

Aneurysmal Bone Cyst

Mechanism • imaging • morphology • differential diagnosis

Pathology teaching lecture

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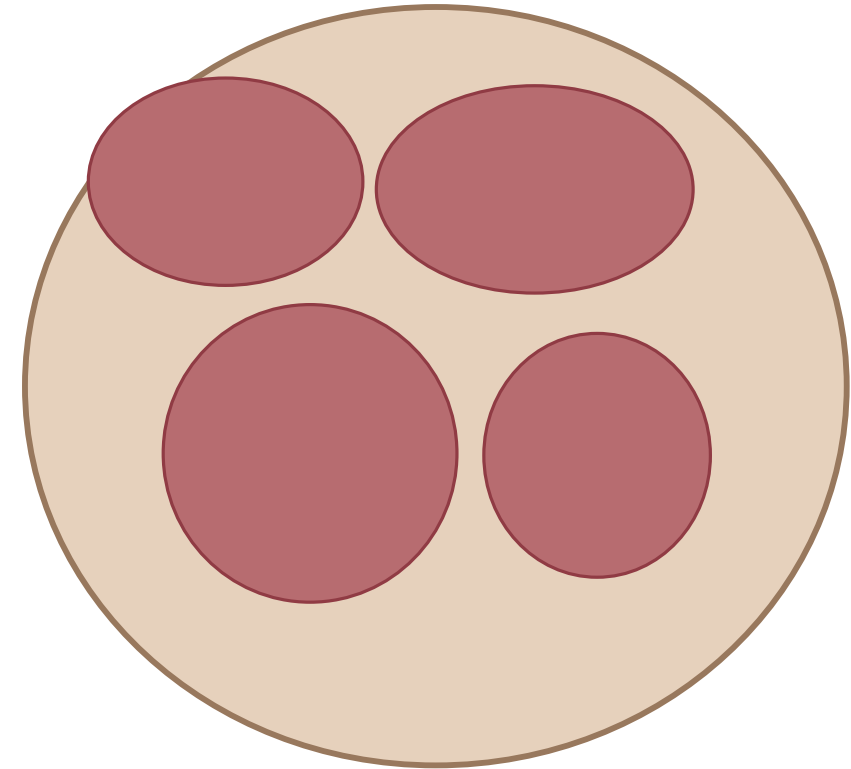
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Learning outcomes

- Define aneurysmal bone cyst and explain why it is neoplastic yet benign.
- Relate USP6 activation to osteolysis and characteristic cystic architecture.
- Interpret imaging, gross appearance and septal microscopic features together.
- Recognize recurrence and critical benign–malignant diagnostic differentials.

Definition: A blood-filled bone neoplasm

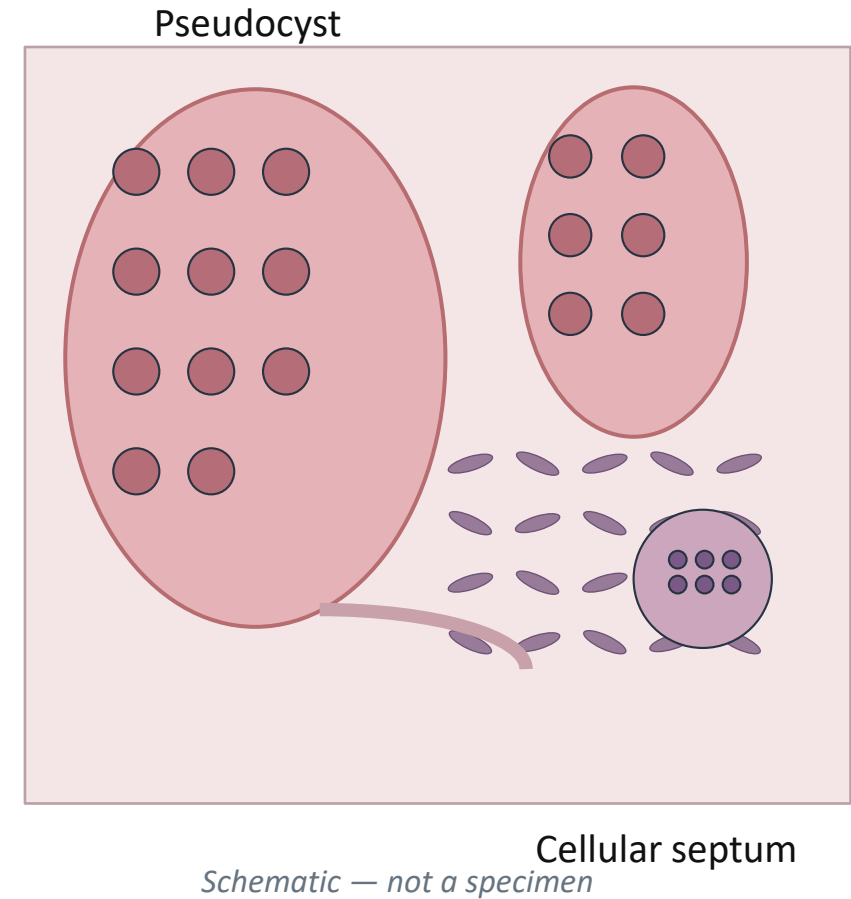
- Aneurysmal bone cyst (ABC) is a benign neoplasm of bone.
- Its defining architecture is multiloculated, blood-filled cyst-like spaces.
- Despite benign classification, tissue expansion and bone resorption can be locally destructive.



Blood-filled spaces Fibrous septa
Schematic — not a specimen

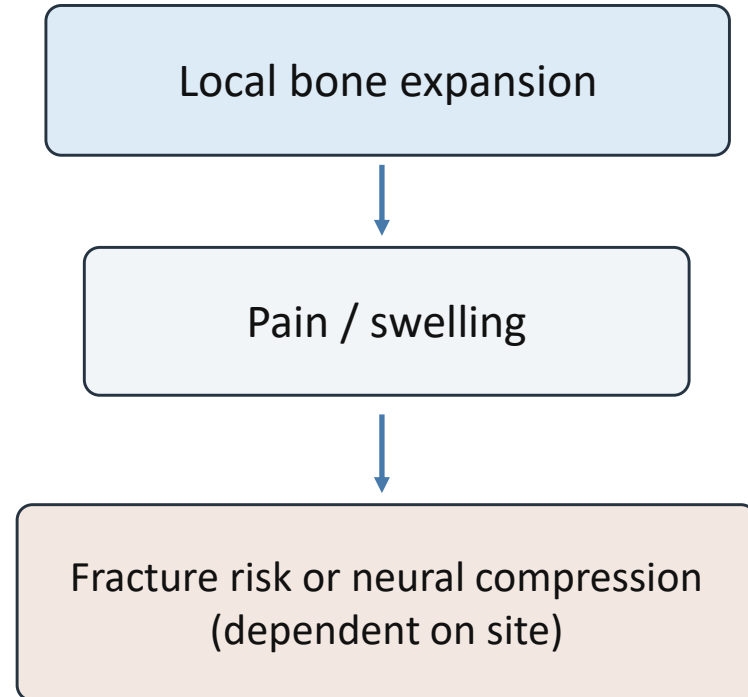
What the name does—and does not—mean

- “Cyst” describes hemorrhagic, cavity-like spaces within bone.
- “Aneurysmal” does not imply a true arterial aneurysm.
- The spaces lack an endothelial lining: They are pseudocystic rather than vascular channels.



Biologic behavior: Benign, not innocuous

- ABC is not classified as a malignant bone tumor.
- Expansile growth can thin and remodel adjacent cortex.
- Local aggressiveness explains symptoms, fracture-related problems and the need for treatment.



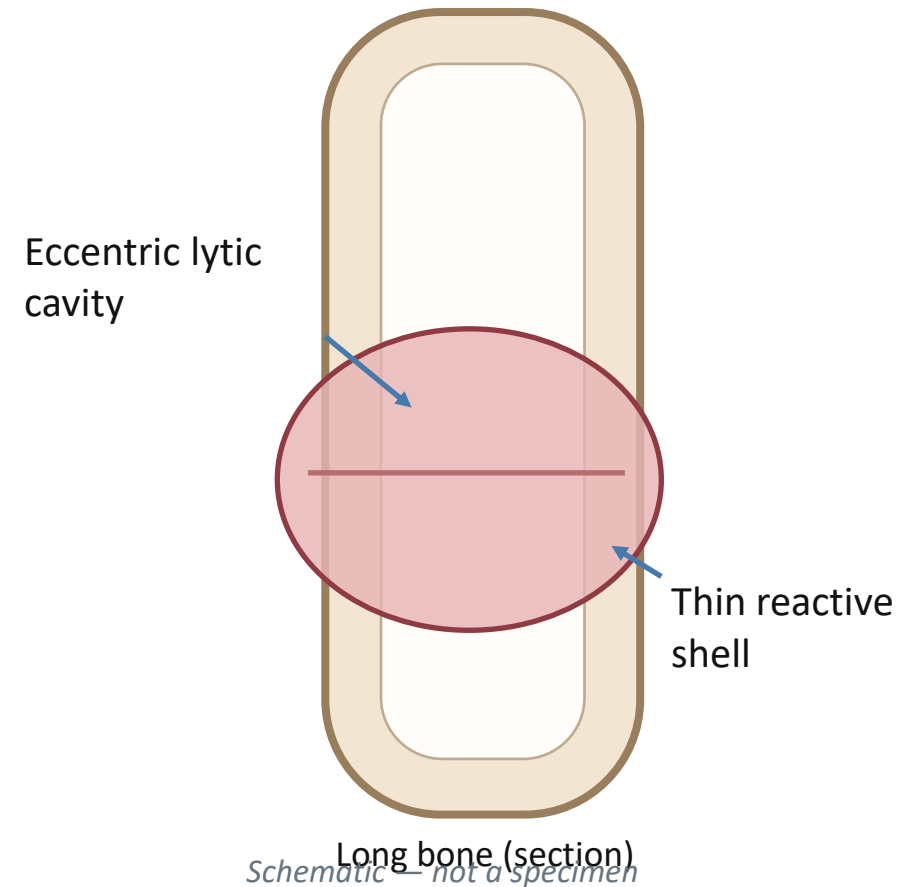
Schematic — not a specimen

Age pattern

- All age groups may be affected.
- Most cases present during adolescence.
- Age supports the clinical context, but cannot establish the diagnosis by itself.

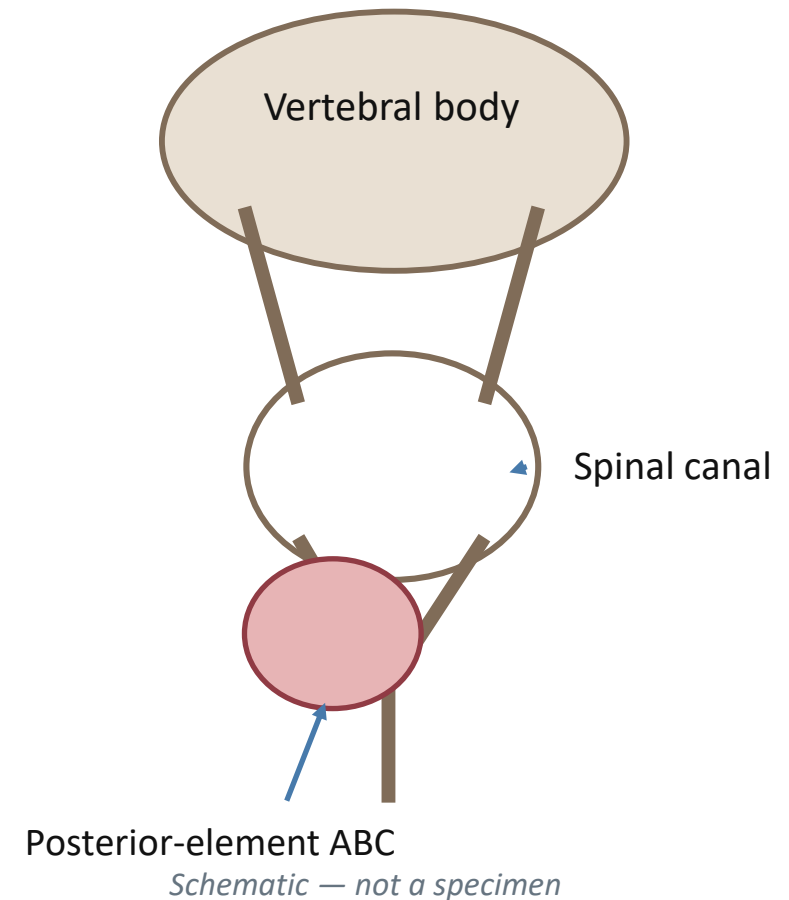
Predilection for major long bones

- The femur and tibia are among the most frequent sites.
- ABC can be considered when a young patient has an expansile lytic lesion in these bones.
- Site is a clue that must be integrated with lesion position and internal architecture.



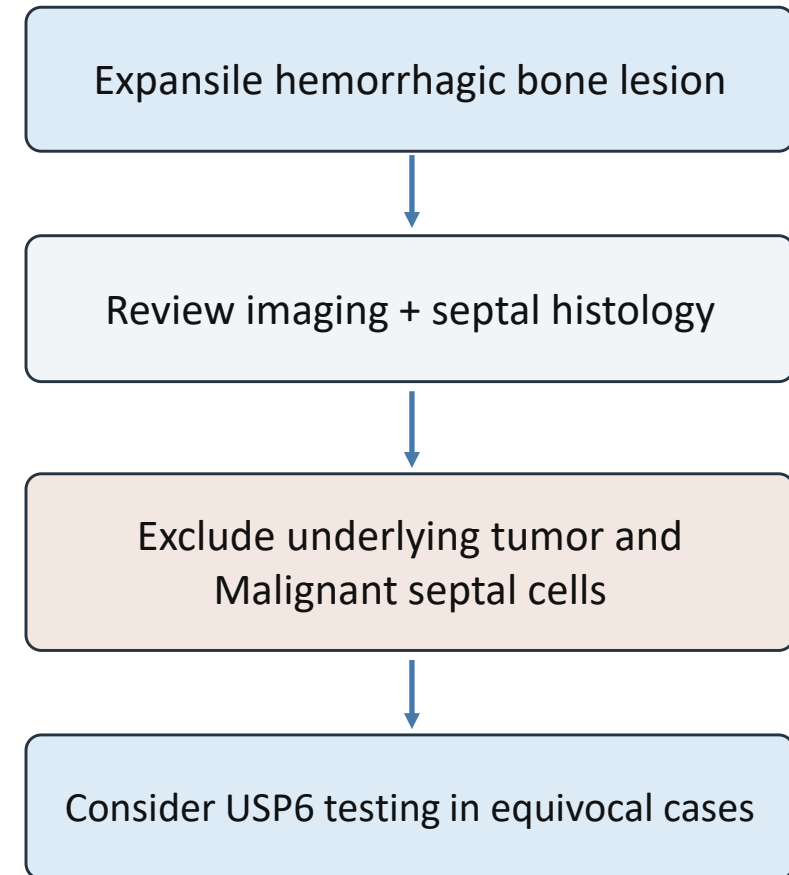
Vertebral involvement: Posterior elements

- In the spine, ABC commonly involves the lamina and pedicles.
- An enlarging lesion in this compartment can compress neural structures.
- Neurologic manifestations depend on the lesion's anatomy, not on malignant histology.



Clinical–pathologic framework

- Bone resorption and expansion explain the radiographic appearance.
- Hemorrhagic compartments account for internal fluid levels and gross cysts.
- Fibroblastic septa, giant cells and woven bone form the diagnostic microscopic pattern.

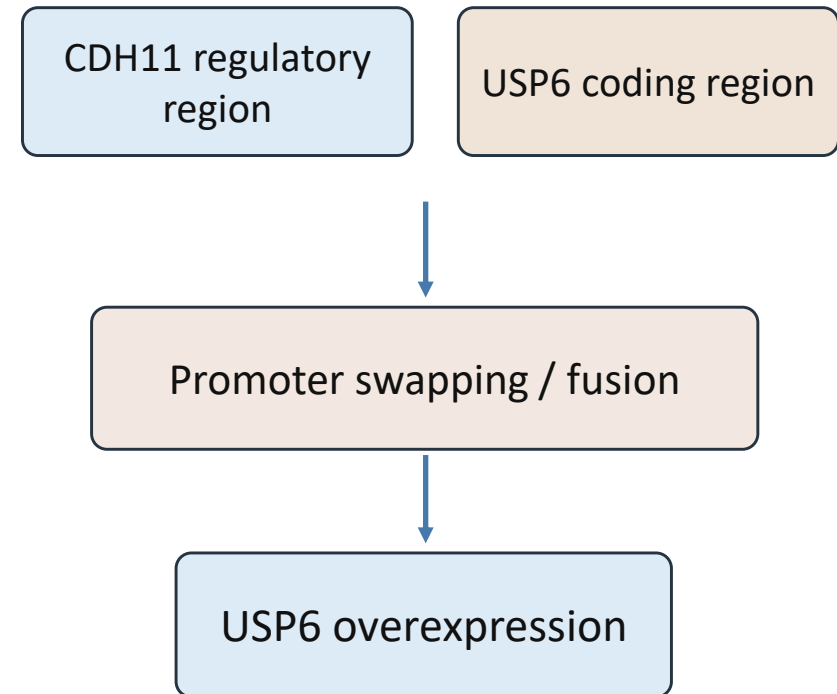


Schematic — not a specimen

How ABC came to be recognized as a neoplasm

- The neoplastic element is a spindle-cell population within the septa.
- Chromosomal rearrangements provide molecular evidence of clonal neoplasia.
- This differs from interpreting a hemorrhagic cavity as a purely passive blood collection.

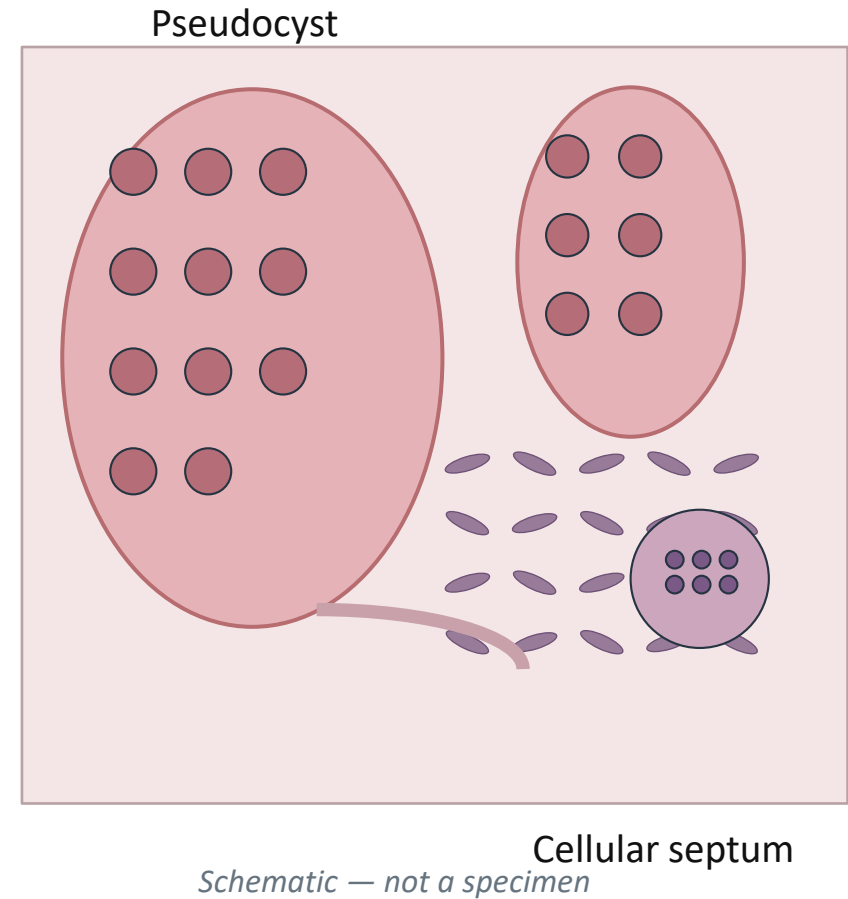
Normal gene regulation



Schematic — not a specimen

Cellular origin remains incompletely defined

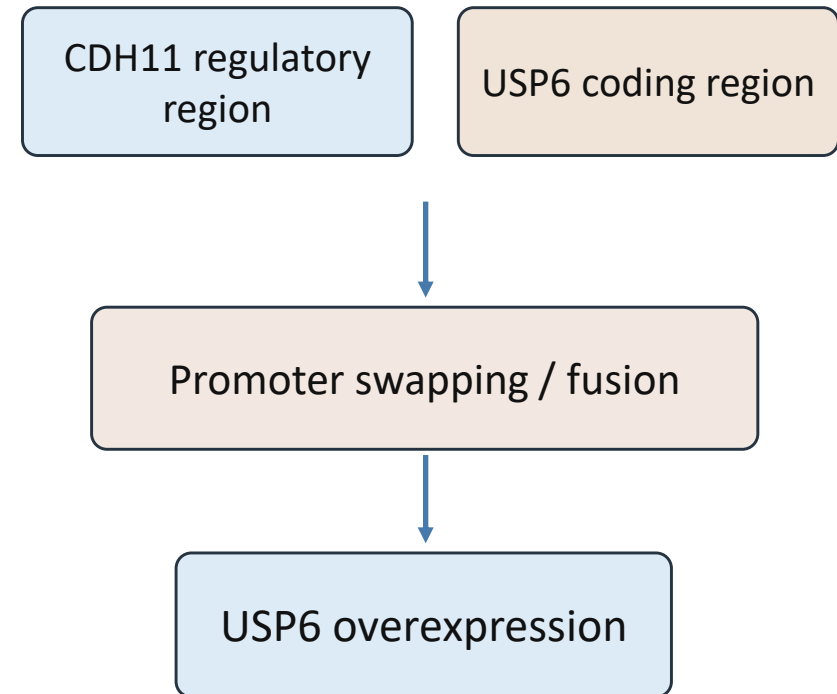
- The spindle-shaped neoplastic cells as being of uncertain origin.
- The spindle cells coexist with osteoclast-like giant cells and osteoblastic bone repair.
- Do not infer a proven specific cell of origin solely from morphology.



Chromosome 17p13 involvement

- The defining molecular mechanism involves rearrangements at chromosome 17p13.
- The locus contains USP6, the gene activated in many primary ABCs.
- These are gene-regulatory rearrangements, not a general rule of chromosome loss.

Normal gene regulation

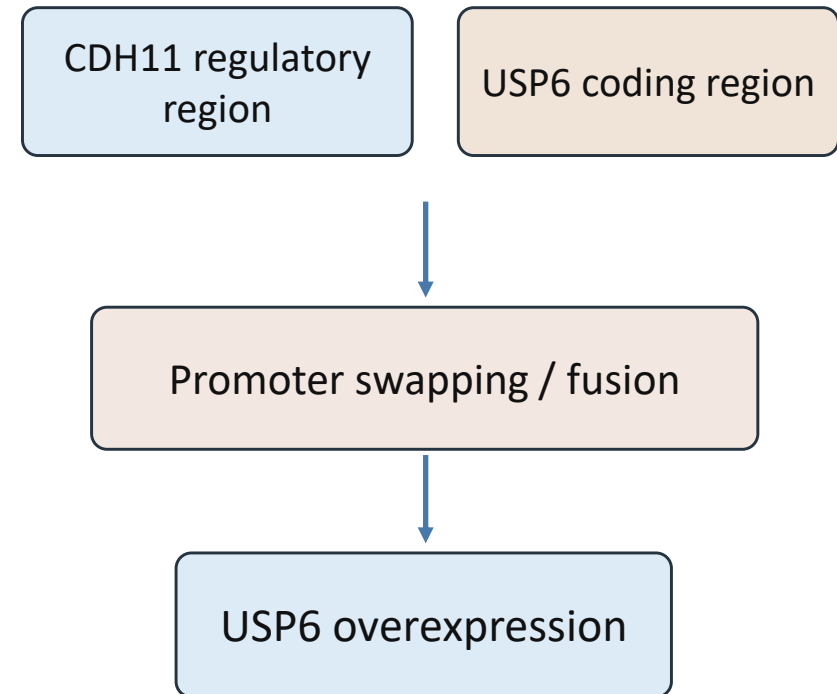


Schematic — not a specimen

USP6 activation: The essential molecular event

- The USP6 coding region becomes juxtaposed to regulatory elements of partner genes.
- The result is overexpression of USP6 protein.
- Partner-gene diversity is compatible with a shared USP6-driven pathway.

Normal gene regulation

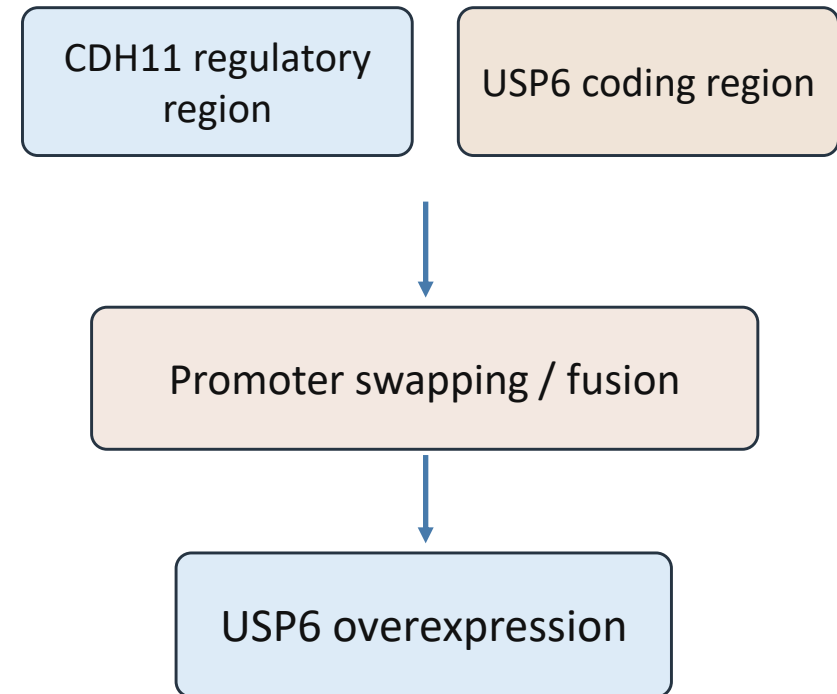


Schematic — not a specimen

CDH11 as a recurrent fusion partner

- CDH11 as the most common USP6 regulatory partner.
- The partner contributes gene-control elements; The USP6 coding sequence remains relevant.
- A CDH11–USP6 example illustrates promoter swapping rather than a new chimeric enzyme domain.

Normal gene regulation

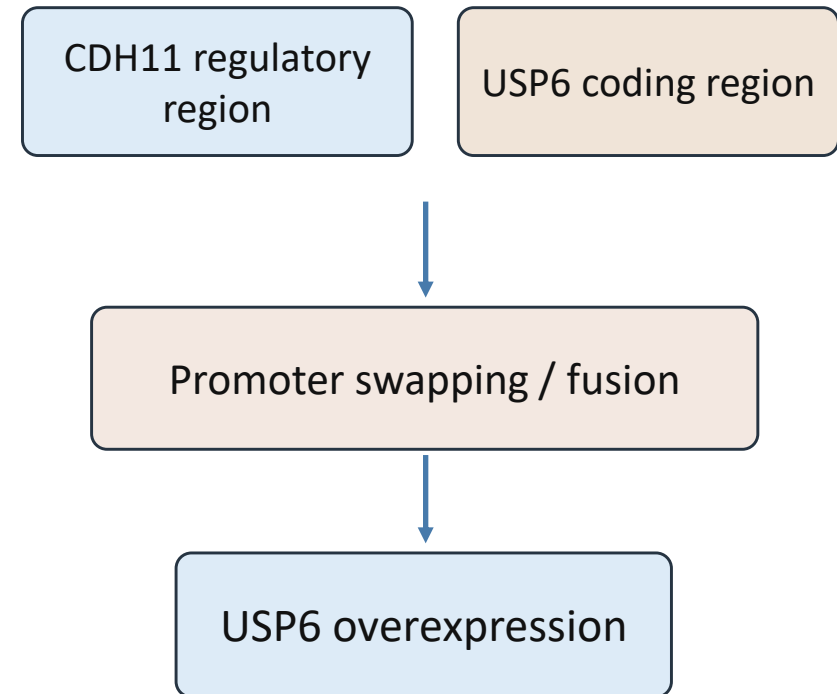


Schematic — not a specimen

Promoter swapping: Mechanism, not mere naming

- A relatively active partner regulatory region becomes linked to USP6.
- USP6 transcription is inappropriately enhanced in neoplastic septal cells.
- The pathogenic point is deregulated expression, even when fusion partners differ.

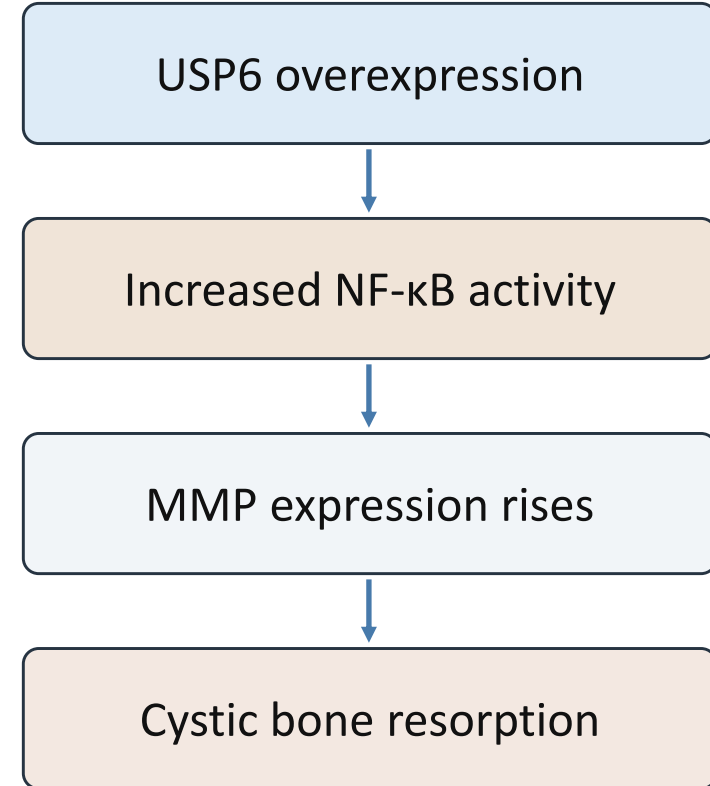
Normal gene regulation



Schematic — not a specimen

USP6 is a deubiquitinating enzyme

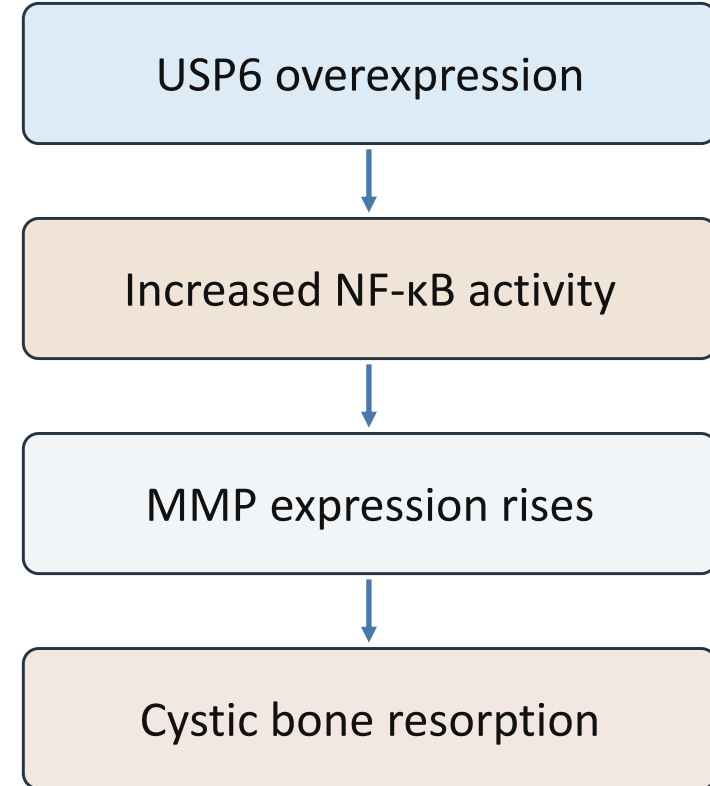
- USP6 encodes a deubiquitinating protein.
- In ABC, its overexpression increases signaling activity downstream.
- The clinically important result is a transcriptional program that promotes matrix breakdown.



Schematic — not a specimen

NF- κ B signaling downstream of USP6

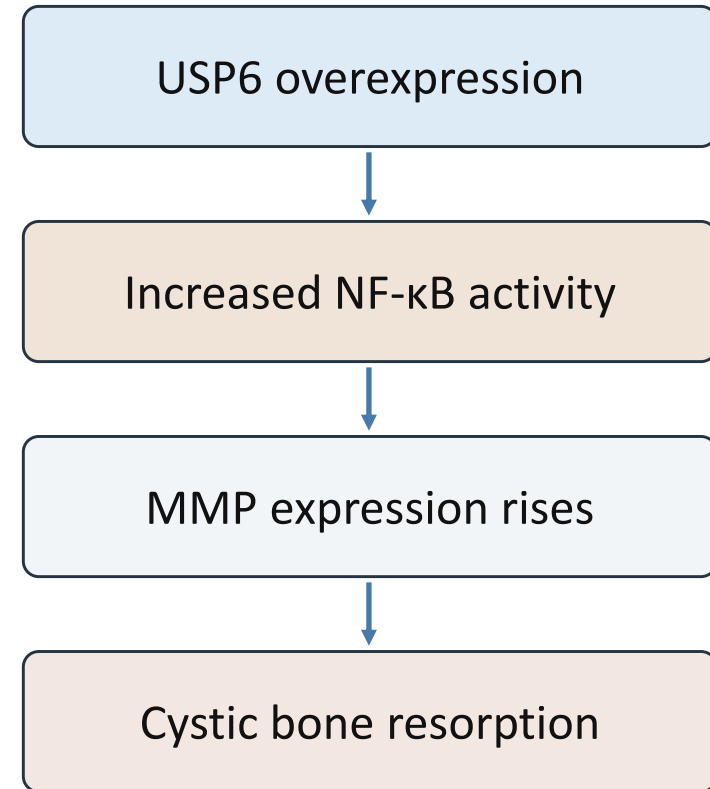
- The Robbins mechanism places increased NF- κ B activity after USP6 overexpression.
- NF- κ B functions as a transcription factor that alters gene expression.
- This links a genetic alteration to a destructive tissue phenotype.



Schematic — not a specimen

Matrix metalloproteinases and osteolysis

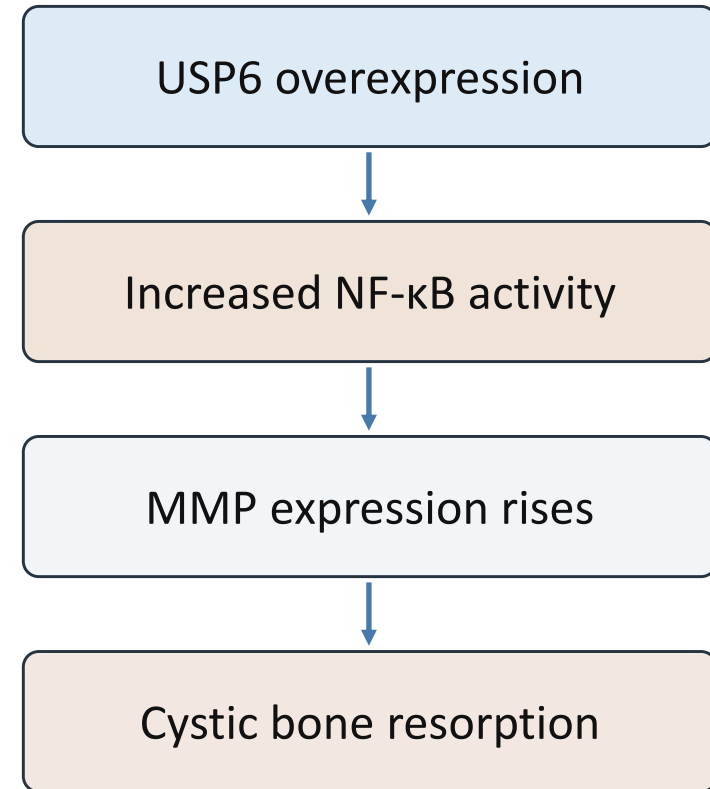
- NF- κ B—associated transcription increases proteins including matrix metalloproteinases.
- These enzymes contribute to extracellular-matrix degradation.
- Their increased activity helps explain cystic resorption of native bone.



Schematic — not a specimen

Pathogenesis: Integrated sequence

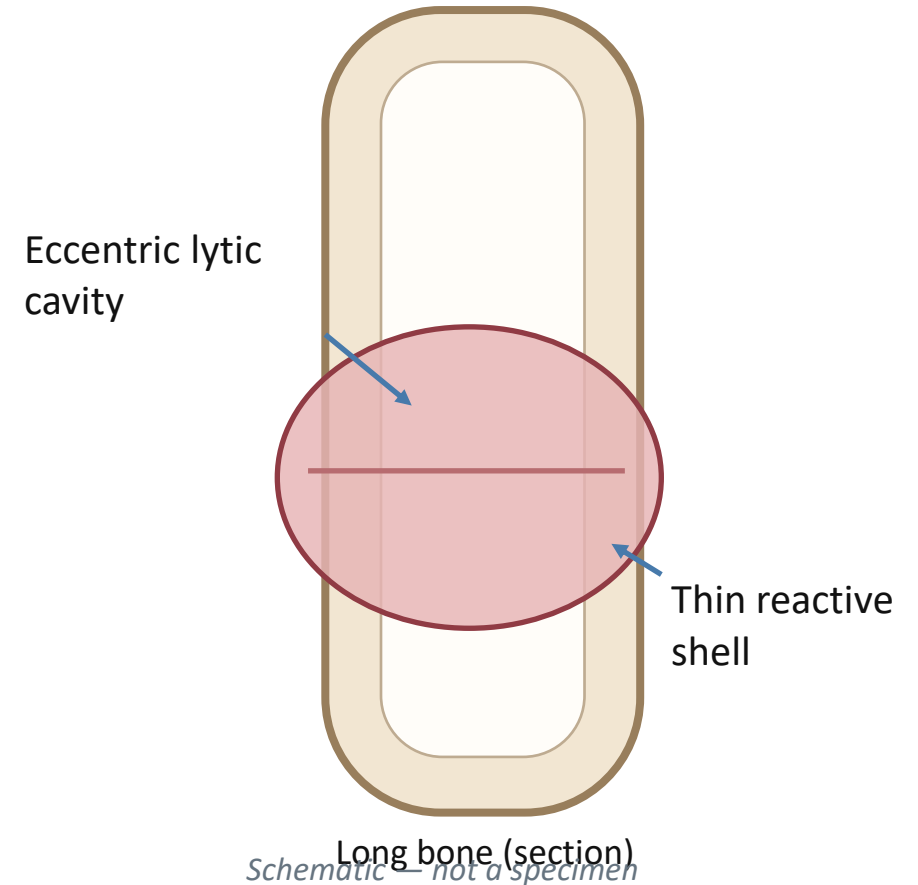
- Regulatory fusion → USP6 overexpression.
- USP6 → enhanced NF-κB activity → matrix metalloproteinase expression.
- Progressive matrix destruction produces characteristic cystic bone resorption.



Schematic — not a specimen

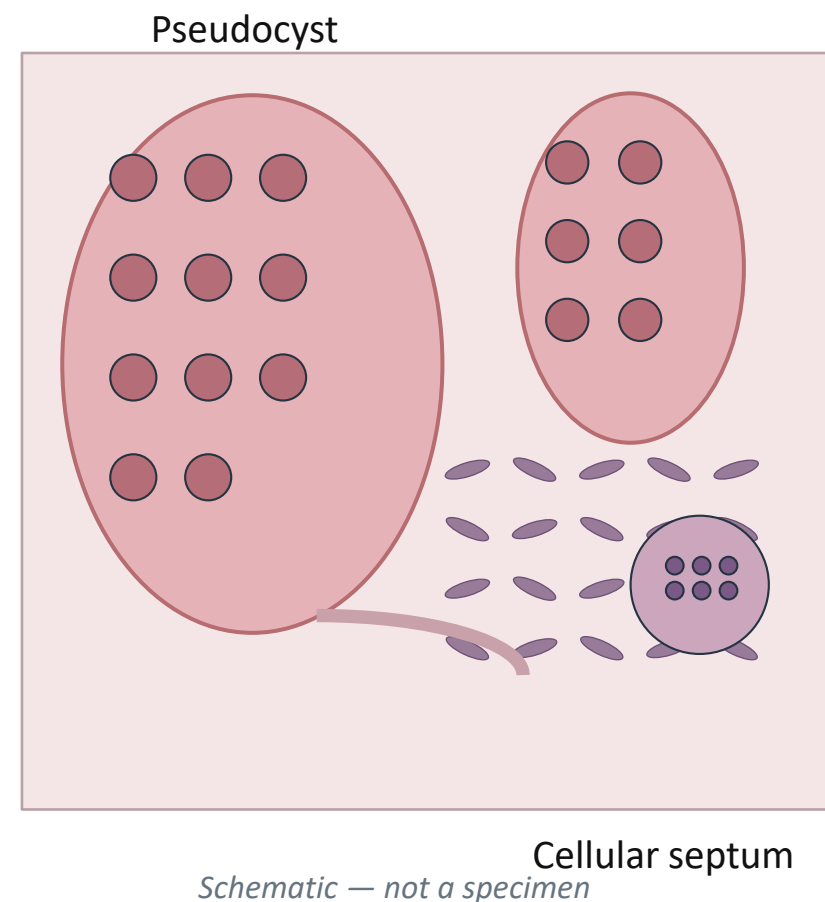
Molecular mechanism explains the imaging

- Resorption creates a lytic compartment in an otherwise mineralized organ.
- Loculated hemorrhagic spaces produce internal structure rather than a single simple cavity.
- Reactive bone at the periphery provides the characteristic thin shell.



Phenotype integrates neoplastic and reactive elements

- Neoplastic spindle cells are embedded in a lesion with extensive secondary tissue responses.
- Osteoclast-type giant cells and osteoblast-rimmed woven bone help shape the histology.
- The presence of reactive structures does not negate the neoplastic USP6 driver.



Primary ABC versus secondary ABC-like change

- A primary ABC is a distinct neoplastic lesion, commonly associated with USP6 rearrangement.
- ABC-like cystic changes may occur within other bone tumors and require identification of that lesion.
- The term “secondary ABC” must not obscure a different underlying diagnosis.

Primary aneurysmal bone cyst

USP6-driven neoplastic septal cells

ABC-like change within another lesion

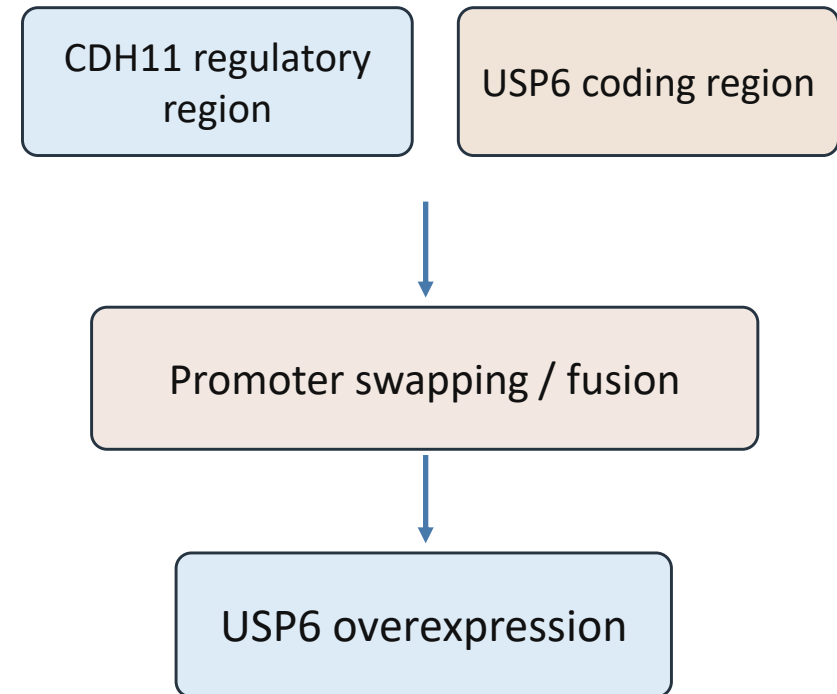
Find and characterize underlying
tumor

Schematic — not a specimen

What USP6 testing can contribute

- Detection of a USP6 rearrangement supports primary ABC in an appropriate context.
- Molecular testing may clarify an equivocal hemorrhagic giant-cell-rich lesion.
- A negative test does not automatically exclude ABC; Assay context and morphology remain necessary.

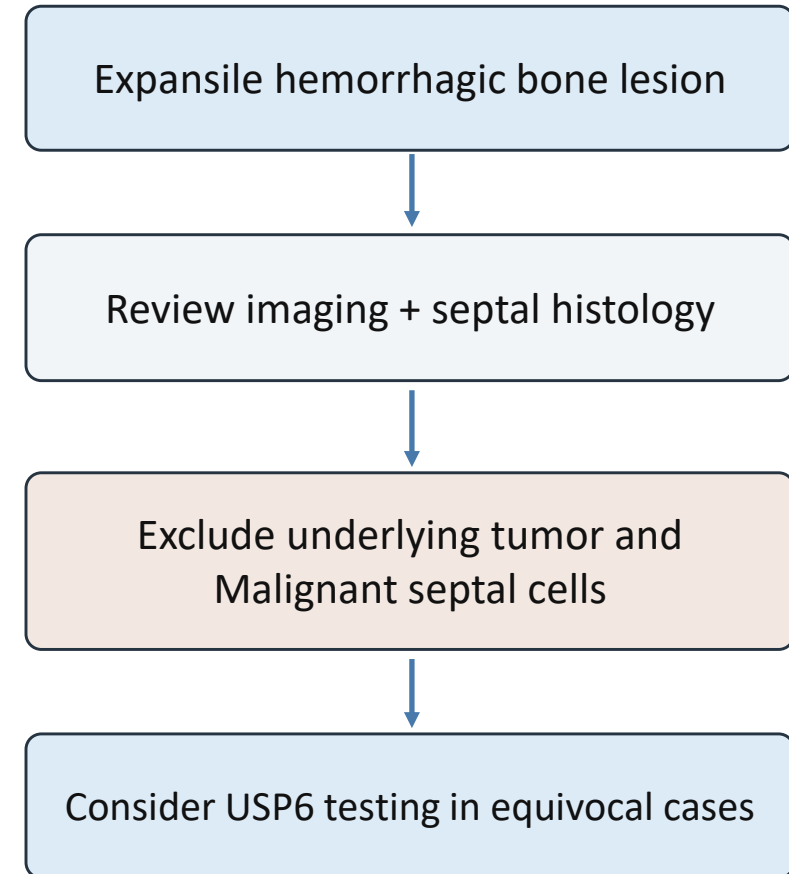
Normal gene regulation



Schematic — not a specimen

Molecular results cannot replace tissue assessment

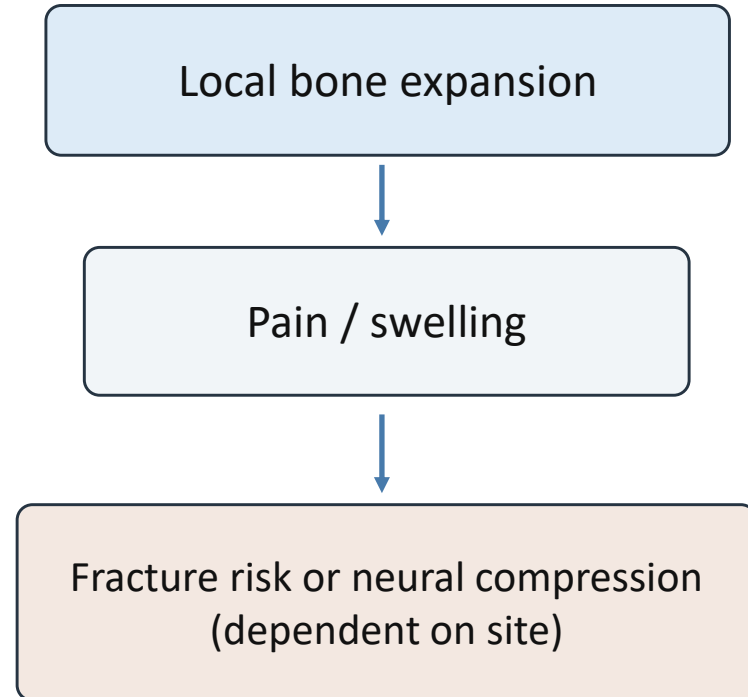
- USP6 activation can be shared across several other USP6-rearranged soft-tissue and bone processes.
- Identify the anatomic site and characteristic architecture before assigning the diagnosis.
- Conversely, hemorrhagic morphology alone does not establish USP6 status.



Schematic — not a specimen

Localized pain: A principal symptom

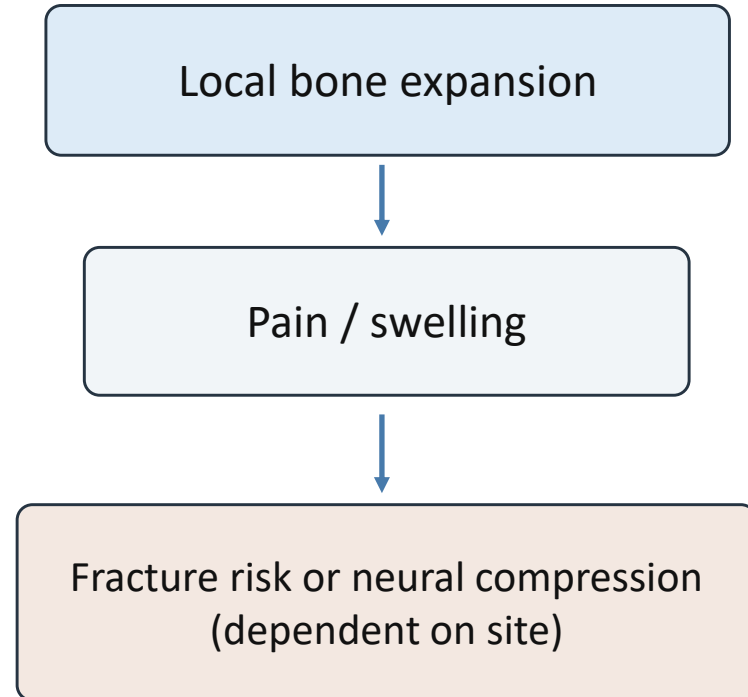
- ABC frequently presents with pain localized to the affected bone.
- Expansile osteolysis and distortion of adjacent structures provide a clinicopathologic explanation.
- Neither pain severity nor duration is specific for ABC.



Schematic — not a specimen

Swelling as a sign of local expansion

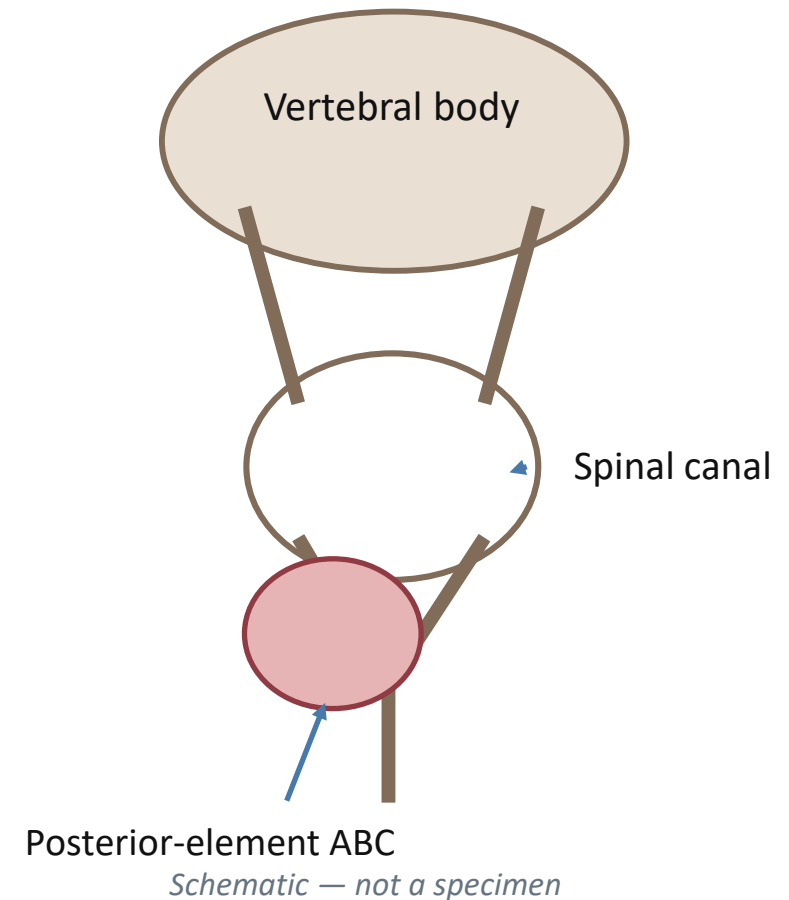
- Local enlargement may produce visible or palpable swelling.
- A locally aggressive lesion can deform the bony outline despite benign classification.
- Examination findings should be interpreted with bone site and imaging.



Schematic — not a specimen

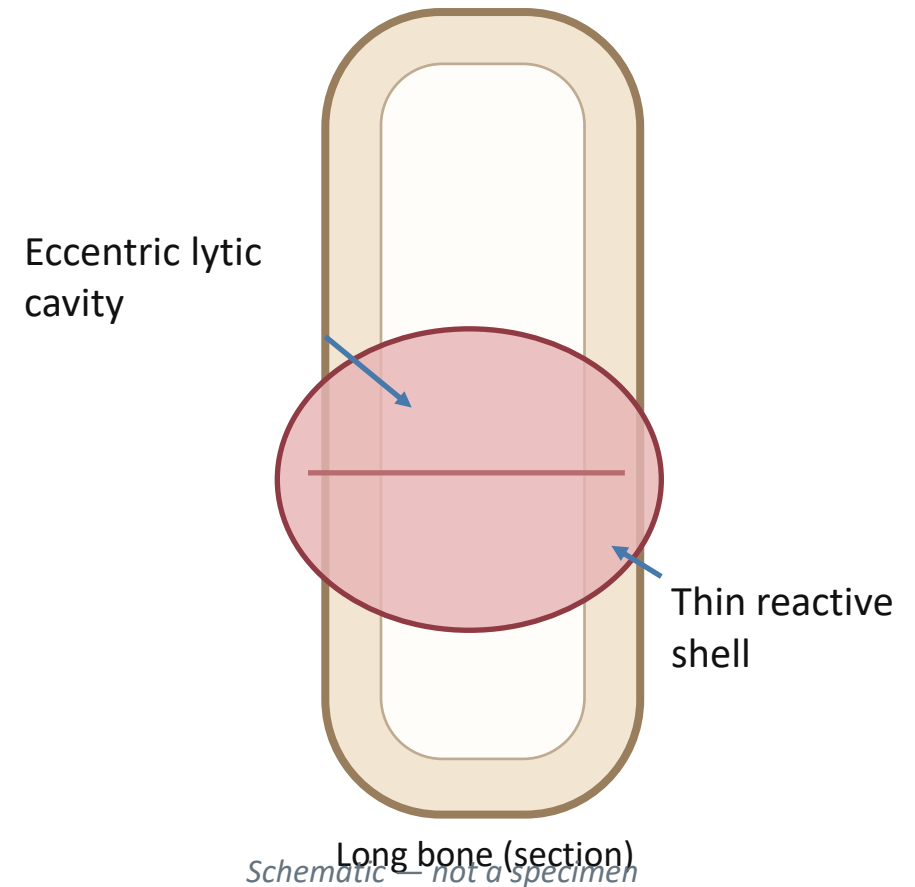
Spinal lesions and neurologic compromise

- Lesions of vertebral posterior elements may compress nerves.
- Clinical assessment should seek neurologic deficits when spine involvement is suspected.
- Benign pathology does not imply an absence of urgent anatomic consequences.



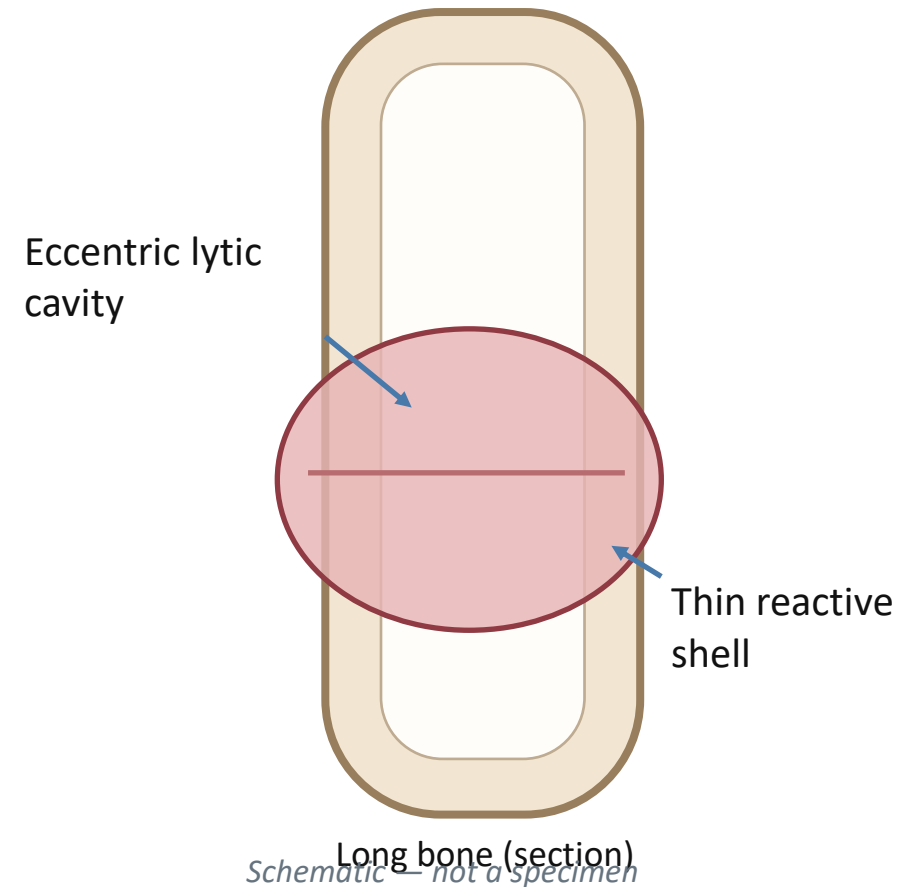
Pathologic fracture and secondary changes

- Cortical attenuation makes fracture a biologically plausible complication of expansion.
- Fracture-related tissue damage can cause necrosis; Robbins otherwise describes necrosis as uncommon.
- In a fractured lesion, do not overinterpret necrosis without the full clinical context.



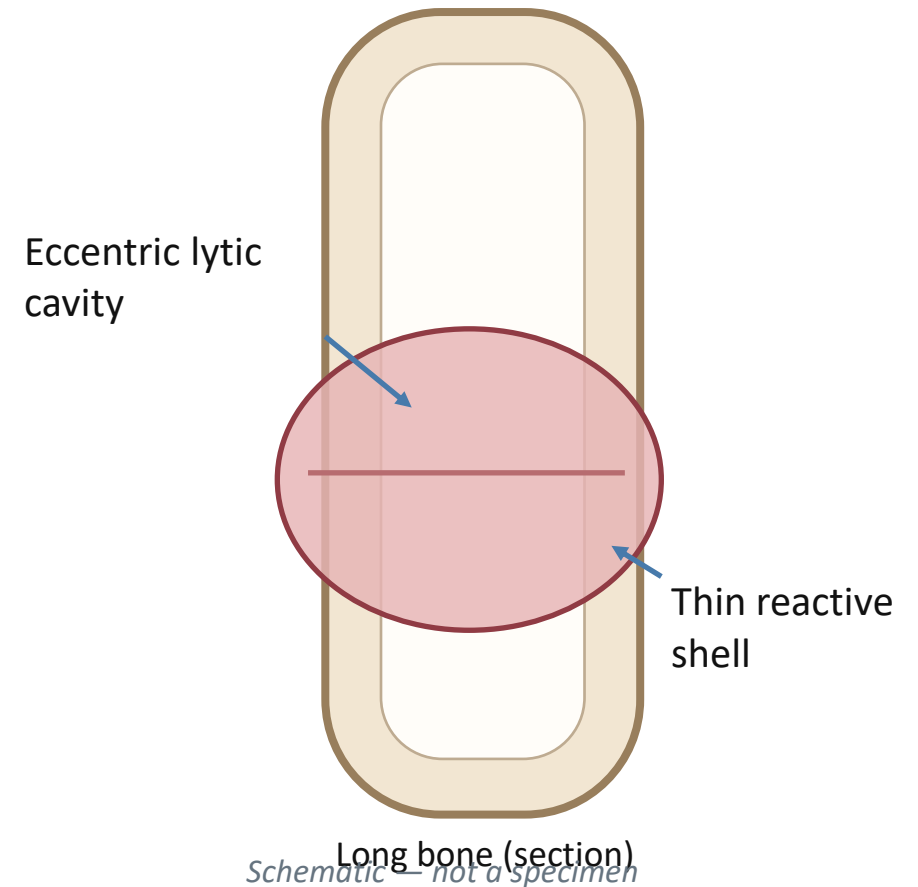
Radiologic evaluation: The lesion as a whole

- Describe location, centricity, margin, cortical shell and internal architecture.
- ABC usually combines an eccentric expansile lytic component with a well-defined boundary.
- Interpretation requires more than the presence or absence of fluid-fluid levels.



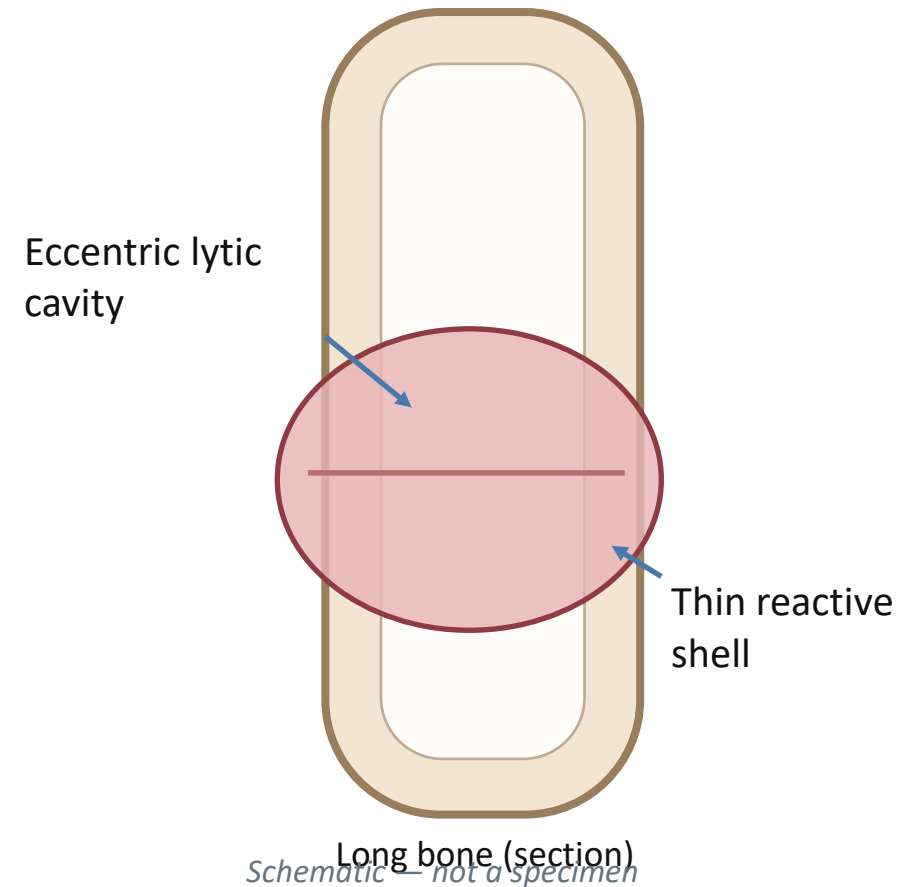
Eccentric lytic pattern

- ABC is generally eccentric rather than uniformly centered within a long bone.
- “Lytic” denotes loss of mineralized bone in the lesion.
- Expansile behavior helps separate the lesion from a small static cortical defect.



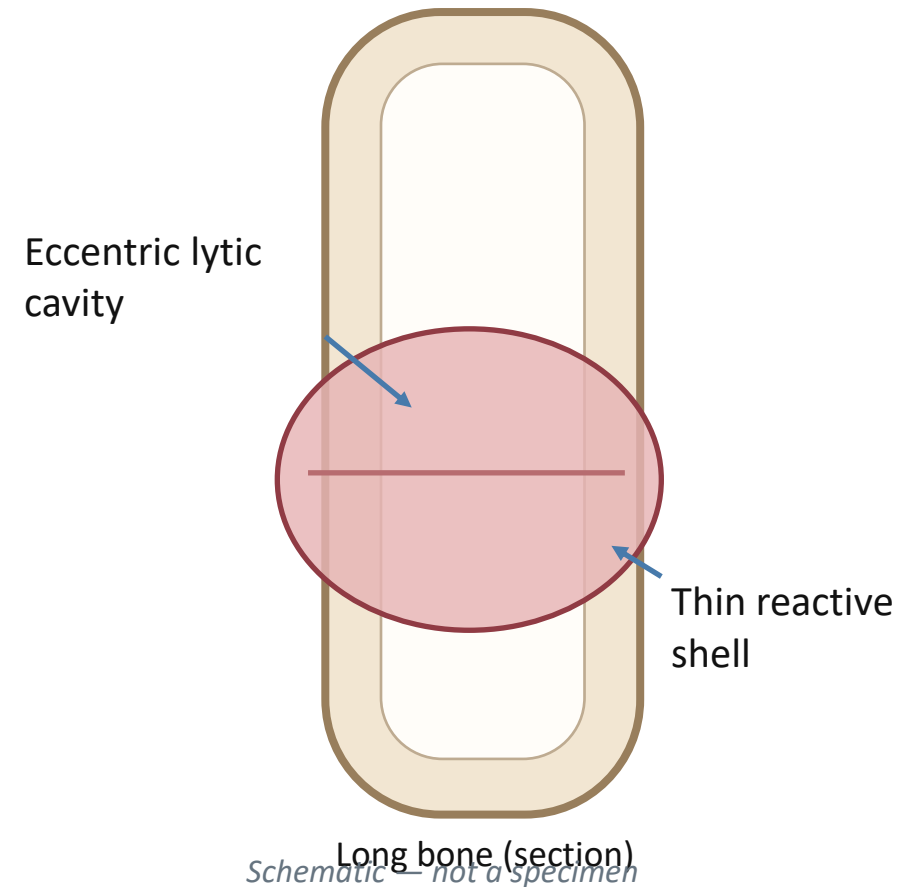
Expansile growth and cortical remodeling

- Growth can produce marked outward expansion of the bone.
- An attenuated peripheral bony shell may remain as the lesion enlarges.
- An expanding benign process can resemble aggressive disease on a single imaging feature.



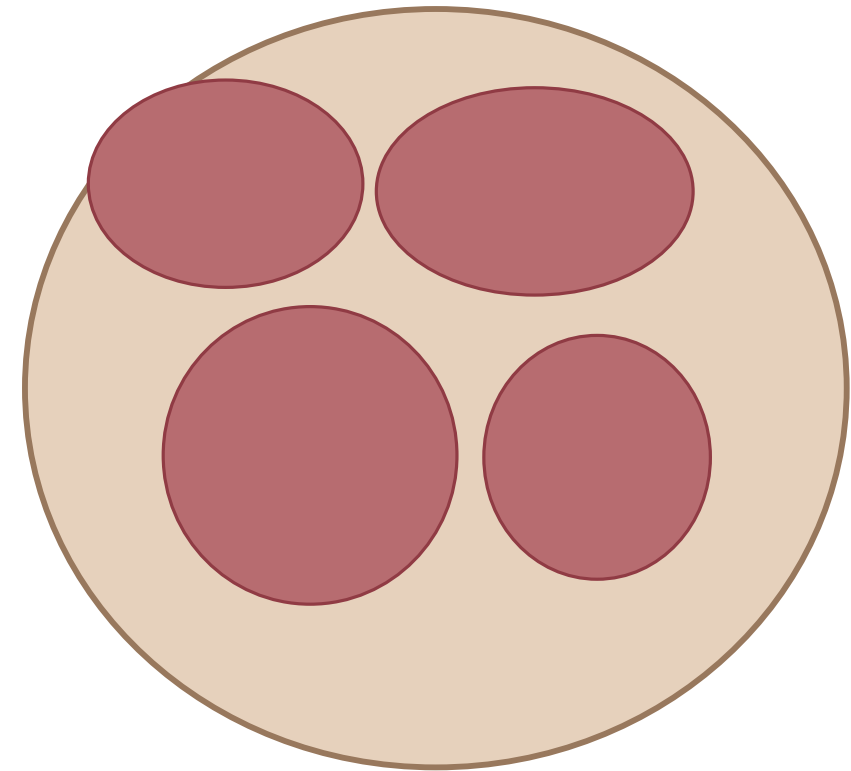
Well-defined margin and reactive eggshell

- Most ABCs are circumscribed and radiographically well defined.
- A thin sclerotic peripheral eggshell reflects reactive bone deposition.
- This rim is a pattern clue; It is not proof of an exclusive diagnosis.



Internal septa on cross-sectional imaging

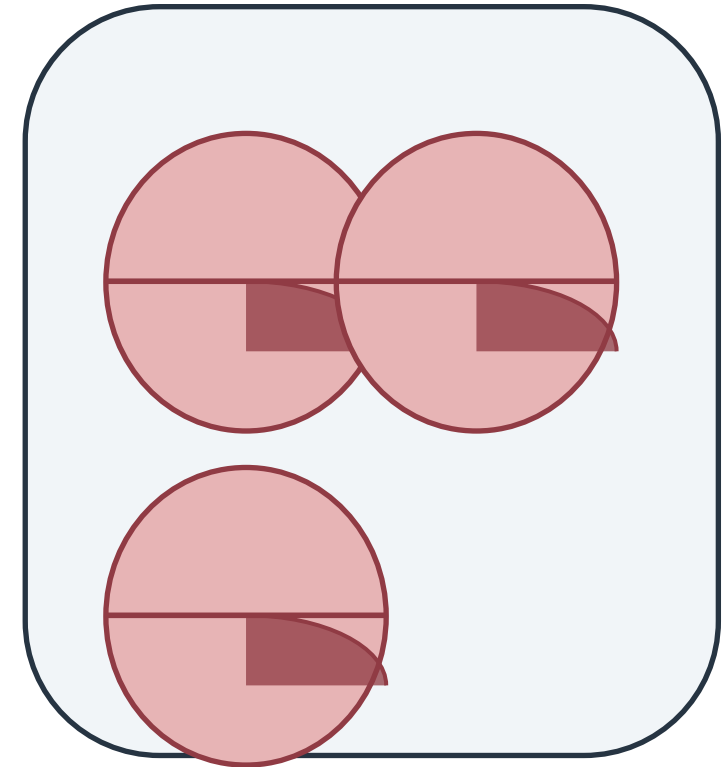
- Computed tomography and magnetic resonance imaging can show internal septation.
- Multiloculation on imaging corresponds to the fibrous partitions visible grossly.
- The septa are relevant targets for histologic examination and differential diagnosis.



Blood-filled spaces Fibrous septa
Schematic — not a specimen

Fluid–fluid levels: Characteristic imaging clue

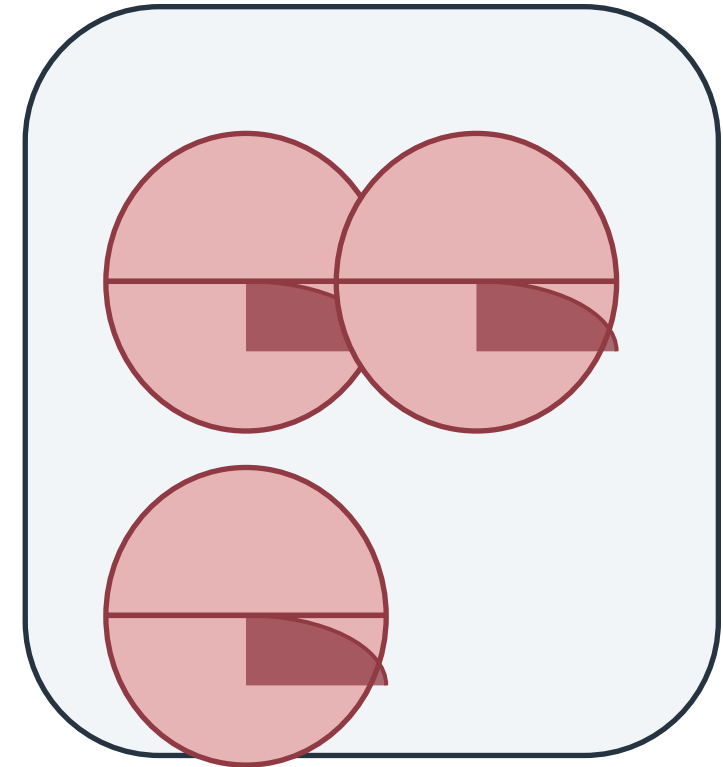
- CT and MRI can reveal fluid–fluid levels within cystic spaces.
- Levels provide a useful clue to compartmentalized hemorrhagic contents.
- They should be interpreted with lesion margins, septa and other imaging features.



Horizontal interfaces between
Schematic — not a specimen
Layered hemorrhagic contents

Why fluid–fluid interfaces develop

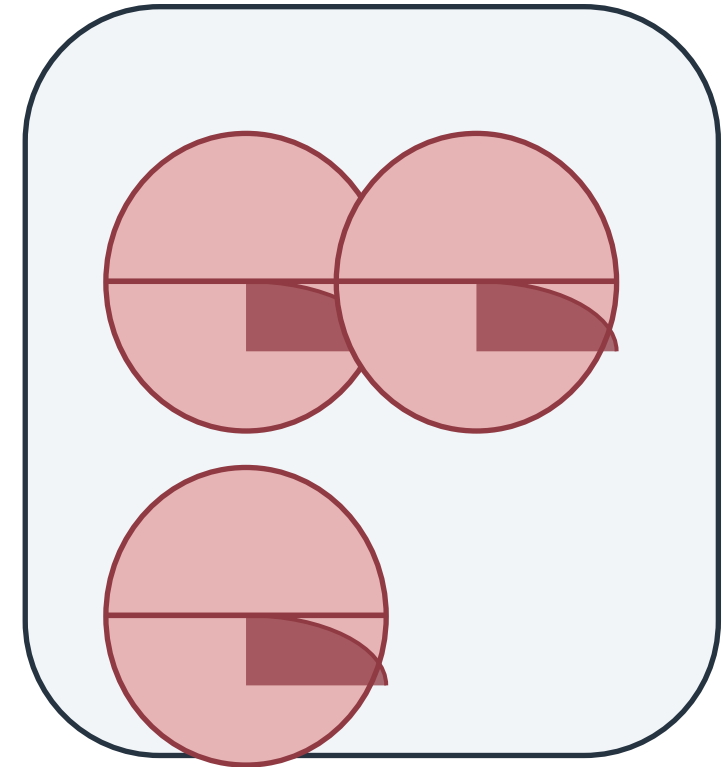
- Different-density hemorrhagic components can settle into layers within a cavity.
- Cross-sectional imaging depicts the resulting interfaces between fluid components.
- This physical interpretation does not prove that the underlying lesion is benign.



Horizontal interfaces between
Schematic — not a specimen
Layered hemorrhagic contents

Fluid levels are not pathognomonic

- Other hemorrhagic bone tumors may also contain fluid–fluid levels.
- Telangiectatic osteosarcoma is an important malignant mimic.
- An indeterminate aggressive lesion requires attention to solid septa and tissue diagnosis.



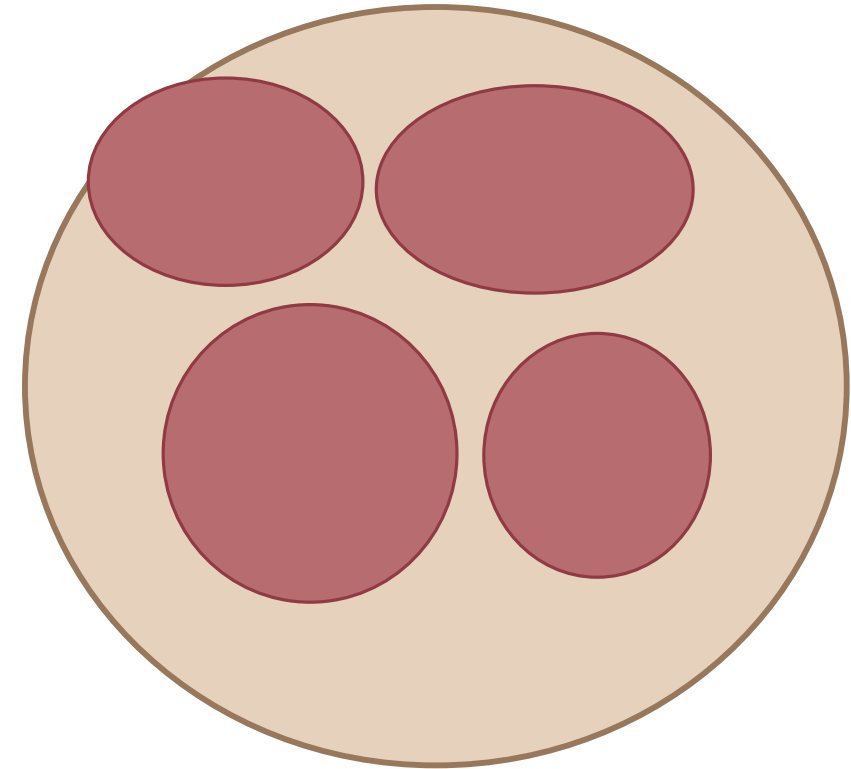
Horizontal interfaces between
Schematic — not a specimen
Layered hemorrhagic contents

Structured imaging report for suspected ABC

- Specify bone, anatomic compartment and distance to adjacent critical structures.
- Describe lesion margins, cortical integrity, expansion and internal septation.
- Report fluid levels and identify solid components requiring scrutiny.

Gross appearance: Multiple blood-filled cavities

- A sectioned ABC has a hemorrhagic, sponge-like appearance.
- Numerous cystic spaces are separated by pale tan-white septa.
- The macroscopic anatomy matches the multiloculated appearance seen on imaging.



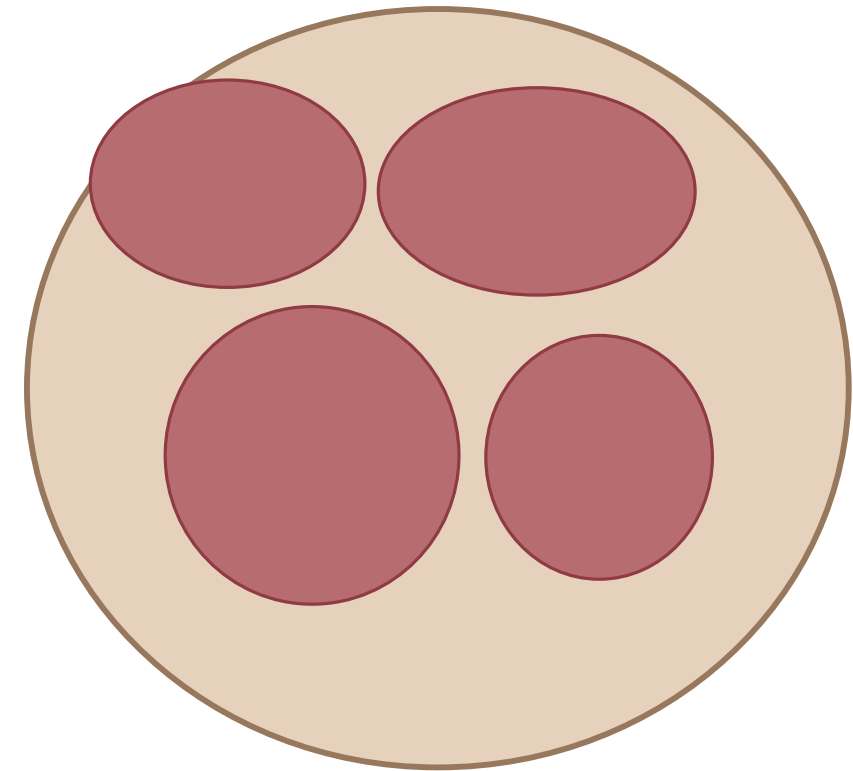
Blood-filled spaces

Fibrous septa

Schematic — not a specimen

Gross septa are diagnostically important

- Blood may dominate a sectioned lesion visually, but the septa contain the tissue architecture.
- Septal tissue is therefore essential for identifying neoplastic and reactive components.
- An isolated blood sample cannot adequately characterize the whole lesion.



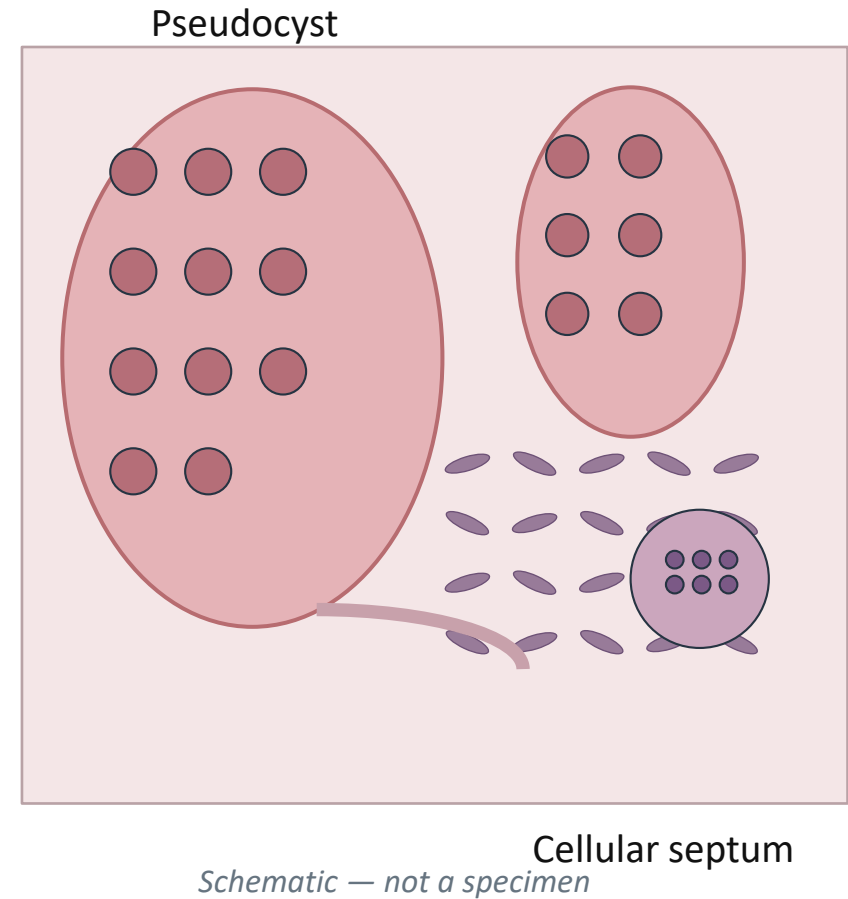
Blood-filled spaces

Fibrous septa

Schematic — not a specimen

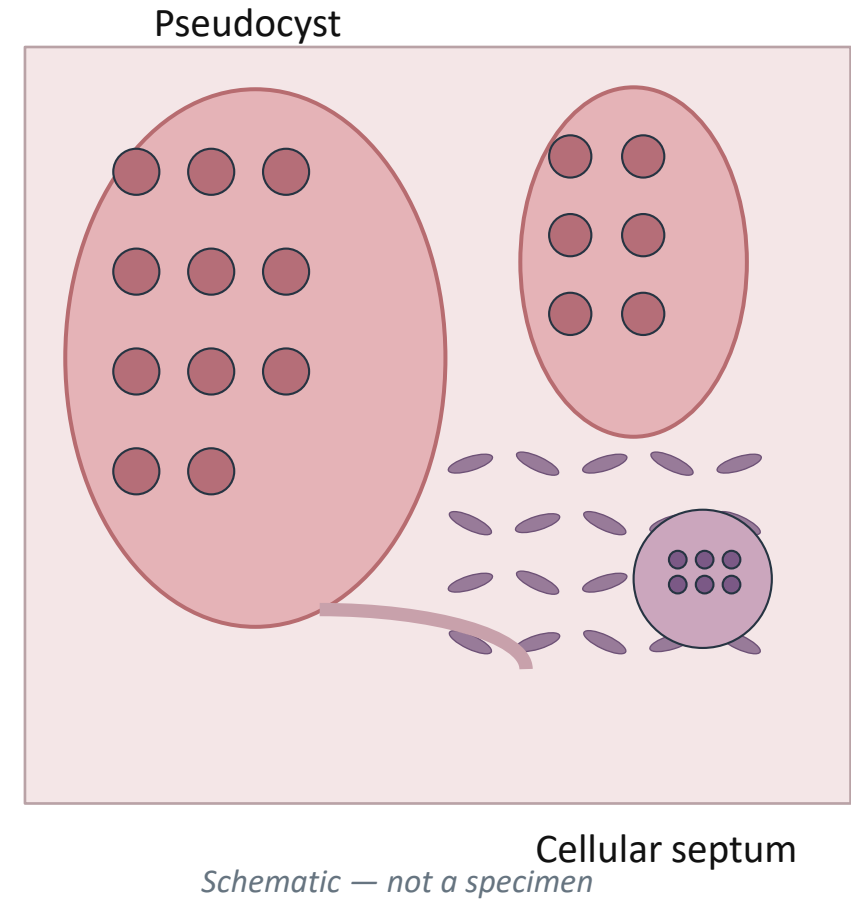
Microscopic architecture: Pseudocysts

- Spaces contain blood yet lack endothelial lining.
- Fibrous, cellular septa partition adjacent cavities.
- The lesion is therefore not a conventional vascular malformation or true endothelial-lined aneurysm.



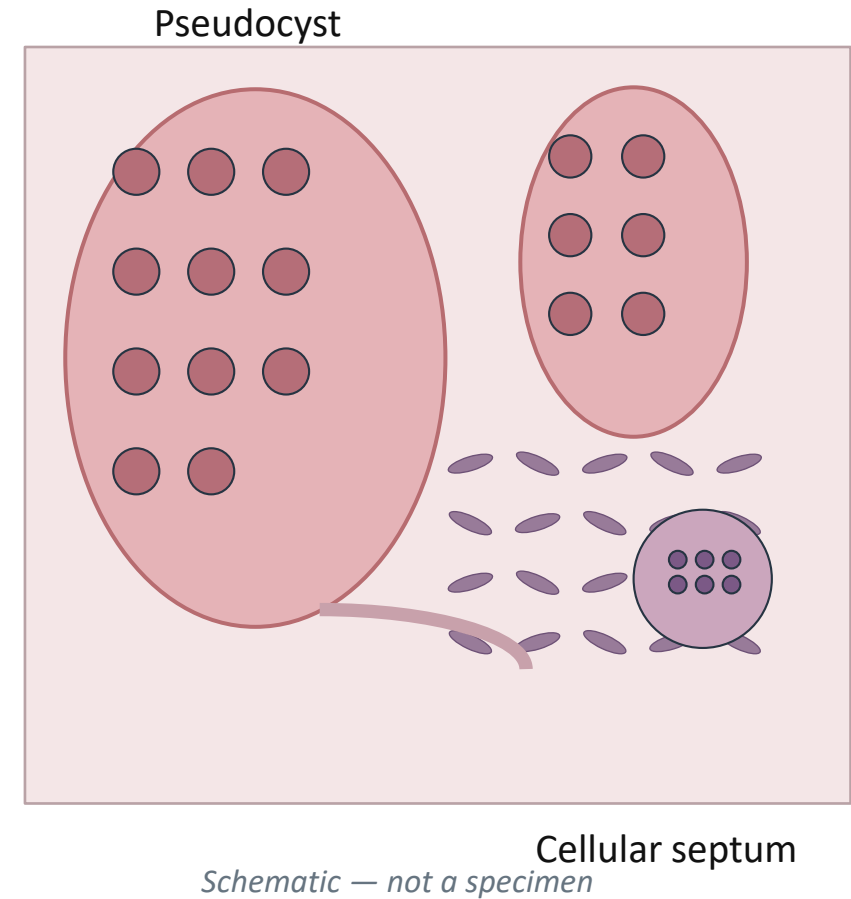
Septal plump spindle cells

- The septa contain plump spindle-shaped lesional cells.
- These form part of the neoplastic tissue compartment.
- Interpret spindle cells in relation to giant cells, woven bone and overall morphology.



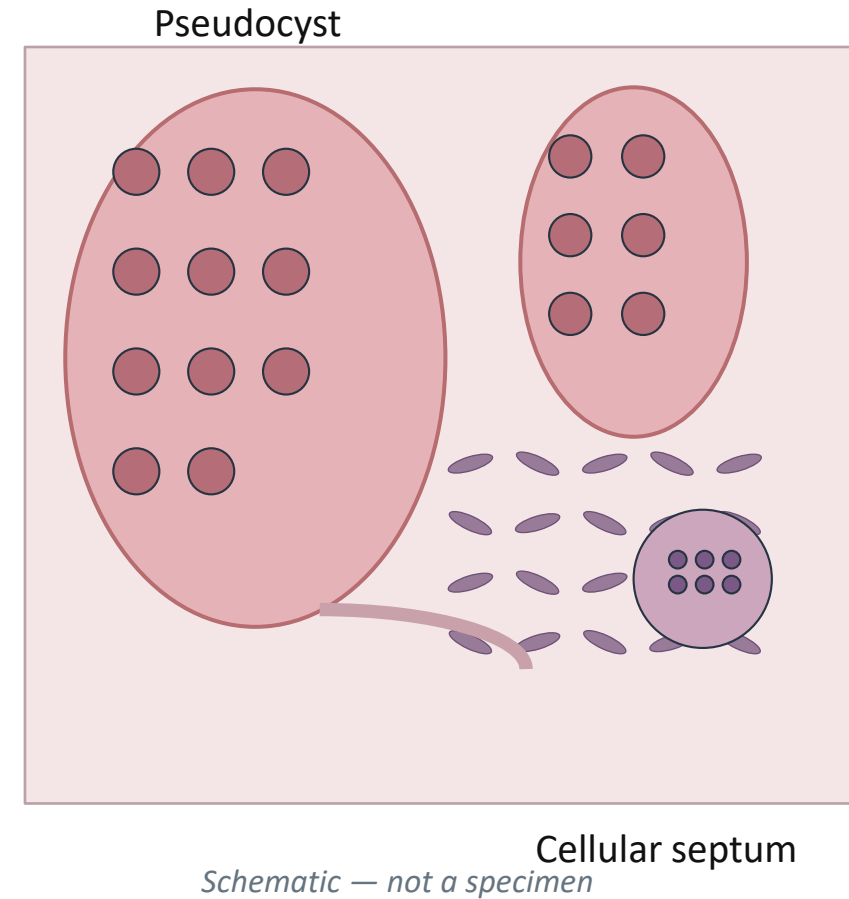
Osteoclast-type multinucleated giant cells

- Multinucleated osteoclast-like cells occur in the septa.
- Giant cells are a morphological feature, not a uniquely diagnostic marker.
- The differential includes other giant-cell-rich bone lesions.



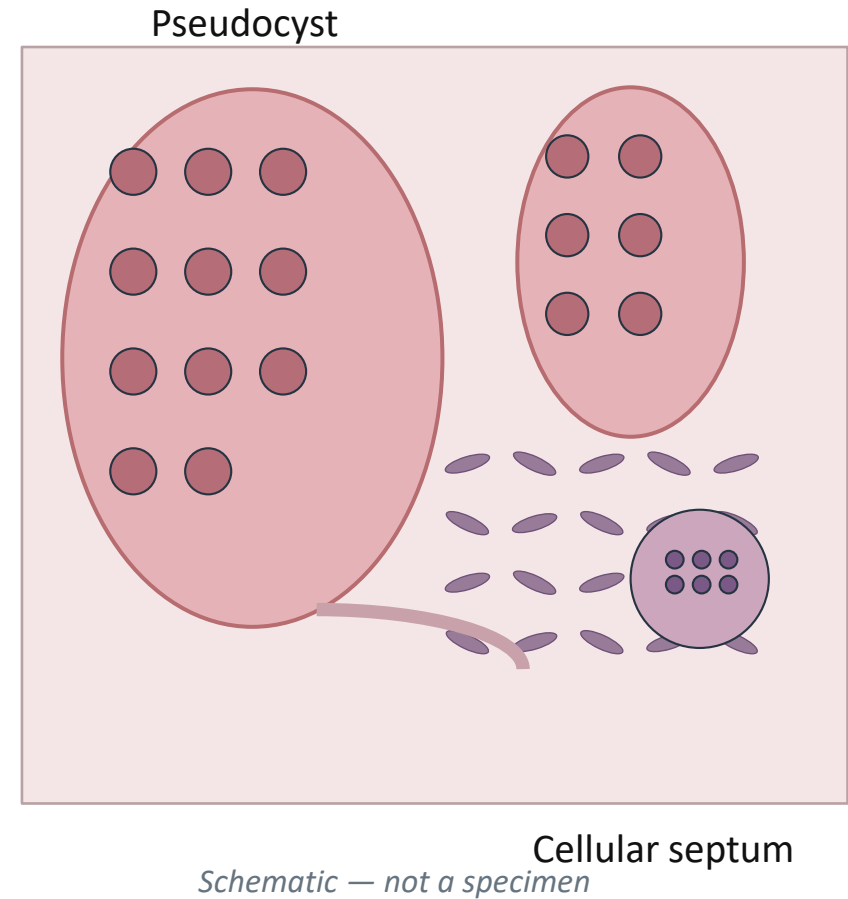
Reactive woven bone in the septa

- Irregular woven bone is present within the fibrous septa.
- Bony deposition often follows the contours of septal structures.
- This pattern helps explain osseous material within a largely hemorrhagic lesion.



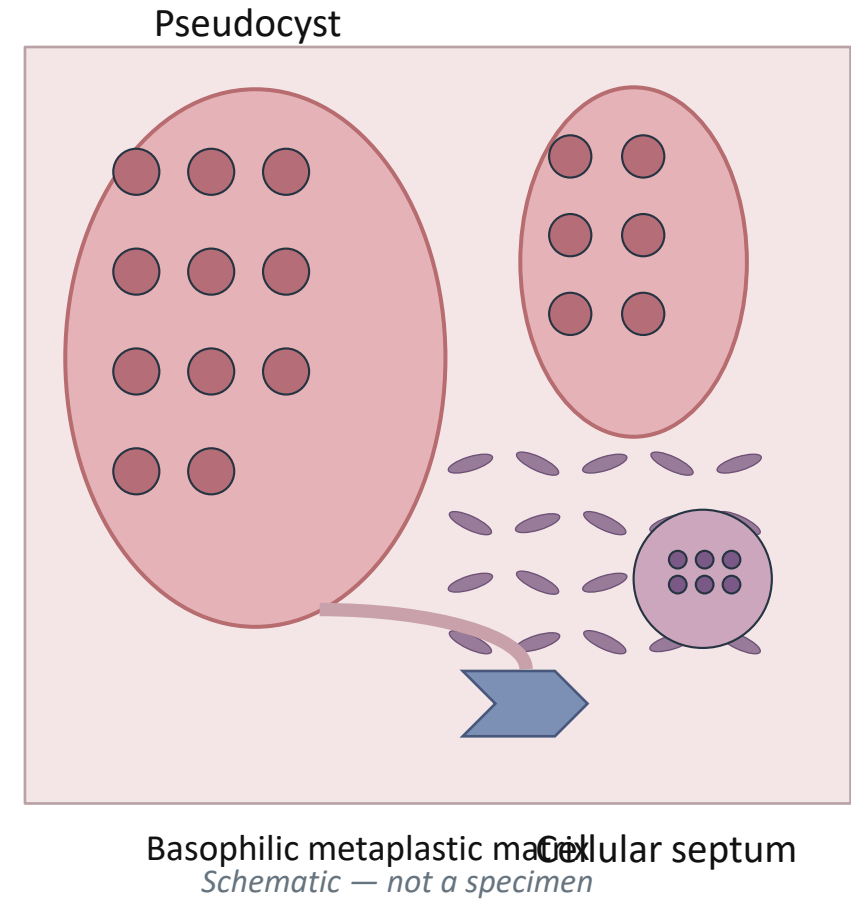
Osteoblastic rimming of reactive bone

- Reactive woven bone lined by osteoblasts.
- This is a recognizable component of the septa, not evidence of malignant osteoid production.
- Evaluate lining cells and matrix together in the context of the full section.



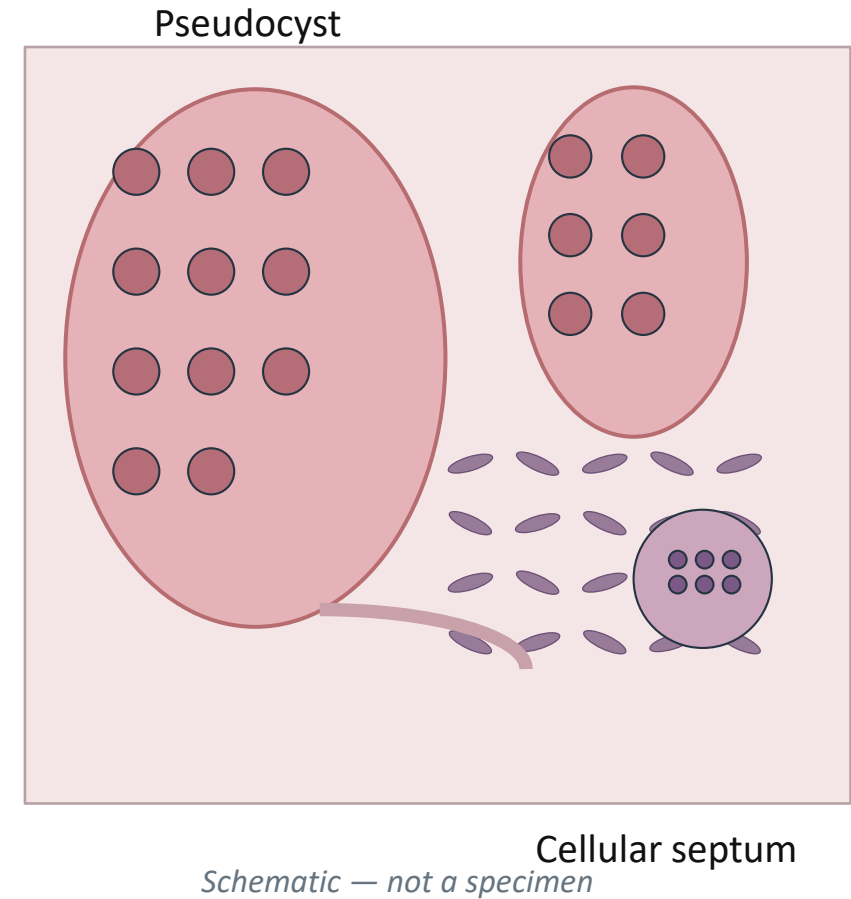
Blue bone: A distinctive metaplastic matrix

- Approximately one-third of ABCs contain densely calcified basophilic metaplastic matrix.
- This material is termed “blue bone”.
- Its presence supports a morphologic pattern but is not a universal requirement.



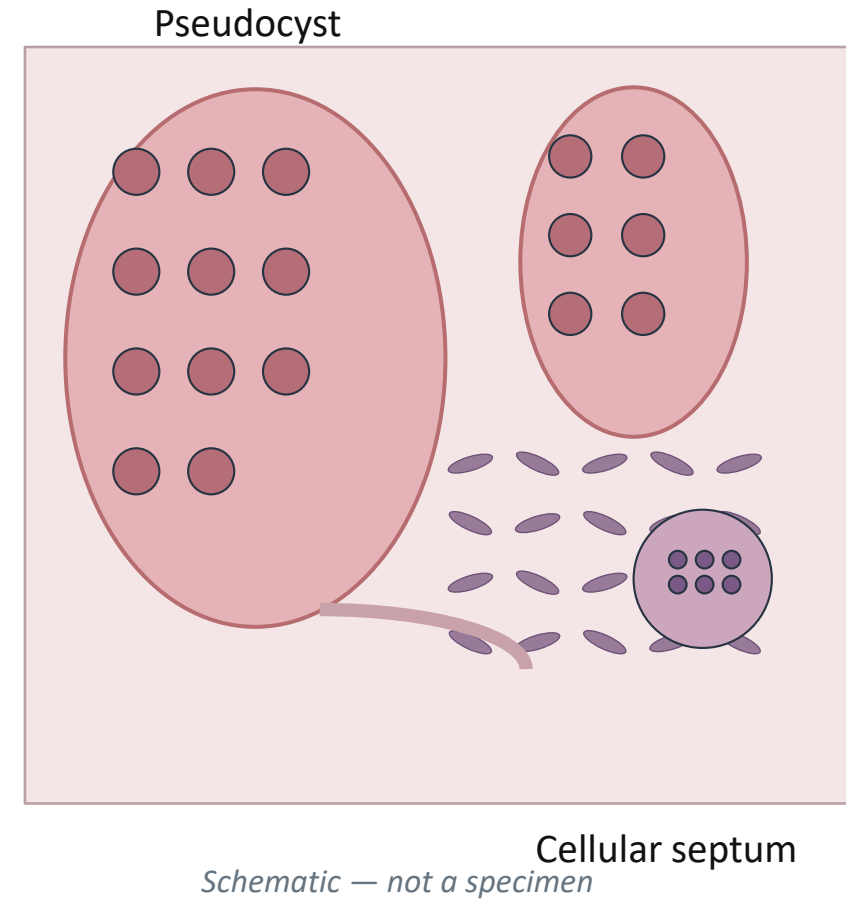
Necrosis: An important contextual observation

- Necrosis is uncommon in ABC without associated pathologic fracture.
- Fracture can produce secondary necrosis within an otherwise benign process.
- Extensive atypia or concerning solid tissue should not be dismissed as a fracture effect.



Integrated microscopic diagnostic pattern

- Blood-filled non–endothelial-lined spaces are separated by cellular septa.
- The septa contain spindle cells, osteoclast-type giant cells and reactive osteoblast-rimmed woven bone.
- A broad specimen and radiologic correlation increase confidence.

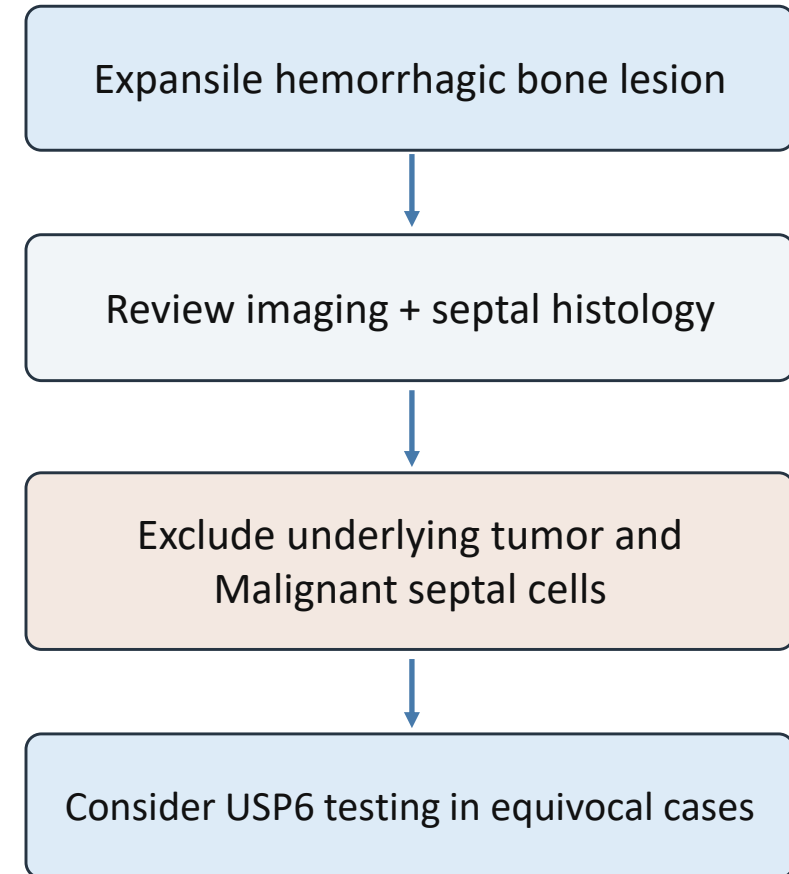


Radiologic–gross–histologic correspondence

Radiology	Gross specimen	Histology
Expansile lysis	Loculated hemorrhagic cavity	Bone resorption and fibrous septa
Fluid–fluid levels	Blood-filled compartments	Hemorrhage within pseudocysts
Thin reactive shell	Peripheral bone remodeling	Reactive bone formation
Internal septa	Tan-white fibrous partitions	Spindle cells, giant cells, woven bone

Why sampling may mislead

- A cavity may yield blood rather than diagnostic septal tissue.
- Cystic change may mask a pre-existing tumor within the same lesion.
- Review discordance between imaging and limited histology before committing to ABC.



Schematic — not a specimen

ABC versus giant cell tumor of bone

Feature	Aneurysmal bone cyst	Giant cell tumor
Typical context	Adolescence; long bones and posterior spine	Usually adults, often epiphysis of long bones
Dominant pattern	Blood-filled pseudocysts with septa	Solid mononuclear stroma with abundant giant cells
Molecular clue	USP6 regulatory rearrangement	H3-3A mutation in neoplastic cells
Clinical note	Expansile and locally aggressive	Locally destructive, may recur

ABC versus nonossifying fibroma

Feature	Aneurysmal bone cyst	Nonossifying fibroma
Typical imaging	Expansile lytic cavity; fluid levels possible	Eccentric metaphyseal lucency with sclerotic rim
Histologic architecture	Blood-filled spaces and cellular septa	Storiform bland fibroblasts and foamy macrophages
Characteristic cells	Spindle cells; osteoclast-type giant cells	Fibroblasts, macrophages, giant cells
Molecular context	USP6 regulatory fusion	RAS-pathway alterations described

ABC versus fibrous dysplasia

Feature	Aneurysmal bone cyst	Fibrous dysplasia
Architecture	Multiloculated hemorrhagic pseudocysts	Fibroblastic stroma with curvilinear woven bone
Woven bone	Reactive; often osteoblast-rimmed	Typically without prominent osteoblastic rimming
Molecular context	USP6 regulatory rearrangement	Somatic activating GNAS alterations
Important caution	May be a distinct primary lesion	May show superimposed ABC-like change

ABC-like change within another bone lesion

- Other benign and malignant tumors may develop secondary hemorrhagic cystic architecture.
- Reported examples include giant cell tumor, fibrous dysplasia and osteosarcoma.
- The final diagnosis should name the underlying process when it is identified.

Primary aneurysmal bone cyst

USP6-driven neoplastic septal cells

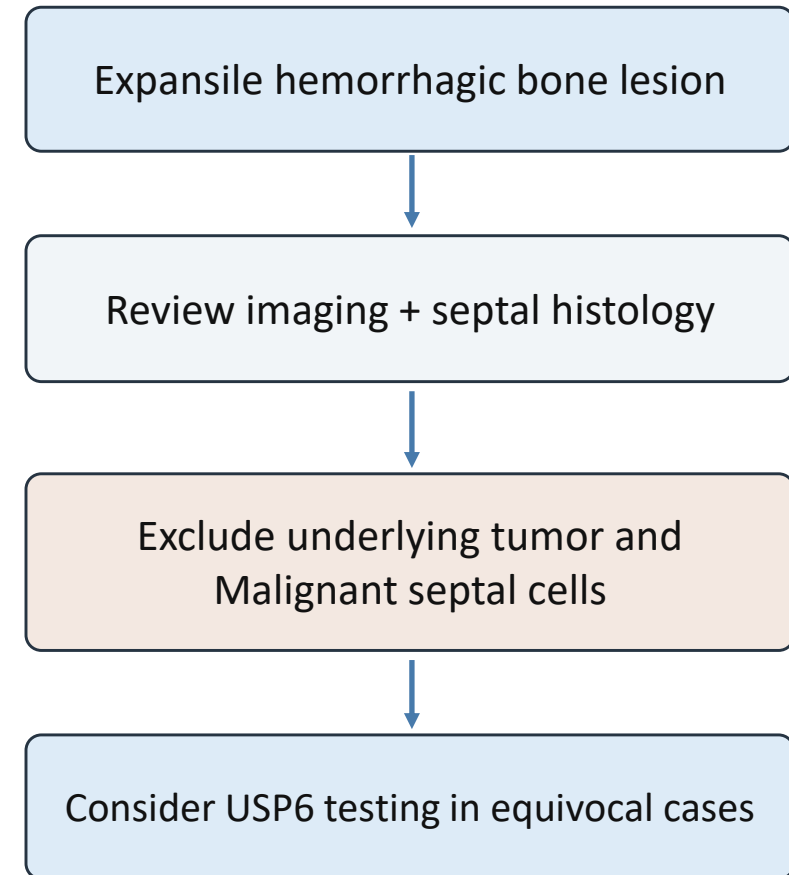
ABC-like change within another lesion

Find and characterize underlying
tumor

Schematic — not a specimen

Telangiectatic osteosarcoma: Do not miss

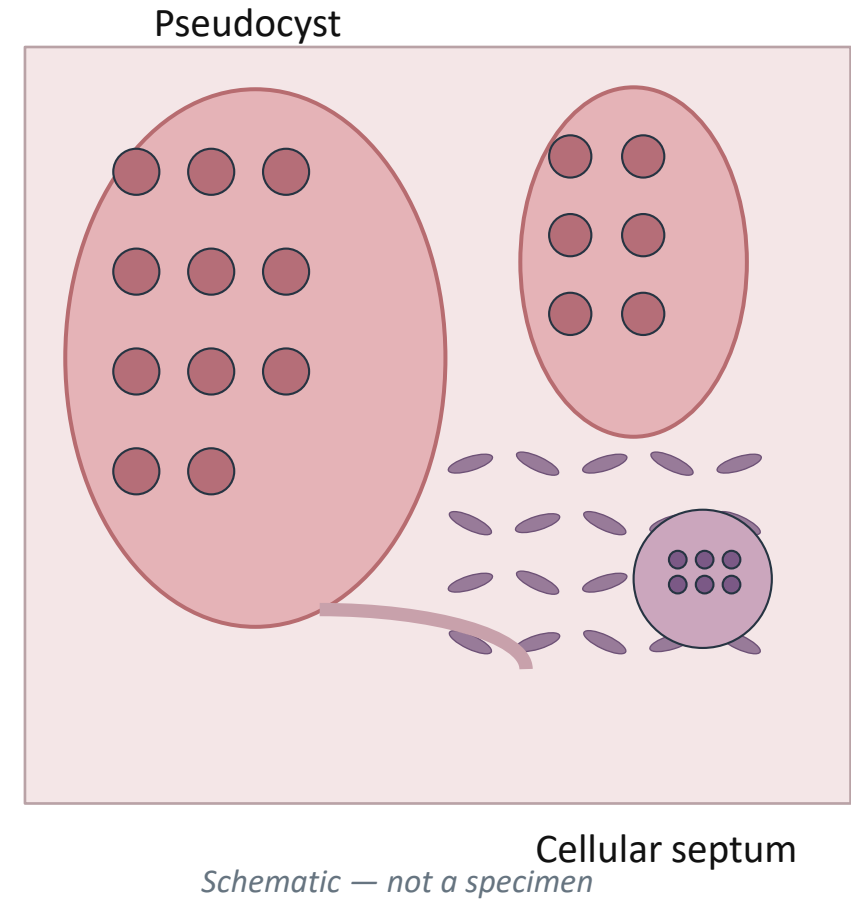
- Both lesions can be expansile, hemorrhagic and show fluid–fluid levels.
- Malignant atypical stromal cells within septa favor telangiectatic osteosarcoma.
- Suspicious enhancing solid components or malignant osteoid demand complete evaluation.



Schematic — not a specimen

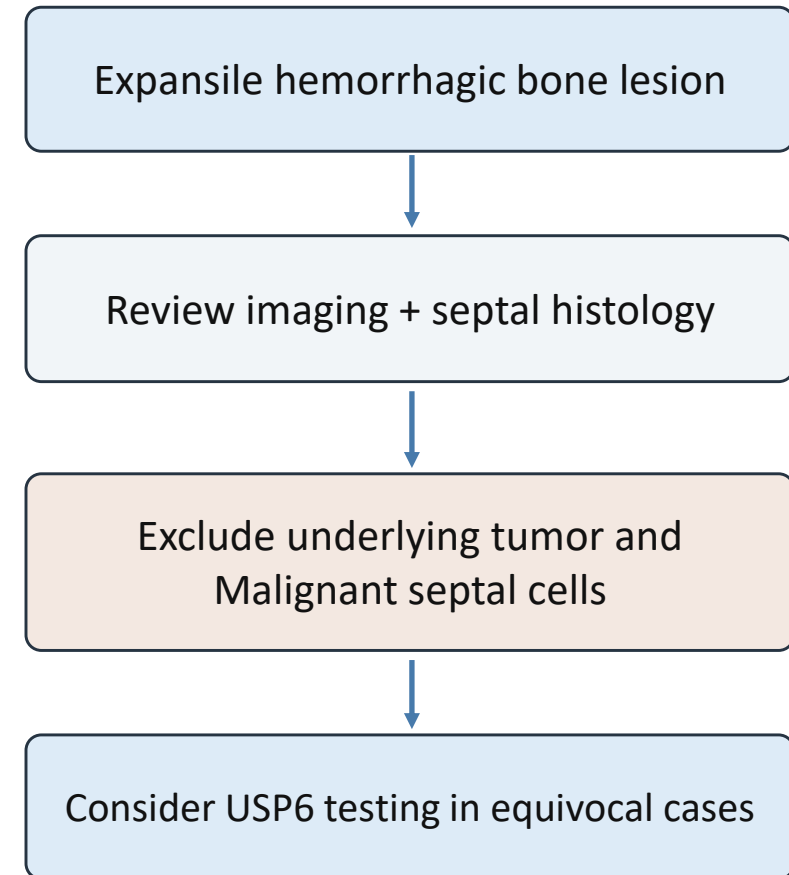
Evaluate the septa, not only the blood

- The central diagnostic distinction often lies in tissue within septa or solid portions.
- Look for bland ABC spindle cells versus cytologically malignant stroma.
- A targeted, representative sample is essential when imaging and histology disagree.



Diagnostic integration: Practical pathway

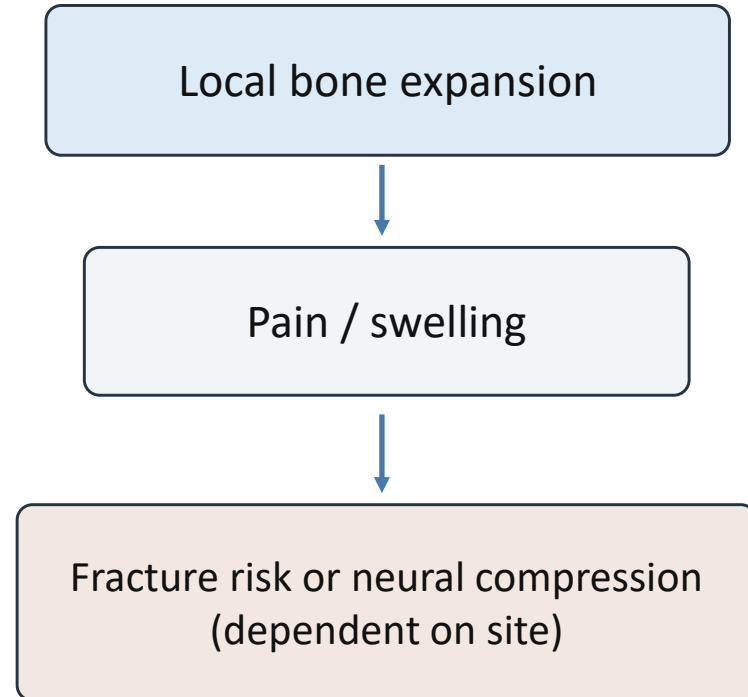
- Begin with clinical age and precise skeletal site.
- Review lesion boundaries, cortical expansion, septa and solid nodules on imaging.
- Examine representative septal tissue; Investigate underlying tumors and use USP6 testing if unresolved.



Schematic — not a specimen

Local aggressiveness without metastasis as a defining feature

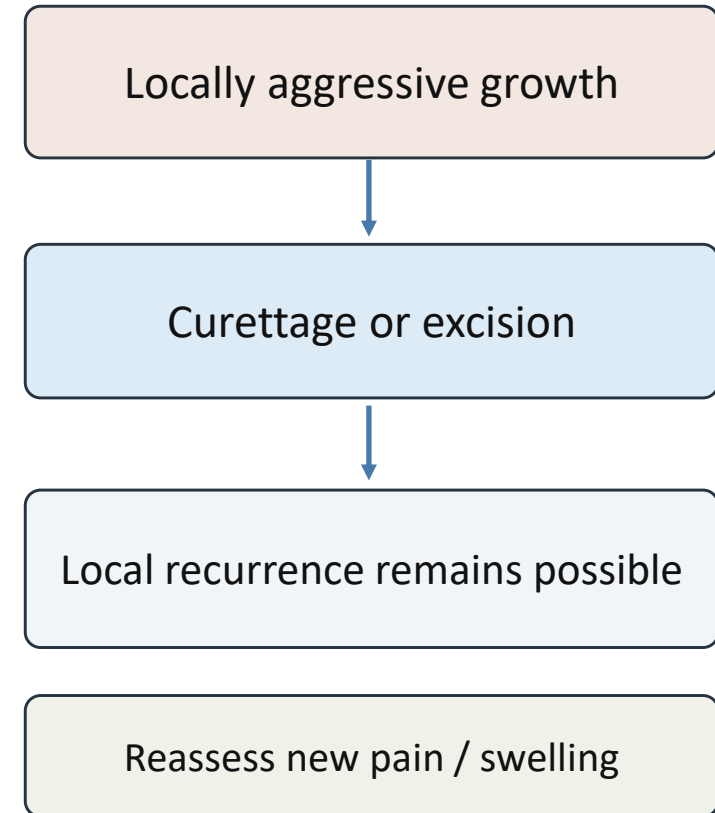
- ABC can be locally destructive despite benign histologic categorization.
- Pain, mass effect and compromised adjacent structures are consequences of location and expansion.
- The principal management issue is local control rather than systemic oncologic staging.



Schematic — not a specimen

Treatment: Curettage or excision

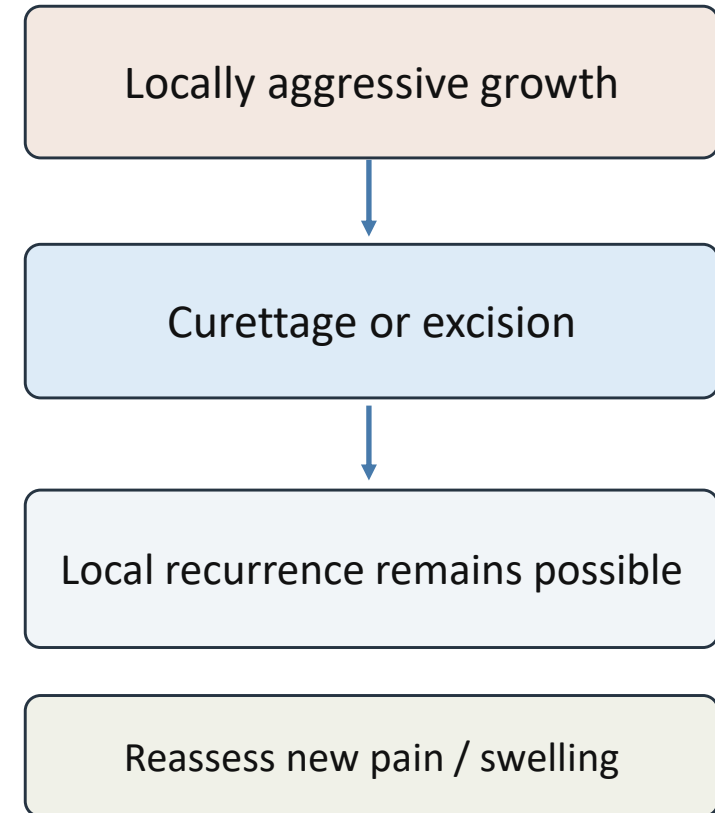
- Curettage or excision as treatment approaches.
- Choice of intervention depends on anatomy and clinical management considerations.
- These treatment names do not imply that every lesion has an identical surgical plan.



Schematic — not a specimen

Recurrence is a clinically important outcome

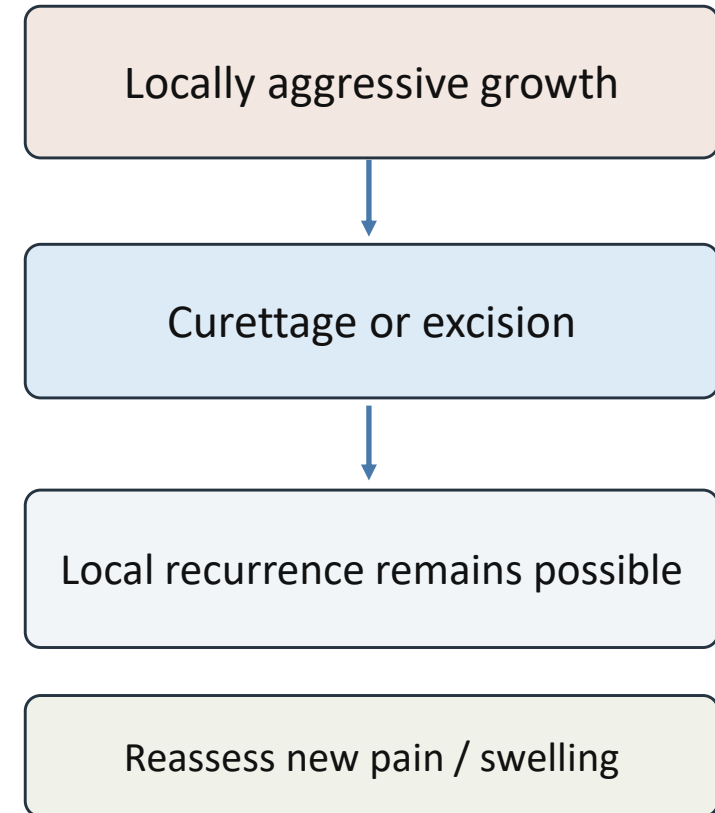
- Local recurrence in 10%–50% of cases.
- The range is broad and should not be presented as an individual-patient probability.
- Return of local symptoms after treatment warrants reassessment for recurrent or residual lesion.



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Follow-up relates to local behavior

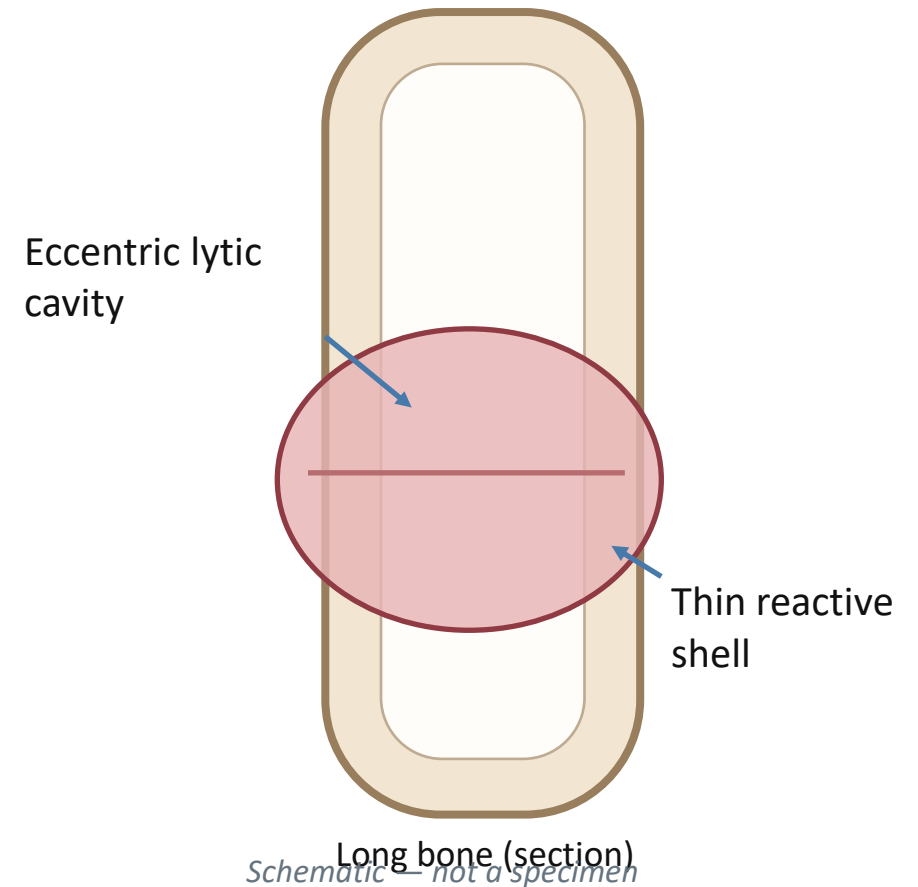
- Clinical surveillance focuses on recurrent pain, swelling and site-specific deficits.
- Imaging is used as indicated to evaluate residual or recurrent expansion.
- A follow-up plan is individualized; Robbins does not provide a universal surveillance interval.



Schematic — not a specimen

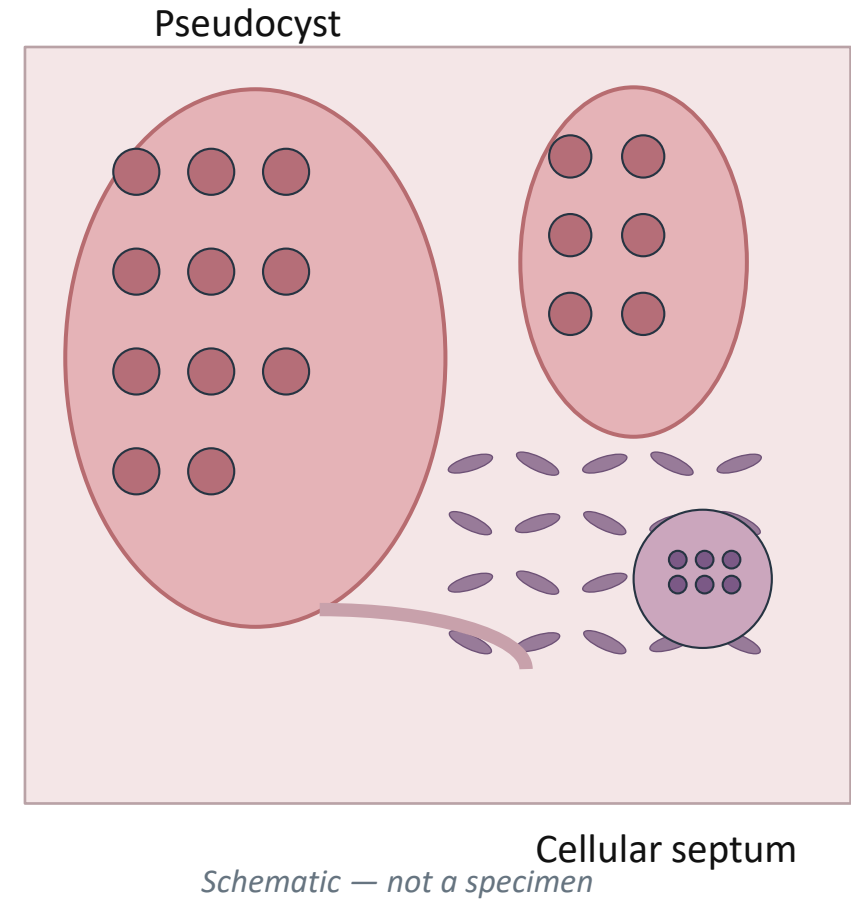
Case 1: Adolescent with distal femoral pain

- A 15-year-old has several months of focal pain and swelling near the knee.
- Imaging shows a circumscribed eccentric expansile lytic lesion with a thin shell.
- MRI demonstrates septated cavities with multiple fluid–fluid levels.



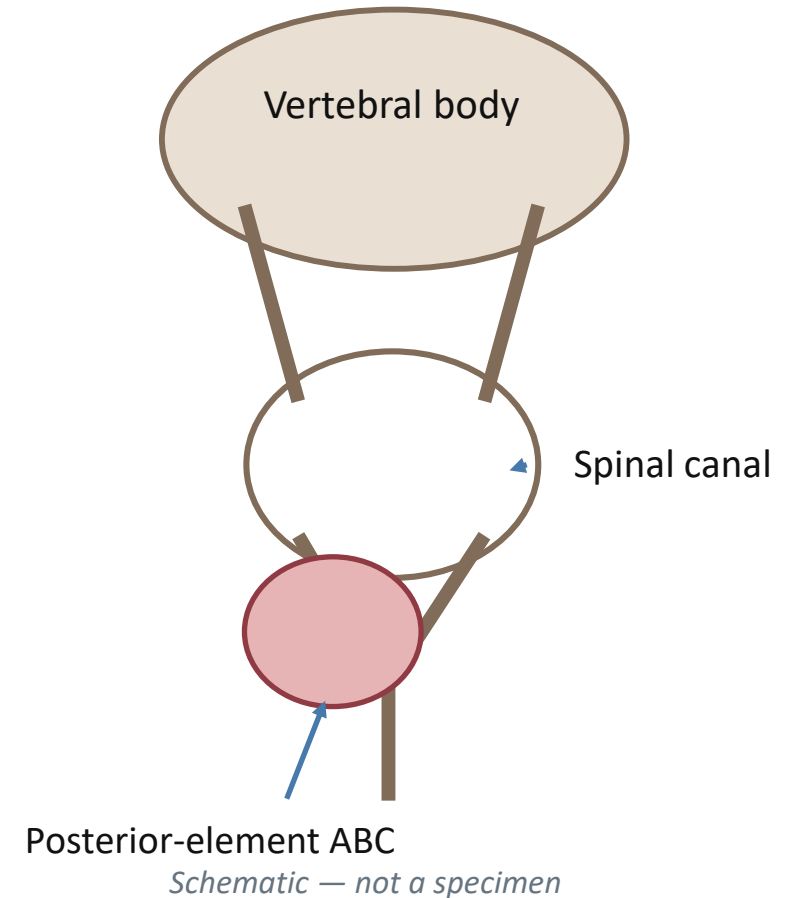
Case 1: What would establish ABC?

- The imaging pattern supports ABC but is insufficient on its own.
- Histology should show hemorrhagic pseudocysts and bland fibroblastic septa with giant cells and woven bone.
- A malignant solid component or marked septal atypia would require reconsideration.



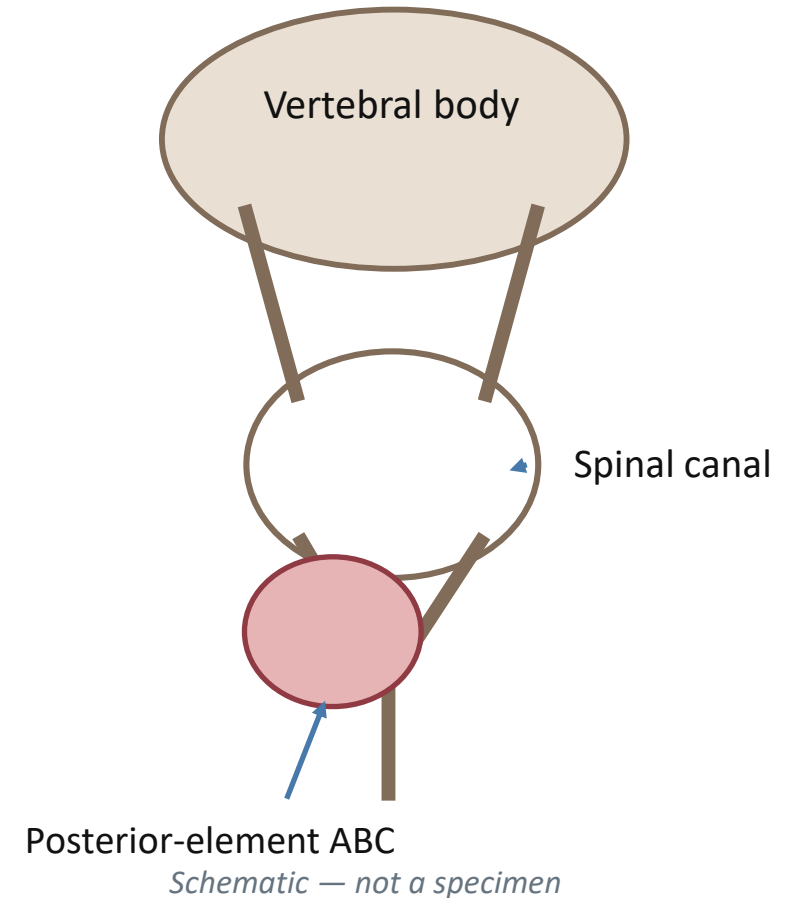
Case 2: Vertebral posterior-element lesion

- An adolescent develops focal spinal pain with progressive nerve-related symptoms.
- Cross-sectional imaging reveals an expansile lesion centered in the posterior elements.
- The diagnostic problem includes both lesion identification and anatomic compression.



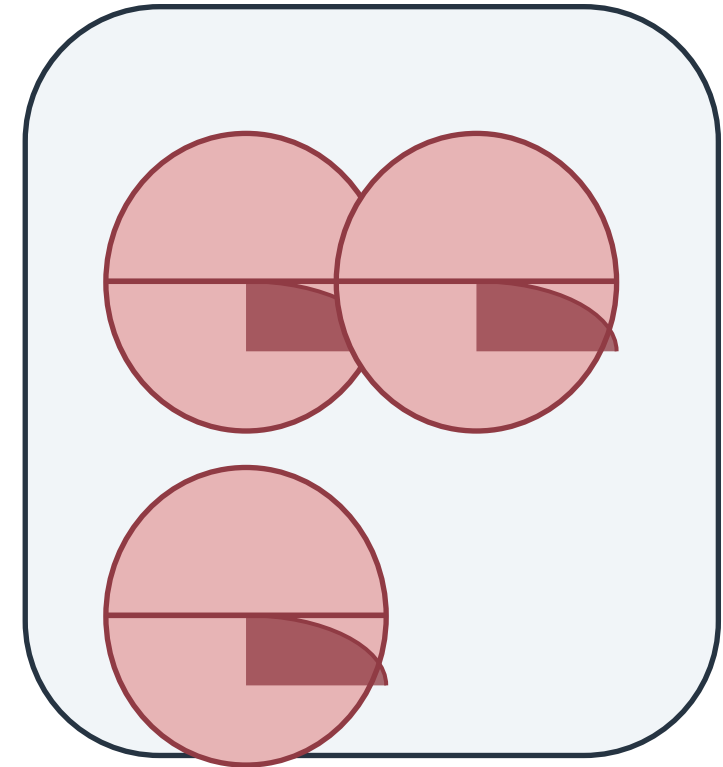
Case 2: Clinicopathologic priority

- Robbins supports ABC in posterior vertebral elements as a recognized site.
- Neural compression can explain neurologic deficits without requiring malignant pathology.
- Urgency follows the neurologic findings and degree of compression.



Case 3: A fluid-level diagnostic trap

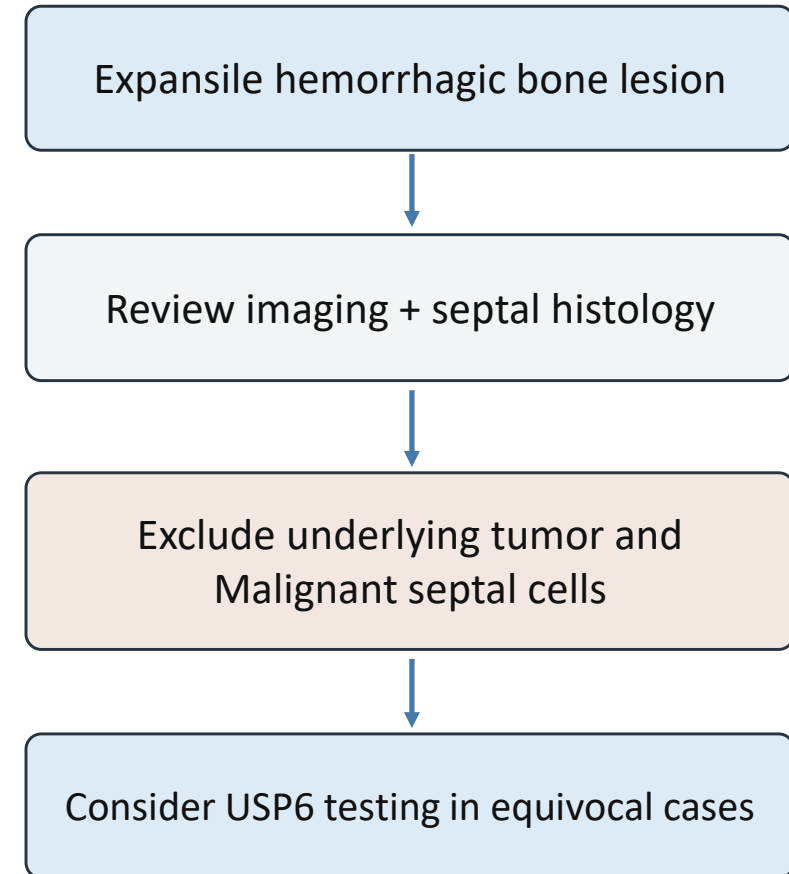
- A rapidly enlarging bone lesion has fluid–fluid levels and thick enhancing internal tissue.
- A limited sample contains mostly blood and a small amount of reactive bone.
- The available material does not safely exclude a malignant hemorrhagic bone tumor.



Horizontal interfaces between
Schematic — not a specimen
Layered hemorrhagic contents

Case 3: Resolving the discrepancy

- Correlate sampling with the suspicious solid or thick septal areas.
- Evaluate for atypical malignant stromal cells and neoplastic osteoid.
- Do not label the entire lesion “ABC” solely because fluid levels and blood are present.

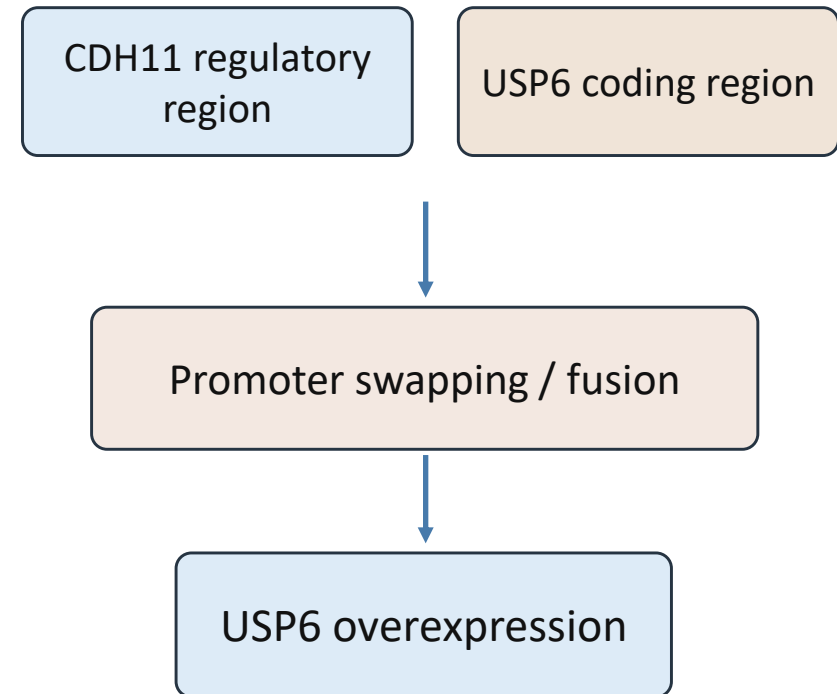


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Knowledge check: USP6 mechanism

- Which molecular change is central to primary ABC?
- USP6 coding sequence becomes controlled by partner-gene regulatory elements.
- The resulting overexpression promotes NF- κ B activity and matrix-degrading proteins.

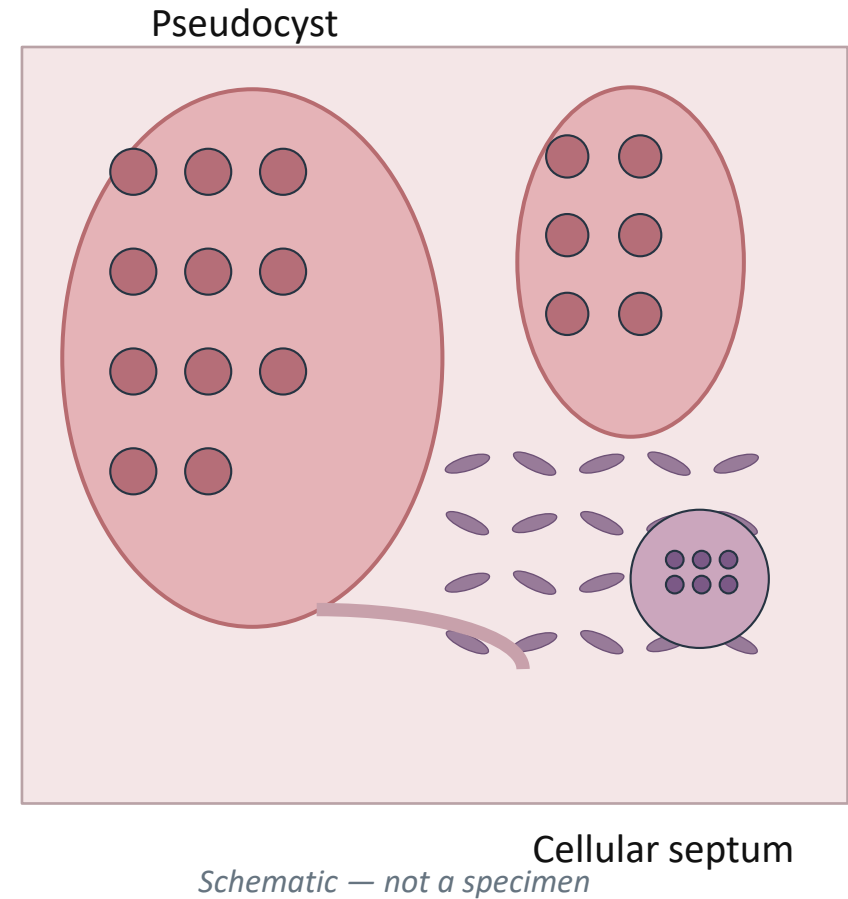
Normal gene regulation



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Knowledge check: Microscopic triad

- What should a representative ABC septum contain?
- Bland plump spindle cells, osteoclast-like giant cells and reactive woven bone.
- The adjacent blood-filled spaces are not lined by endothelium.



Diagnostic synthesis

- The lesion is benign but can be locally aggressive.
- USP6-driven signaling and matrix degradation underpin the neoplastic mechanism.
- Morphologic diagnosis depends on septa and blood-filled pseudocysts, not fluid levels alone.
- A malignant mimic or underlying tumor must be excluded when findings are discordant.

Expansile hemorrhagic bone lesion



Review imaging + septal histology



Exclude underlying tumor and
Malignant septal cells



Consider USP6 testing in equivocal cases

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References and source boundaries

Primary textbook

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. Chapter 26: Bones, Joints, and Soft Tissue Tumors. pp. 1084–1086.

Supplementary diagnostic context

Nasri E, Reith JD. Aneurysmal bone cyst: a review. J Pathol Transl Med. 2023;57:81–87. doi:10.4132/jptm.2023.02.23.

Restrepo R, Zahrah D, Pelaez L, et al. Update on aneurysmal bone cyst: pathophysiology, histology, imaging and treatment. Pediatr Radiol. 2022;52:1601–1614. doi:10.1007/s00247-022-05396-6.

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