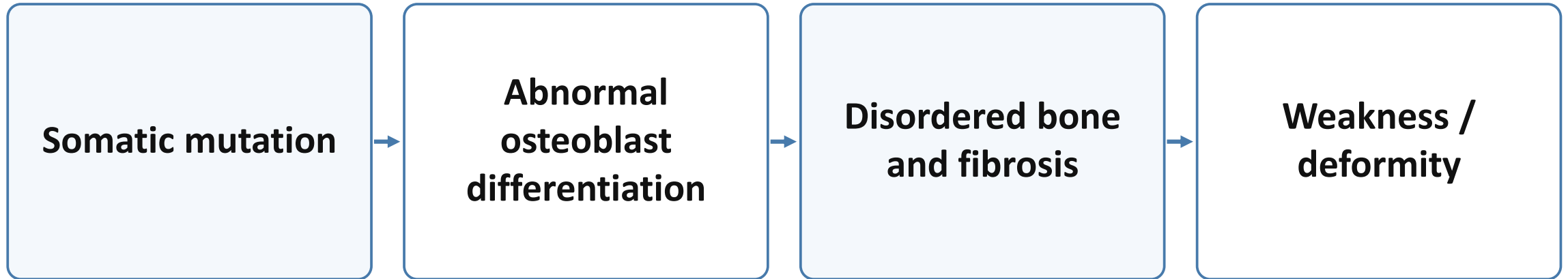
Learning objectives

- Connect GNAS1 activation to abnormal skeletal differentiation.
- Identify the radiologic and microscopic pattern of fibrous dysplasia.
- Distinguish monostotic, polyostotic and syndromic presentations.
- Apply morphology and clinical context to focused cases.

Fibrous dysplasia is a benign bone neoplasm

- The lesion contains disorganized, inadequately mineralized bone.
- Intervening fibrous tissue replaces normal skeletal architecture.
- The process arises during skeletal development.

From developmental lesion to clinical problem



Clinical expression depends on when and where the mutated cells arise.

Four recognized clinical presentations

Monostotic

A single bone is involved.

Polyostotic

Multiple bones are involved.

Mazabraud

Fibrous dysplasia accompanied by soft tissue myxomas.

McCune–Albright

Polyostotic lesions with skin pigmentation and endocrinopathy.

Monostotic versus polyostotic: First distinction

Feature	Monostotic	Polyostotic
Extent	One affected bone	Several affected bones
Typical onset	Early adolescence	Slightly earlier
Course	Often stabilizes at growth plate closure	May remain clinically active into adulthood
Consequences	Often incidental; Pain/fracture possible	Deformities and fractures may require repair

Sporadic and syndromic disease share a pathway

- Sporadic lesions and both named syndromes arise from somatic activating mutations.
- The anatomical distribution reflects developmental mosaicism.
- A molecular mechanism can therefore yield very different clinical patterns.

GNAS1 is the initiating gene

- Somatic gain-of-function mutations in GNAS1.
- GNAS1 encodes the stimulatory G-protein α subunit ($Gs\alpha$).
- Mutations occur during fetal development.

Constitutive activation of Gsα

GNAS1 gain-of-function



Gsα remains active



Intracellular cAMP rises

CAMP is the signaling intermediate directly emphasized.

Normal signaling versus mutated signaling

Regulated signaling

Gs α activity is controlled; Downstream cAMP signaling is stimulus-dependent.

Fibrous dysplasia

Constitutively active Gs α increases intracellular cAMP signaling.

Downstream signaling changes

Increased cAMP



**Altered pathways,
including Wnt**



More proliferation

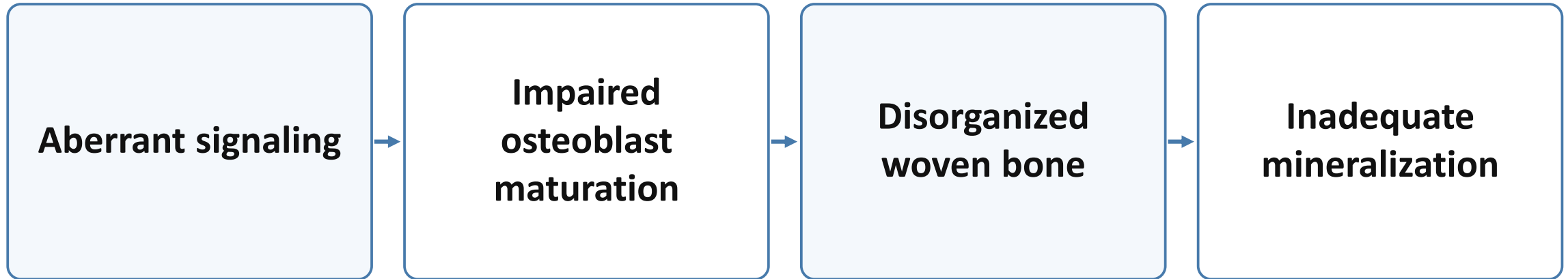


**Less osteoblast
differentiation**

The cellular phenotype has two linked components

- Cellular proliferation is promoted.
- Osteoblast differentiation is inhibited.
- Together, these changes favor fibrous stroma with structurally abnormal bone.

Why the bone has abnormal architecture



The morphologic pattern reflects defective bone formation, not simply bone destruction.

Developmental timing controls the phenotype

- The stage of embryogenesis at mutation acquisition matters.
- The eventual differentiation fate of the mutant cell also matters.
- These variables govern tissue distribution and clinical expression.

Early versus later embryonic mutation

Very early embryogenesis

Mutation may affect a broad cellular population, producing multisystem McCune–Albright syndrome.

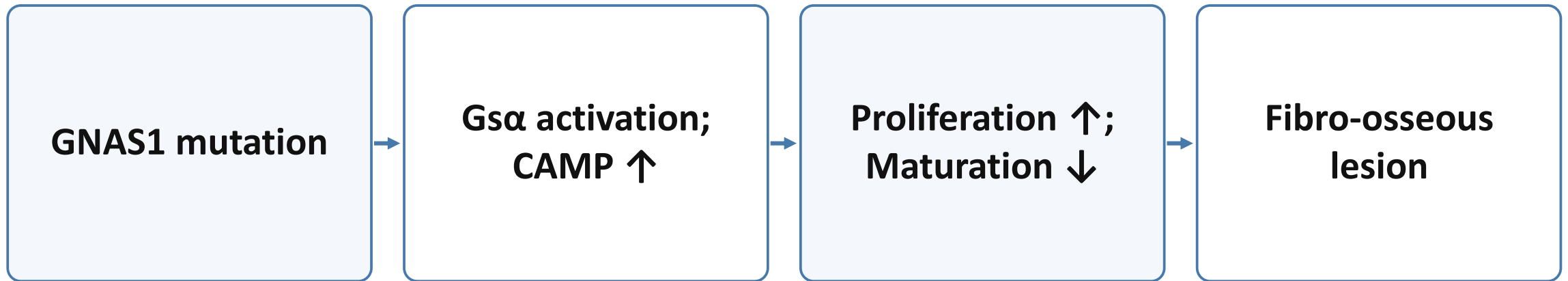
Osteoblast precursor, later

Mutation confined to skeletal precursors may produce monostotic fibrous dysplasia.

Distribution reflects the fate of the mutant cell

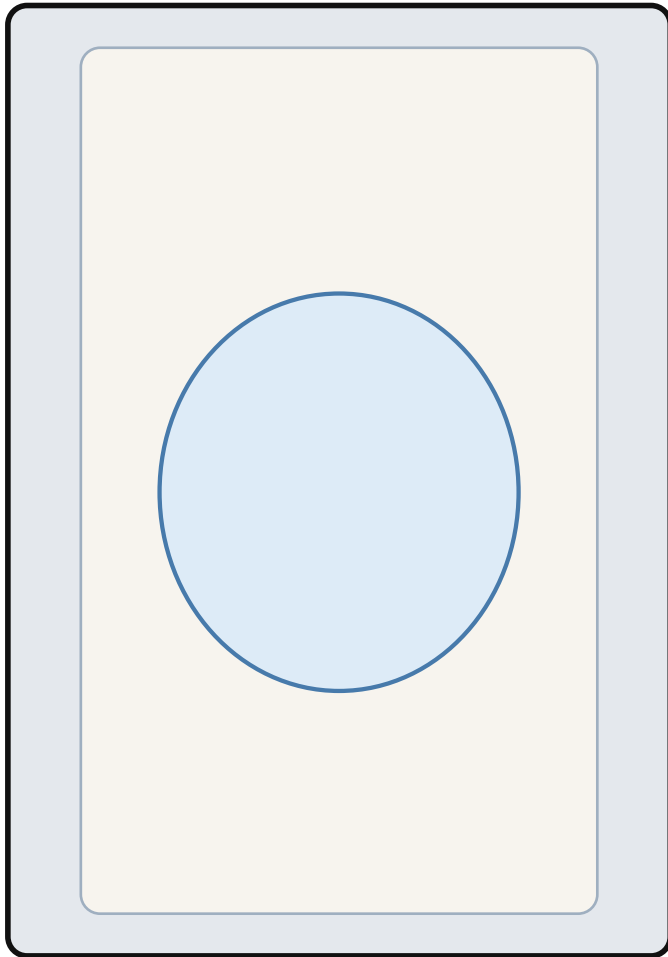
- An early mutation may persist in derivatives of several tissues.
- A later mutation can be restricted to a skeletal lineage.
- Hence clinical form does not imply a different initiating signaling defect.

Pathogenesis: The complete teaching model



Schematic causal summary of the textbook description.

An intramedullary origin



Schematic — not a radiograph

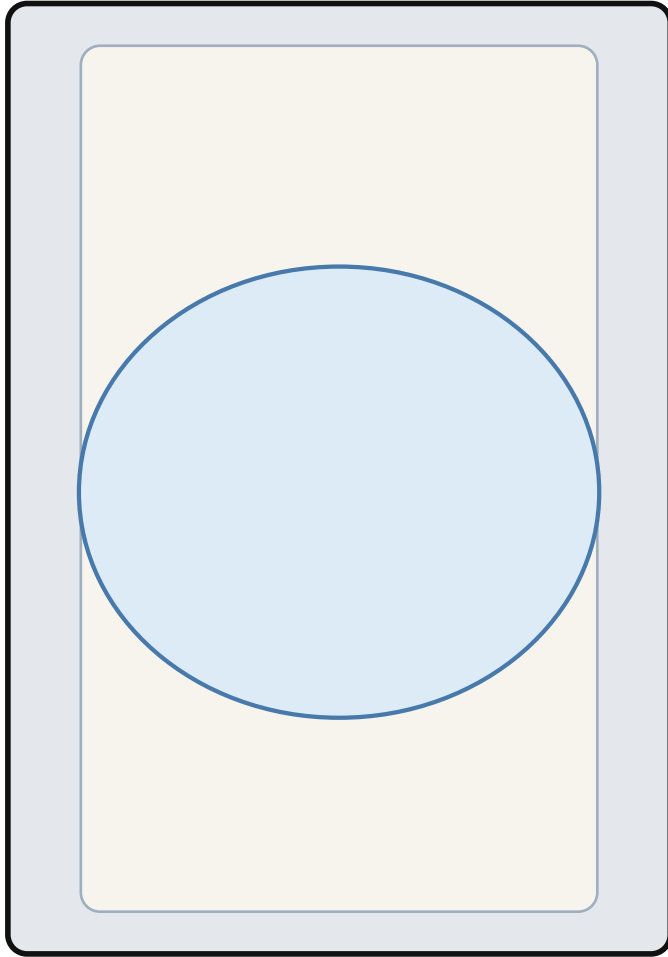
Intramedullary focus

- The lesion arises in the marrow cavity, rather than at the surface.
- Its location explains the central osseous replacement.

A lytic lesion is seen on imaging

- The radiographic lesion is described as intramedullary and lytic.
- Its extent can be assessed by the change in bone architecture.
- Interpret lysis in the context of expansion and clinical distribution.

Expansile remodeling of the affected bone

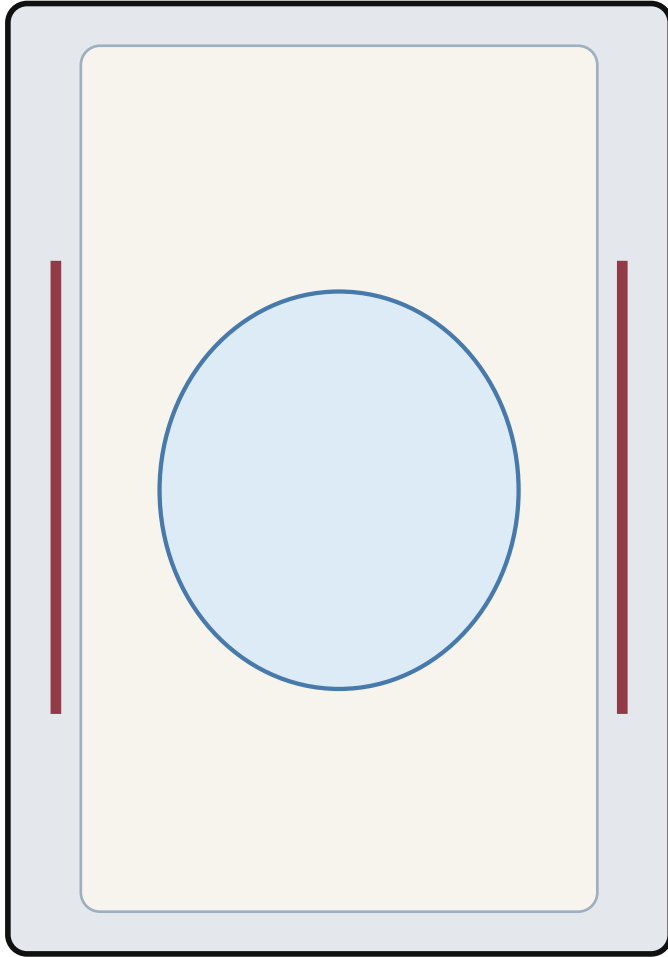


Schematic — not a radiograph

Progressive intramedullary expansion

- Expanding dysplastic tissue broadens the affected bone.
- Cortical architecture may be altered as the lesion grows.

Cortical thinning indicates structural vulnerability



Schematic — not a radiograph

Thin supporting cortex

- Expansion may attenuate the cortical shell.
- Structural weakness contributes to fracture risk.

Bowing follows altered bone mechanics

- Expanding fibrous dysplasia may bend the affected bone.
- Deformity follows progressive distortion of the cortical shell.
- Bowing links imaging findings to the functional burden of the disease.

Periosteal reaction is usually absent

- That a periosteal reaction usually is not present.
- This is one element of the typical imaging profile, not an isolated diagnostic criterion.
- Correlate with location, expansion and cortical thinning.

Gross morphology: Tan-white, gritty tissue

- The lesional material is described as tan-white.
- Its gritty character reflects abnormal mineralized tissue within fibrous proliferation.
- Gross texture should be interpreted with histology, not used alone.

Curvilinear trabeculae of woven bone



Schematic — not a histology specimen

Curvilinear woven bone

- Irregularly shaped trabeculae are embedded in fibrous tissue.
- The bone pattern is disordered, not mature lamellar architecture.

Prominent osteoblastic rimming is absent



Schematic — not a histology specimen

Osteoblastic rimming

- Prominent osteoblast layers around the trabeculae are absent.
- Interpret rimming together with trabecular shape and stroma.

The intertrabecular tissue is fibroblastic



Schematic — not a histology specimen

Cellular fibroblastic stroma

- A moderately cellular proliferation occupies spaces between bone trabeculae.
- Loose collagen accompanies the fibroblasts.

Loose collagen accompanies the fibroblasts

- The intervening fibrous tissue includes loose collagen.
- Cellular fibroblastic tissue surrounds the curvilinear trabeculae.
- The combination differs from the architecture of organized lamellar bone.

Combine architectural clues, not isolated features



Schematic — not a histology specimen

Composite histological pattern

- Irregular woven bone + fibroblasts + loose collagen.
- Lack of prominent osteoblastic rimming reinforces the pattern.

Secondary microscopic changes to recognize

Cystic degeneration

Cystic alteration may occur within the lesion.

Hemorrhage

Blood may be present as a secondary finding.

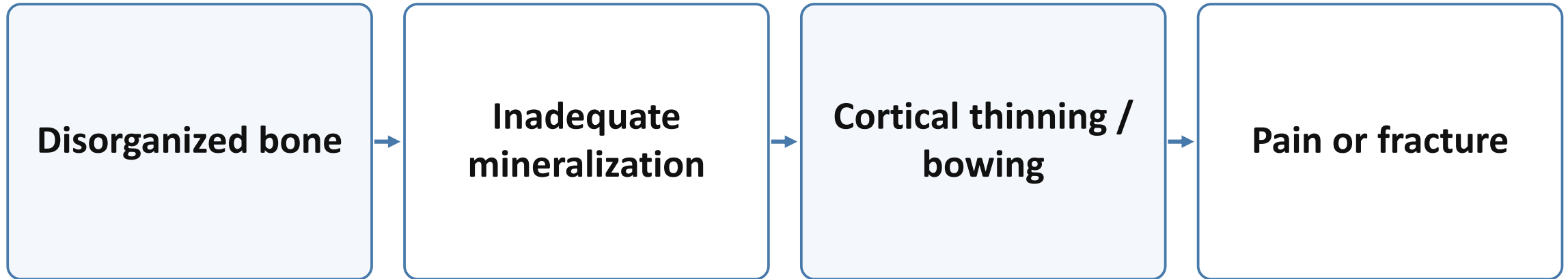
Foamy macrophages

Lipid-laden histiocytes may accompany degenerative changes.

An integrated fibrous dysplasia morphology checklist

Domain	Source-described finding
Imaging location	Intramedullary lytic lesion
Bone outline	Possible expansion, bowing, cortical thinning
Periosteum	Periosteal reaction usually absent
Gross examination	Tan-white and gritty
Microscopy	Curvilinear woven bone, minimal osteoblastic rimming
Background	Fibroblasts, loose collagen; Possible cysts, hemorrhage, foamy cells

From microscopic pattern to mechanical failure



Clinicopathologic inference from the source-described morphology and clinical effects.

Monostotic disease: Usual time of presentation

- Monostotic lesions appear in early adolescence.
- Clinical visibility often coincides with skeletal growth.
- Growth may stop when the growth plate closes.

Common bones affected in monostotic disease

Long bones

Femur and tibia

Axial skeleton

Ribs

Craniofacial skeleton

Jawbones and calvarium

Monostotic lesions are often incidental

- Many patients have no symptoms.
- A lesion may be detected on imaging performed for another indication.
- An asymptomatic presentation does not mean normal bone architecture.

Monostotic disease can cause symptoms

- Pain may arise from an affected bone.
- Pathologic fracture may complicate compromised structural integrity.
- Clinical assessment therefore considers symptoms and the risk posed by an expanding lesion.

Growth plate closure often limits enlargement

- Many monostotic lesions stop enlarging at skeletal maturity.
- This trend is not a guarantee of a symptom-free outcome.
- Evaluate clinical course separately from the benign histologic classification.

Surgical treatment does not ensure permanence

- Curettage for symptomatic monostotic lesions.
- Recurrence following curettage is common.
- Recurrence is not equivalent to malignant transformation.

Polyostotic disease begins earlier

- Polyostotic disease manifests at a slightly earlier age than monostotic disease.
- Its distribution involves multiple bones.
- Problems may continue into adult life.

Frequent sites in polyostotic disease

Femur / tibia

Weight-bearing long bones are frequently affected.

Skull

Craniofacial involvement is common.

Shoulder / pelvis

Girdle involvement can be especially deforming.

Craniofacial involvement alters disease burden

- Craniofacial bones are commonly involved in polyostotic disease.
- The anatomical distribution contributes to the clinical phenotype.
- Assess burden by site and extent rather than lesion count alone.

Girdle involvement may be progressively deforming

- Shoulder and pelvic girdles can be affected.
- Progressive disease may produce structural deformity.
- Fractures and deformities can require surgical repair.

Polyostotic disease: Clinical progression

**Multiple bone
lesions**



**Persistent
mechanical effects**



**Progressive
deformity**



**Fractures / surgical
repair**

Bisphosphonates target bone pain

- Bisphosphonates may reduce the severity of bone pain.
- Analgesic benefit is distinct from correction of the mutant cell population.
- Skeletal deformities and fractures may still require surgical management.

Malignant transformation is uncommon

- A rare complication is conversion of a lesion to sarcoma.
- The textbook associates this mainly with polyostotic disease.
- The rarity should be retained: Fibrous dysplasia itself is benign.

Mazabraud syndrome: Bone and soft tissue

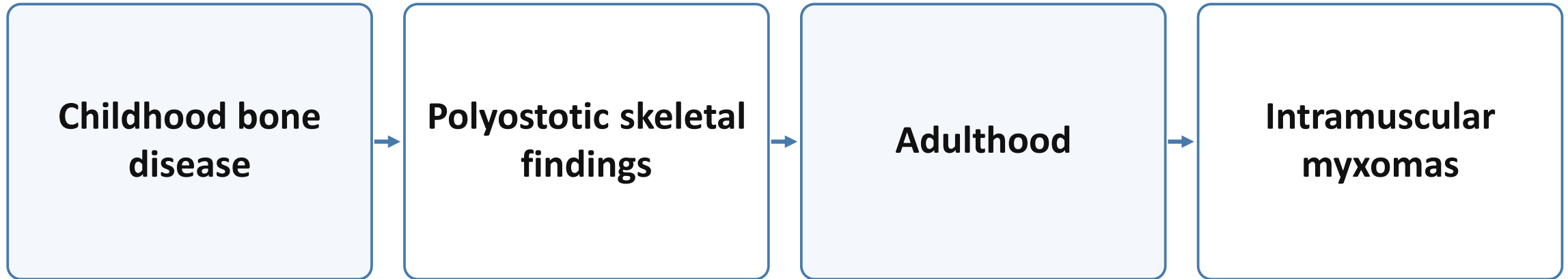
Bone component

Fibrous dysplasia, commonly with polyostotic skeletal features.

Soft-tissue component

Intramuscular myxomas, typically appearing later.

Mazabraud syndrome: Temporal sequence



The soft-tissue masses often occur near the anatomical region containing fibrous dysplasia.

Why intramuscular myxomas matter

- The myxomas are benign.
- They may cause local compression symptoms or limb deformity.
- Surgical excision as curative for these myxomas.

McCune–Albright syndrome: Diagnostic triad

Skeletal

Polyostotic fibrous
dysplasia

Cutaneous

Café-au-lait pigmentation

Endocrine

Abnormal hormone
activity, notably
precocious puberty

Precocious puberty is a common presentation

- The most common clinical presentation is precocious sexual development.
- This particularly among girls.
- Endocrine manifestations may prompt the diagnosis before skeletal symptoms.

Other endocrine abnormalities in McCune–Albright

Thyroid

Hyperthyroidism

Pituitary

Growth-hormone–
secreting pituitary
neuroendocrine tumor

Adrenal

Primary adrenal
hyperplasia

The distribution may be asymmetric

- Bone involvement in McCune–Albright is often unilateral.
- Café-au-lait lesions, when present, may be limited to the same side.
- This sided pattern is consistent with a developmental mosaic process.

McCune–Albright requires multisystem care

Clinical component	Textbook-described approach
Skeletal lesions	Manage as for polyostotic fibrous dysplasia
Endocrinopathy	Medical therapy directed at the endocrine disorder
Example: Precocious puberty	Robbins mentions aromatase inhibitors as one therapy

Clinical phenotype comparison

Form	Bone distribution	Associated feature	Course
Monostotic	One bone	Usually sporadic	Often stabilizes at maturity
Polyostotic	Multiple bones	Deformity / fractures	Problems may persist
Mazabraud	Usually polyostotic	Intramuscular myxomas	Myxomas often appear later
McCune–Albright	Polyostotic	Pigmentation + endocrinopathy	Early, multisystem

Case: Incidental long-bone lesion

An adolescent undergoes radiography for an unrelated reason. A solitary intramedullary lytic lesion expands the bone with mild cortical thinning. There is no reported periosteal reaction.

Which form is most compatible with this distribution?

Case interpretation: Monostotic fibrous dysplasia

A single-bone presentation is consistent with monostotic disease.

Reasoning

- One affected bone supports the monostotic category.
- The radiographic description matches Robbins' lesion pattern.
- Histology and clinical correlation remain relevant if diagnosis is uncertain.

Case: Multiple lesions and skeletal deformity

A young patient has lesions involving the femur, tibia and skull. Over time, a pelvic lesion causes increasing deformity and a fracture requiring surgical repair.

Which clinical form and consequence are illustrated?

Case interpretation: Progressive polyostotic disease

Multiple-bone fibrous dysplasia with deformity.

Reasoning

- The distribution is polyostotic rather than monostotic.
- Pelvic/shoulder girdle lesions may cause progressive deformity.
- Fracture and deformity can require surgical repair.

Case: Bone lesions followed by muscle masses

Fibrous dysplasia is recognized during childhood. Later, a benign intramuscular myxoma becomes apparent in the same anatomical region as affected bone.

Name the syndrome and explain its chronology.

Case interpretation: Mazabraud syndrome

Fibrous dysplasia plus intramuscular myxoma.

Reasoning

- Bone manifestations commonly precede the myxomas.
- The myxoma often arises near an existing bone lesion.
- Compression symptoms, if present, may be treated by excision.

Case: Precocious puberty and bone lesions

A young girl develops precocious sexual development. She has multiple bone lesions and unilateral café-au-lait pigmentation.

Identify the syndrome and link the systems involved.

Case interpretation: McCune–Albright syndrome

Skeletal, pigmentary and endocrine features occur together.

Reasoning

- Polyostotic bone involvement is the skeletal component.
- Pigmentary and endocrine findings support the syndrome.
- The initiating early somatic mutation can affect more than one tissue lineage.

Morphology exercise: Identify the defining pattern

Bone tissue contains irregular curvilinear trabeculae of woven bone, a moderately cellular fibroblastic stroma and loose collagen. Osteoblastic rimming is inconspicuous.

What diagnosis is this pattern designed to suggest?

Morphology exercise: Architectural integration

The combined microscopic findings support fibrous dysplasia.

Reasoning

- Curvilinear woven-bone trabeculae are characteristic.
- A fibroblastic background and weak osteoblastic rimming are complementary findings.
- Secondary hemorrhage or cystic change need not exclude the diagnosis.

Adjacent benign bone lesions: Different architecture

Feature	Fibrous dysplasia	Nonossifying fibroma	Aneurysmal bone cyst
Typical location	Intramedullary	Eccentric metaphysis	Often eccentric / expansile
Dominant tissue	Woven bone + fibrous stroma	Storiform fibroblasts + macrophages	Blood-filled spaces + fibrous septa
Useful distinction	Curvilinear trabeculae; Little rimming	Foamy macrophages / hemosiderin	Fluid–fluid levels may be seen

A diagnostic reasoning sequence

**Determine bone
distribution**



**Assess imaging
pattern**



**Recognize
microscopic
architecture**



**Seek syndromic
clues**

Do not use a single morphologic or clinical sign in isolation.

Final synthesis: Five findings to retain

- Somatic activating GNAS1 mutation increases Gs α –cAMP signaling.
- Disordered woven bone and fibroblastic tissue replace normal bone.
- Curvilinear trabeculae generally lack prominent osteoblastic rimming.
- The spectrum extends from solitary lesions to multisystem syndromes.
- Fracture/deformity, pain and rare sarcomatous change shape the clinical course.

Principal source and image policy

Primary reading

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026). Chapter 26, “Bones, Joints, and Soft Tissue Tumors”; Fibrous Dysplasia, printed pp. 1085–1087.

Illustration provenance

Native editable diagrams are original conceptual schematics derived from the assigned textbook material. They are not clinical radiographs or histological specimens.