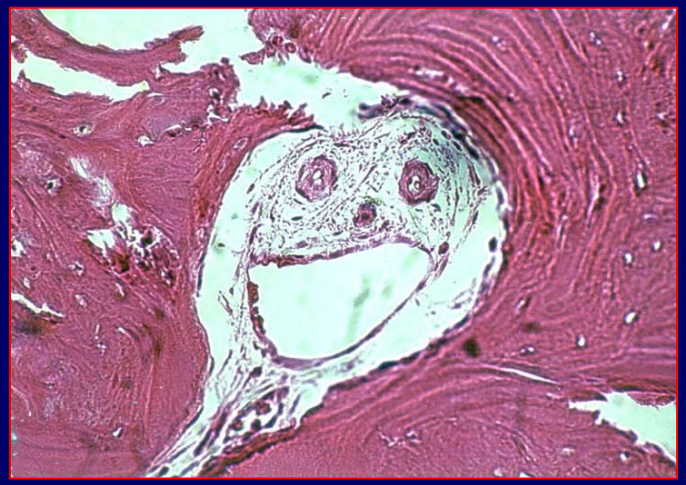
COMMON NON NEOPLASTIC BONE DISORDERS



A Prof Fiona Bonar

Douglass Hanly Moir Pathology

Sydney

IAP Jordan

October 2018

Mesenchymal stem cells

- progenitor cells for all mesenchymal components

Variable proportions

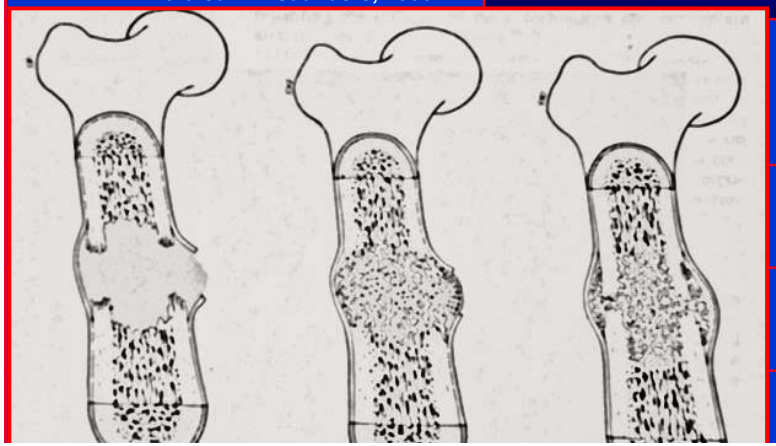
- Osteoblasts / osteocytes
- Chondrocytes
- Endothelial cells/ pericytes
- Fibroblasts / myofibroblasts

- Bone
- Cartilage
- Fibrous tissue
- Vascular tissue

Fracture repair….orderly complex process …over time

week 1	week 2	week 3	thereafter
Inflammatory phase			
Haemorrhage			
Necrosis	**Reparative phase**		
Fibrin clot			**Remodelling ….**
Macrophage infiltration			
Fibroblastic proliferation			
Capillary proliferation			
	Plump mesenchymal cells		
	Periosteal cellular proliferation		
	Periosteal new bone formation		
		Medullary new bone formation	
		Chondroblastic proliferation	
		Periosteal cartilagenous callus	
		Medullary cartilage callus	

Resnick D. Diagnosis of Bone and Joint Disorders
3rd ed WB Saunders; 1995



Fracture Healing : 1st Week

- periosteum
- medulla
- soft tissue

◆ haematoma

- fibrin mesh
- platelet degranulation
- inflammatory cells
- fibroblastic proliferation
- capillary proliferation
- macrophage infiltration

CYTOKINES

BMP
PDGF
FGF
TGF β
IGF

➢ mesenchymal cell activation osteoprogenitor cells

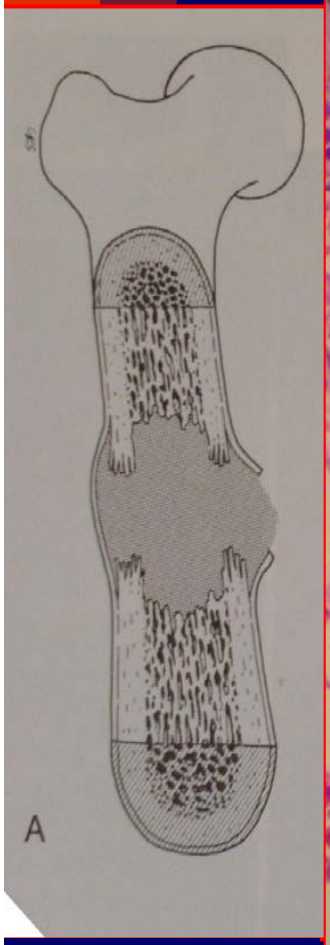
➢ **osteoblasts^{++}**

➢ fibroblasts
➢ chondroblasts

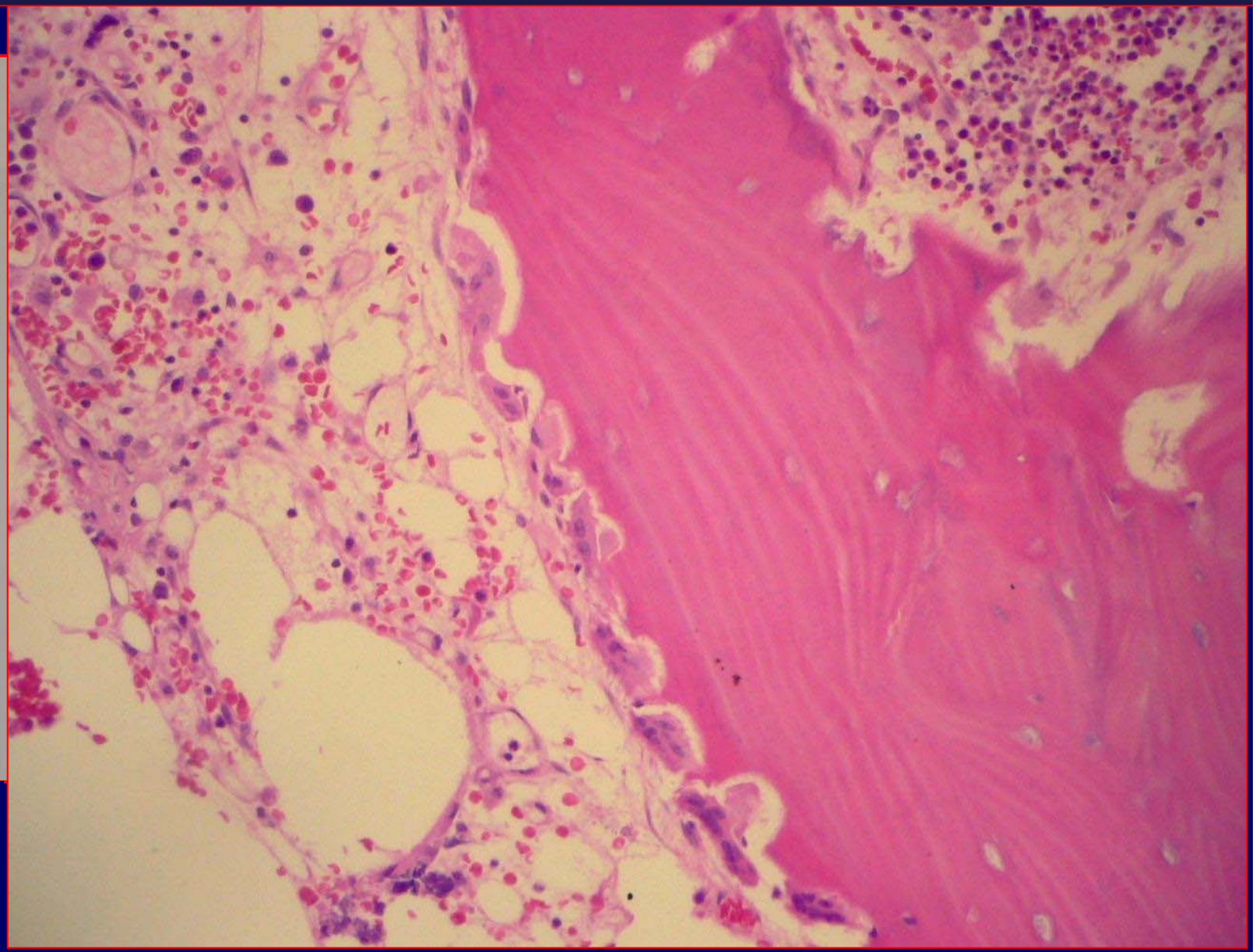
➢ woven bone
➢ cartilage
➢ fibrosis

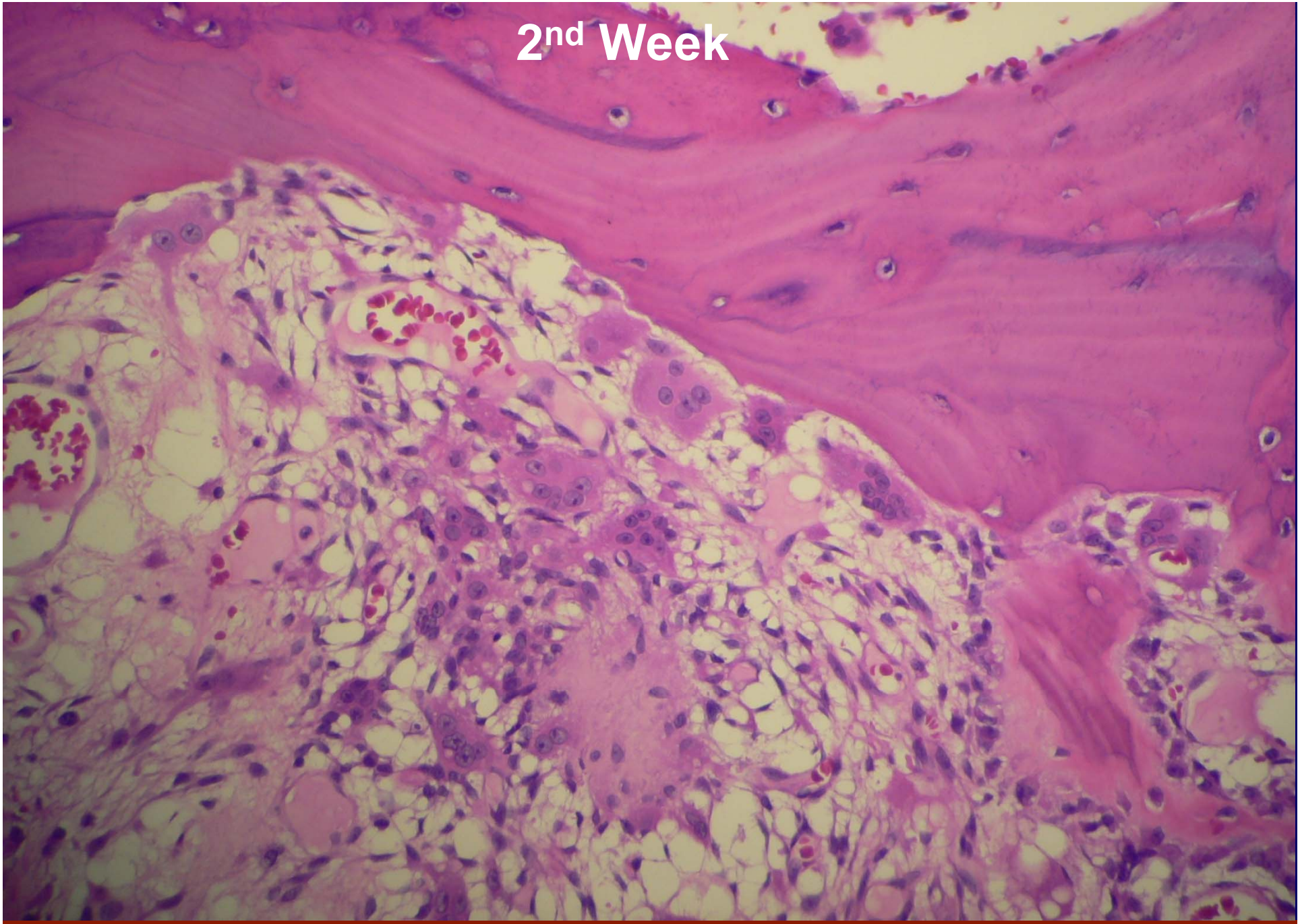
soft callus

- macrophage infiltration
- osteoclast formation



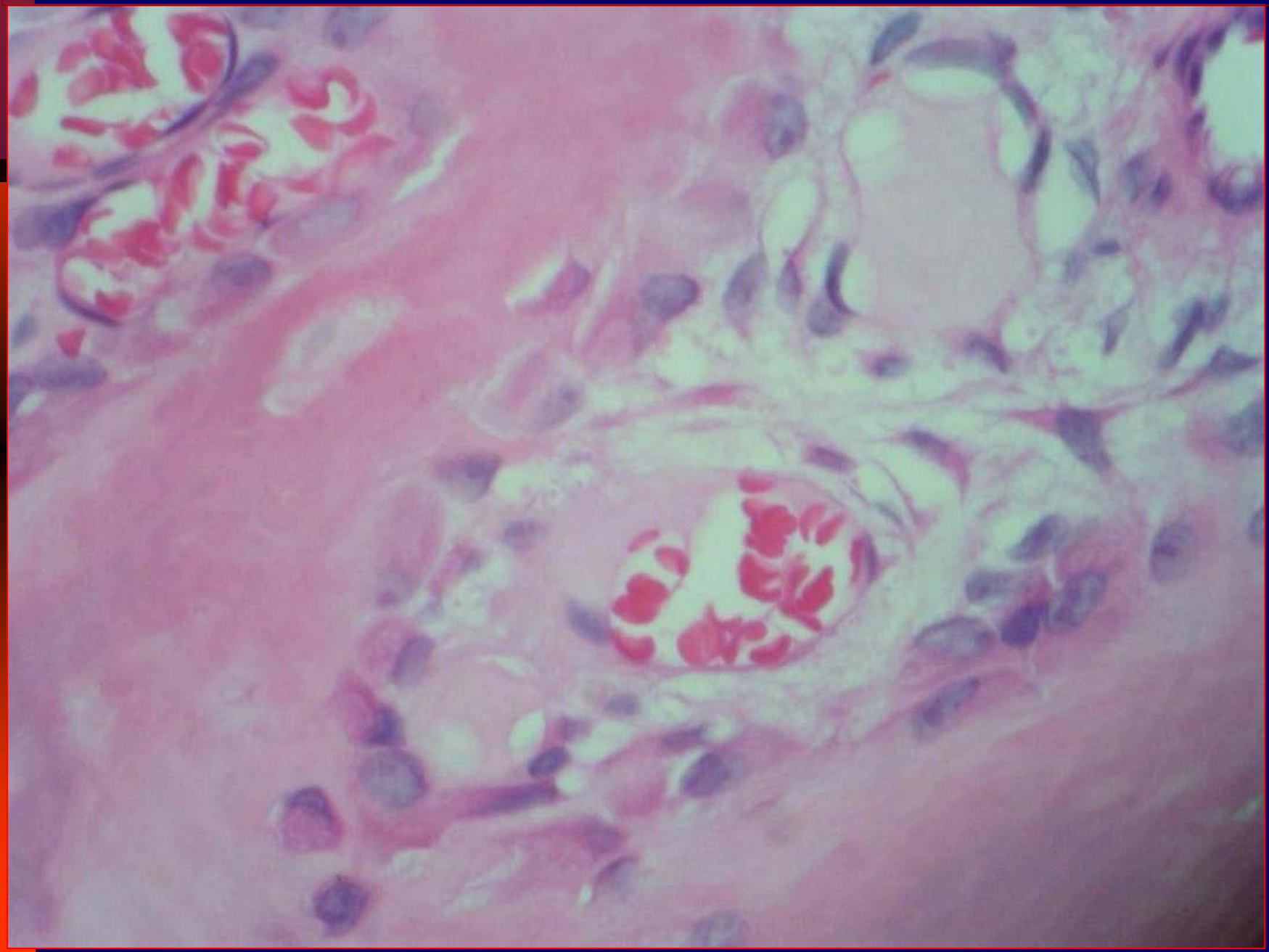
Resnick "diseases of bones and joints " 3rd ed



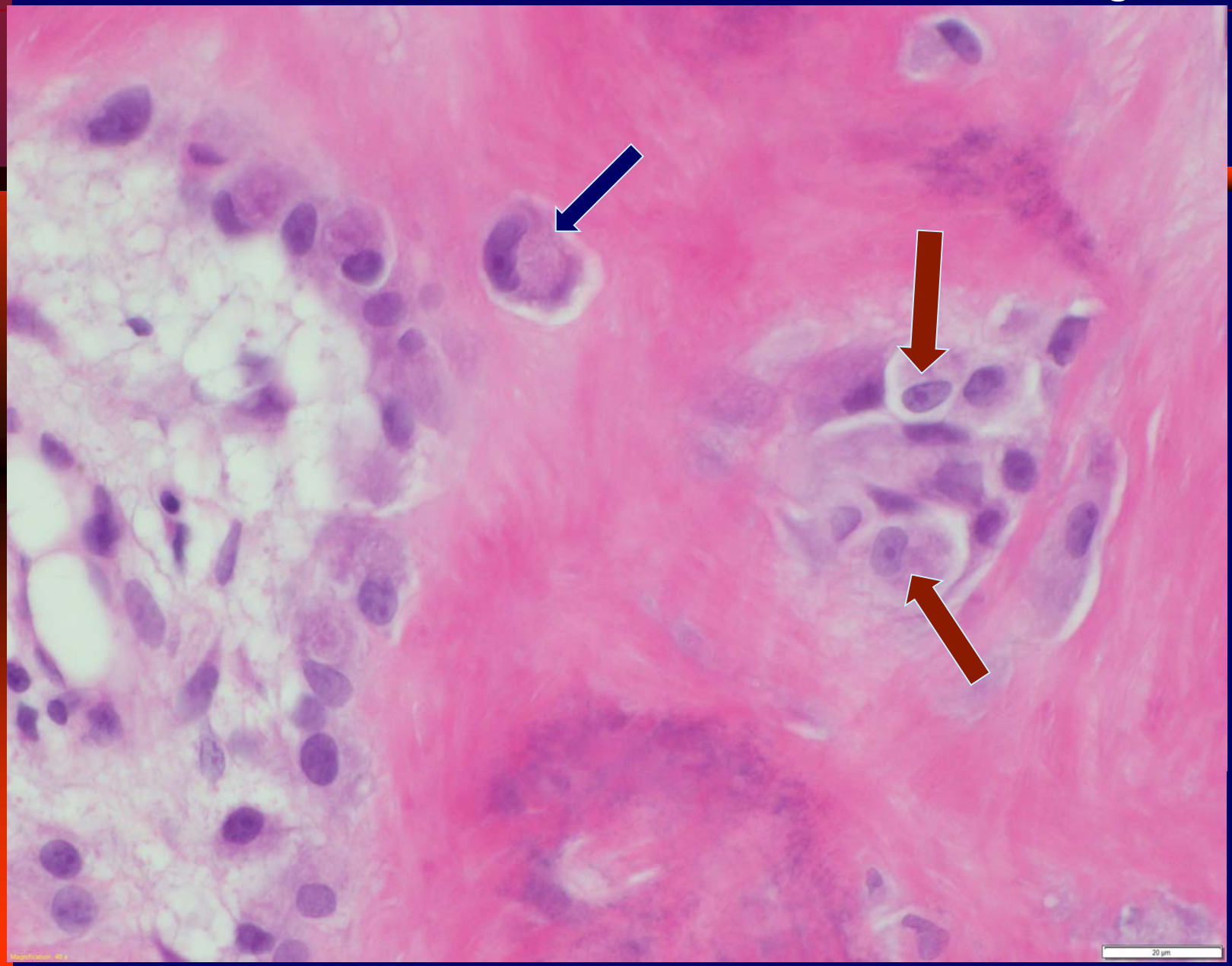


concurrent osteoclast resorption, early ossification rimmed by plump osteoblasts

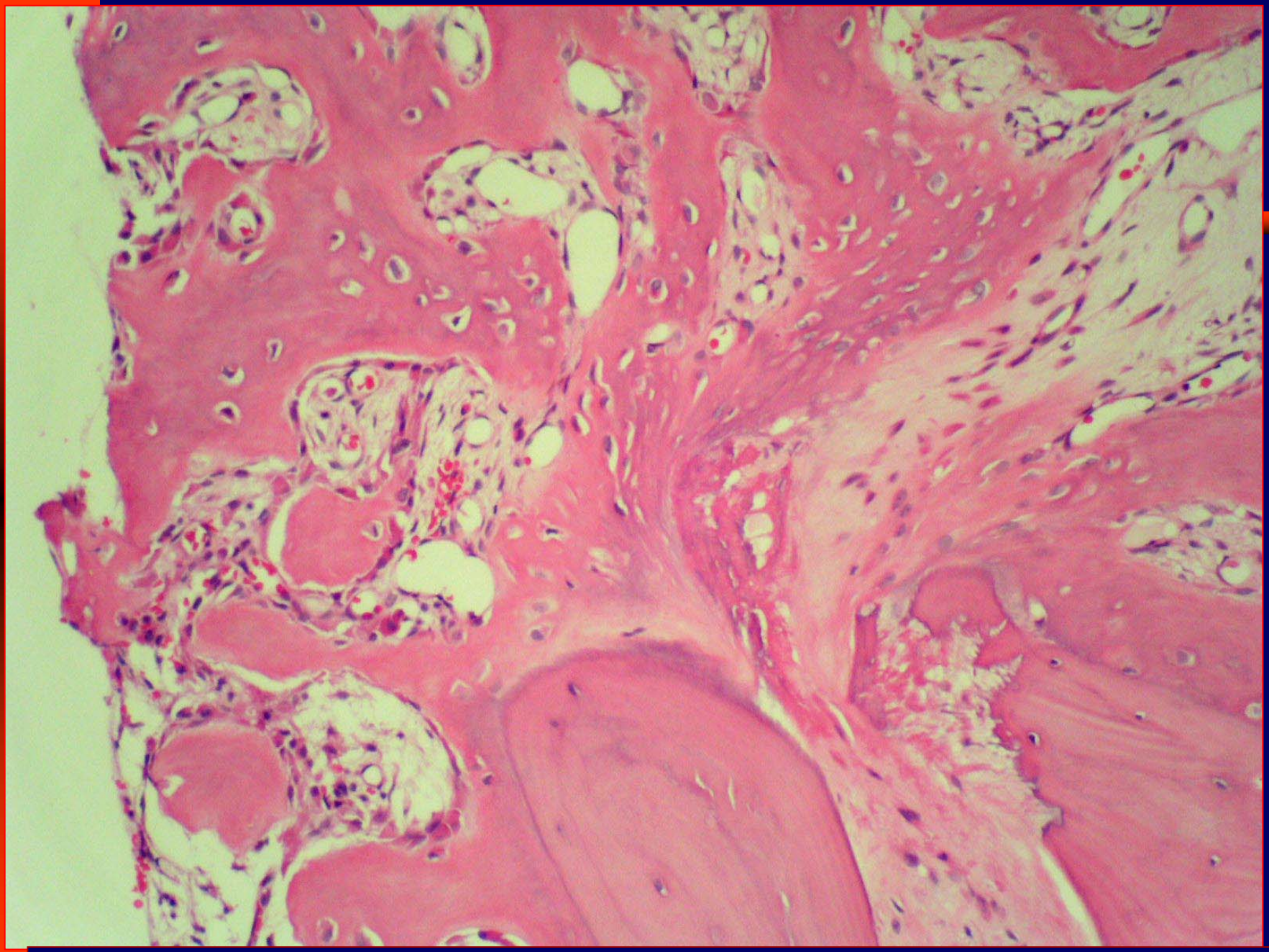
- osteoid with single layer plump osteoblasts in vascular stroma



◆vescicular nuclei , small nucleoli, normal NCR, Golgi

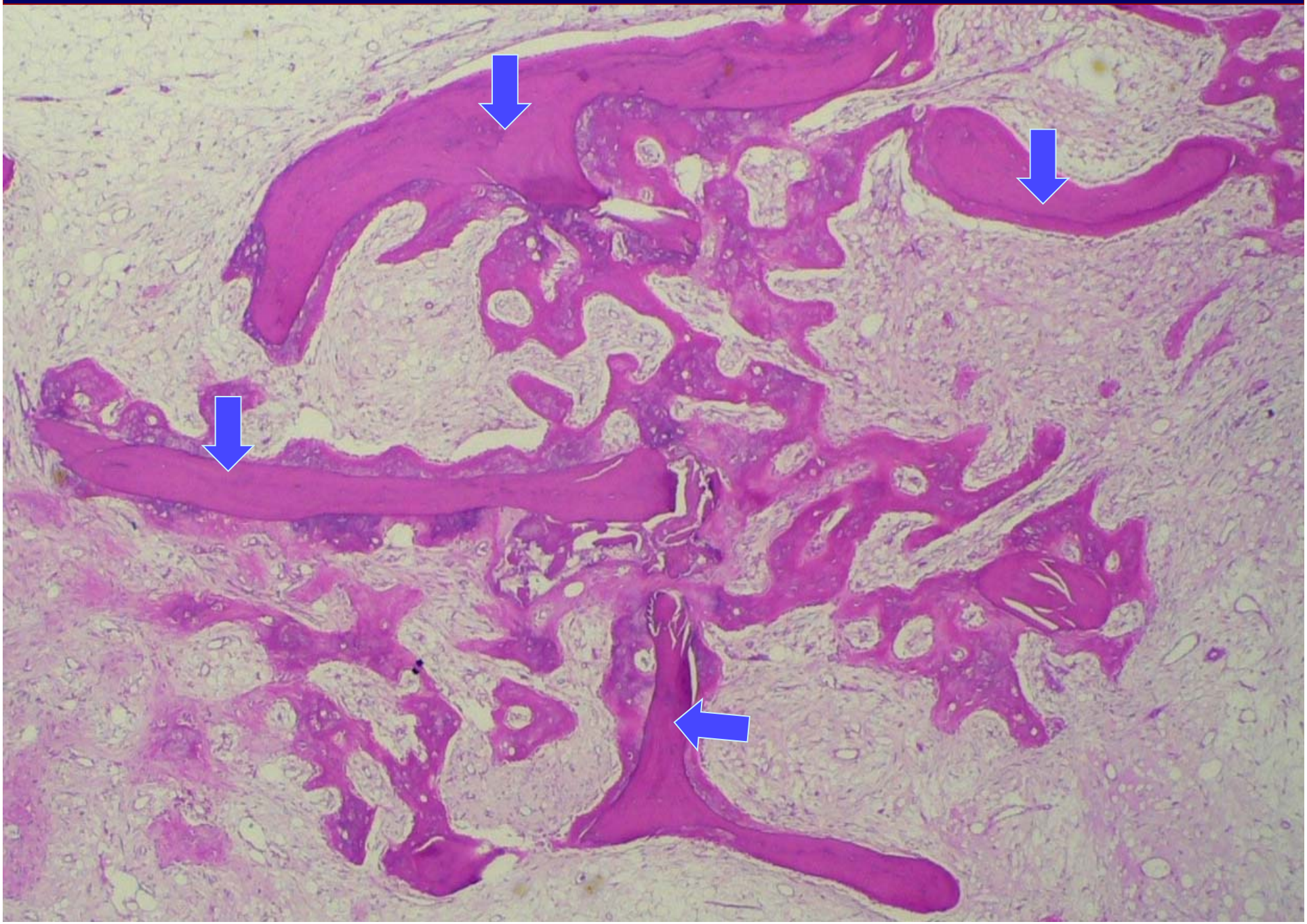


mitoses very rare in reactive osteoblasts

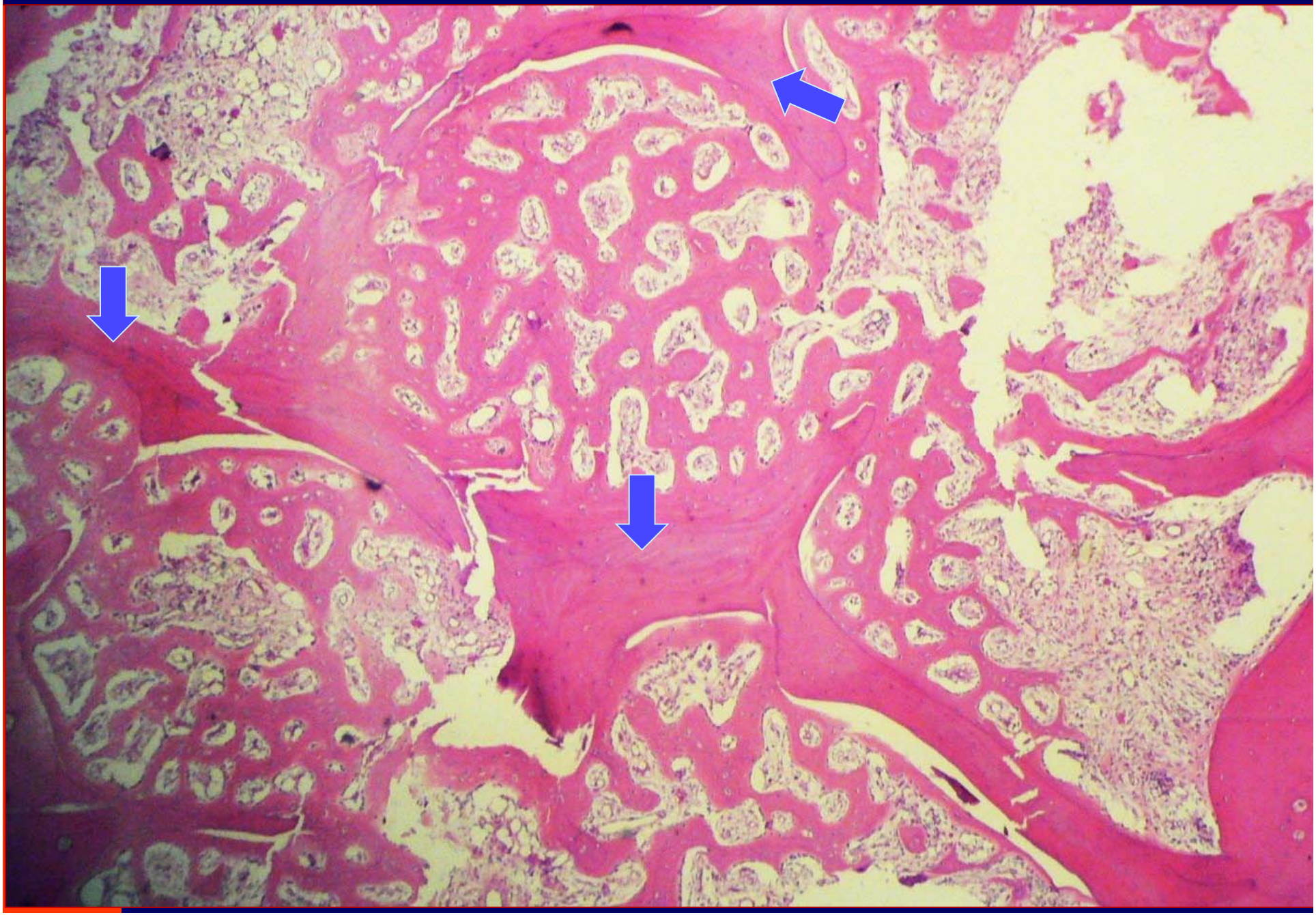


◆reactive trabeculae are interconnected and purposeful: scaffold

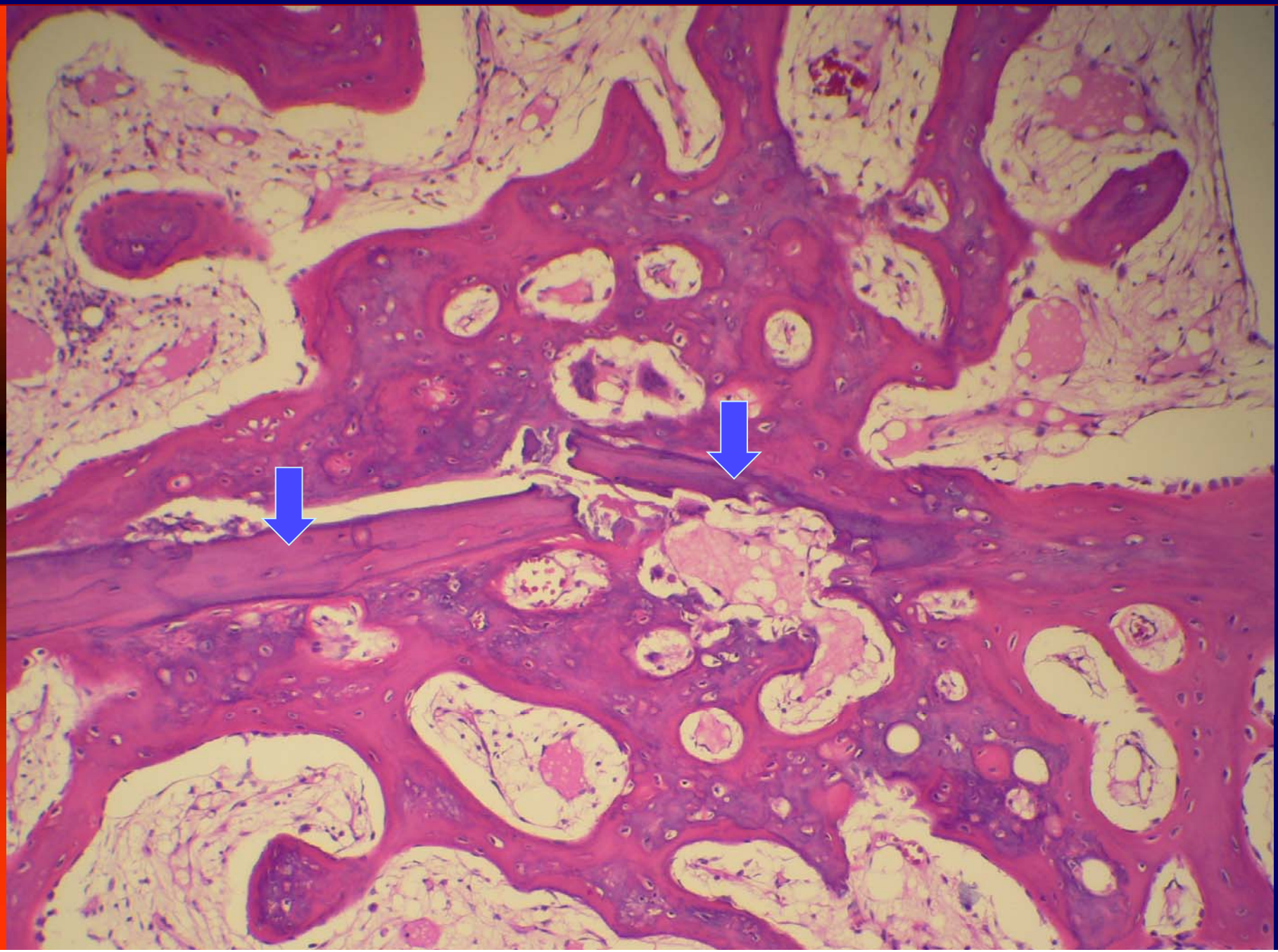
◆ early callus connecting original host trabeculae (blue arrows)



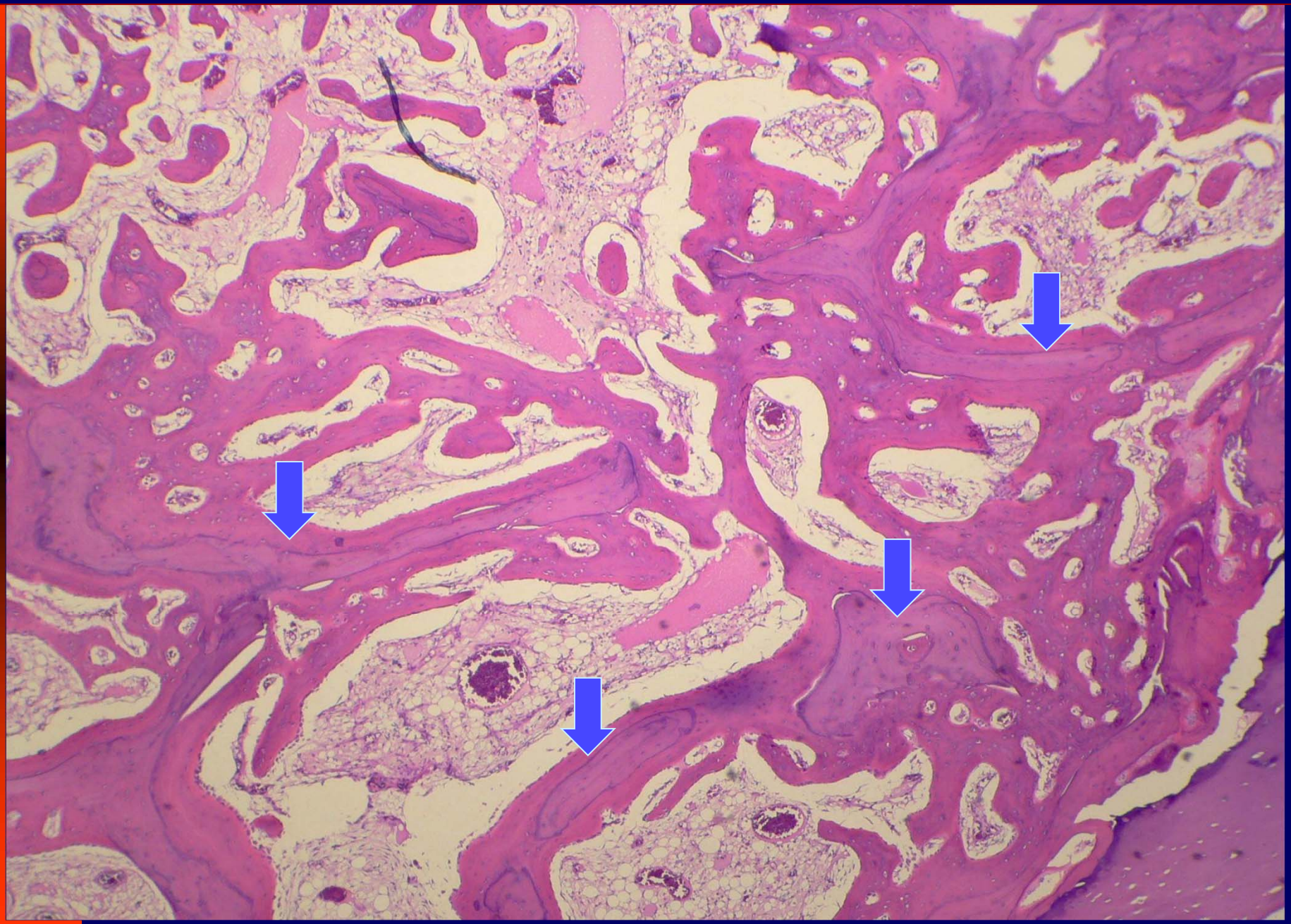
◆scaffold connecting multiple bone fragments



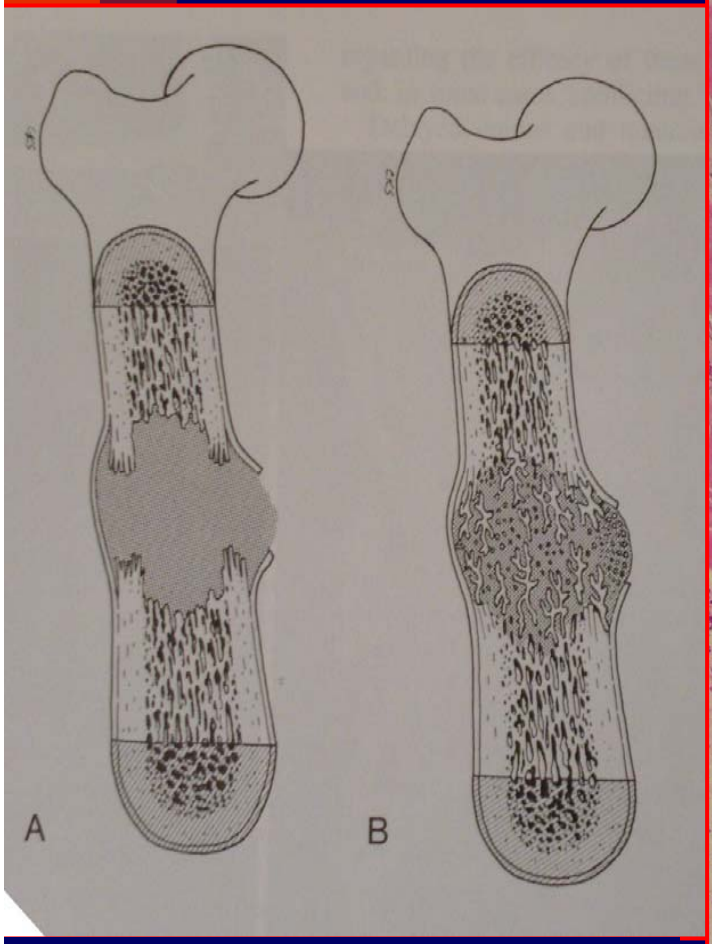
◆ thickening of callus with woven bone becoming lamellar



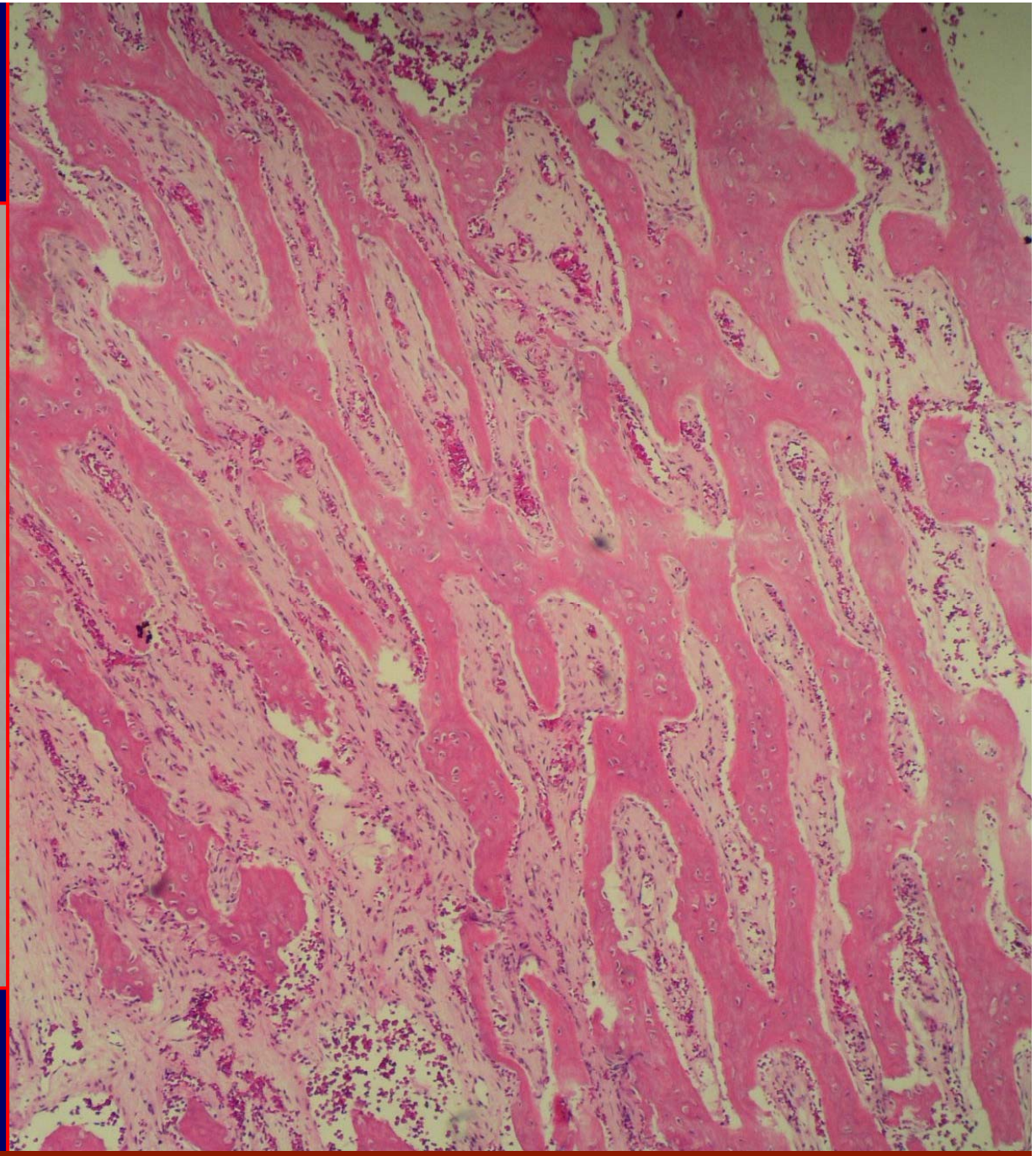
◆ thickening of callus with woven bone becoming lamellar



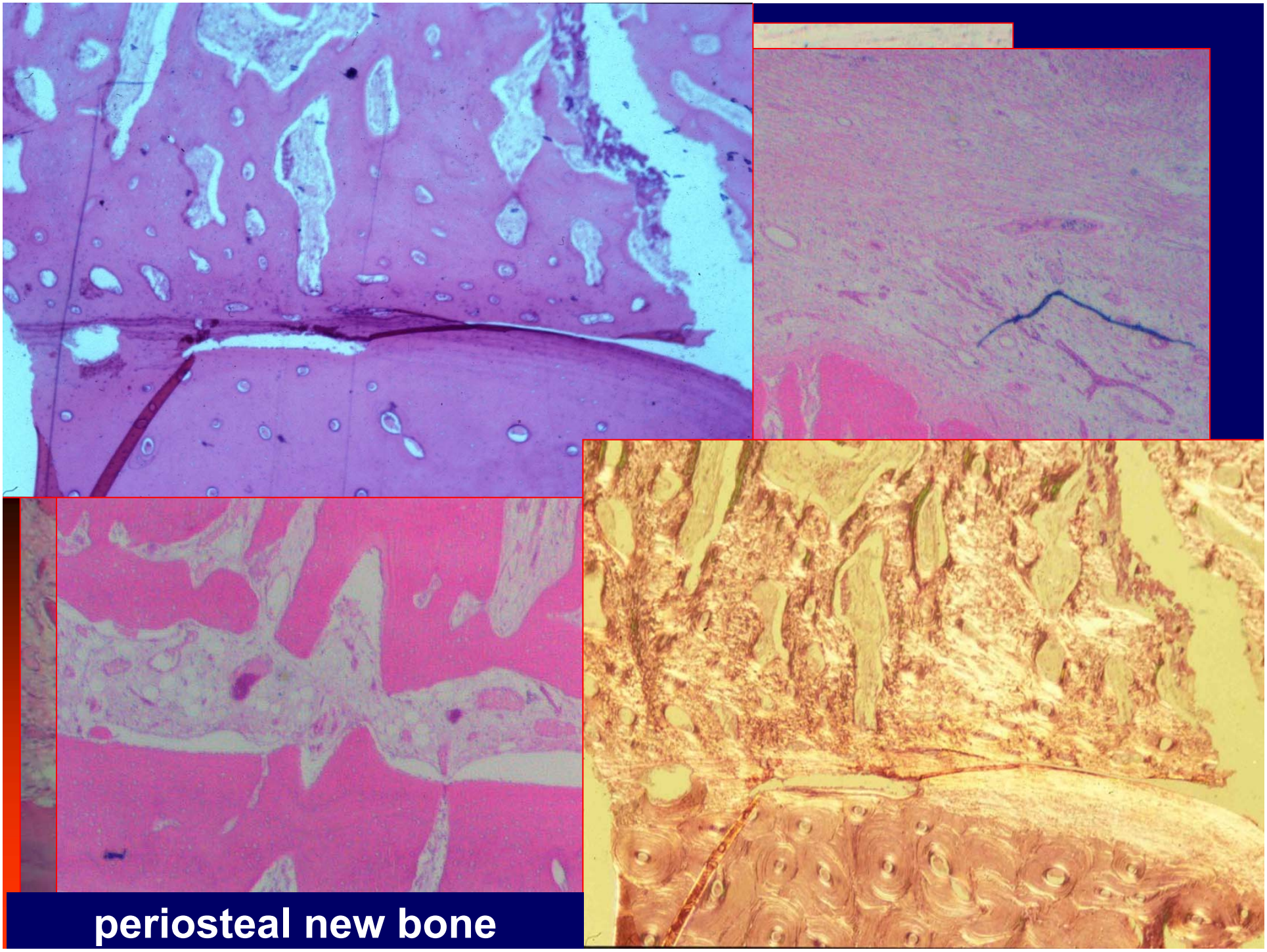
3rd week onwards

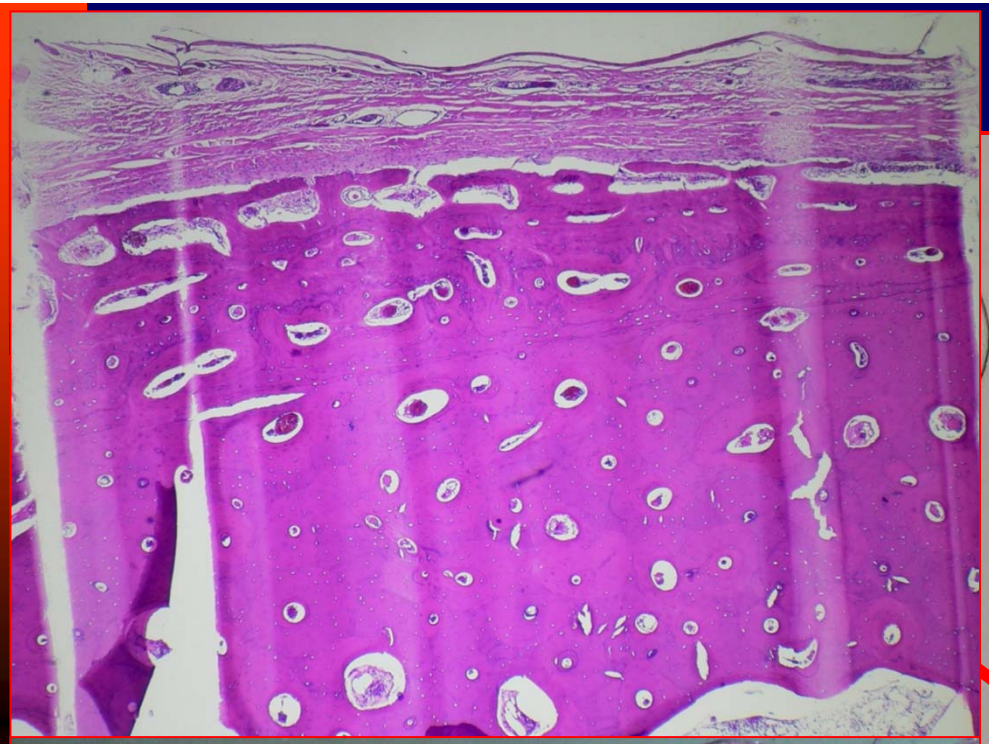


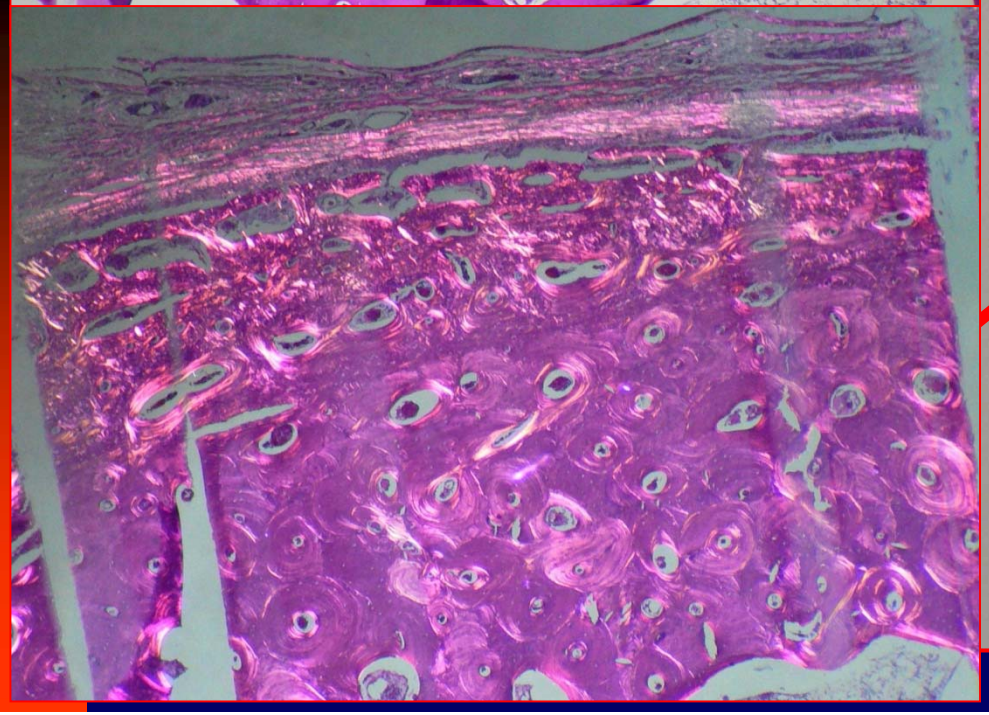
Resnick "diseases of bones and joints "3rd ed

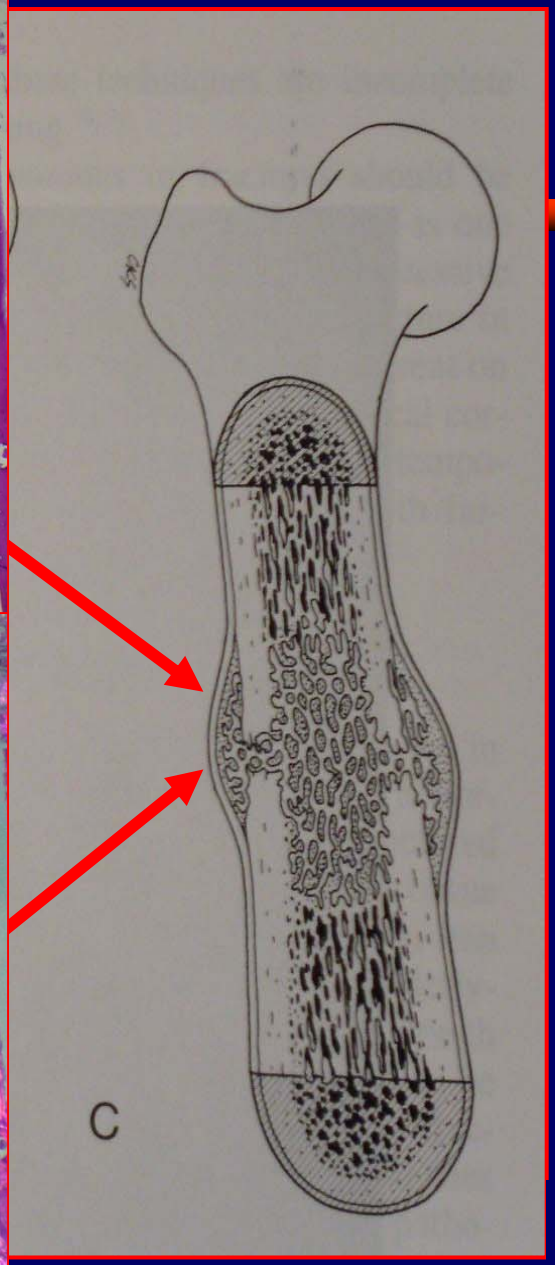


- increasing orderliness of distribution with appropriate forces


periosteal new bone







Resnick "diseases of bones and joints " 3rd ed

Fracture Healing

- adequate blood supply
- mechanical stability and appropriate interfragmentary strain

EARLY HISTOLOGICAL AND ULTRASTRUCTURAL CHANGES IN MEDULLARY FRACTURE CALLUS 833

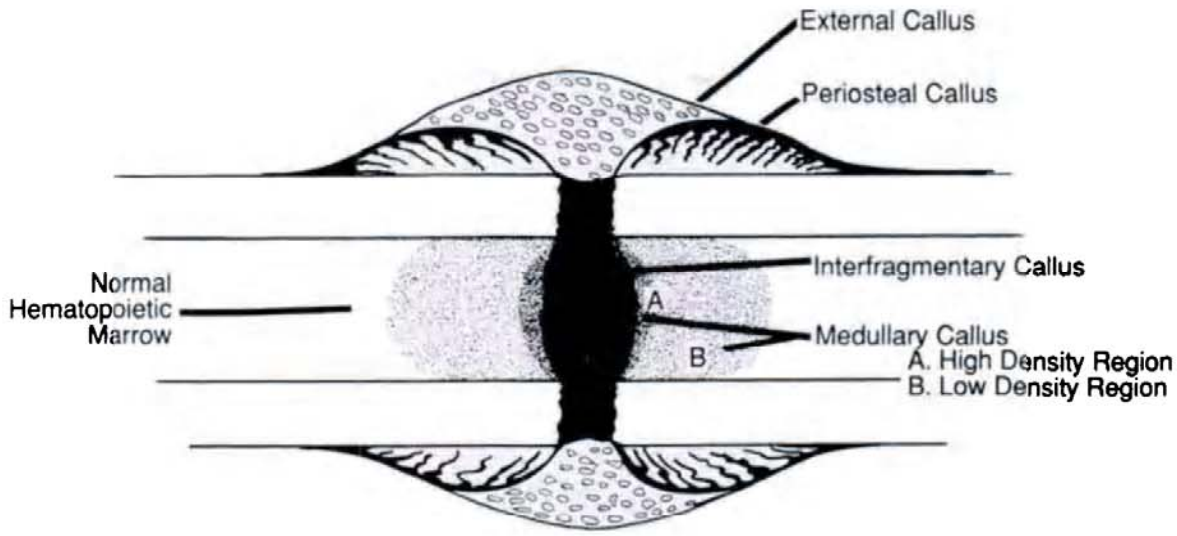


FIG. 1

Drawing depicting the regions of a typical fracture of a rib in the rabbit.

Fracture Healing requirments:

- Strain and shear stresses guide mesenchymal differentiation
- Exact load / stress / strain is critical;
  small movements promote osteogenesis
- Excess strain and shear movements deleterious

USUAL FRACTURE : IRREGULAR GEOMETRY
COMPLEX LOAD
TEMPORALLY VARIABLE

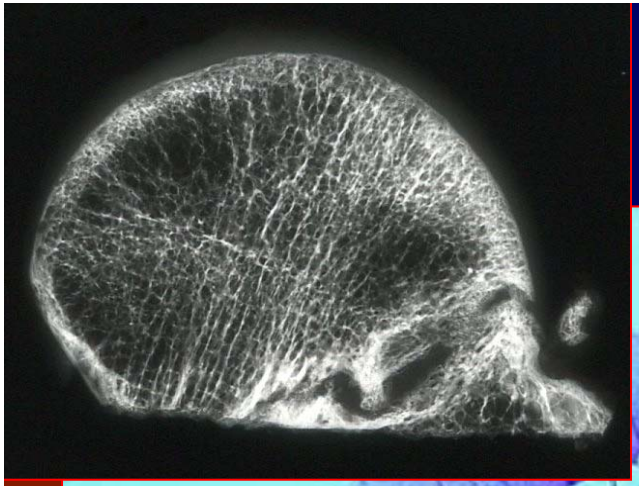
Fracture Healing

Adequate blood supply Appropriate strain / stability	Bone formation	Osseous union
Adequate blood supply ↑ Instability / Strain	Fibrosis	Fibrous non-union
↓ Blood supply Instabilty /abnormal strain	Cartilage Fibrocartilage	Fibrocartilagenous nonunion +/- pseudarthrosis

complicated by:

- Nature / site # / age / nutritional status
- Infection/ bone necrosis/ tumour
- Dxt / steroid

- fibrous non union
- sclerosis of adjacent bone



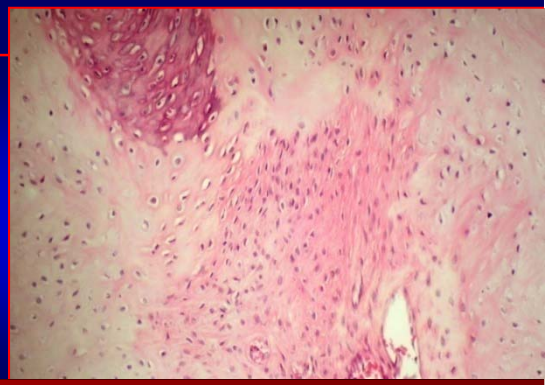

• fibrosis extending through articular cartilage
• sclerosis of adjacent bone

Cartilagenous Callus

osteochondroid

all stages of cartilage development

endochondral ossification

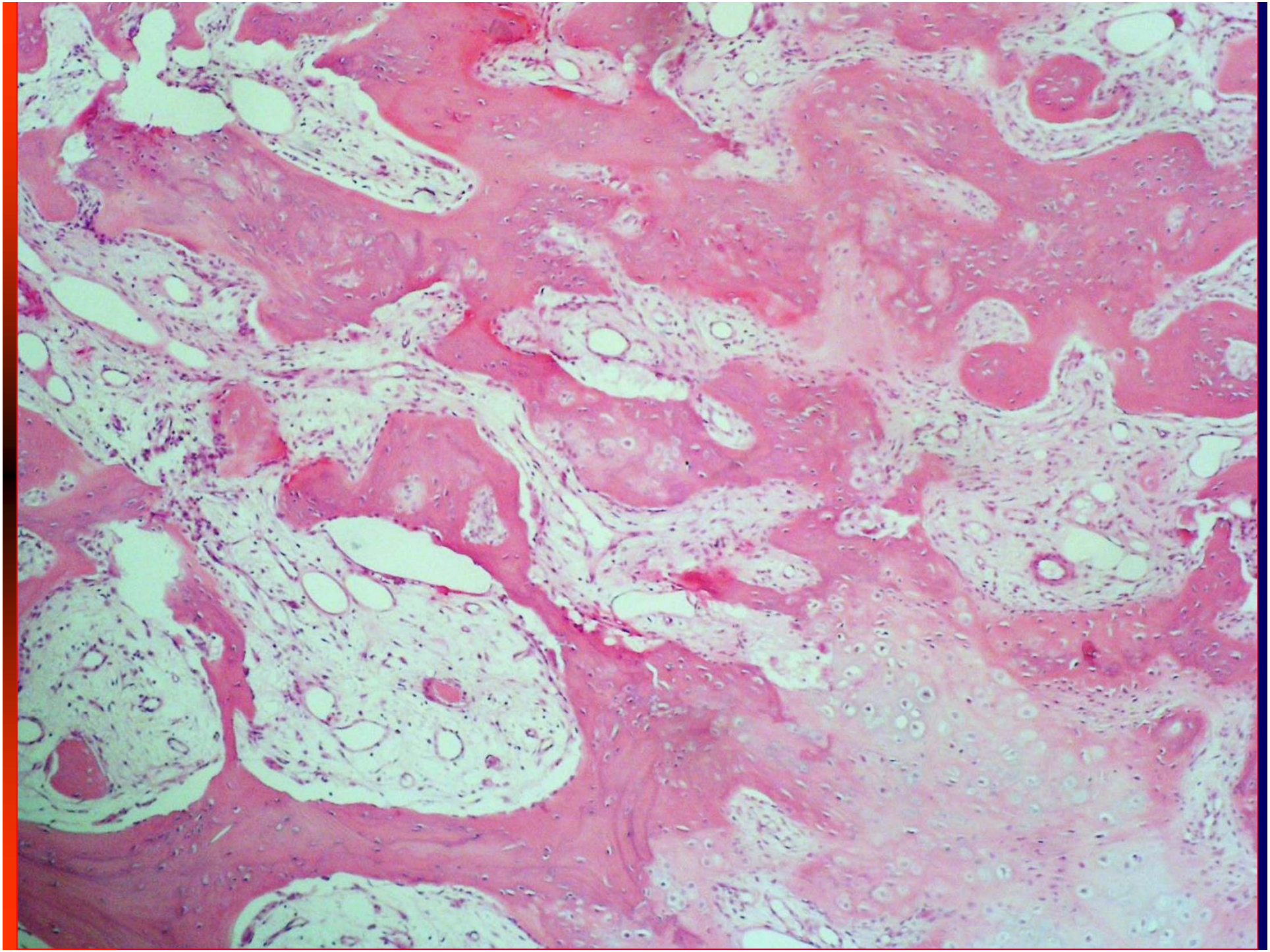


exuberant proliferation: “pseudosarcomatous”

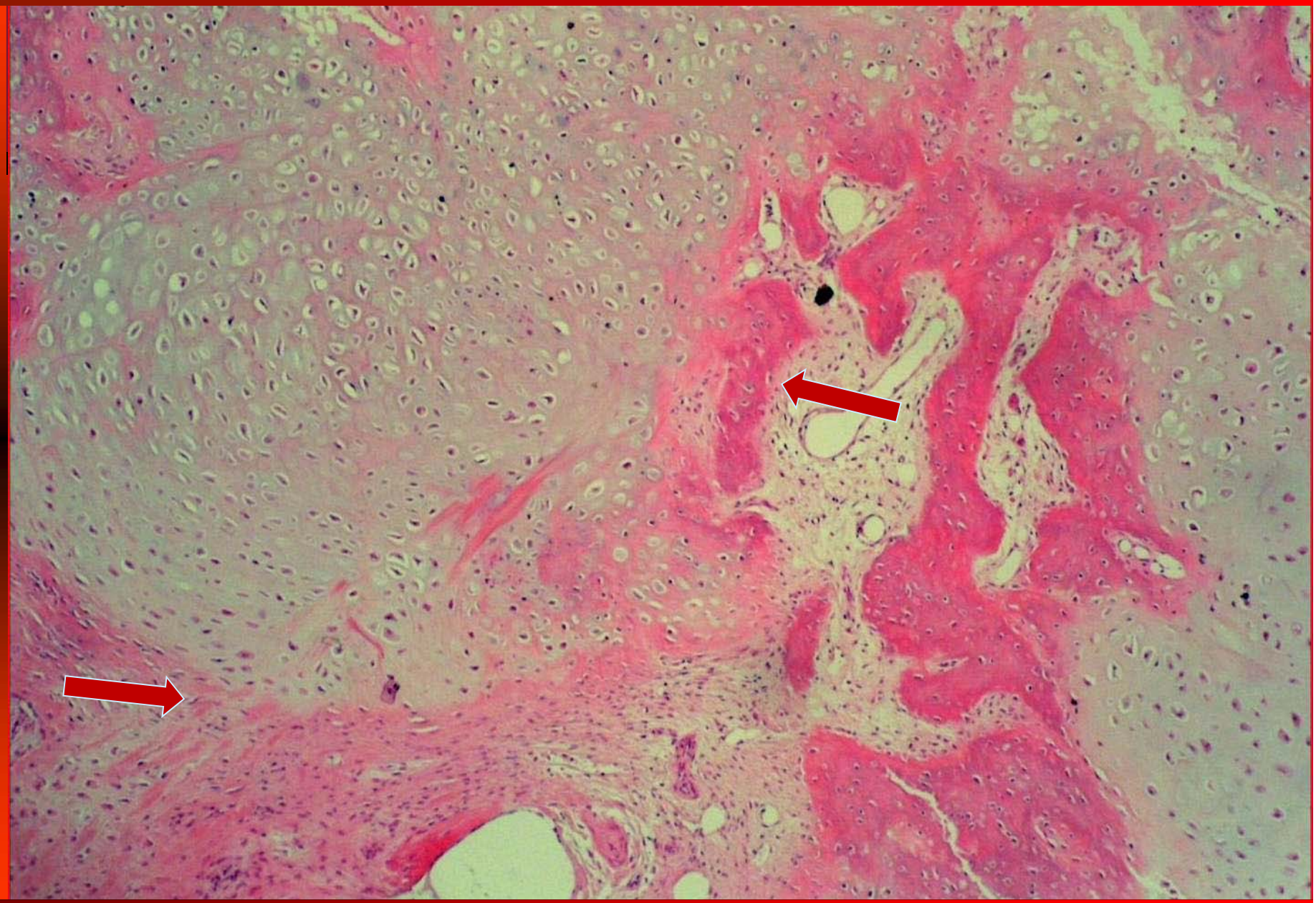
- bone
- cartilage
- fibrous tissue
- angiogenesis

- cellular chondroid
- reactive new bone
- muscle incorportion
- spindle cell proliferation
- variably myxoid

- Oxygen tension ↓
- Mechanical stimuli ↑

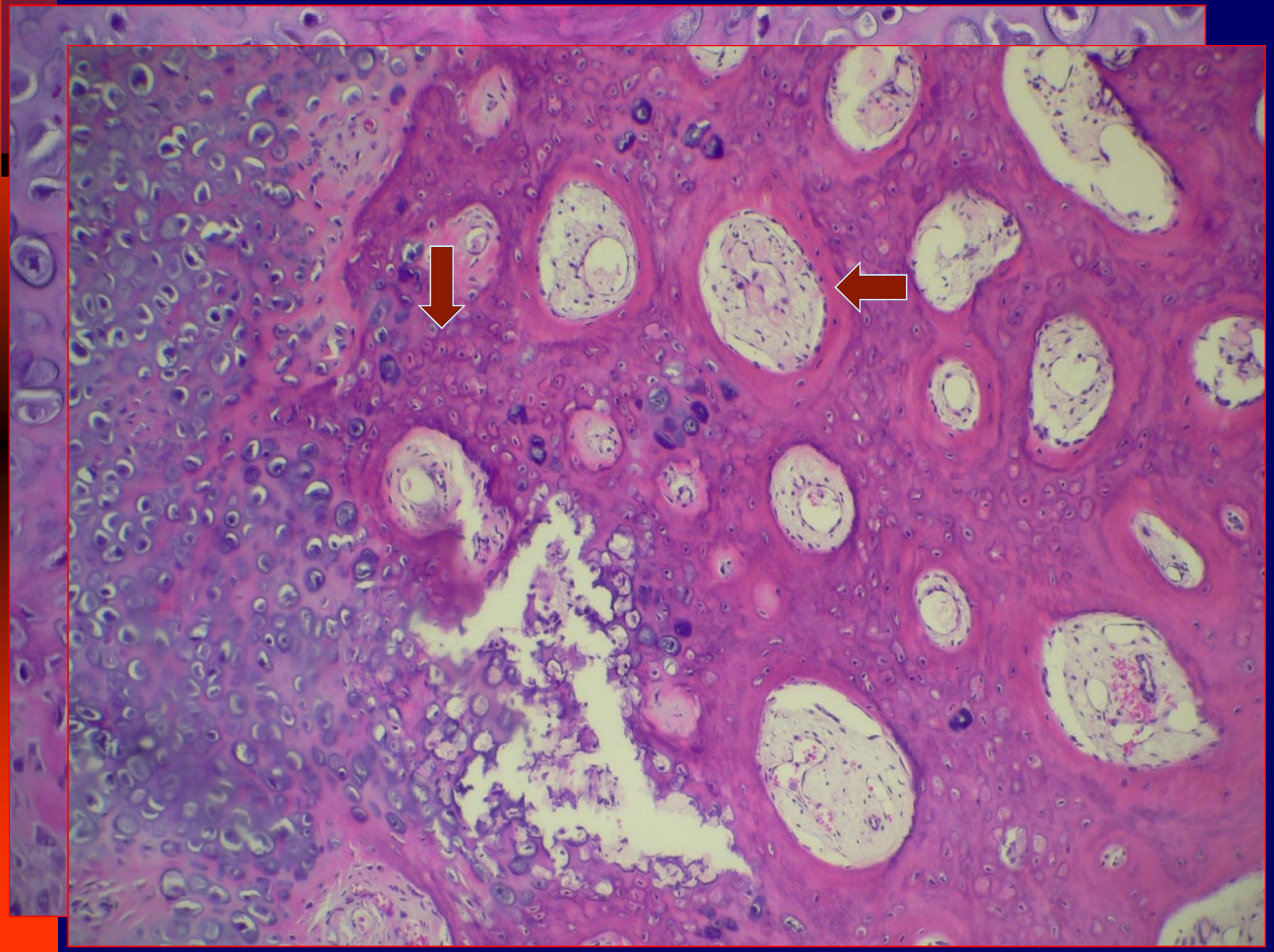


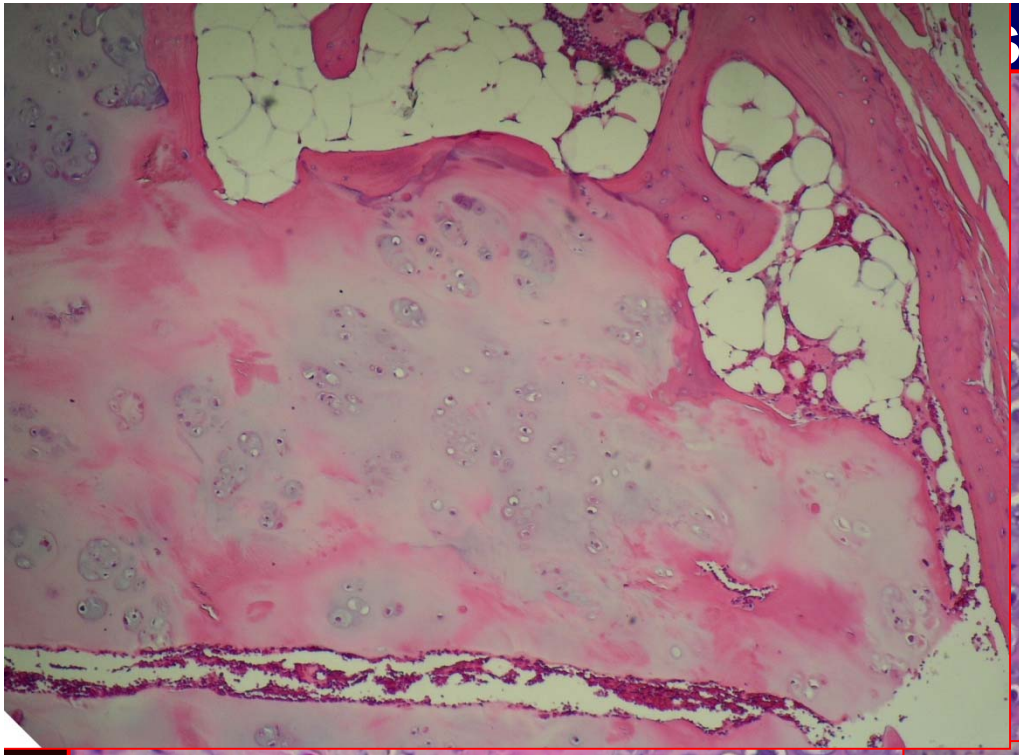
zonal change characteristic of reactive lesions



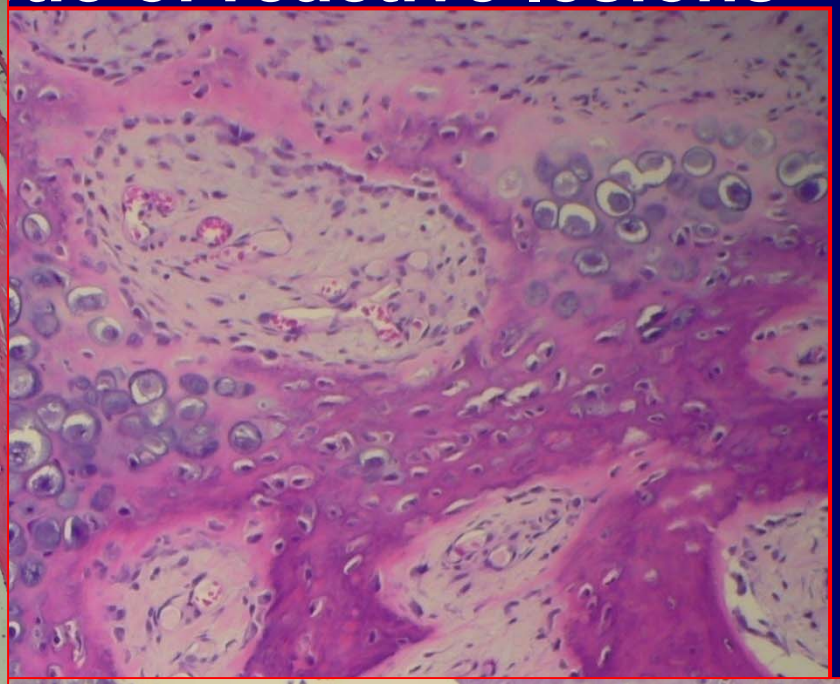
↓ oxygen tension ↑ mechanical stimuli

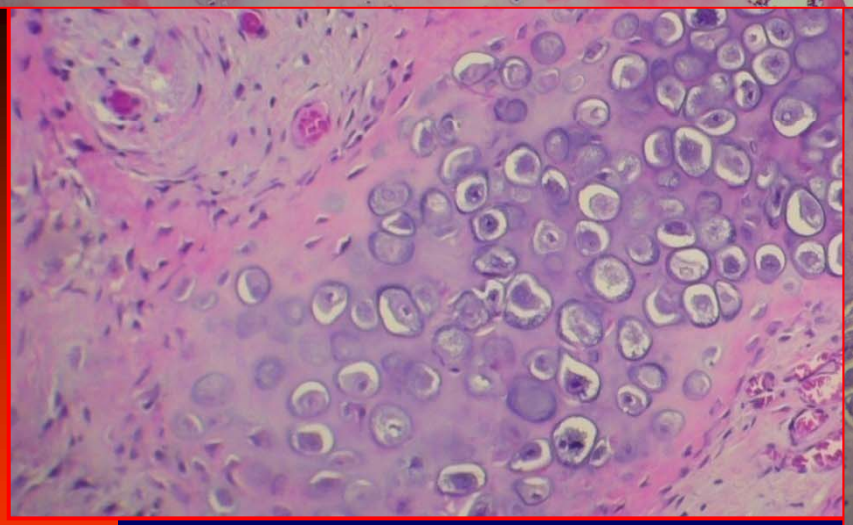
zonal change characteristic of reactive lesions



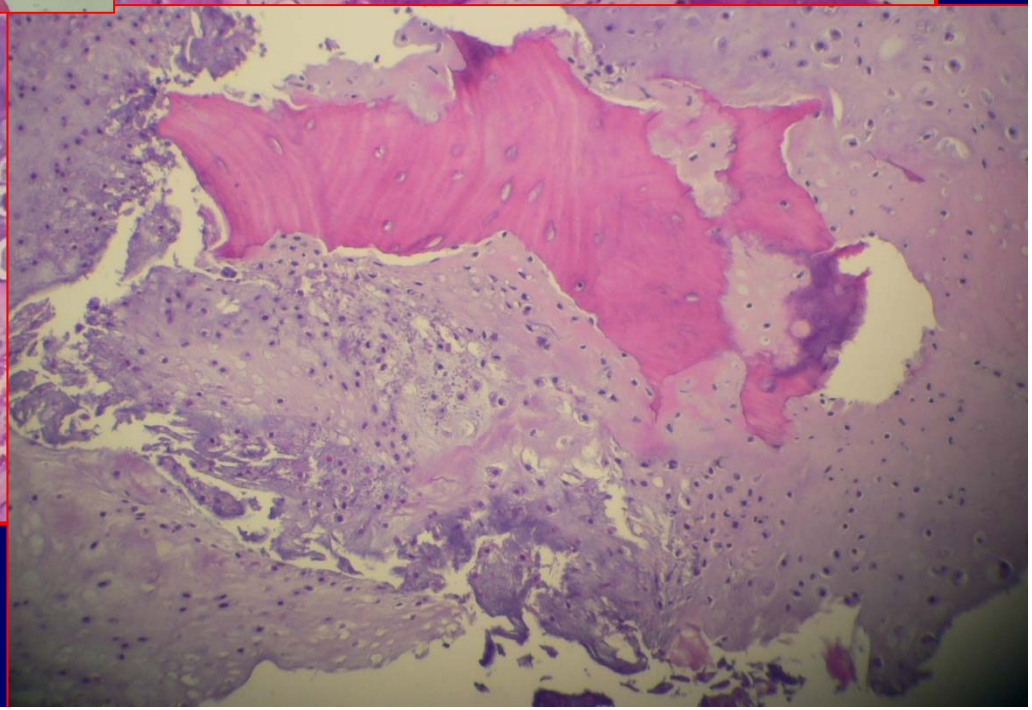


stic of reactive lesions

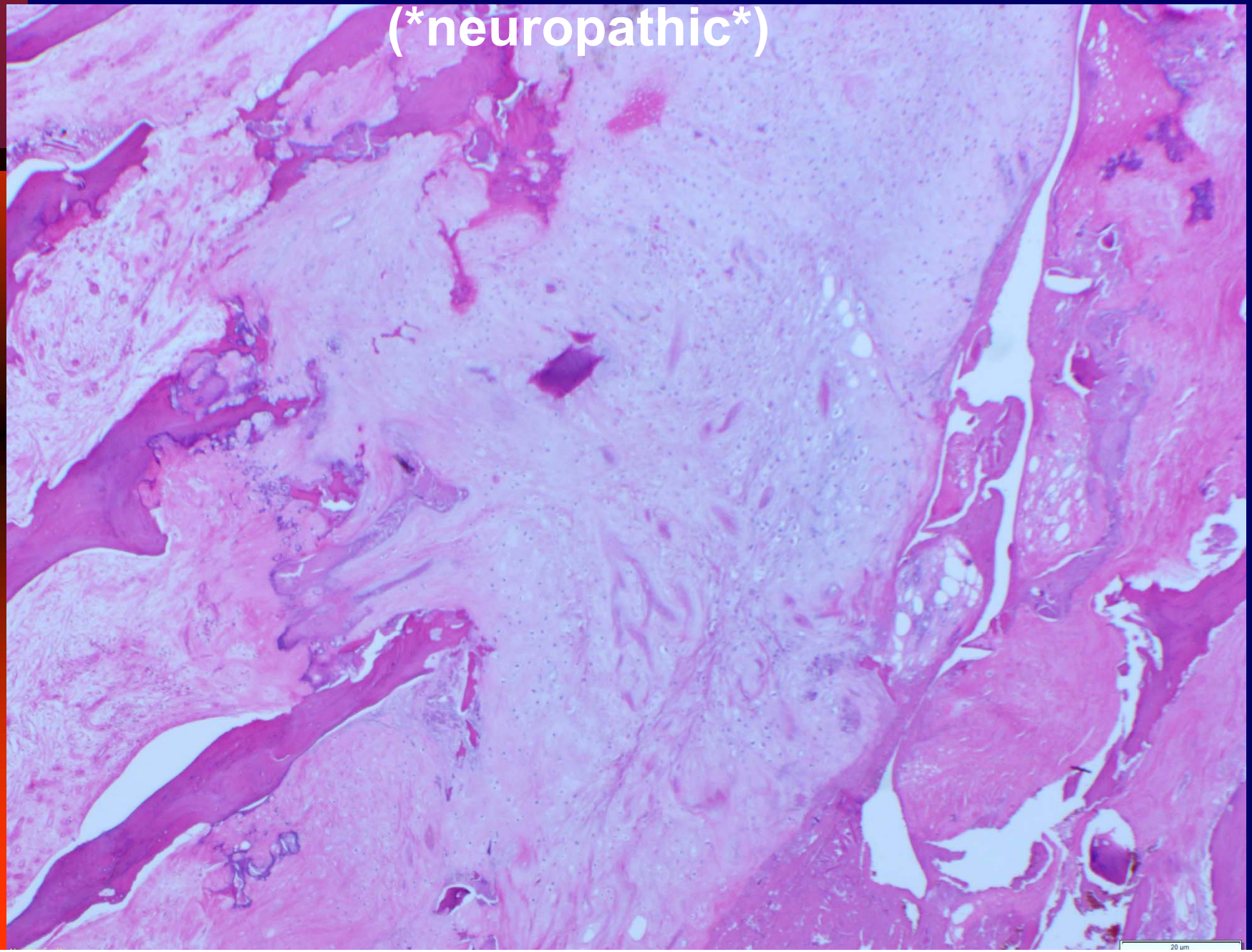




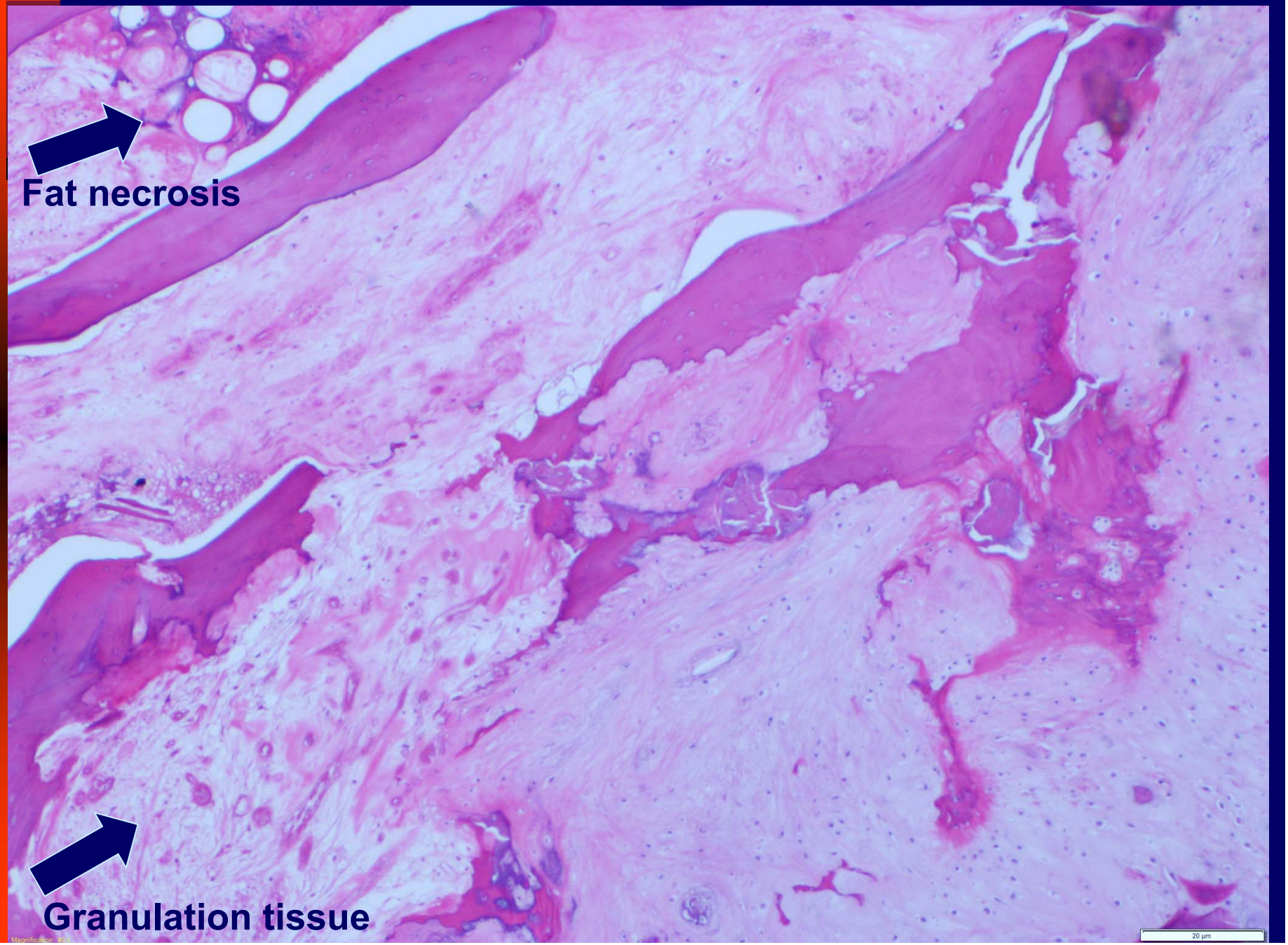
contrasting with
tumours of cartilage



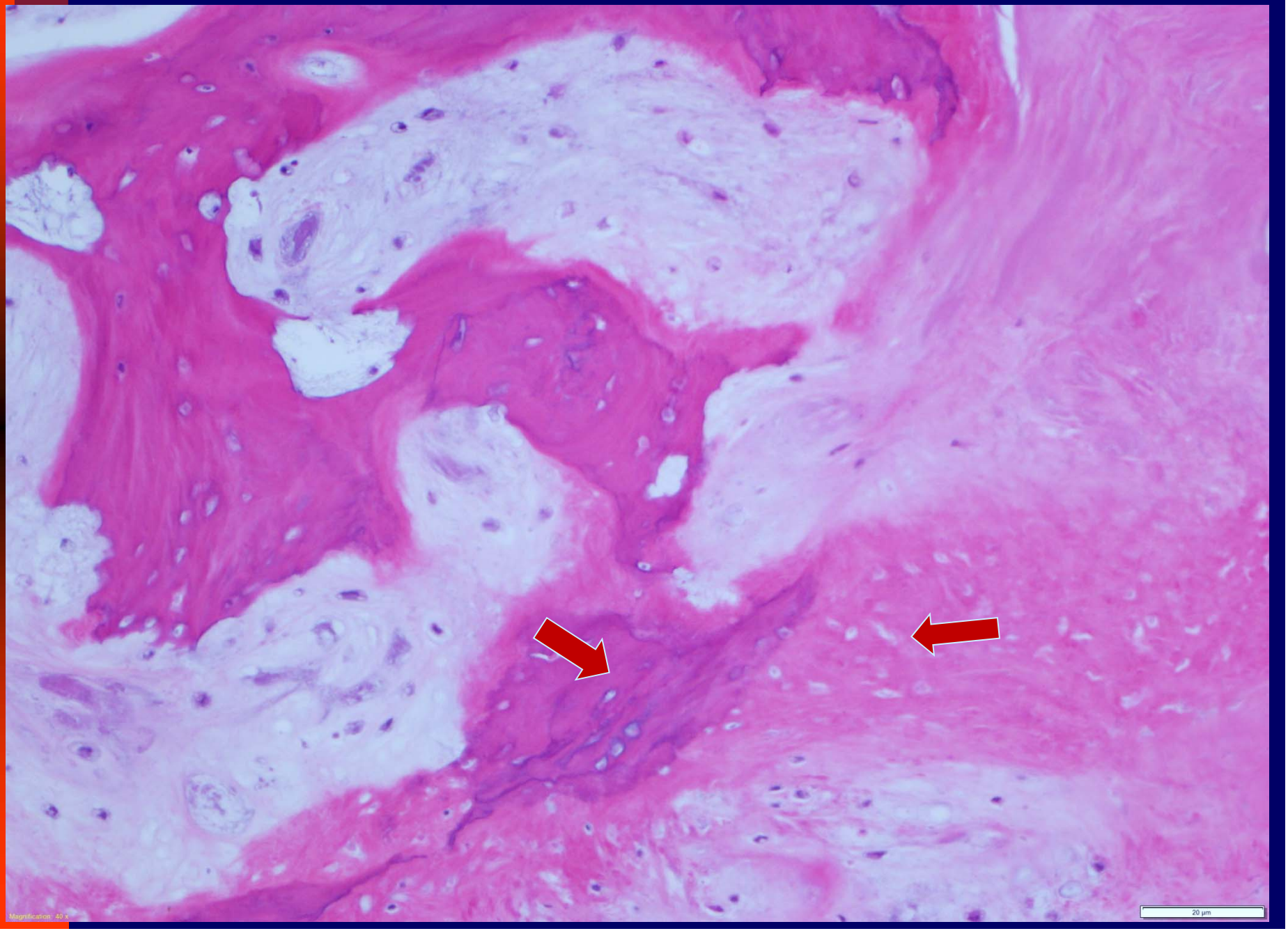
ongoing excess mobility, diminished oxygen tension (*neuropathic*)



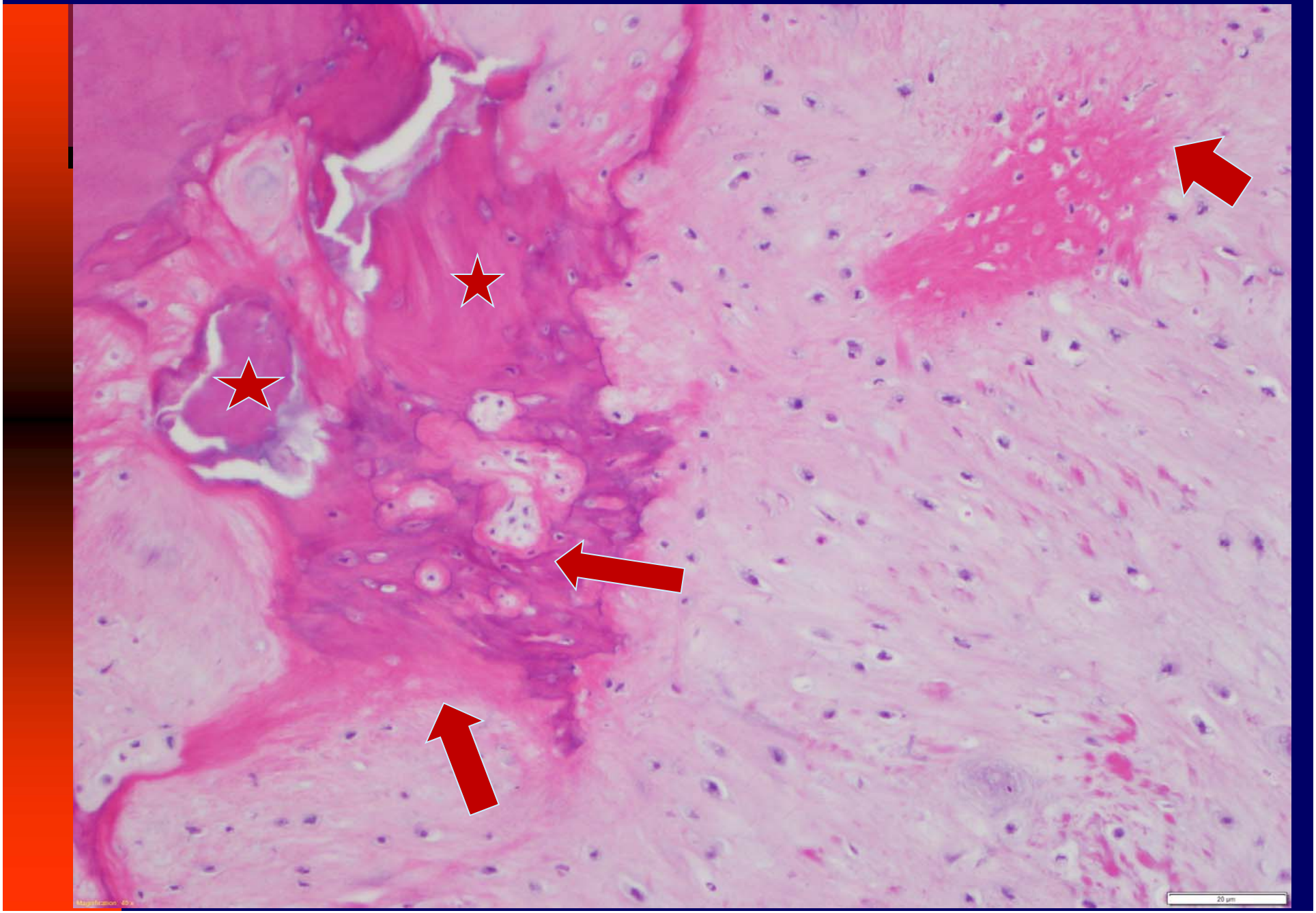
fragmented partly resorbed fragmented bone and cartilage



Subtle zonation, osteoid,woven bone, reactive stromal components

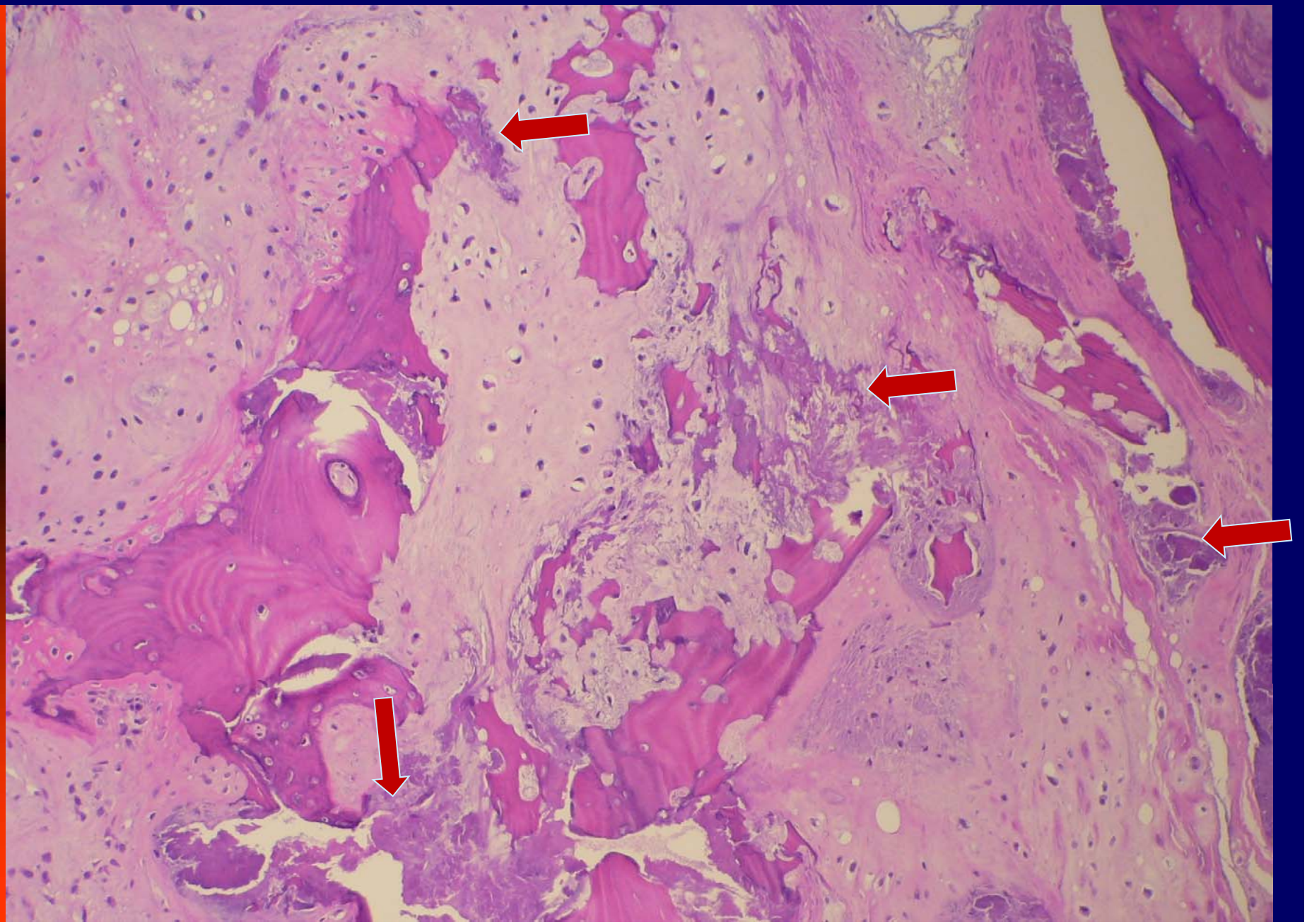


osseous debris,subtle zonation, osteoid,woven bone, reactive stromal components

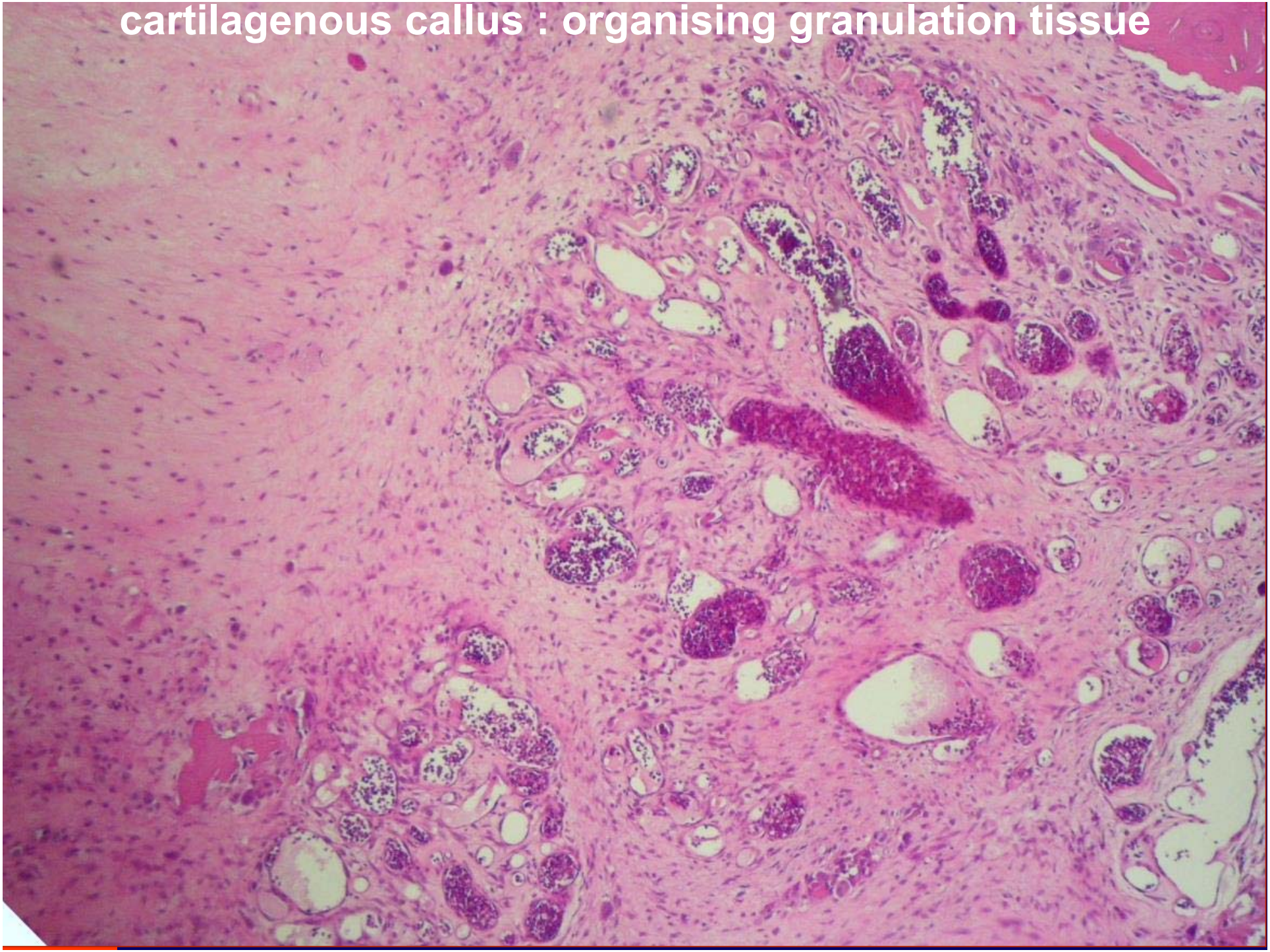


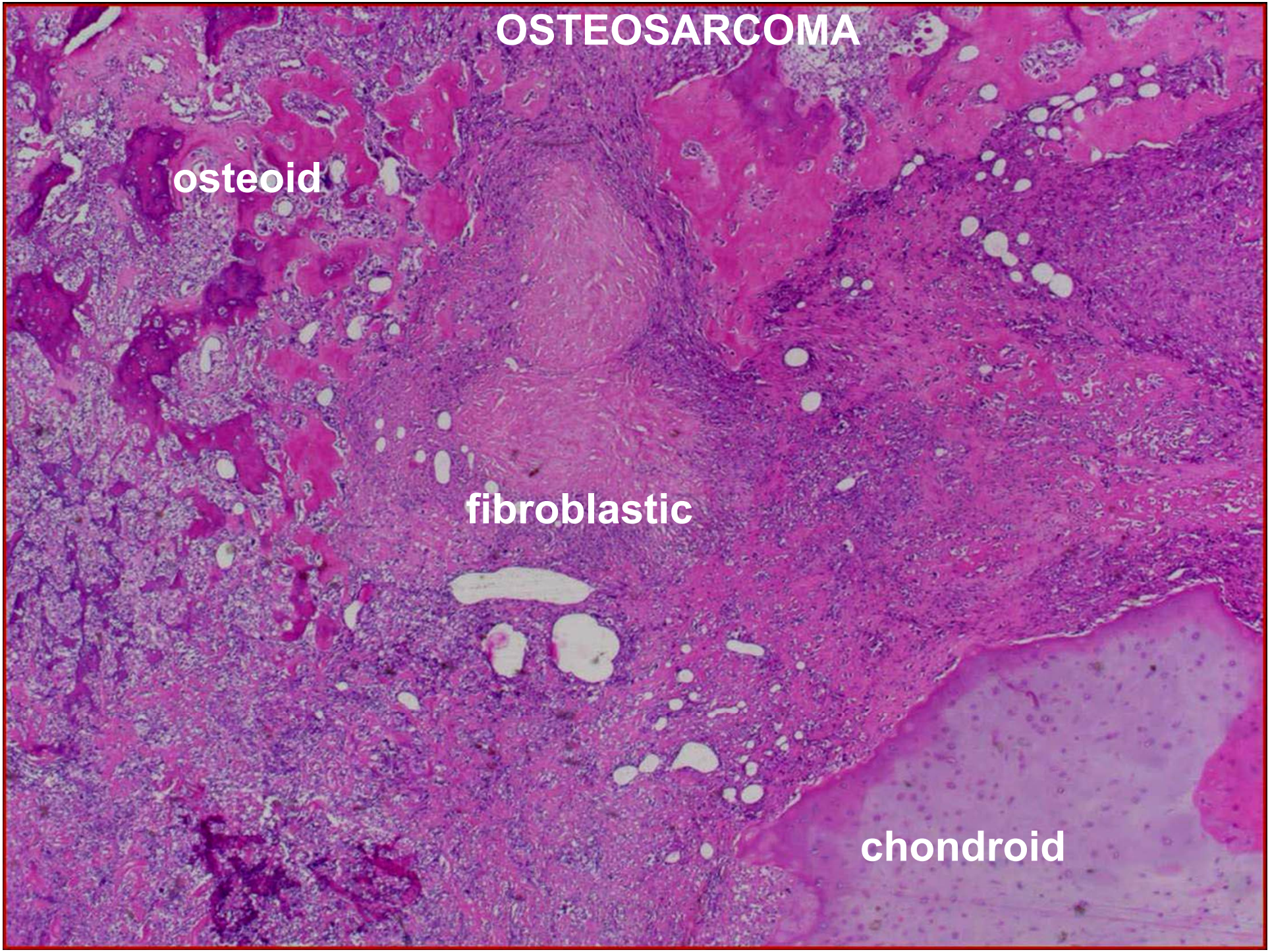
cartilagenous callus: background bone fragmentation, resorption

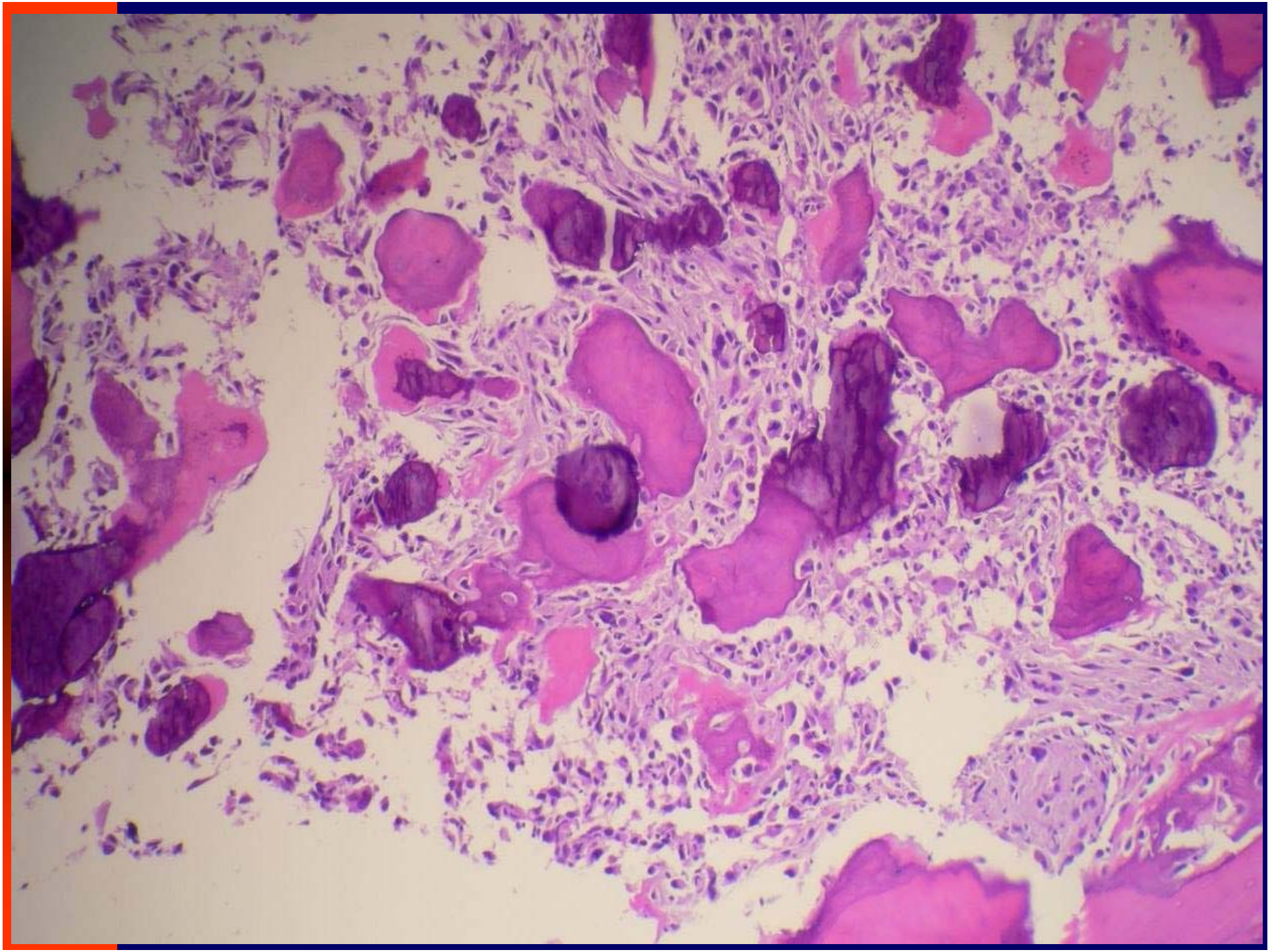
powdery / granular detritic debris (arrows)

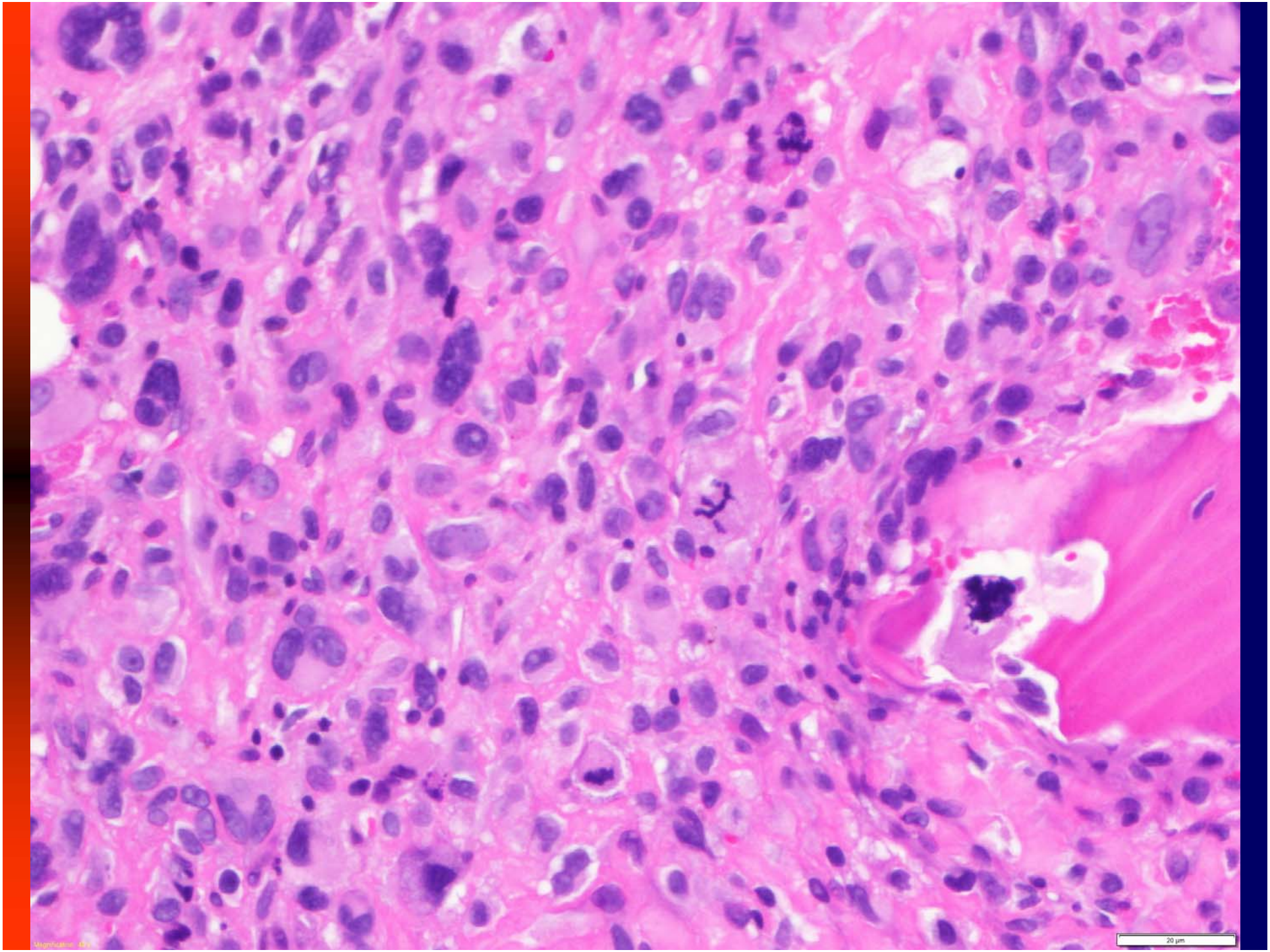


cartilagenous callus : organising granulation tissue



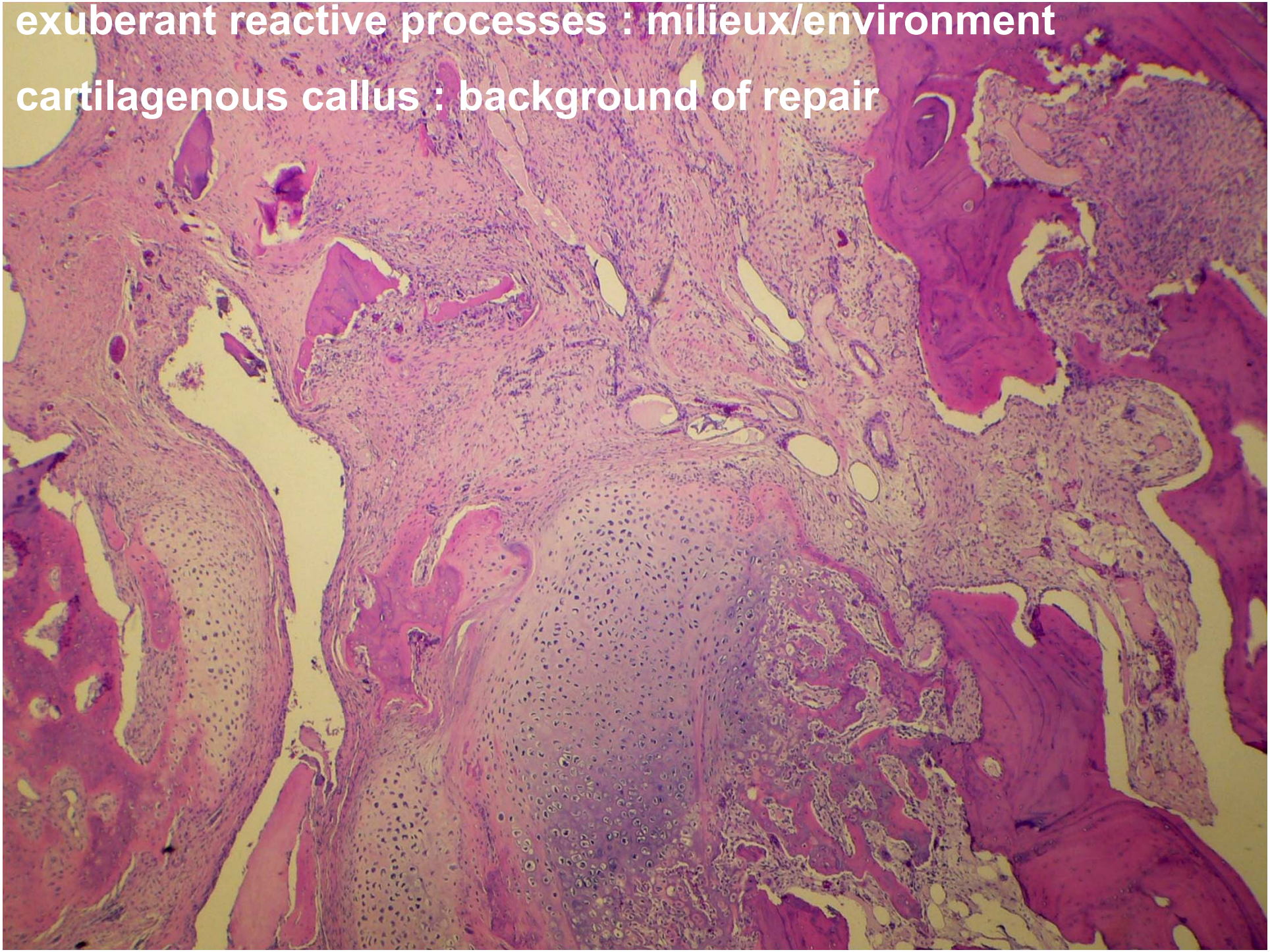

OSTEOSARCOMA
osteoid
fibroblastic
chondroid




20 µm

exuberant reactive processes : milieux/environment

cartilagenous callus : background of repair

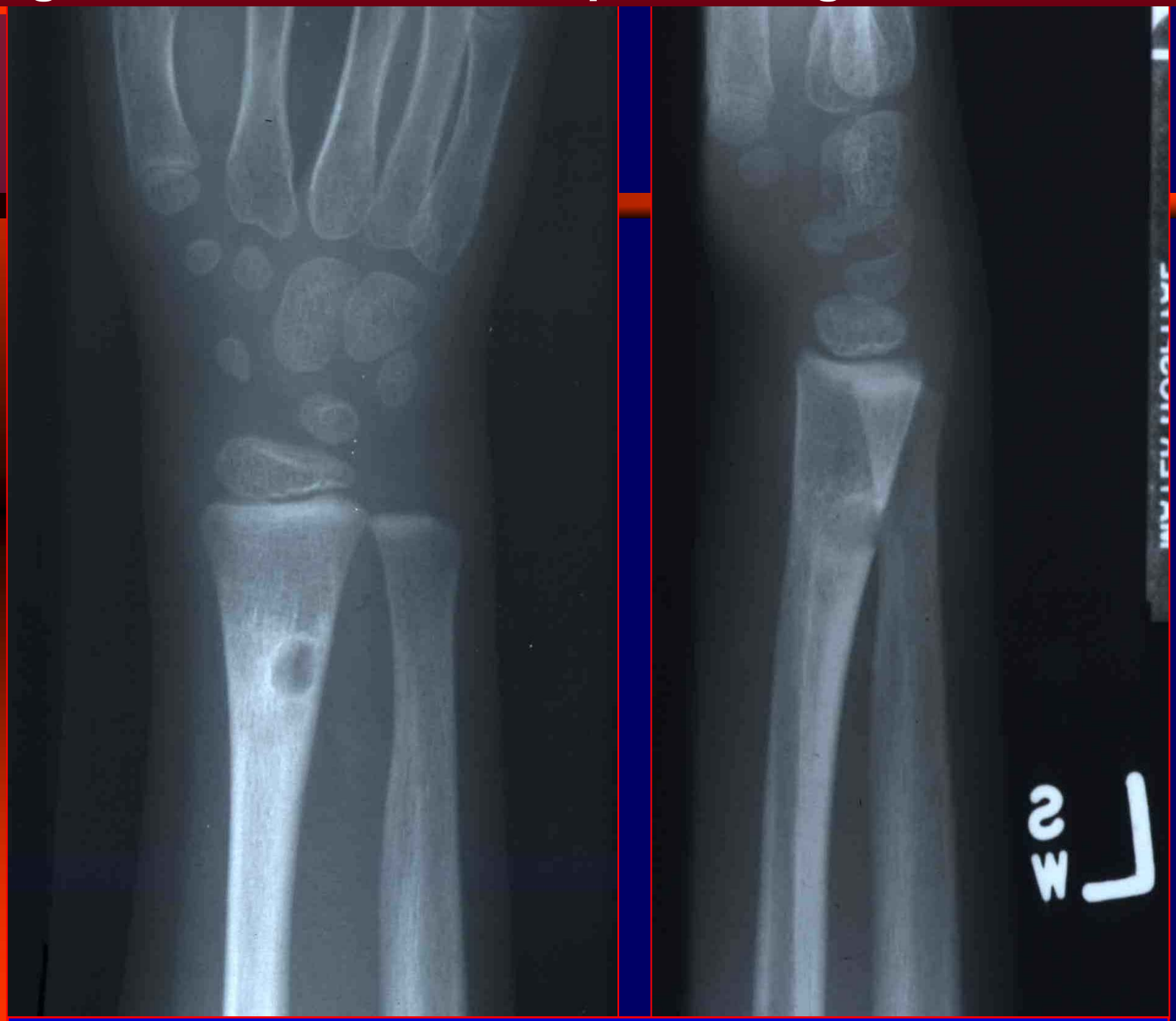


Biopsies performed

Commonly by non tumour surgeons

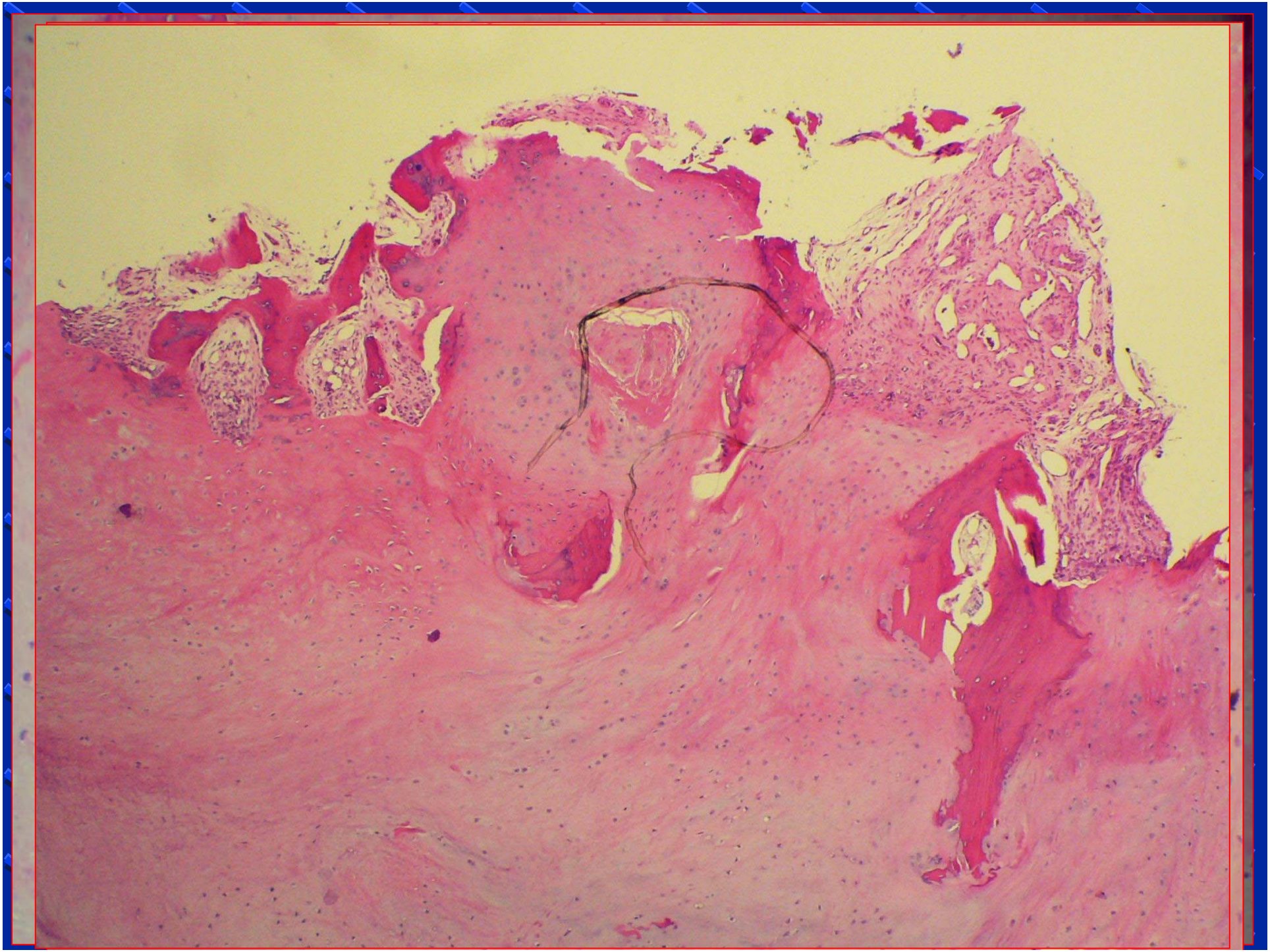
- variable quantities of tissue
  (often miniscule!!)
- variable artefact (often bad!)
- variable clinical information
  - (lucky to be given the name of the bone!)

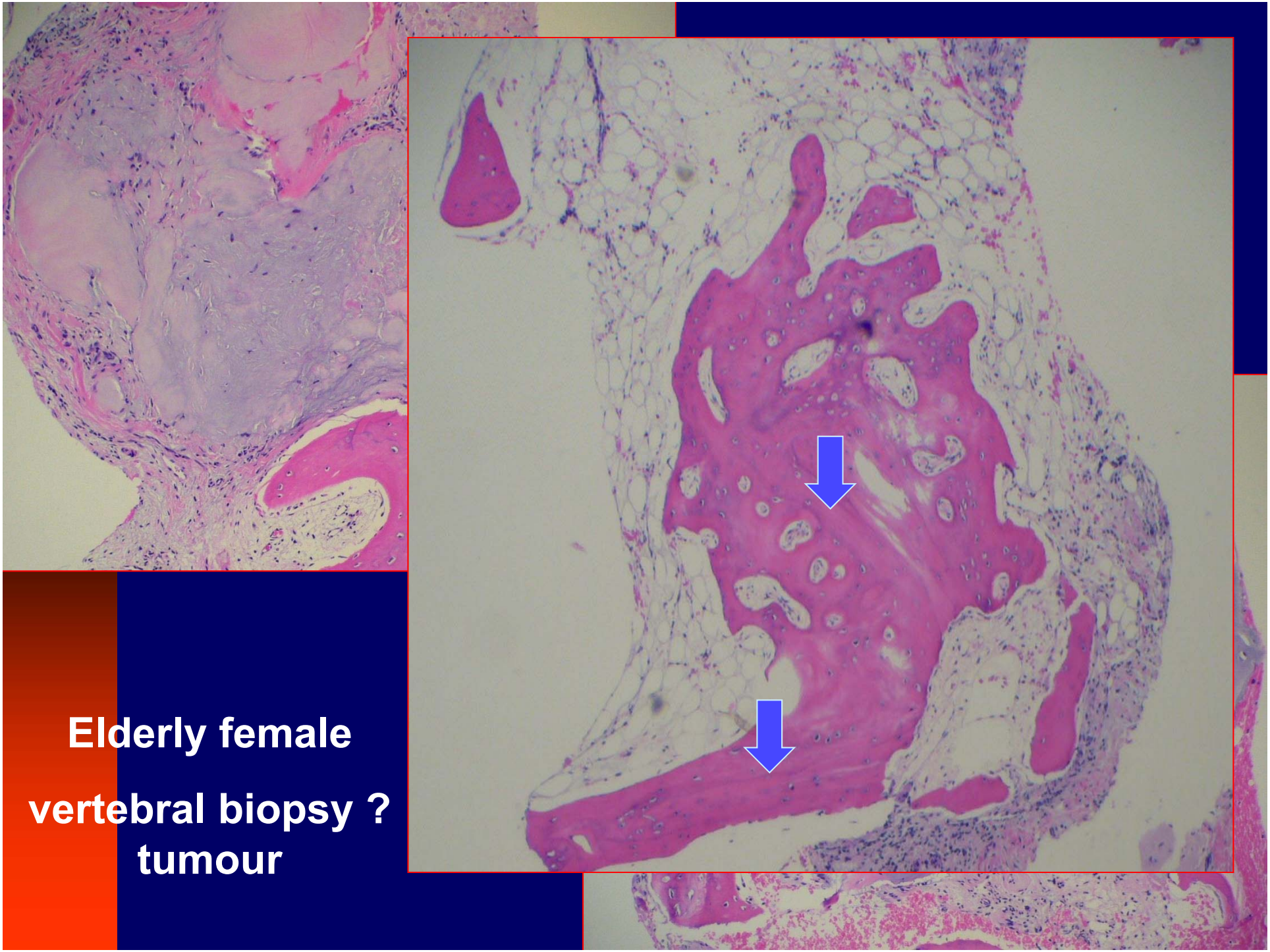
Neglected to mention the previous greenstick fracture



Clinical history: female age 3, lytic lesion distal radius

Clinical history: ? enchondroma scaphoid

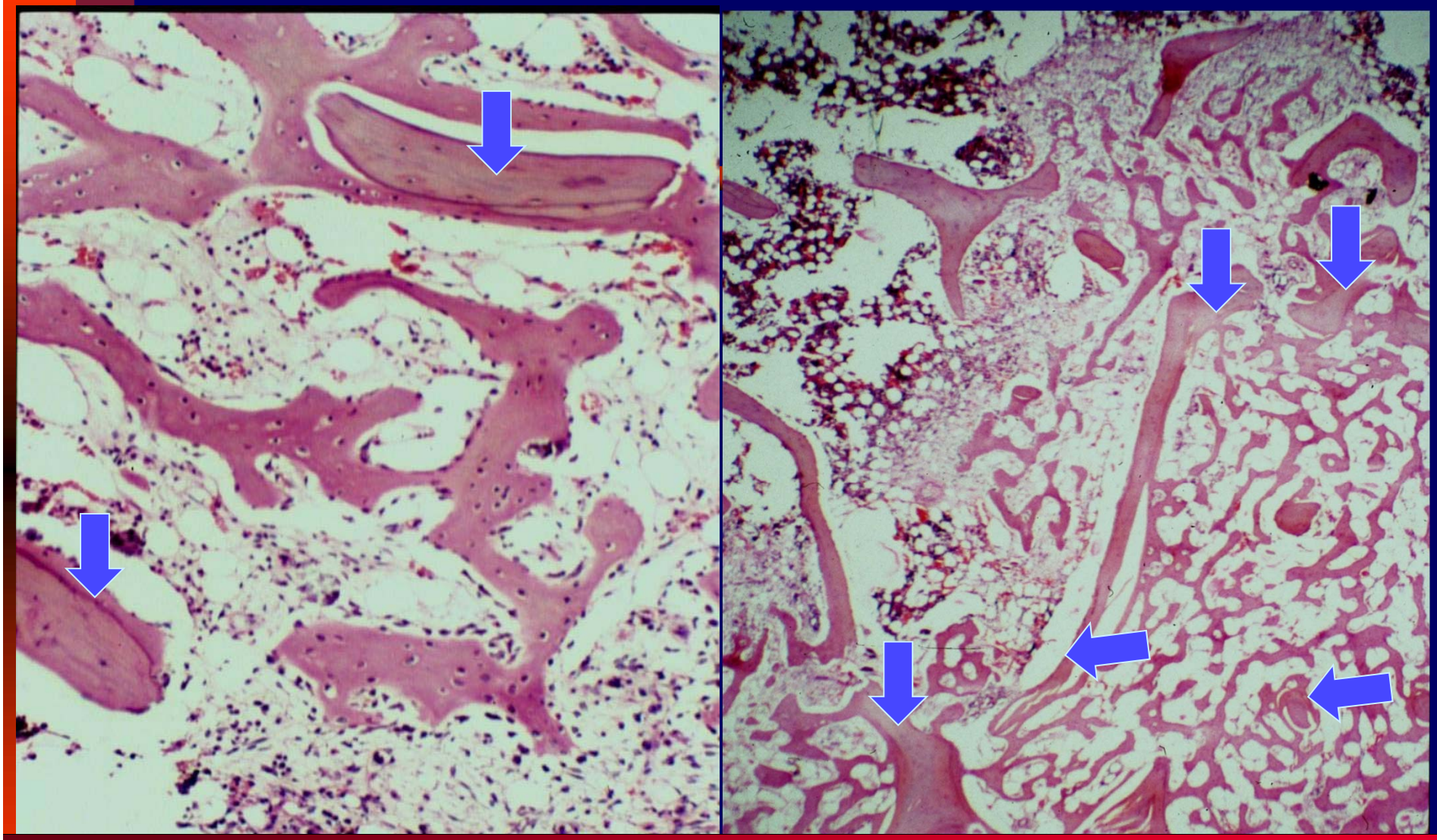




Elderly female

vertebral biopsy ?
tumour

Female 76 vertebral lesion ? tumour ? osteoblastoma



I strongly recommend:

- Biopsies performed
- Commonly by non tumour surgeons

Be pushy!

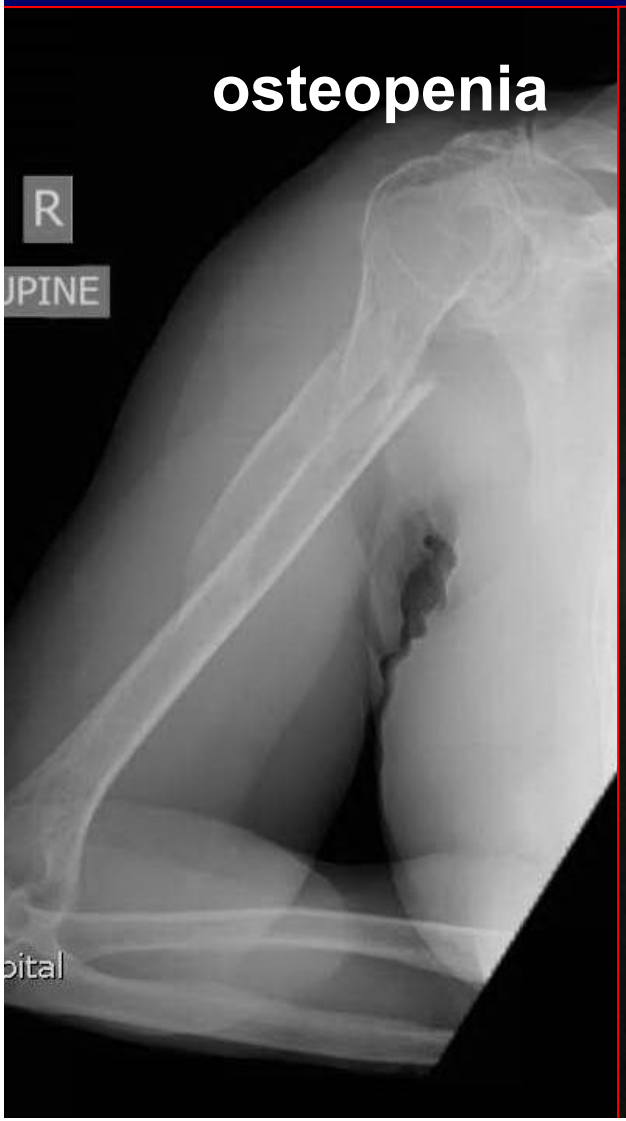
Call the referring doctor

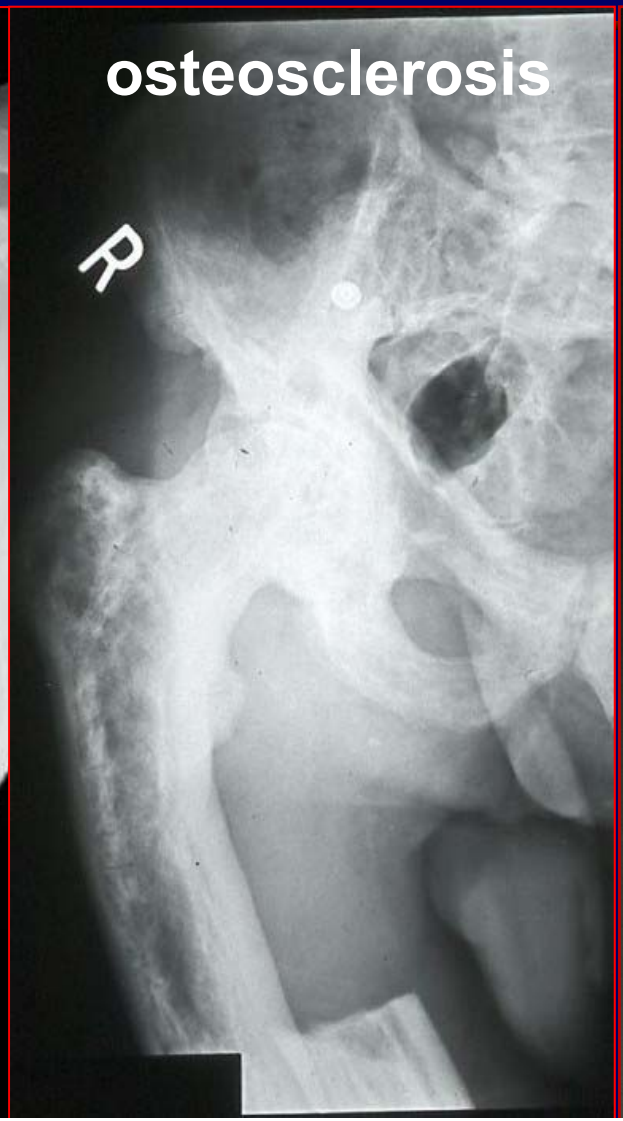
complete clinical history, imaging

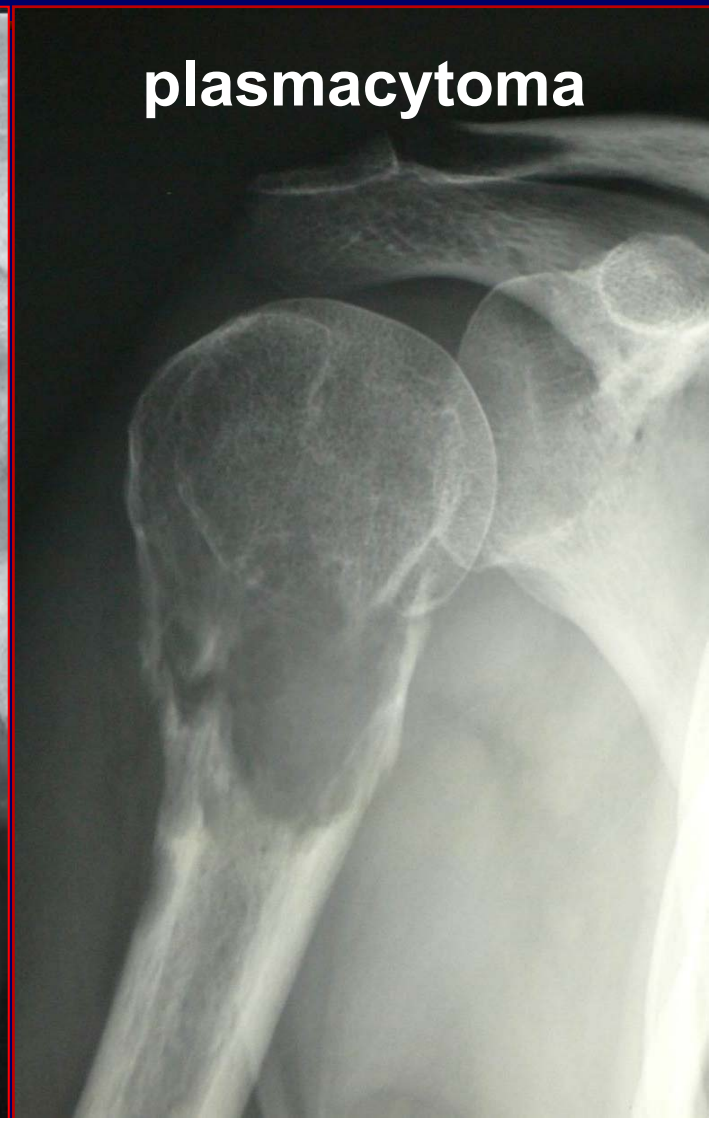
and keep calling …

… until you are satisfied..

- **pathological fracture**
  - abnormal matrix
  - tumour
    - minor trauma
    - no trauma

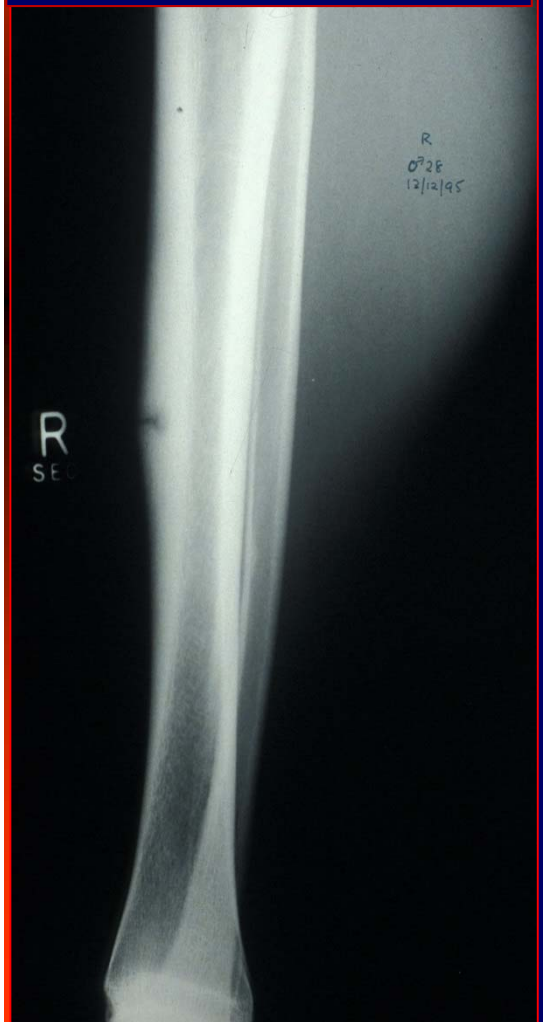




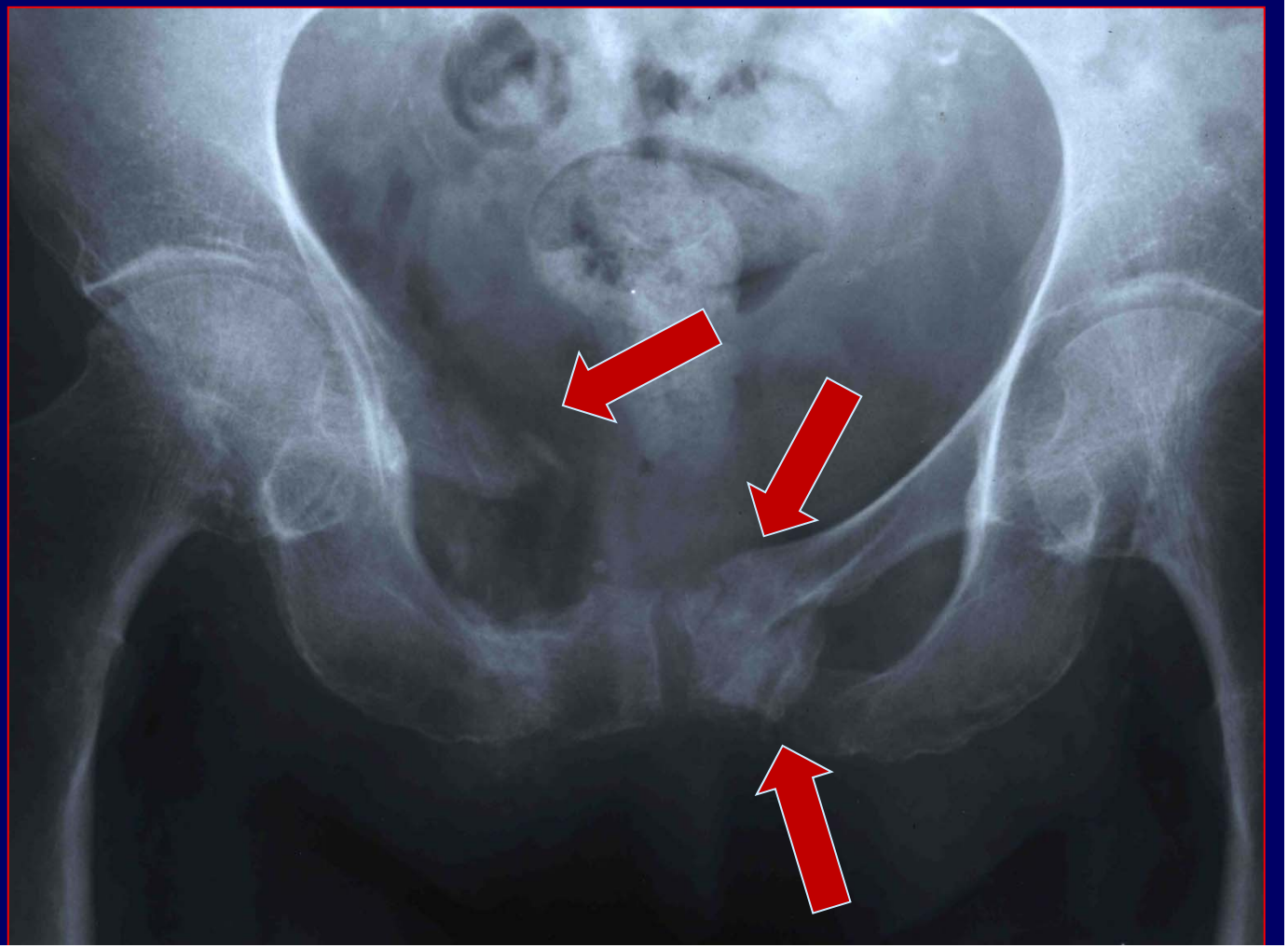


- **stress fracture** → **recurrent, cyclic trauma**
  - **normal bone** → **fatigue fracture**
  - **abnormal (osteopenic+)** → **insufficiency fracture**

fatigue fracture



insufficiency fracture



BONE STRENGTH

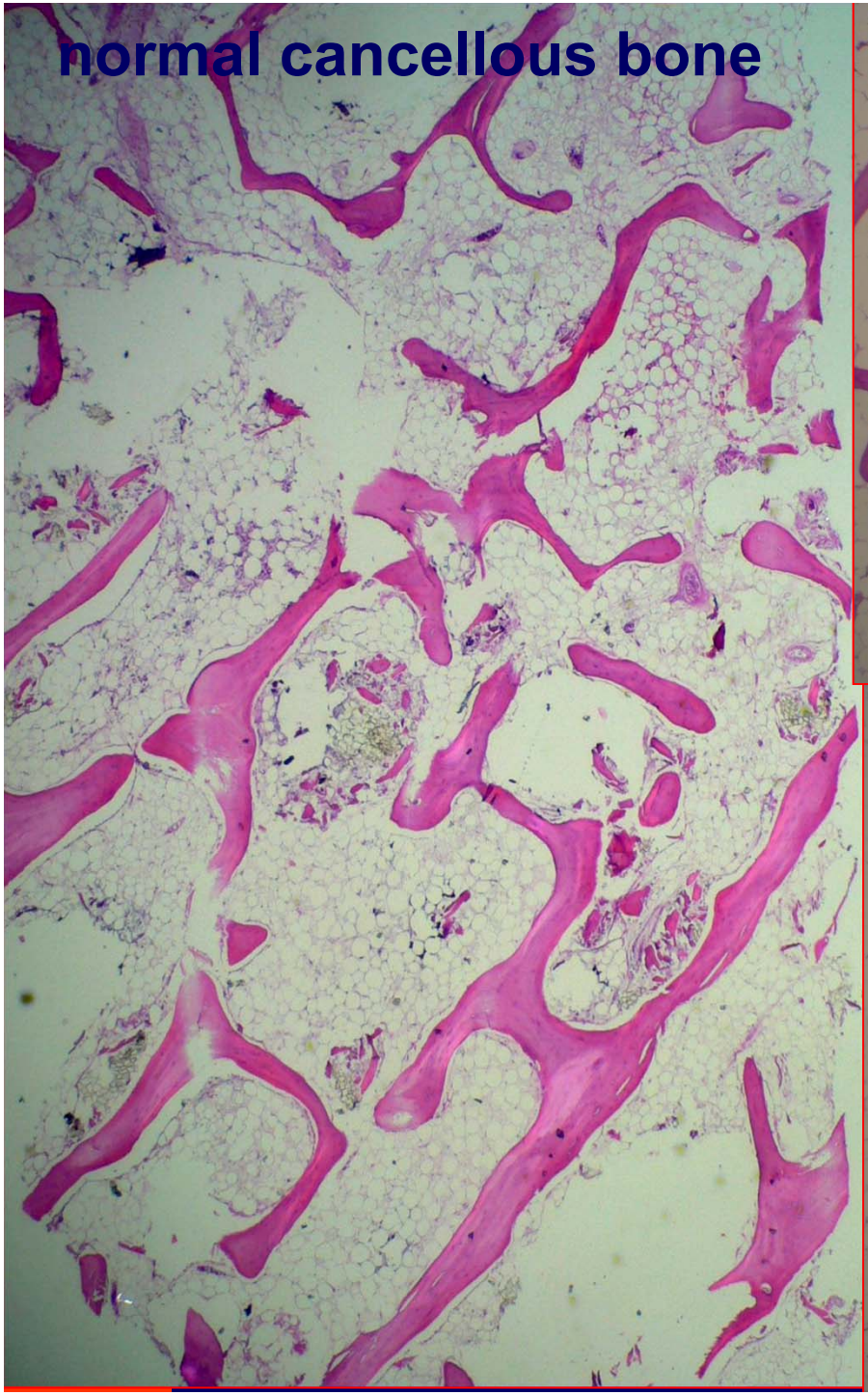
- density
- mineral content
- distribution of collagen

- **trabecular bone**

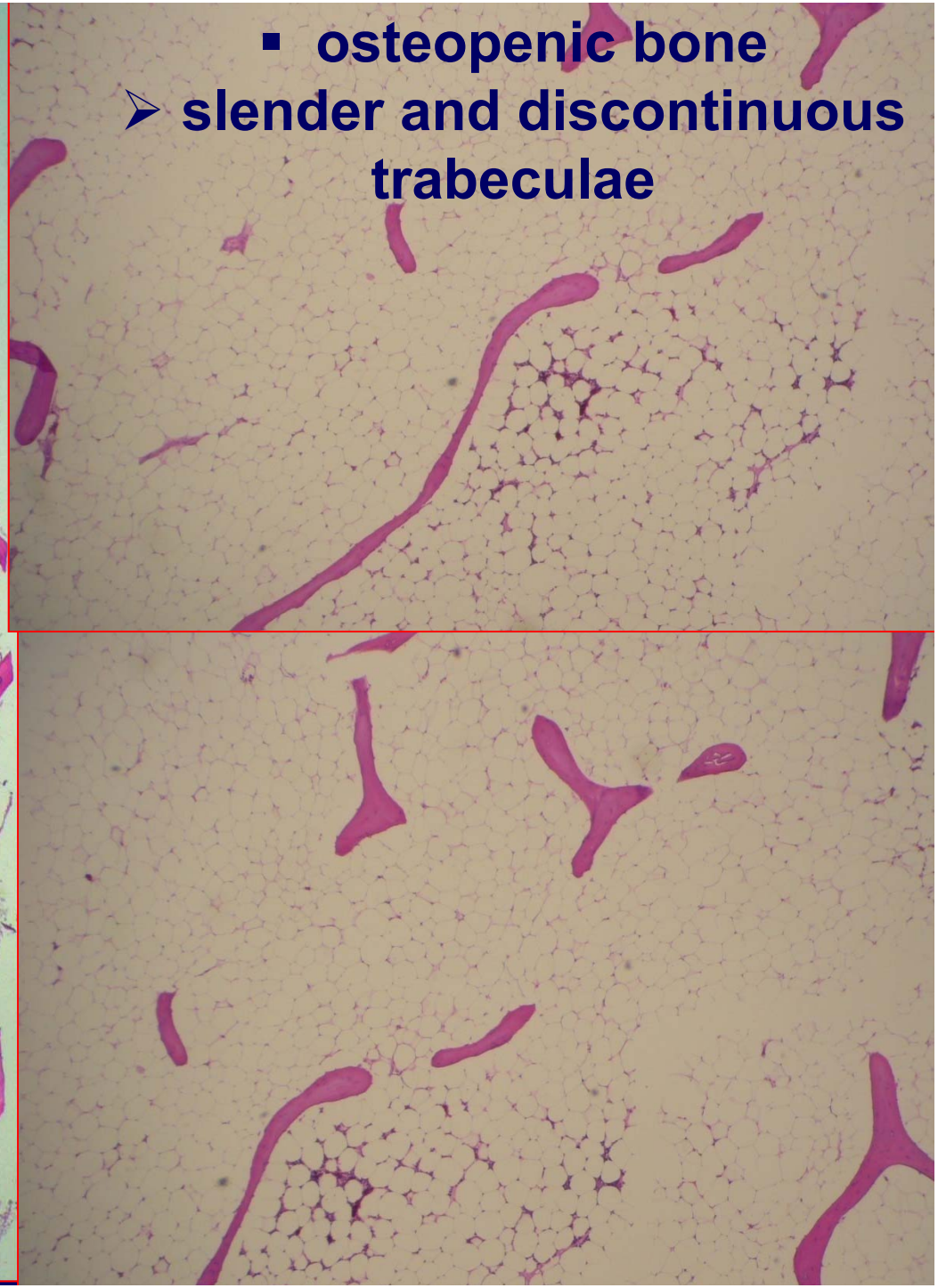
- compressive strength α square of density

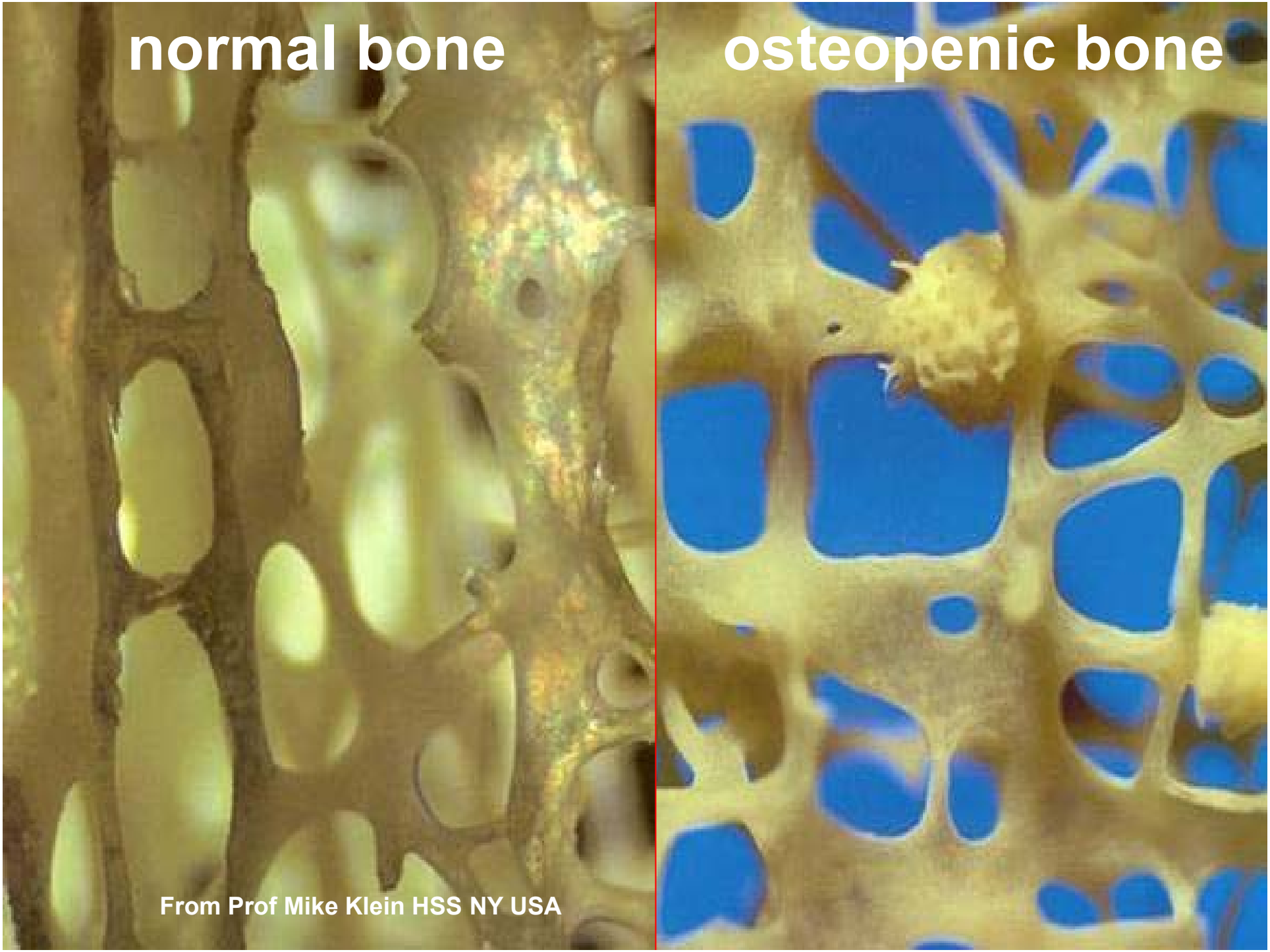
↓ density x 2

↓ compressive strength x 4



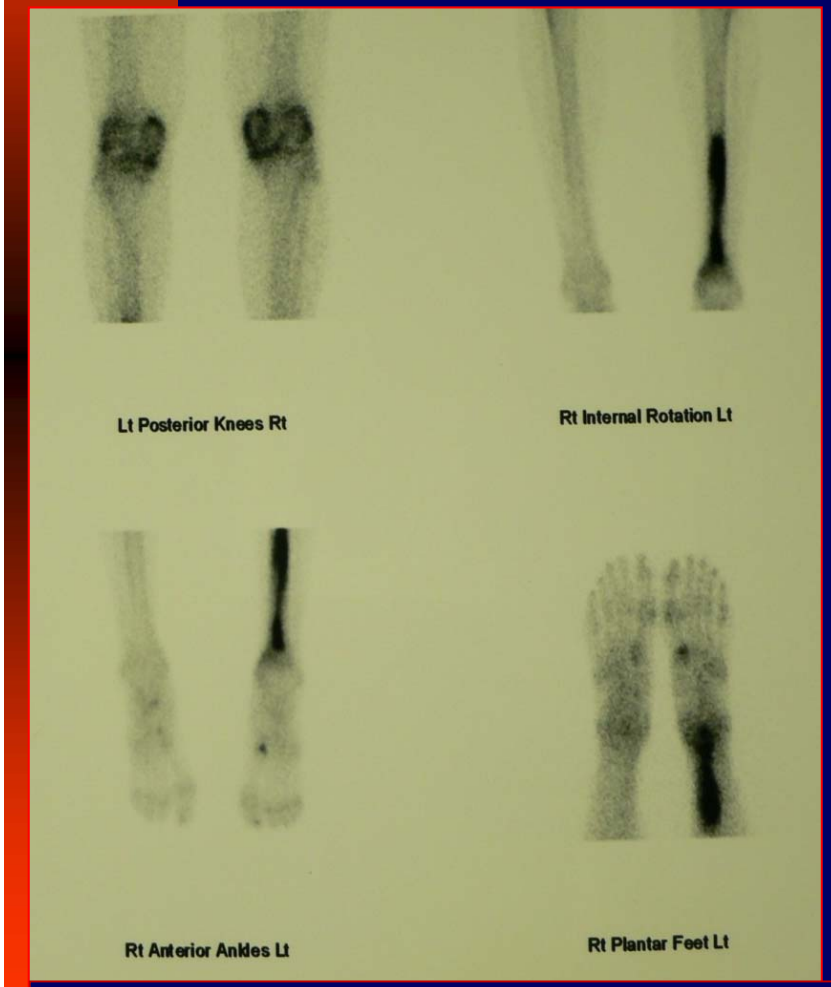
- osteopenic bone
  - slender and discontinuous trabeculae

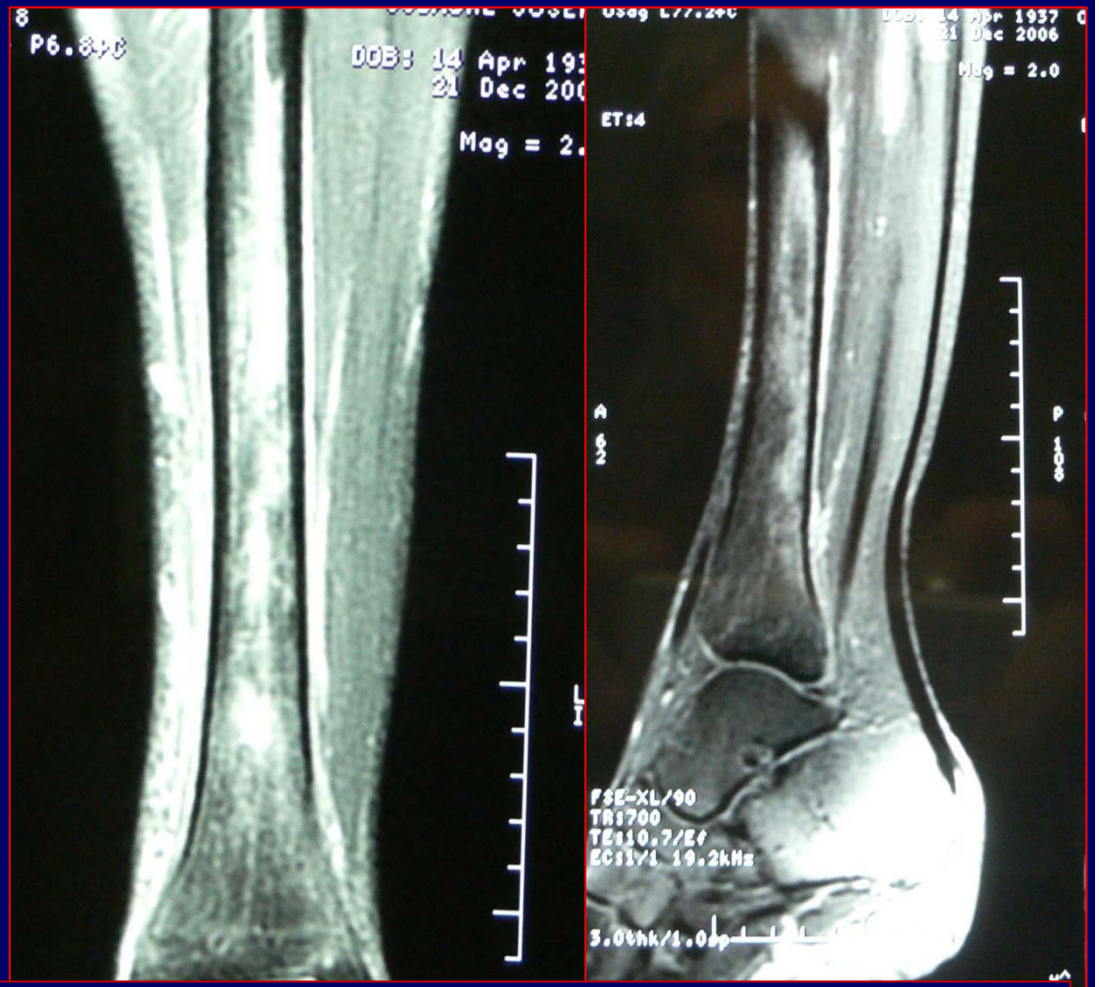



normal bone
osteopenic bone
From Prof Mike Klein HSS NY USA

- **microtrabecular fracture: bone “bruise”**
  - ➢ **abnormal usually osteopenic bone**

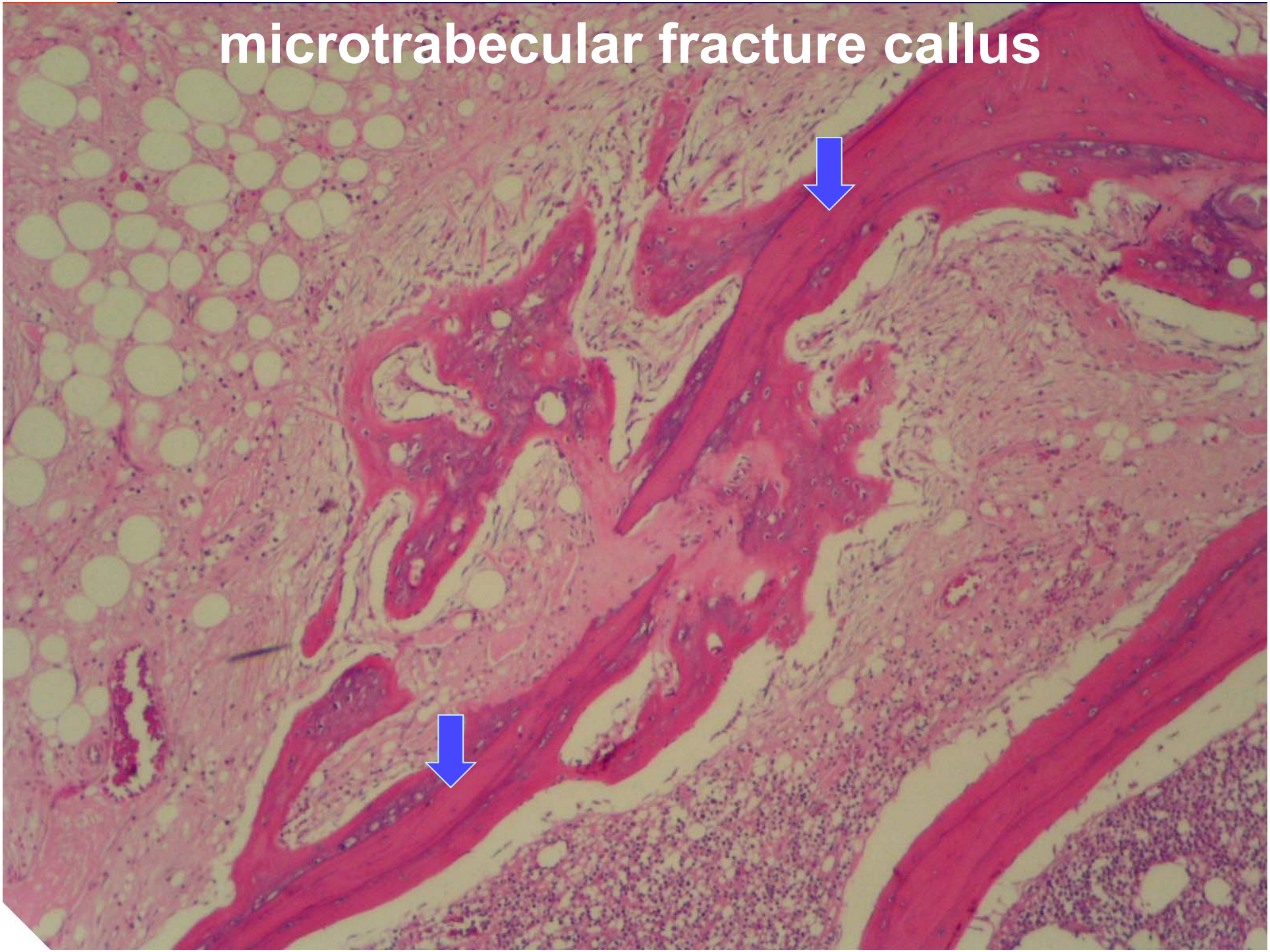
may mimic intramedullary tumour/sepsis





female aged 70 ?

microtrabecular fracture callus

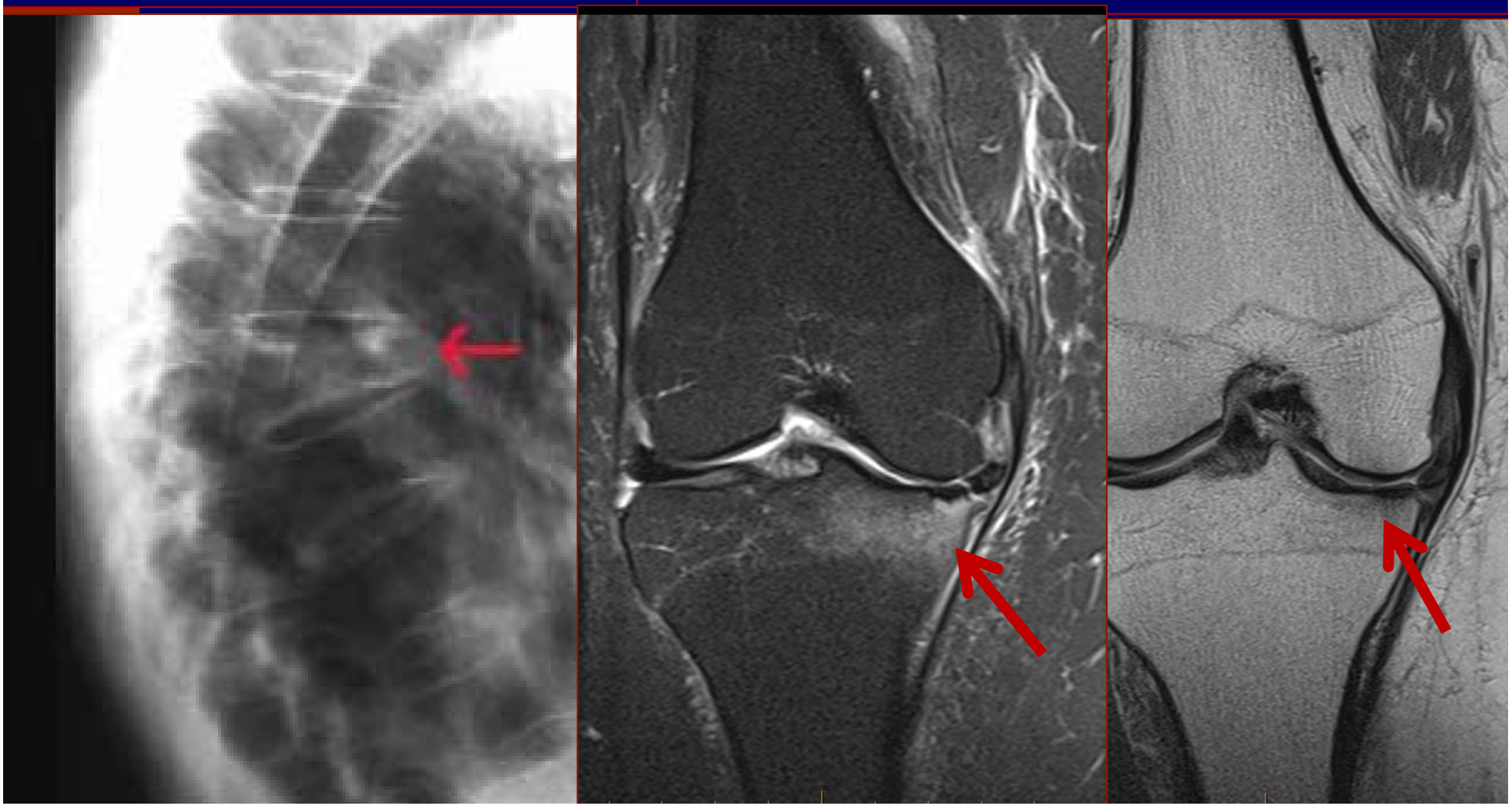


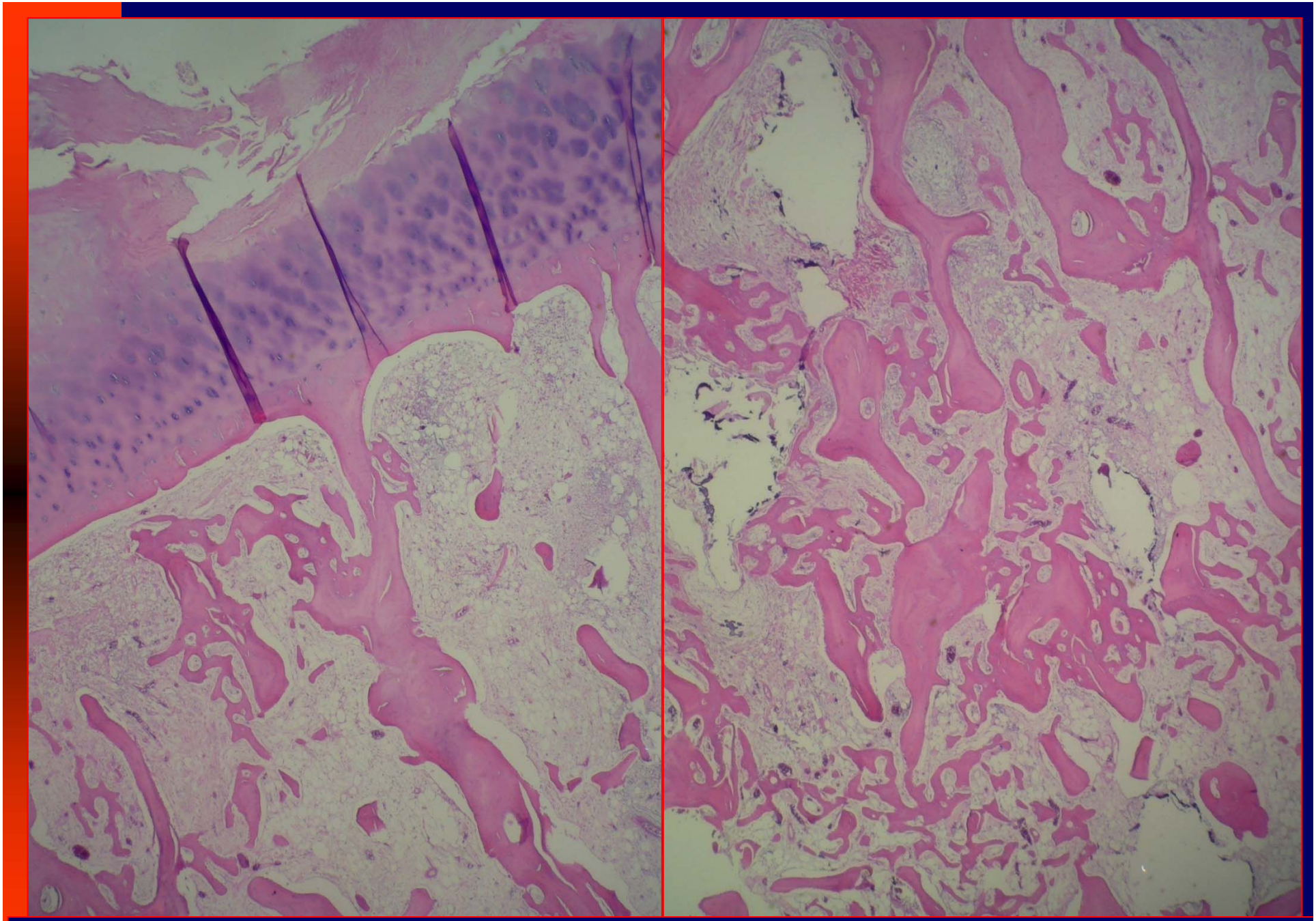
➢ compression/impaction

- ➢ normal /abnormal bone
- ➢ close to joint

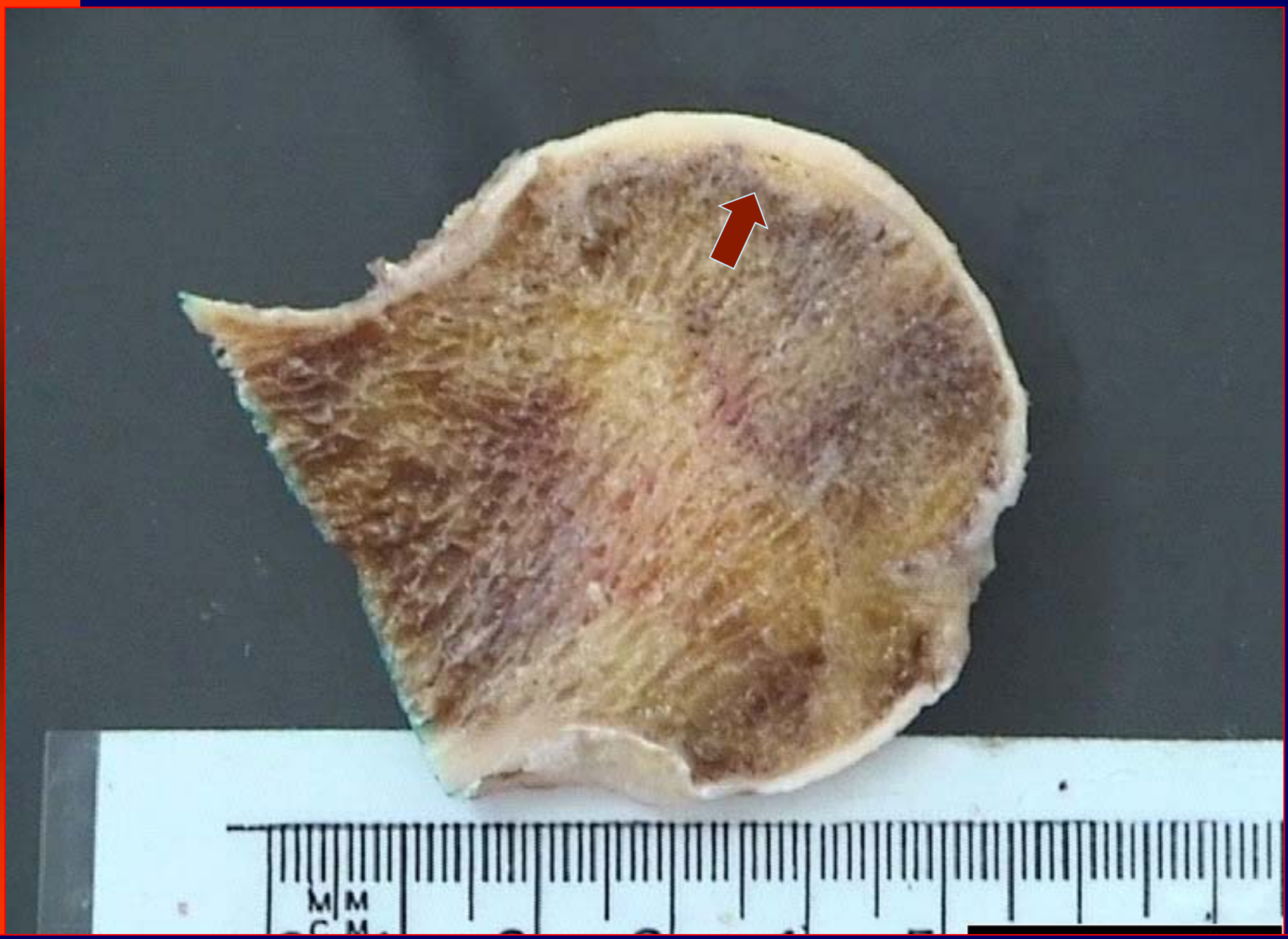
compression/impaction

subchondral fracture

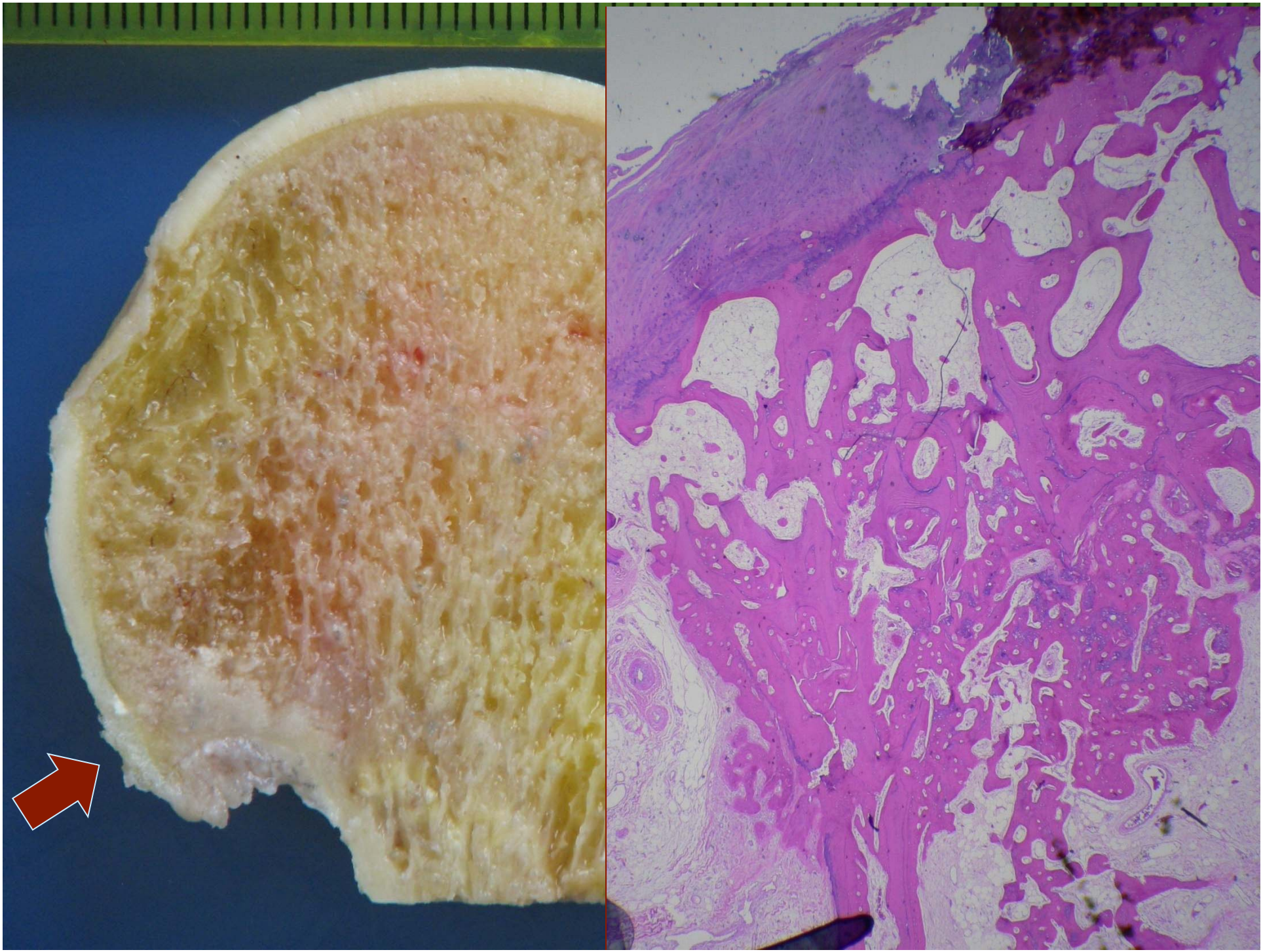


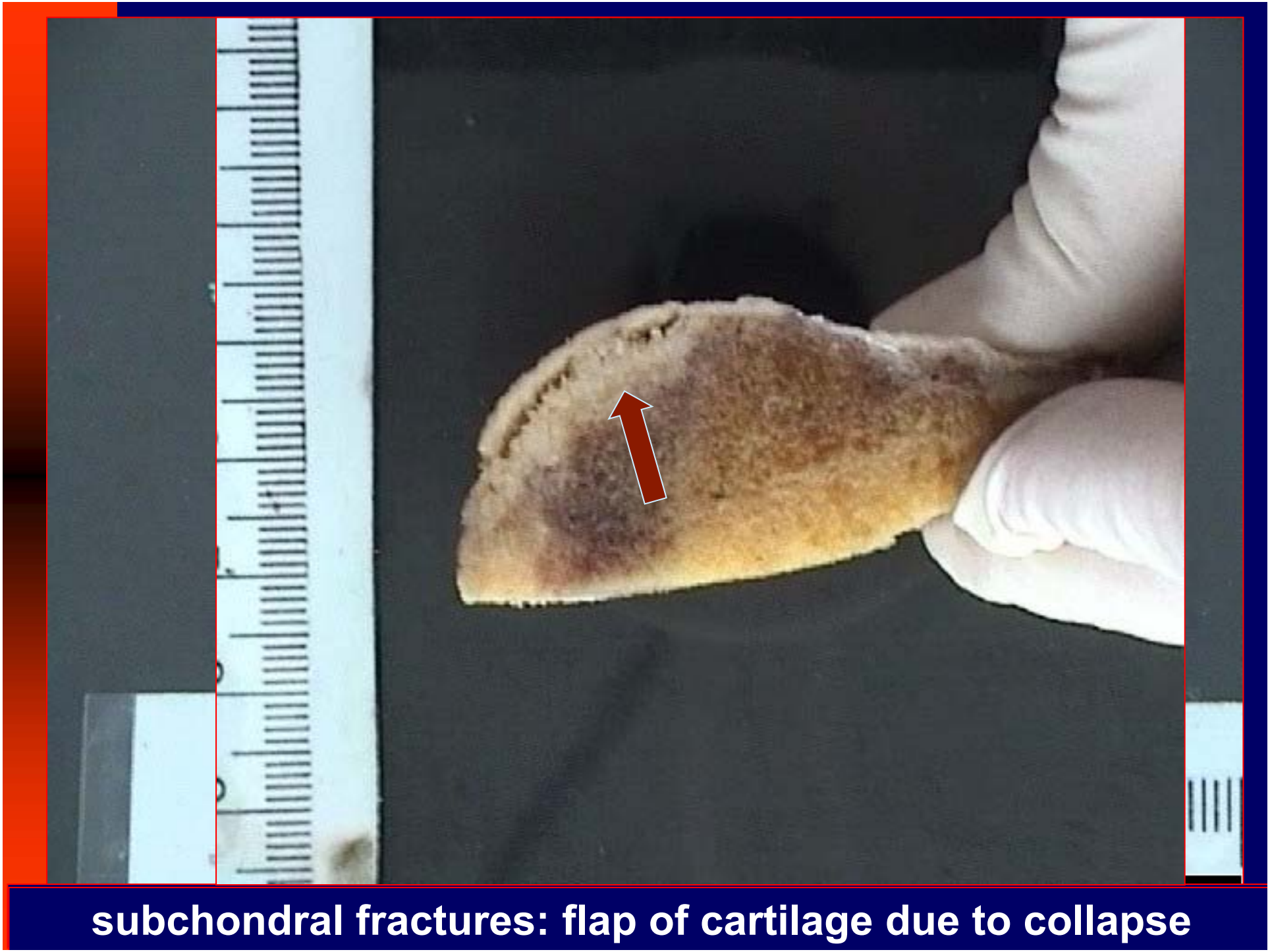


subchondral fractures



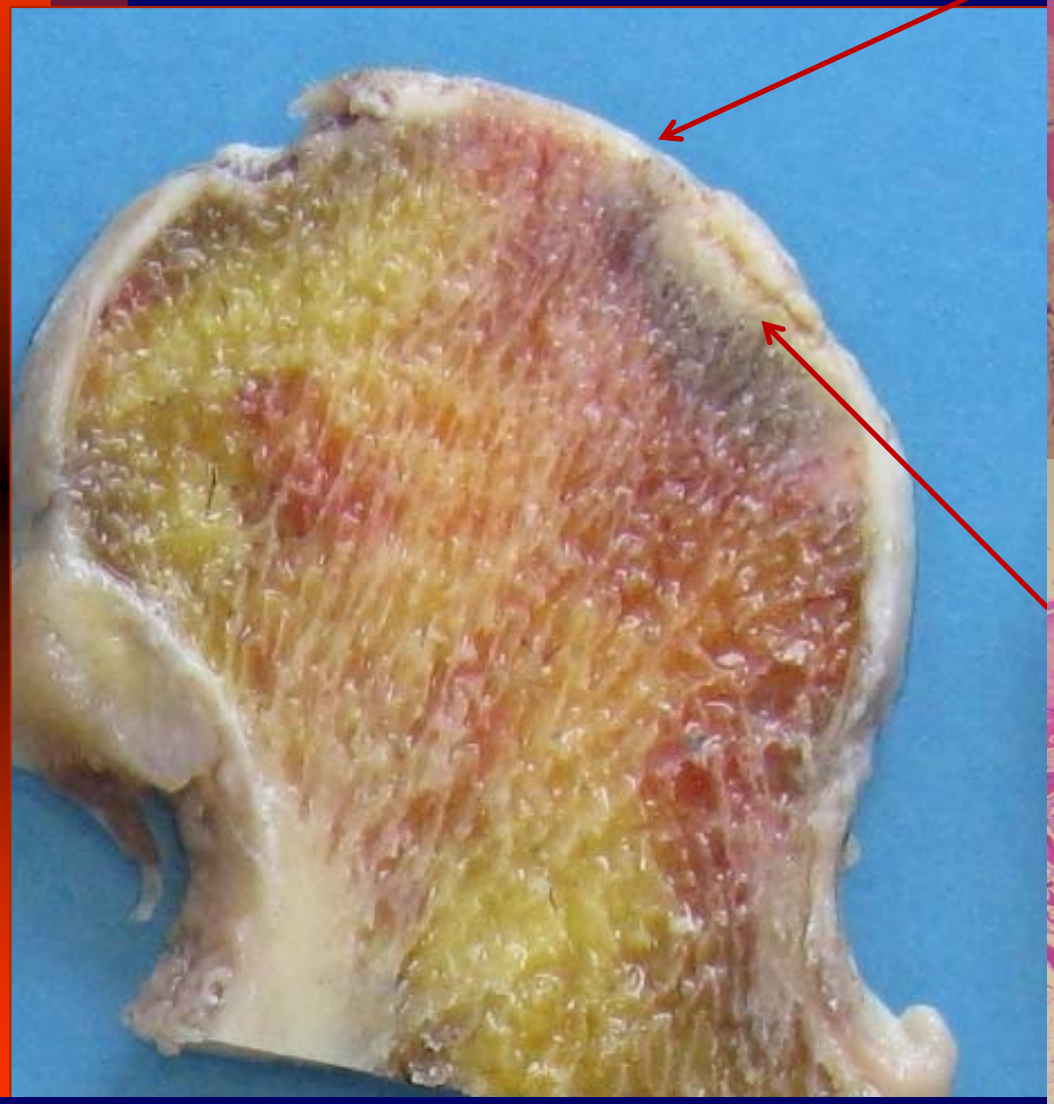
subchondral fractures: subtle linear zone sclerosis

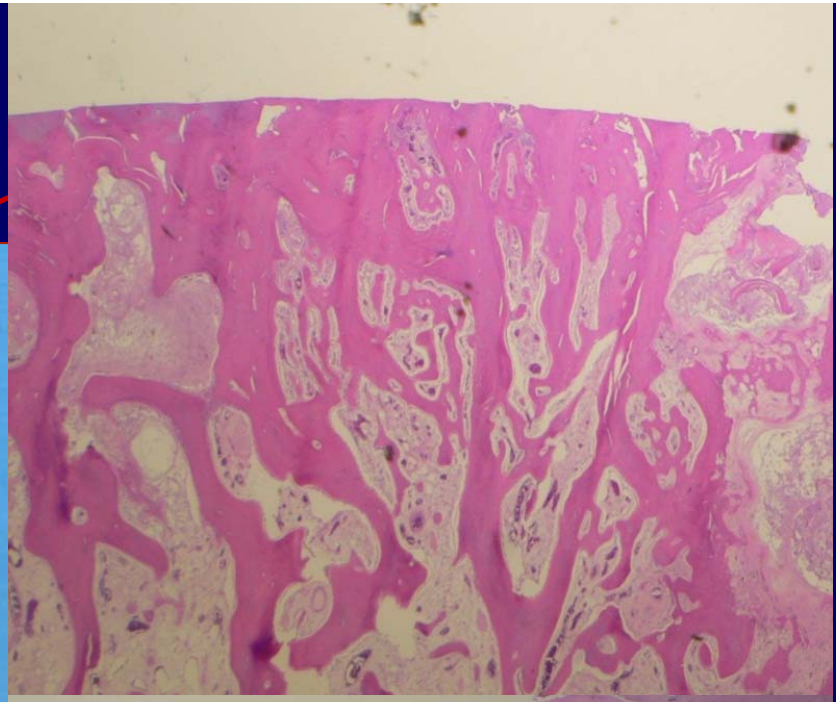


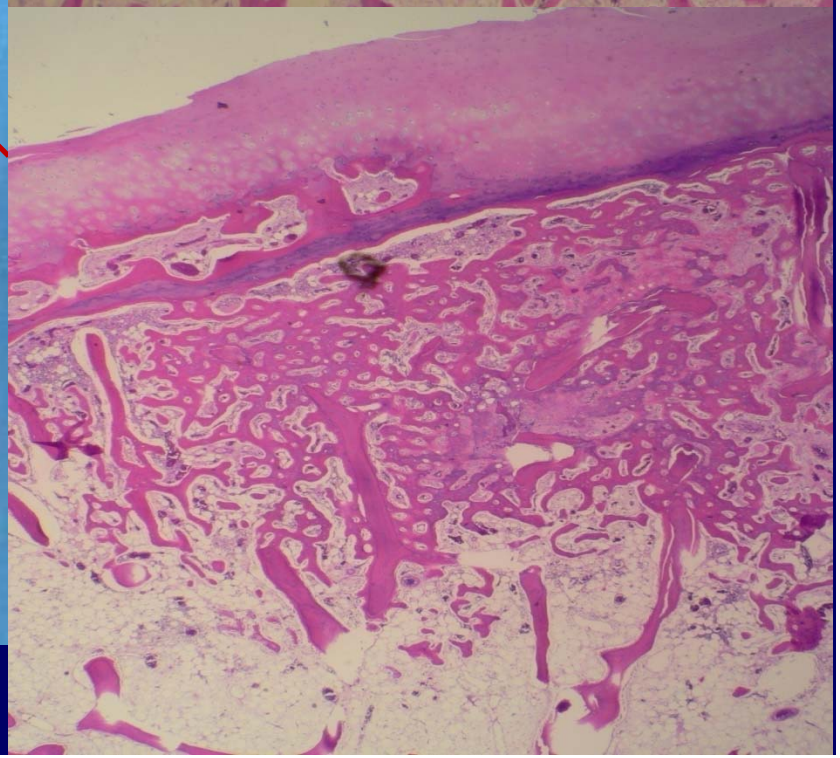


subchondral fractures: flap of cartilage due to collapse

- 7-10% arthroplasty specimens
- “osteoarthritis”

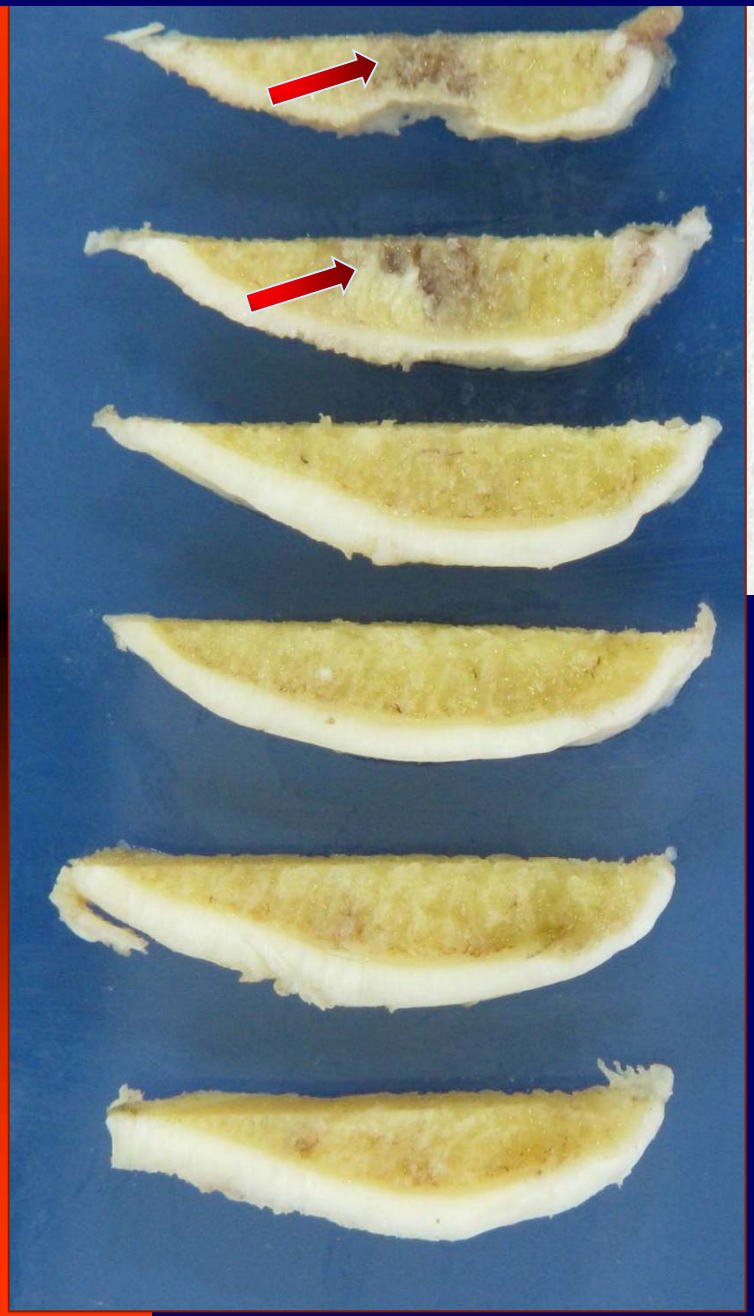


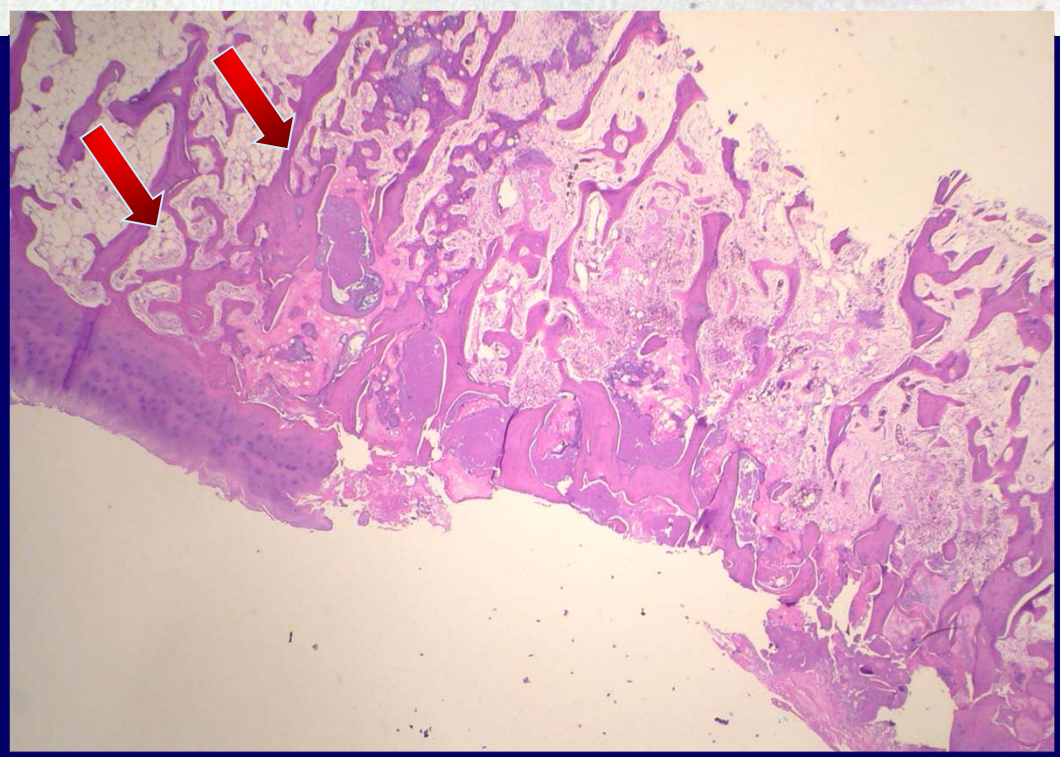




subchondral # - collapse: OA

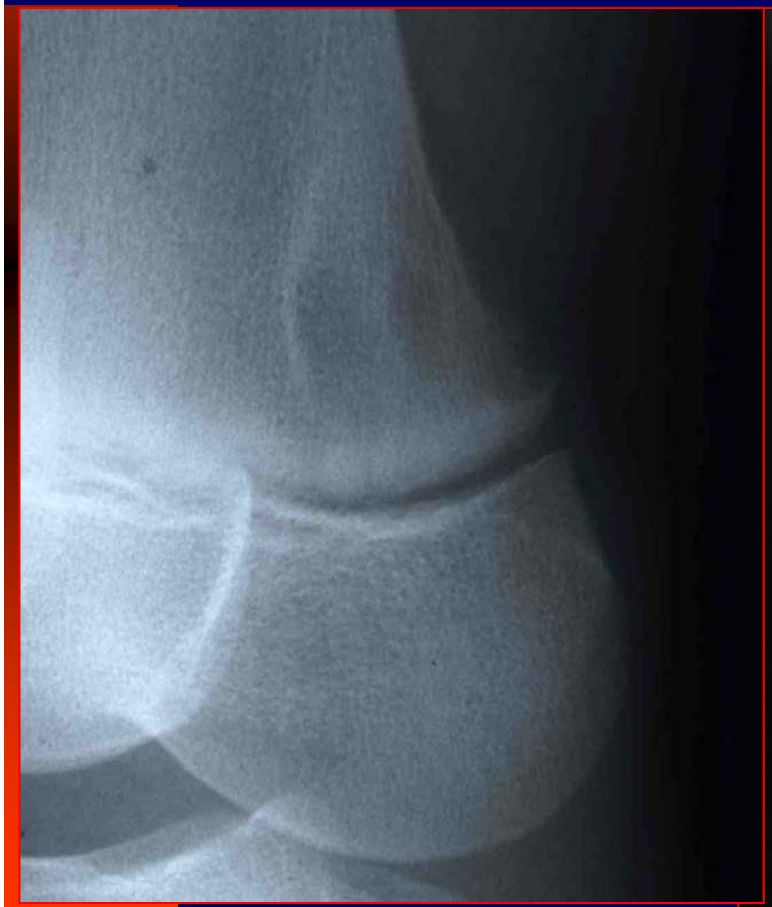
Medial femoral condyle female 62 ?AVN

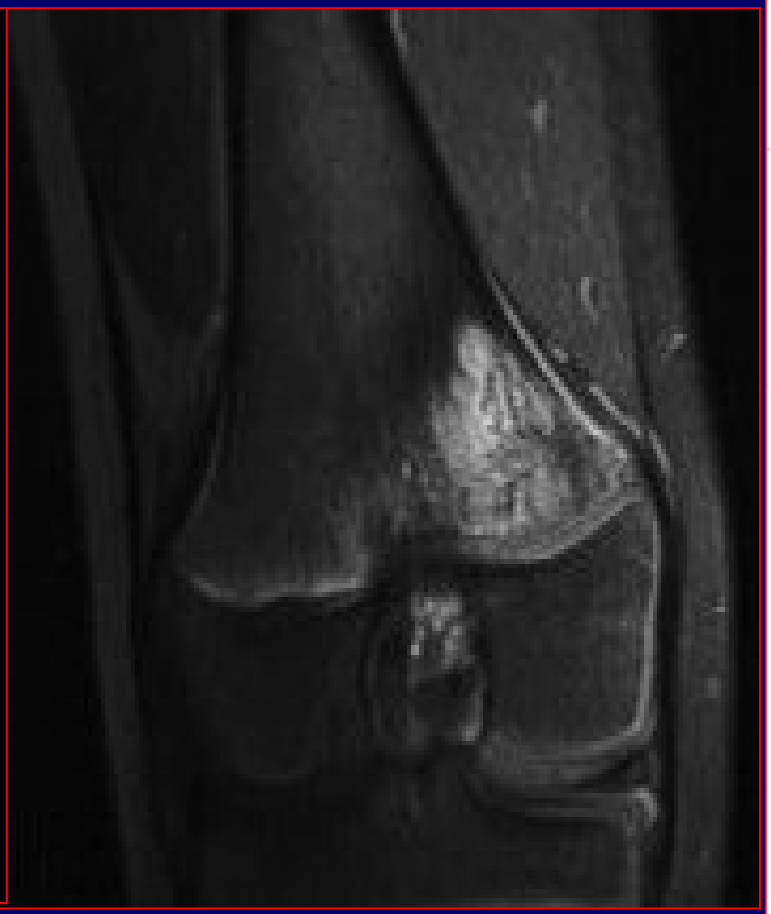




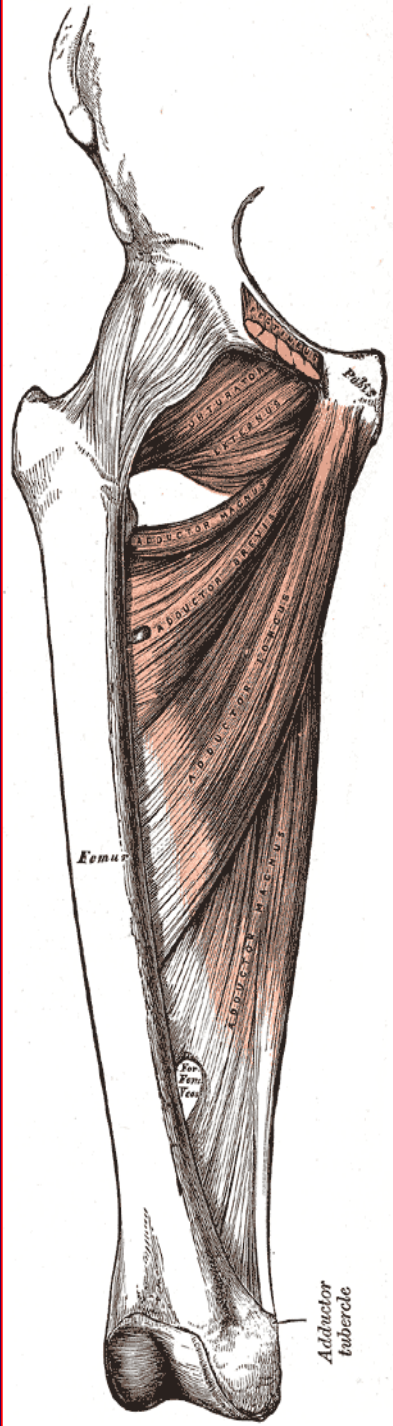
Avulsive / Tug lesions

- repetitive forceful traction
- ligamentous and tendon insertion
- often athletic adolescents

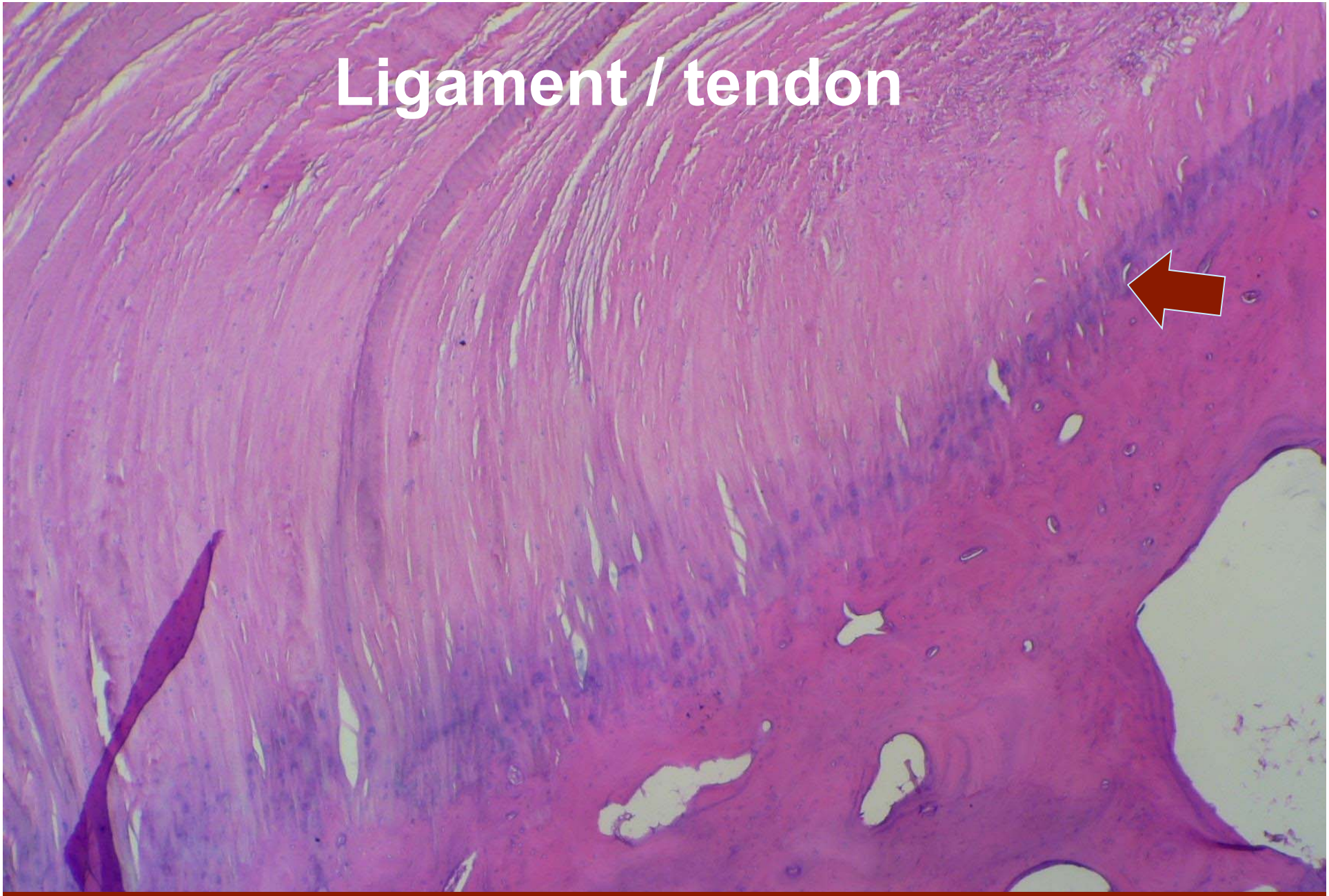




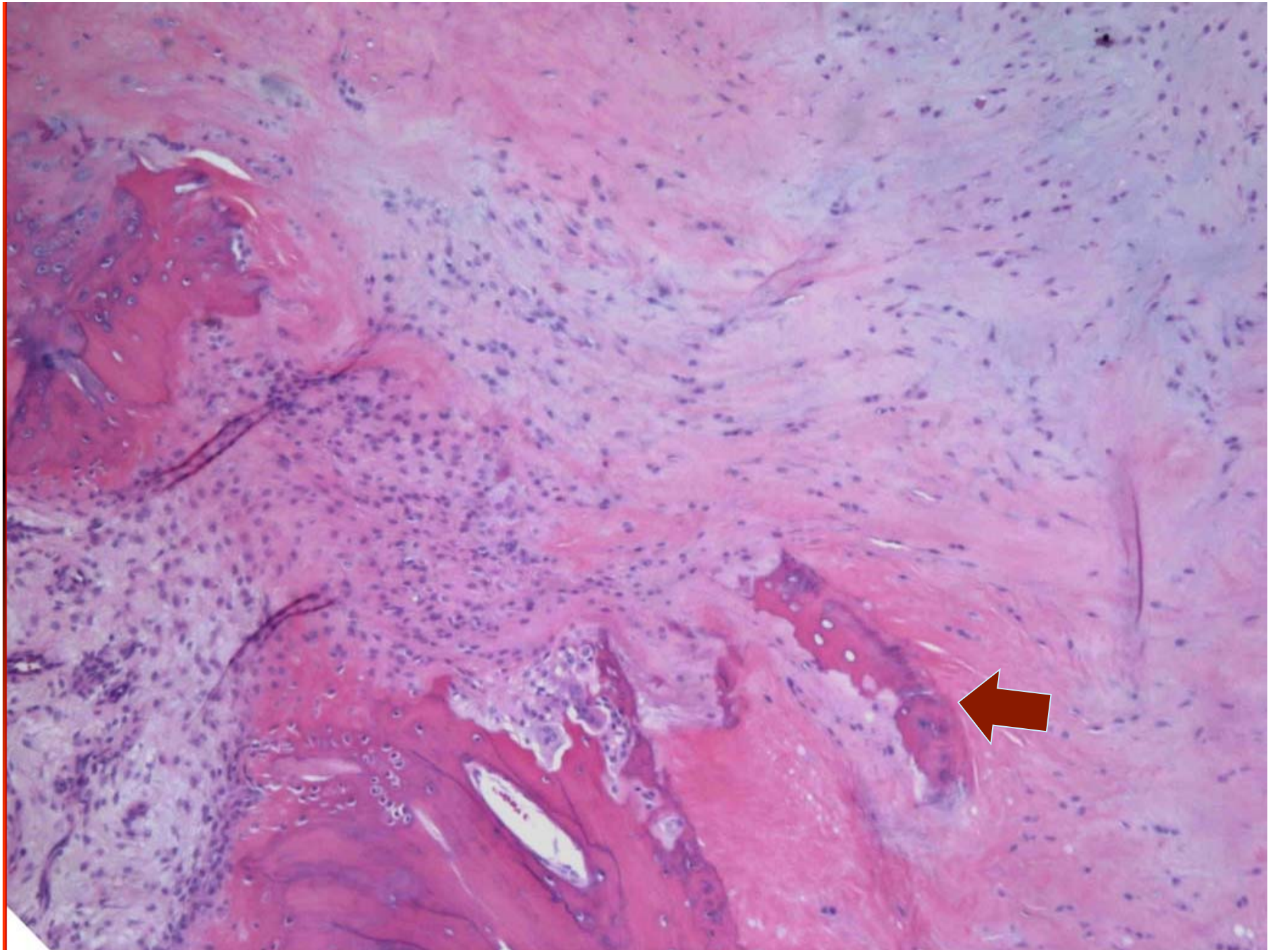
Boy aged 13 …"?OS"

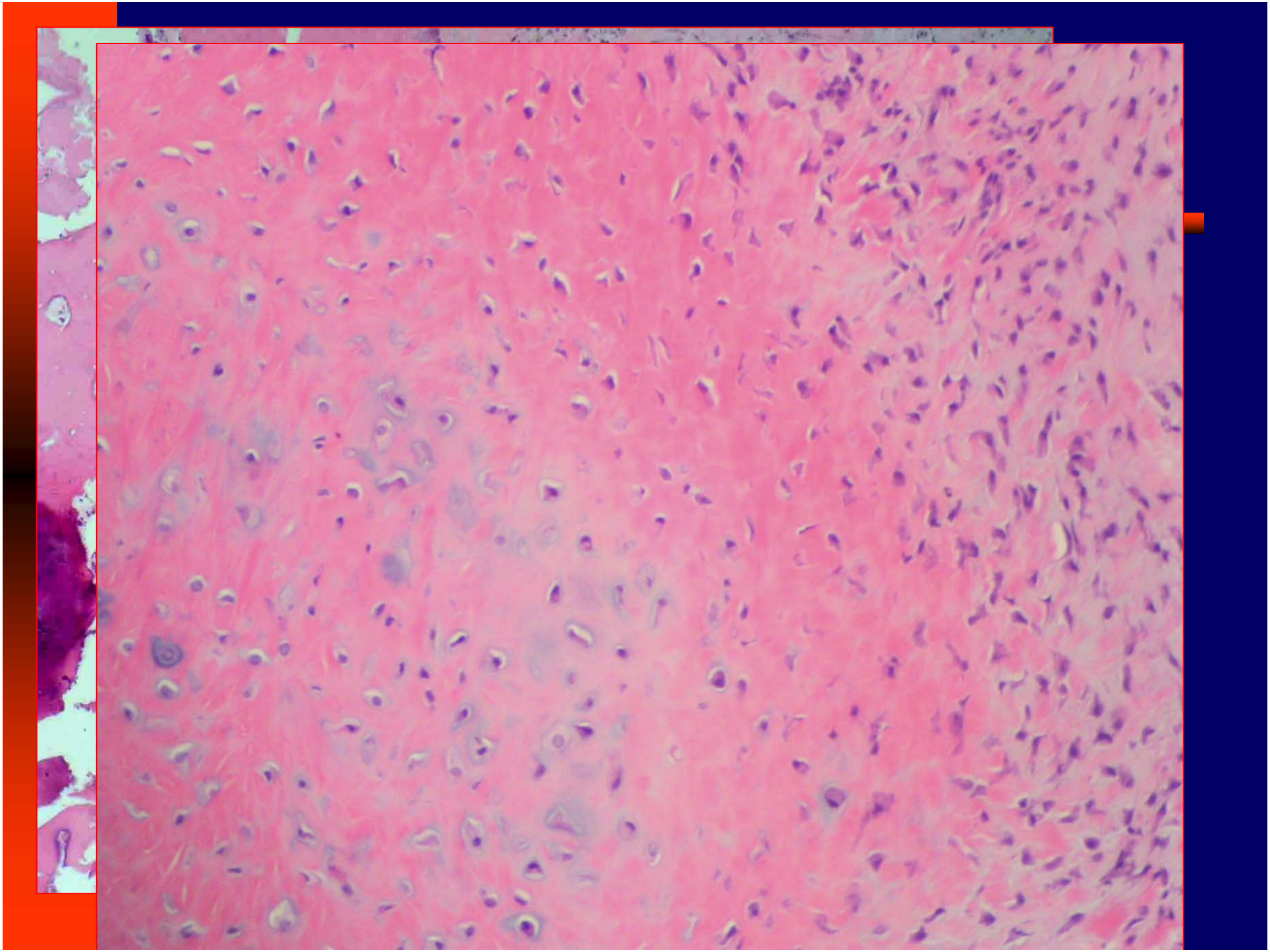


Ligament / tendon

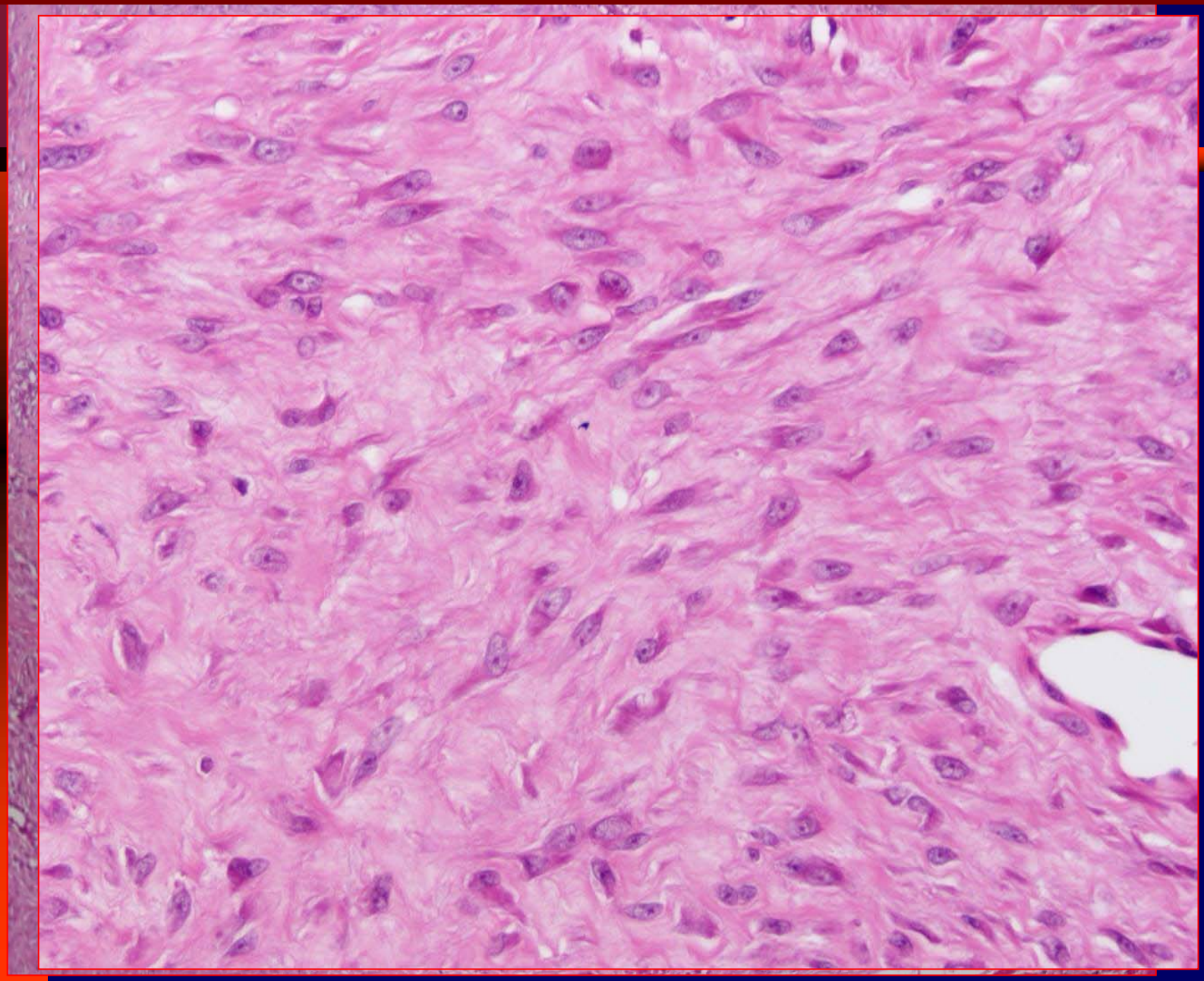


complete continuous bony end plate
orderly calcified tidemark with no remodelling





Avulsive cortical irregularity (“periosteal desmoid”)

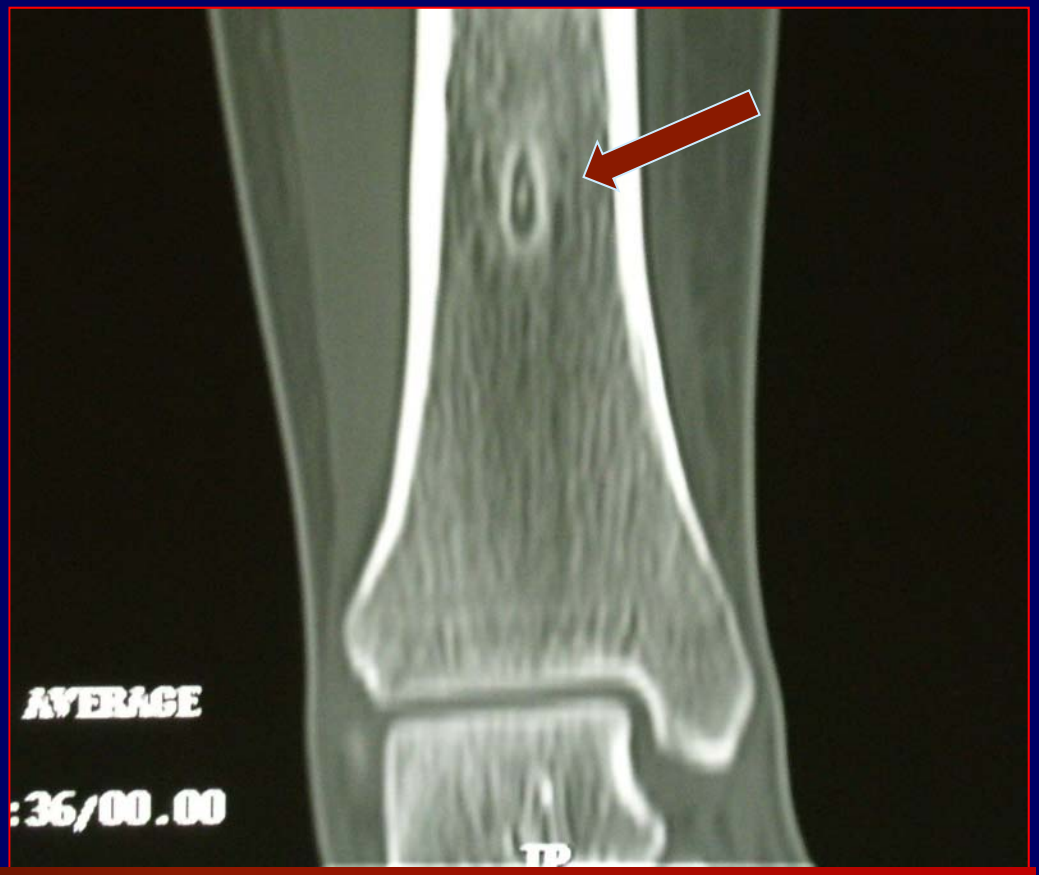


Osteomyelitis

- most haematogenous
- < 20 years of age
- 75% long bones extremities

➢ infection in bone

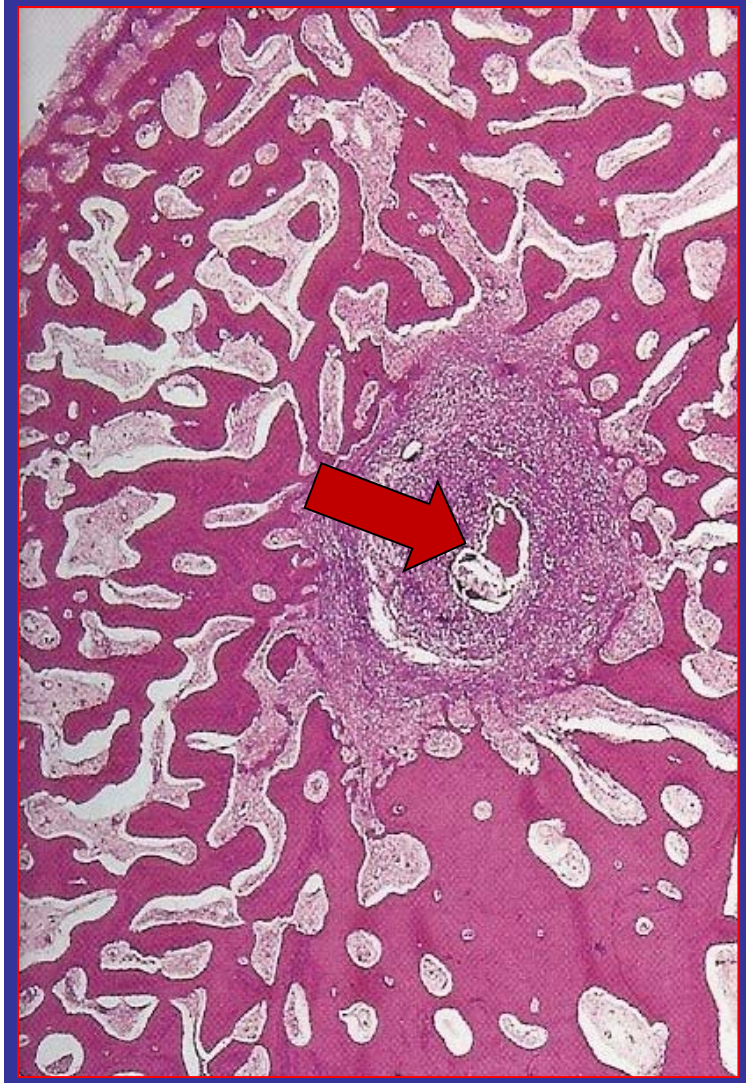
➢ Brodie abscess



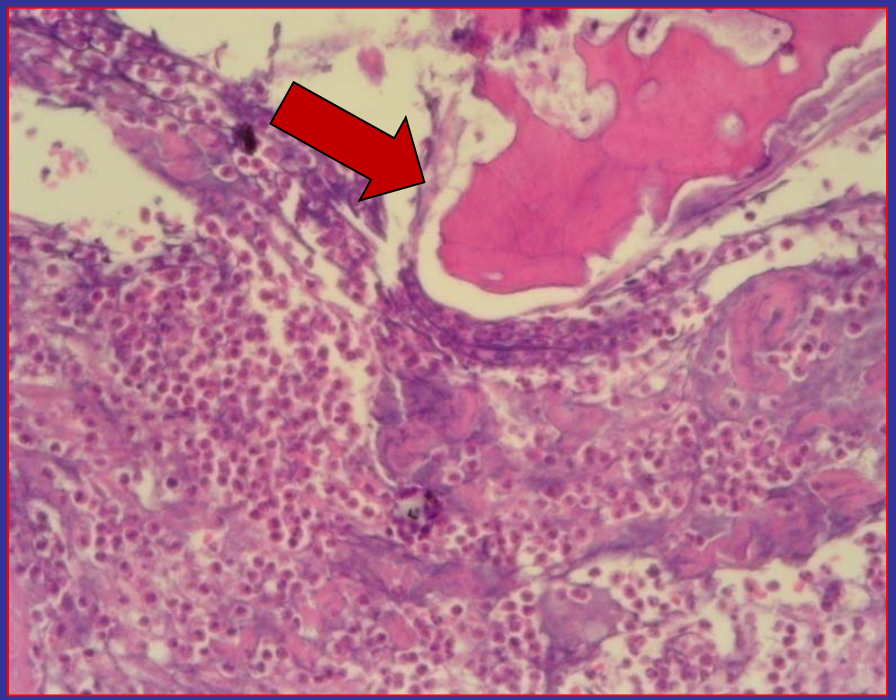
- acute
- subacute
- chronic

➢ Staph Aureus commonest organism

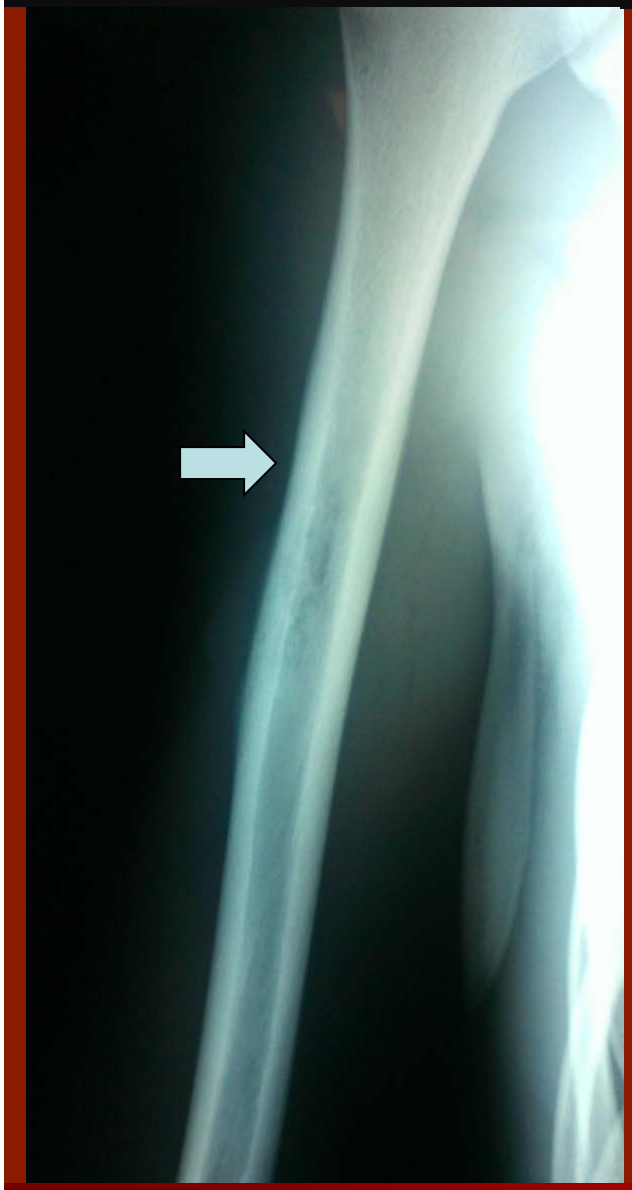
Acute osteomyelitis…….



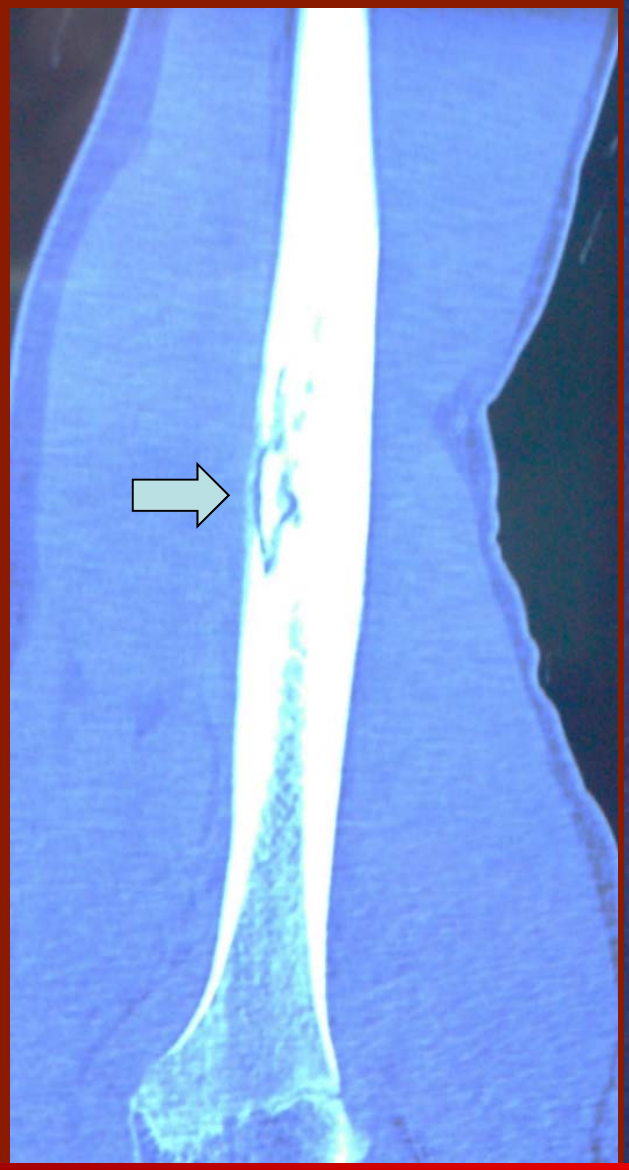
Brodie abscess



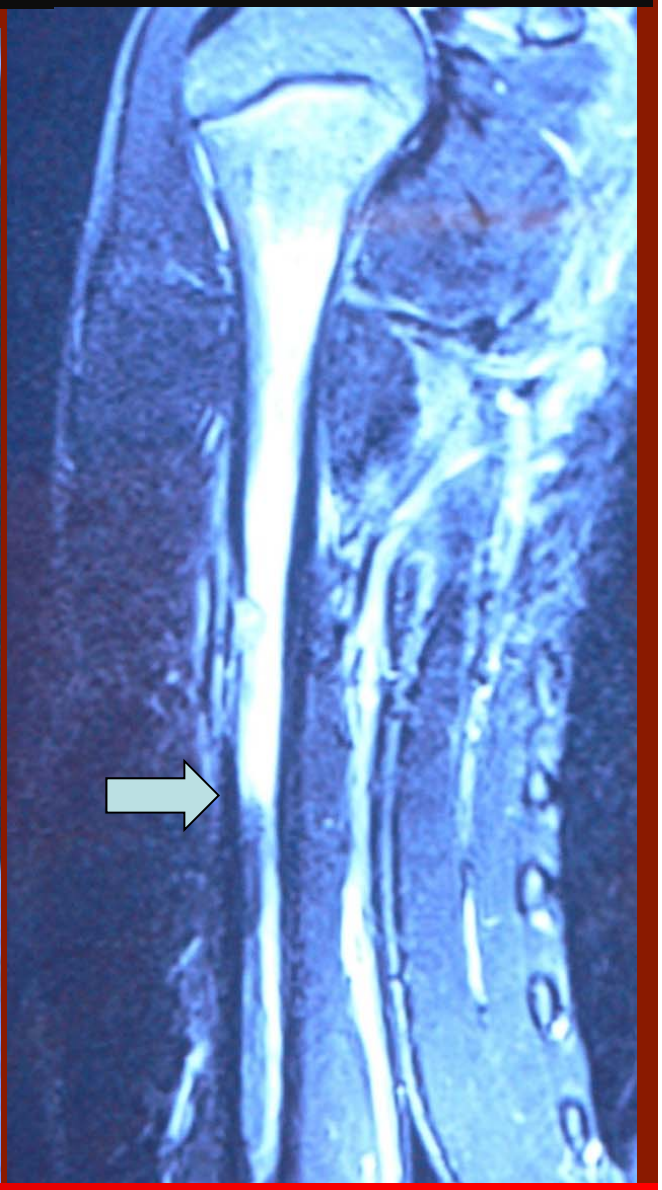
permeative lucency



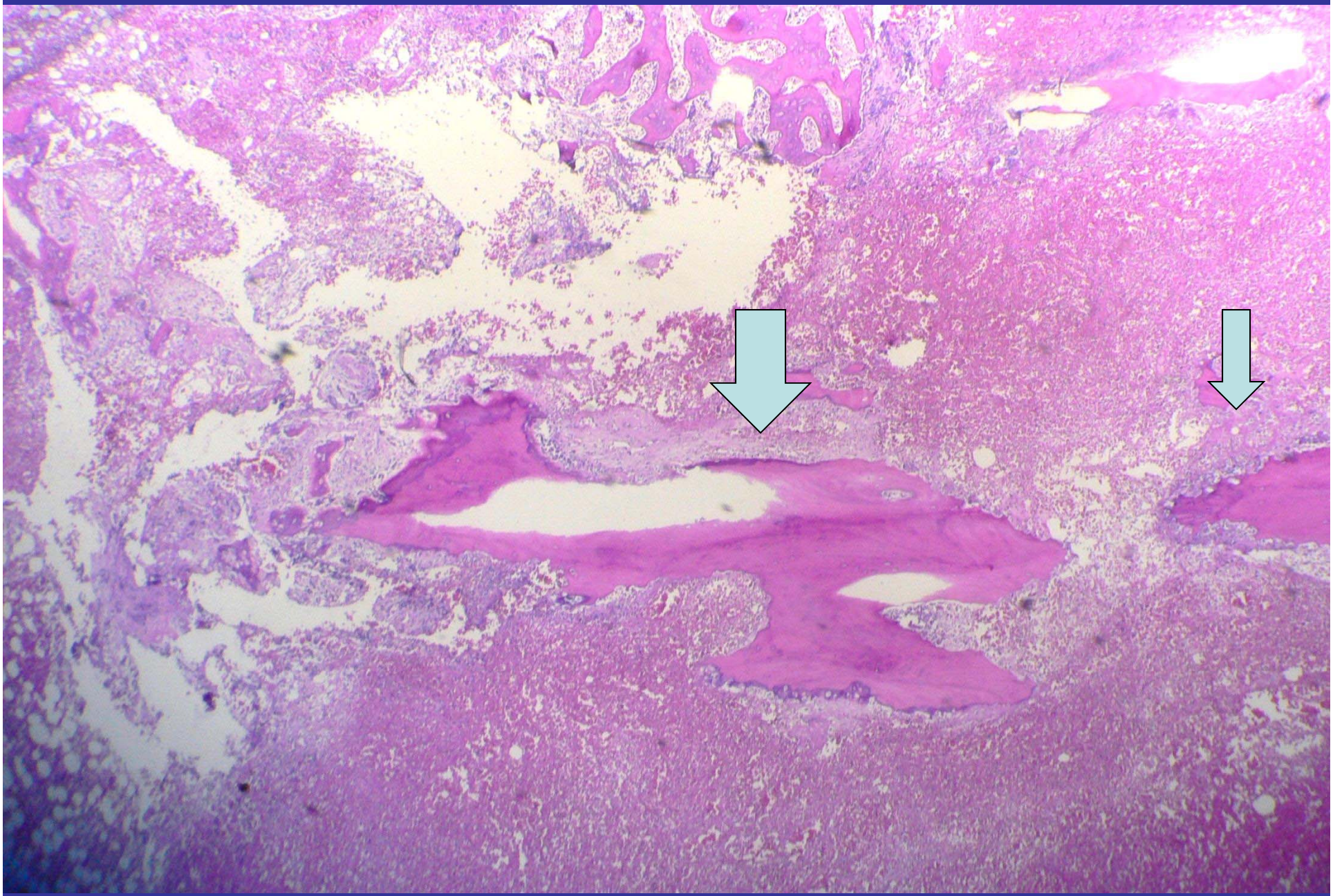
CT scan: bone sequestrum



MR: bone sequestrum

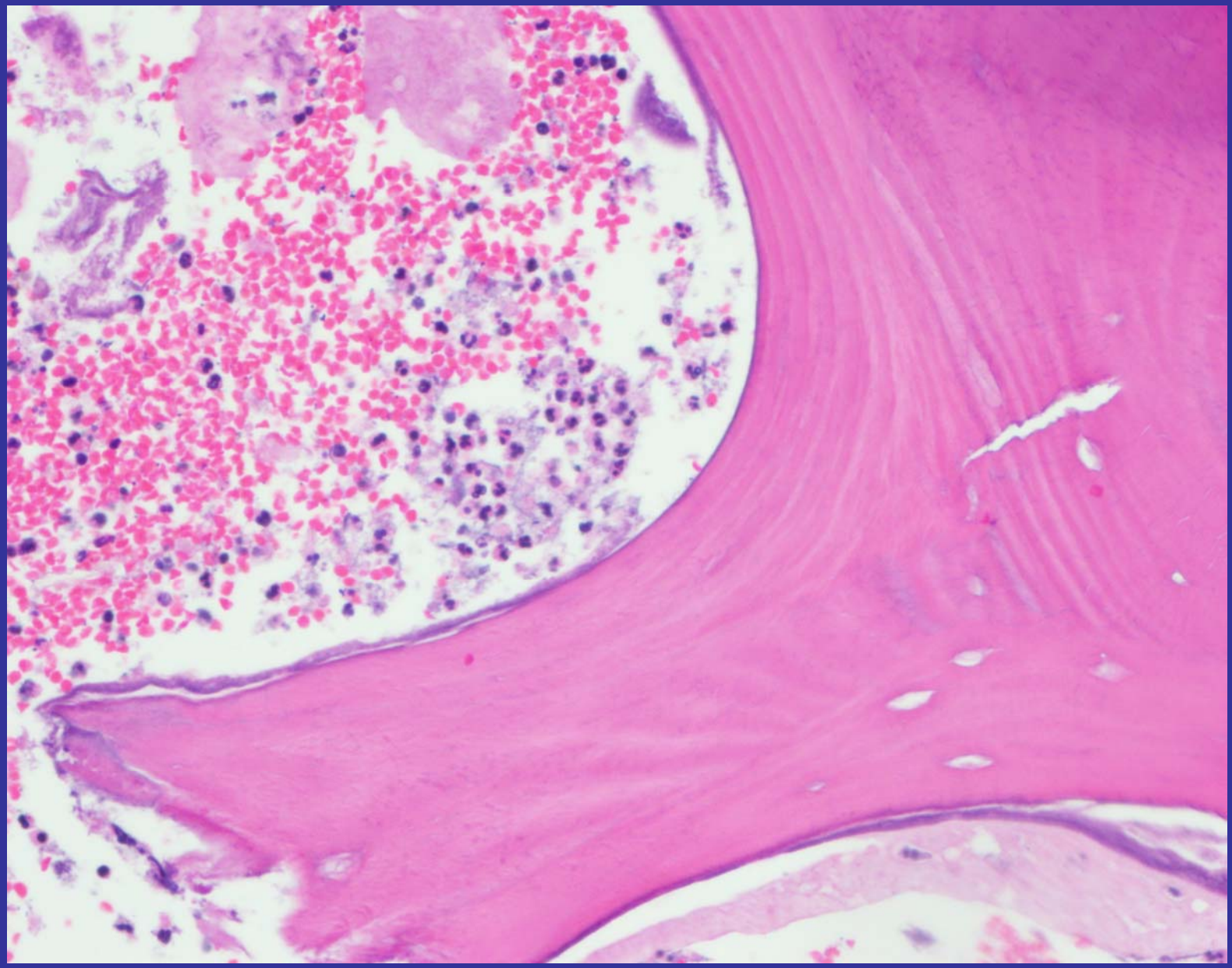


Acute osteomyelitis male 16
acute tonsillitis several weeks previously.

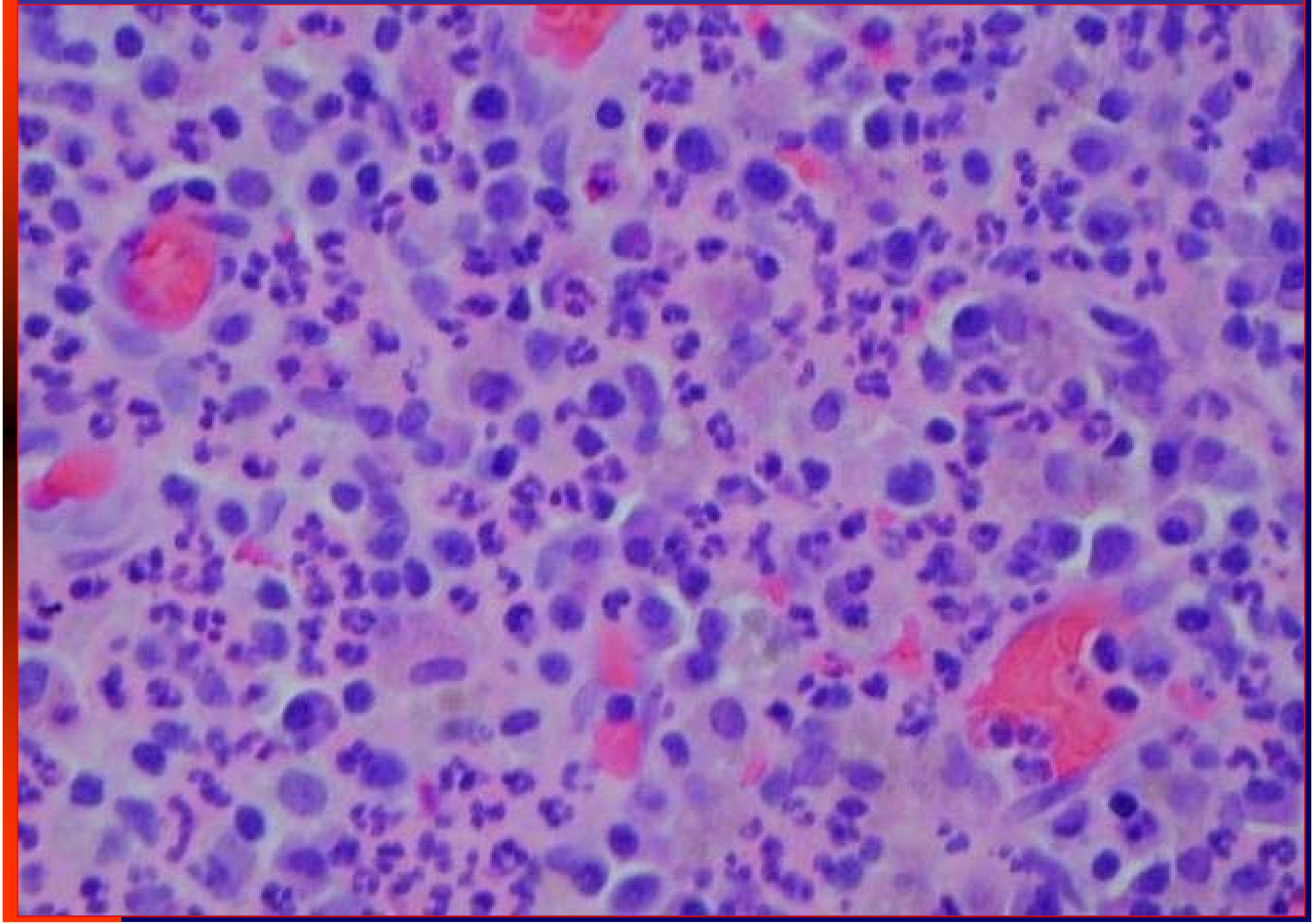


granulation tissue with sequestrum

sequestrum …necrotic bone in suppurative background

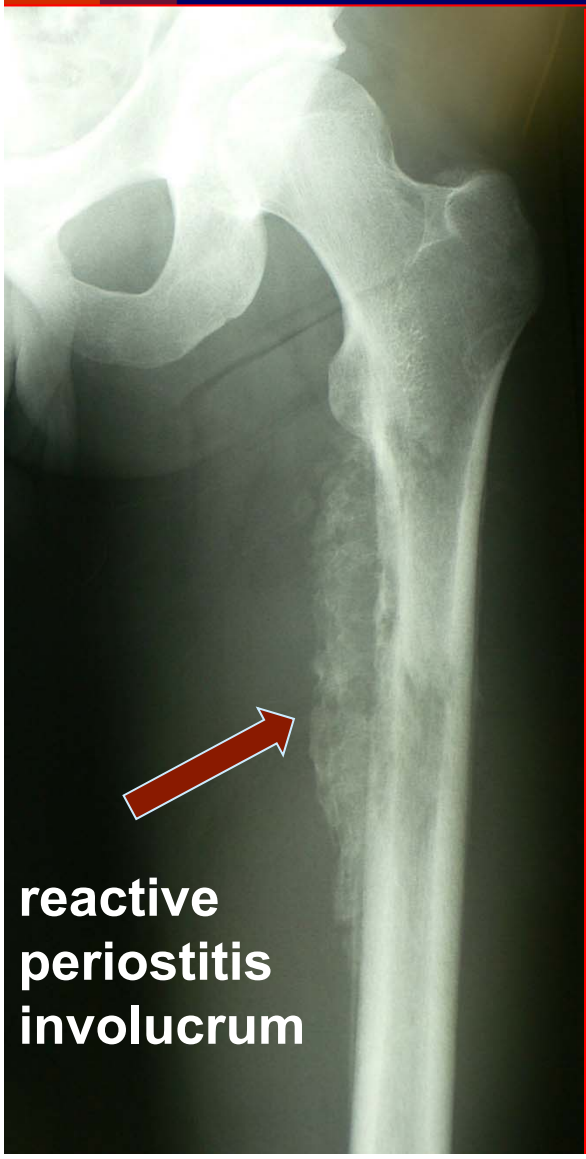


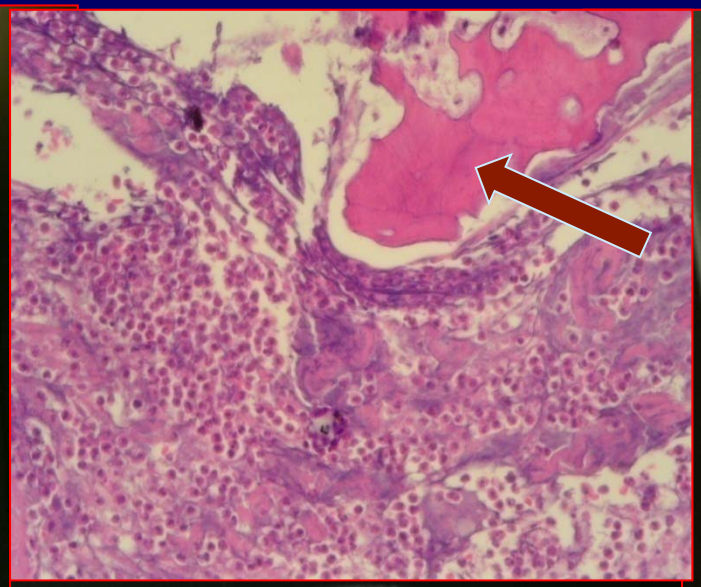
◆ acute suppurative inflammation

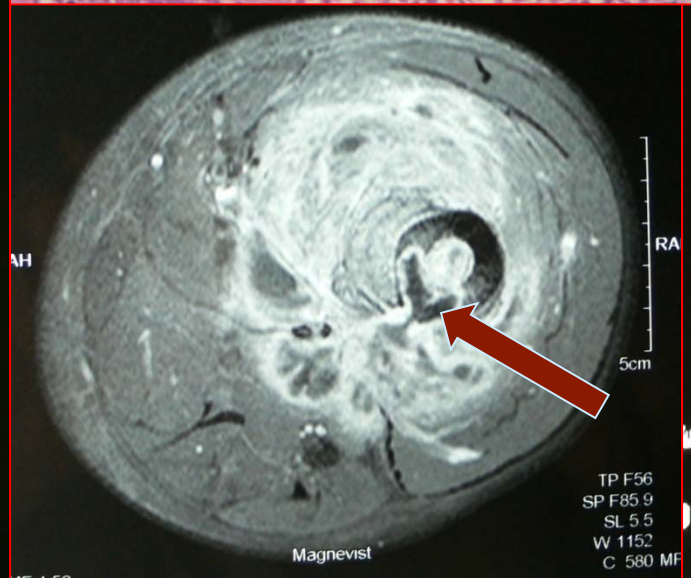


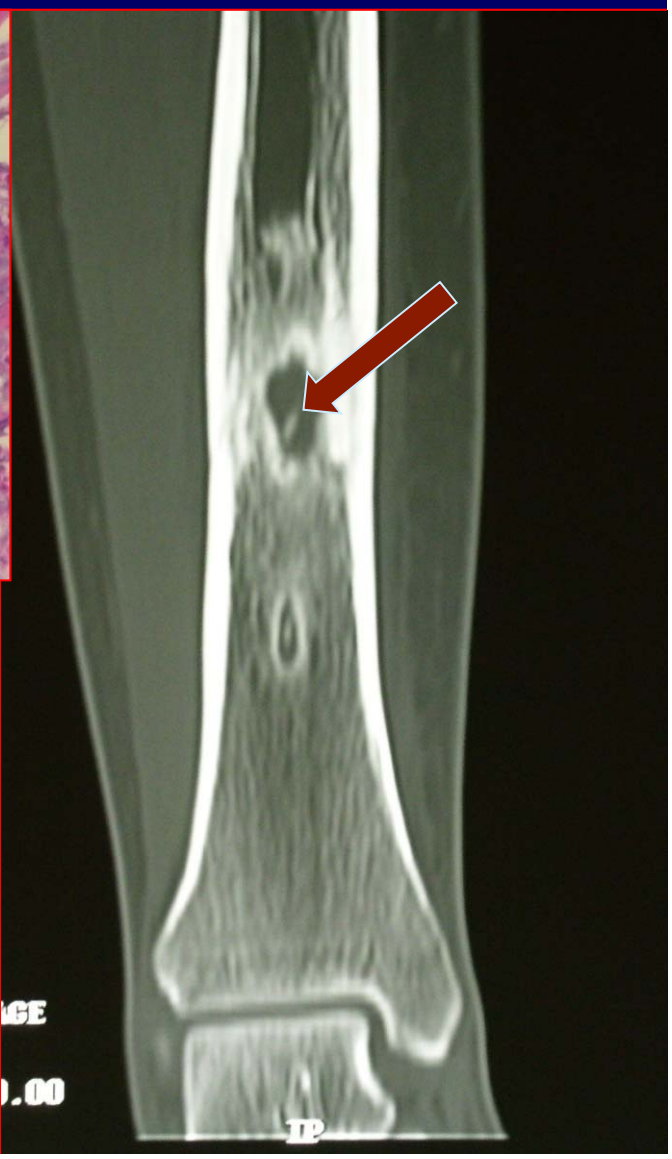
osteomyelitis

- necrosis of medulla…..sequestrum
- permeation through cortex..cloaca
- reactive periostitis …. Involucrum
- progression to chronicity



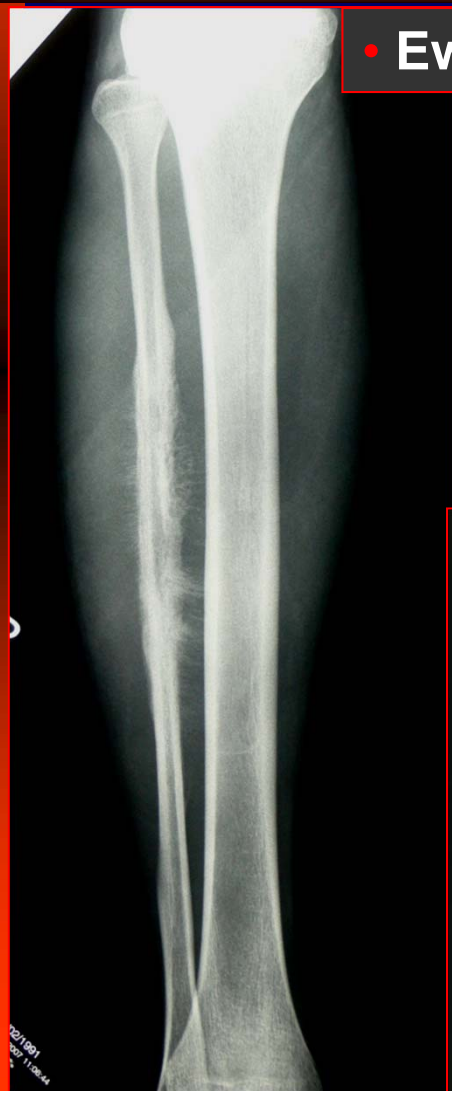




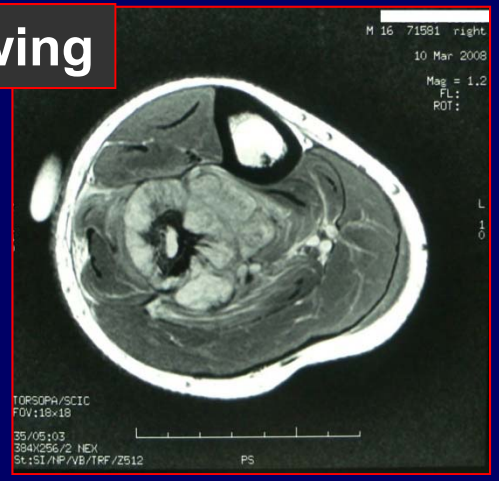


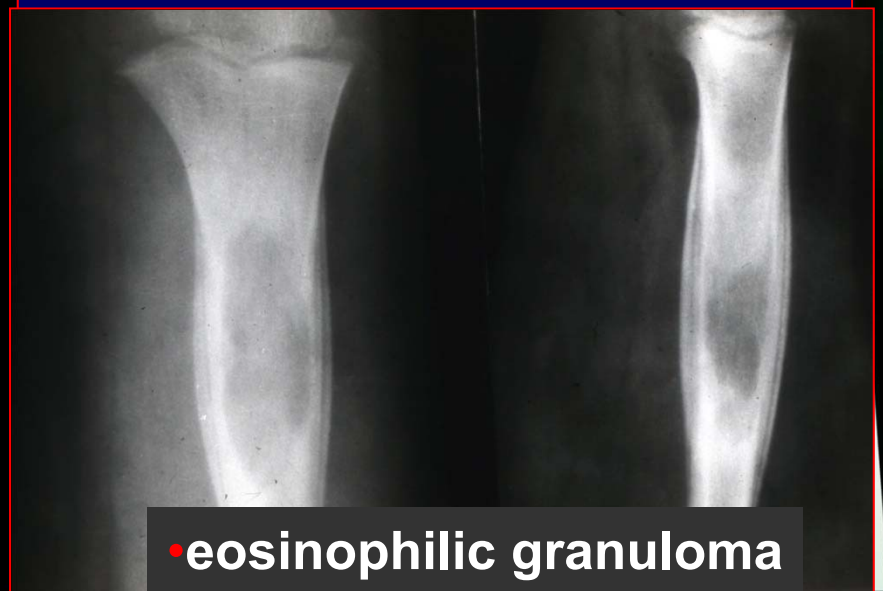
Chronic osteomyelitis

- mimics other aggressive disorders
  - eosinophilic granuloma
  - Ewing sarcoma
  - osteosarcoma

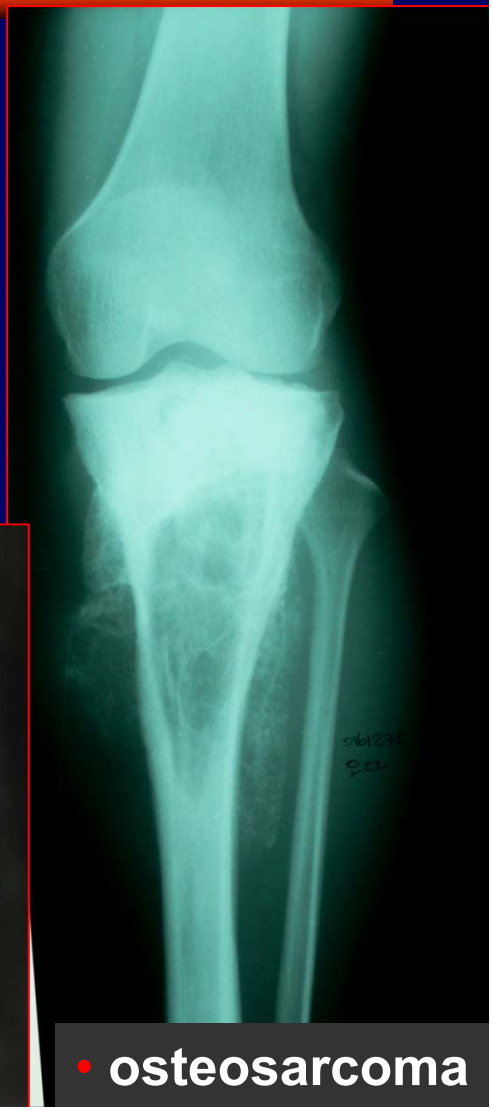


• Ewing





•eosinophilic granuloma



• osteosarcoma

Chronic non bacterial osteomyelitis (CNO)

autoinflammatory, non-infectious disorder of skeletal system

- Giedion et al 1972
- Bjorksten et al 1978

Chronic non bacterial osteomyelitis (CNO) (one bone affected)

- Acquired hyperostosis syndrome
- Chronic multifocal cleidometaphyseal osteomyelitis
- Chronic multifocal symmetrical osteomyelitis
- Chronic plasmacellular osteomyelitis
- Chronic recurrent multifocal osteomyelitis
- Chronic sclerosing osteomyelitis
- Chronic symmetric osteomyelitis
- Condensing osteomyelitis
- Diffuse sclerosing osteomyelitis
- Intersternocostoclavicular ossification
- Lymphoplasmacellular osteomyelitis
- Multifocal sterile osteomyelitis
- Plasmacellular osteomyelitis
- Primary chronic osteomyelitis
- Primary chronic sclerosing osteomyelitis
- Pustulotic arthro-osteitis
- Sclerosis and hyperostosis
- Sternoclavicular hyperostosis
- Sternocostoclavicular hyperostosis
- Tumorous osteomyelitis

Chronic recurrent multifocal osteomyelitis (CRMO)

Cimolai M 2011 Journal of infection and public health 4:157-168

Chronic non bacterial osteomyelitis (CNO and CRMO)

- culture negative
- no organisms identifiable
- no response to antibiotics (most)

- Stern SM, Ferguson PJ Rheum Dis Clin Noth Am Nov 2014

Chronic non bacterial osteomyelitis

- ANY AGE
  - NO SEQUESTRA
  - NO ABSCESS
  - CULTURE NEGATIVE

- most in childhood (often around age 10)
- often recurrent
- slight female predominance

- relapses and remissions
- systemic symptoms rare
- fever +/-
- ESR,CRP +/- mild

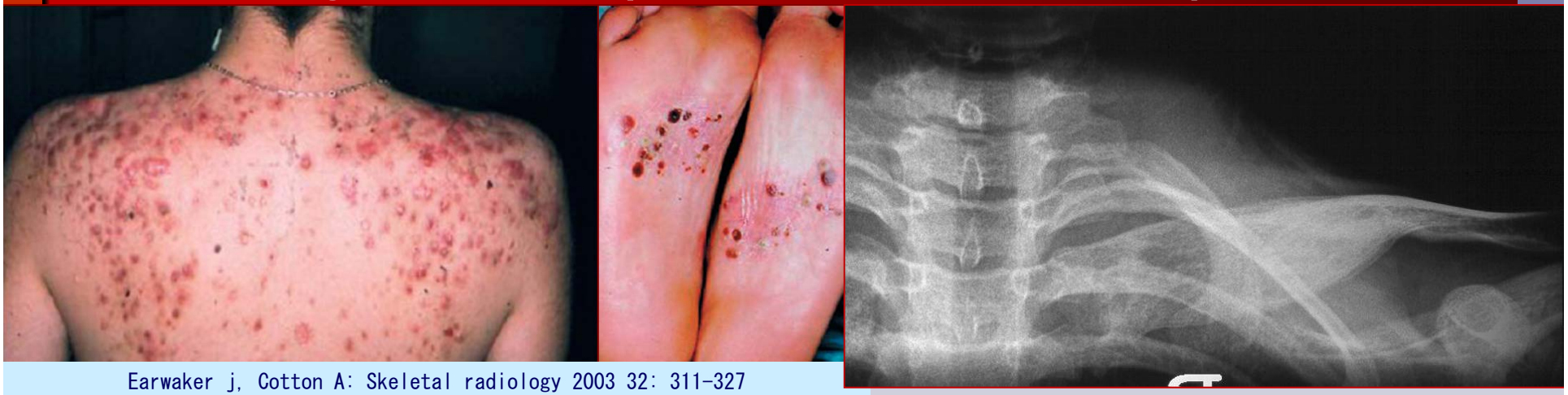
Chronic non bacterial osteomyelitis (CNO and CRMO)

- can occur at any any age
  - one bone: CNO
    - more often in adults
    - 40's…….. 70's **
    - female > male
  - multiple bones : CRMO
    - most in childhood (often around age 10)
    - often recurrent
    - slight female predominance

** Okuno H et al Modern Rheumatology 2017; 67 cases

▪ chronic non bacterial osteomyelitis "CNO"

SAPHO syndrome (prevalence 1/10000)



Earwaker j, Cotton A: Skeletal radiology 2003 32: 311-327

◆ young adults

- Synovitis
- Acne (fulminans and conglobata, hidradenitis suppurativa)
- Pustulosis (palmoplantar pustulosis / psoriasis)
- Hyperostosis
- Osteitis

synchronous

metachronous

Chronic non bacterial osteomyelitis

- osteitis with hyperostosis cortex and medulla
  - clavicles
  - sternum
  - sternoclavicular joints
  - spine
  - sacroiliitis
  - ilium
  - mandible

  → 70 -90%

  → older age group

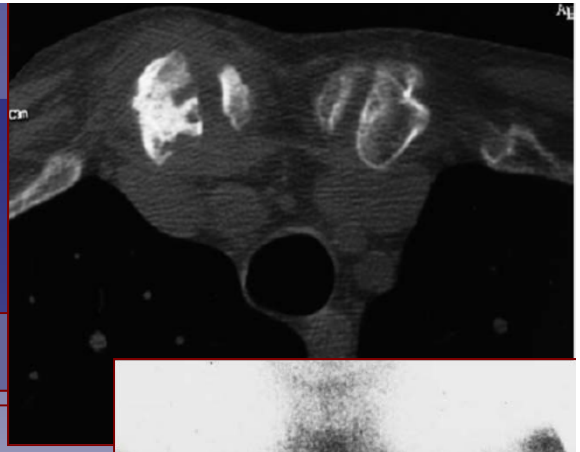
  → 50%

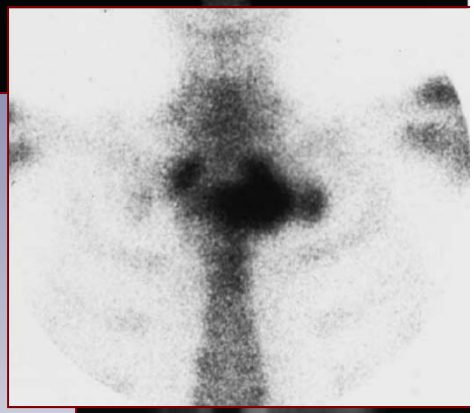
  → 10%

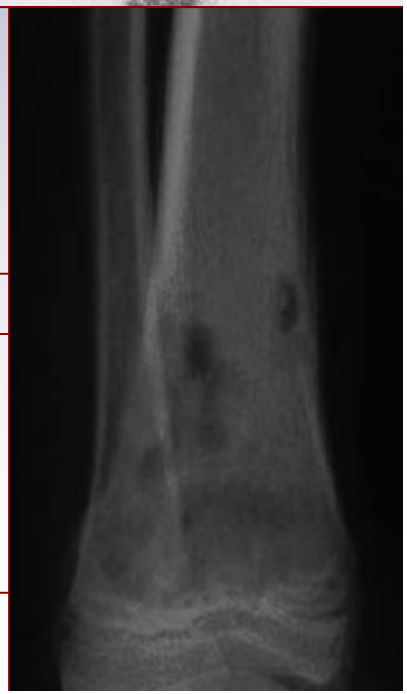
- clavicle
- metaphysis femur
- tibia

→ 63%

→ childhood

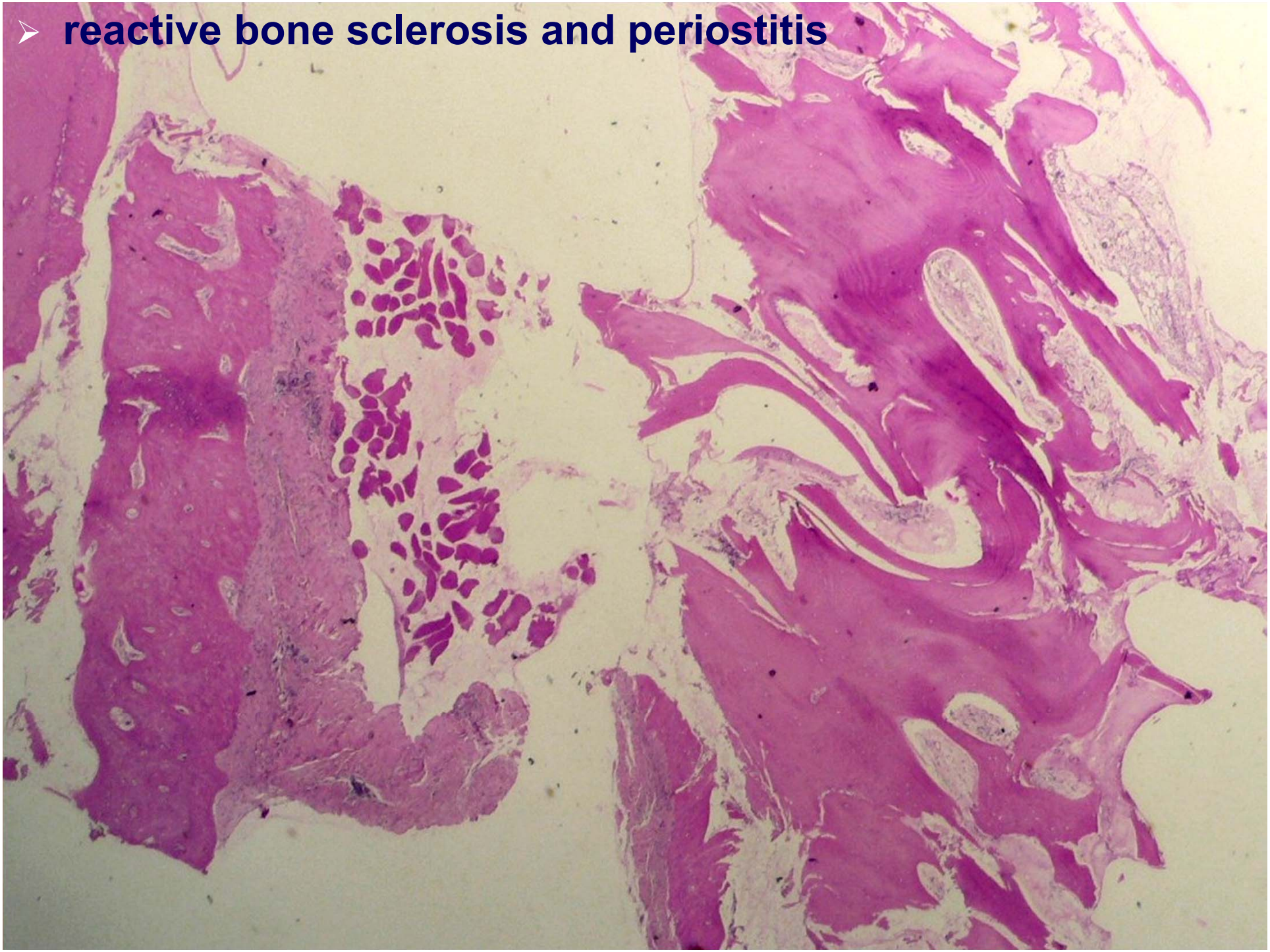




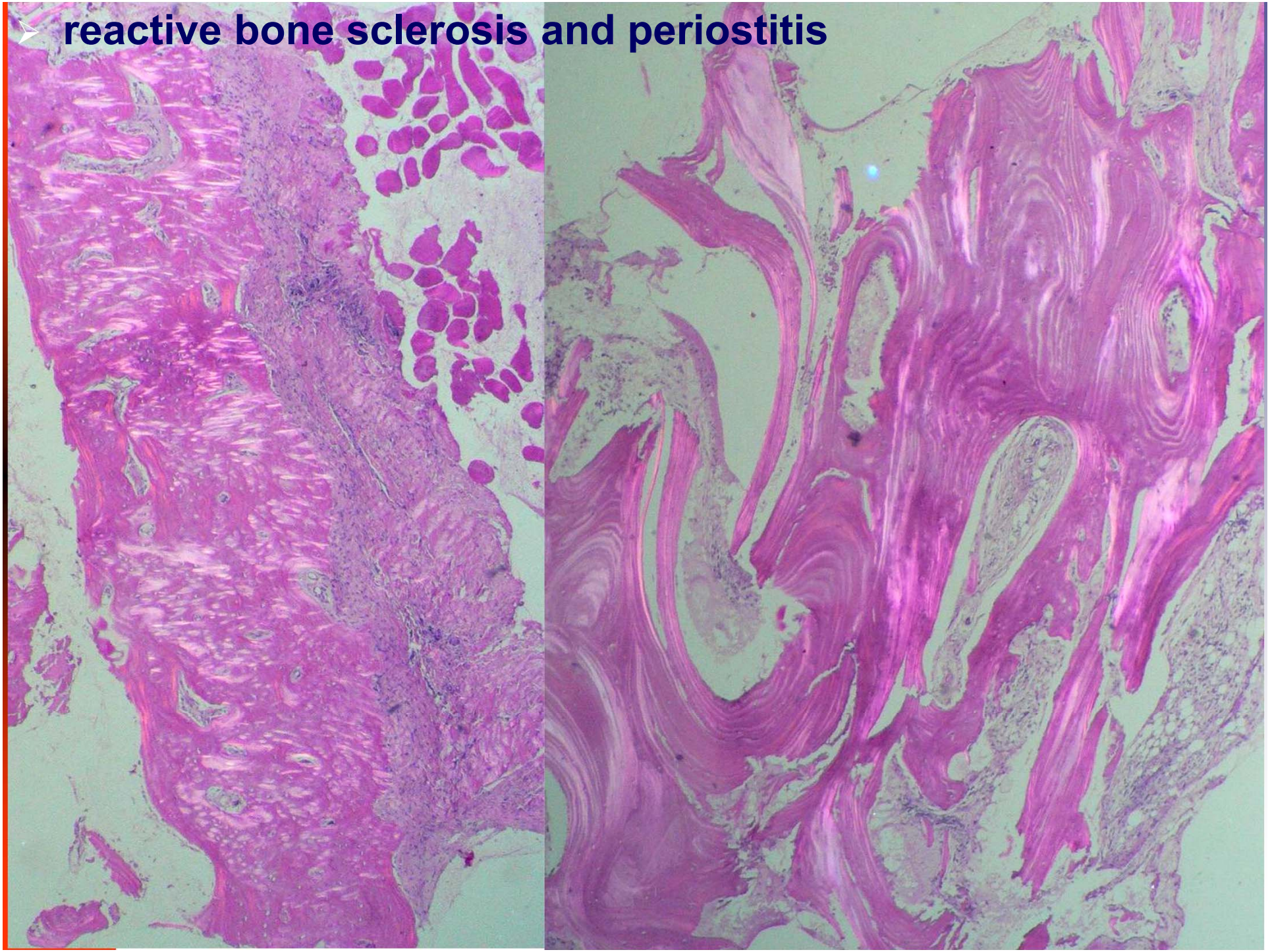


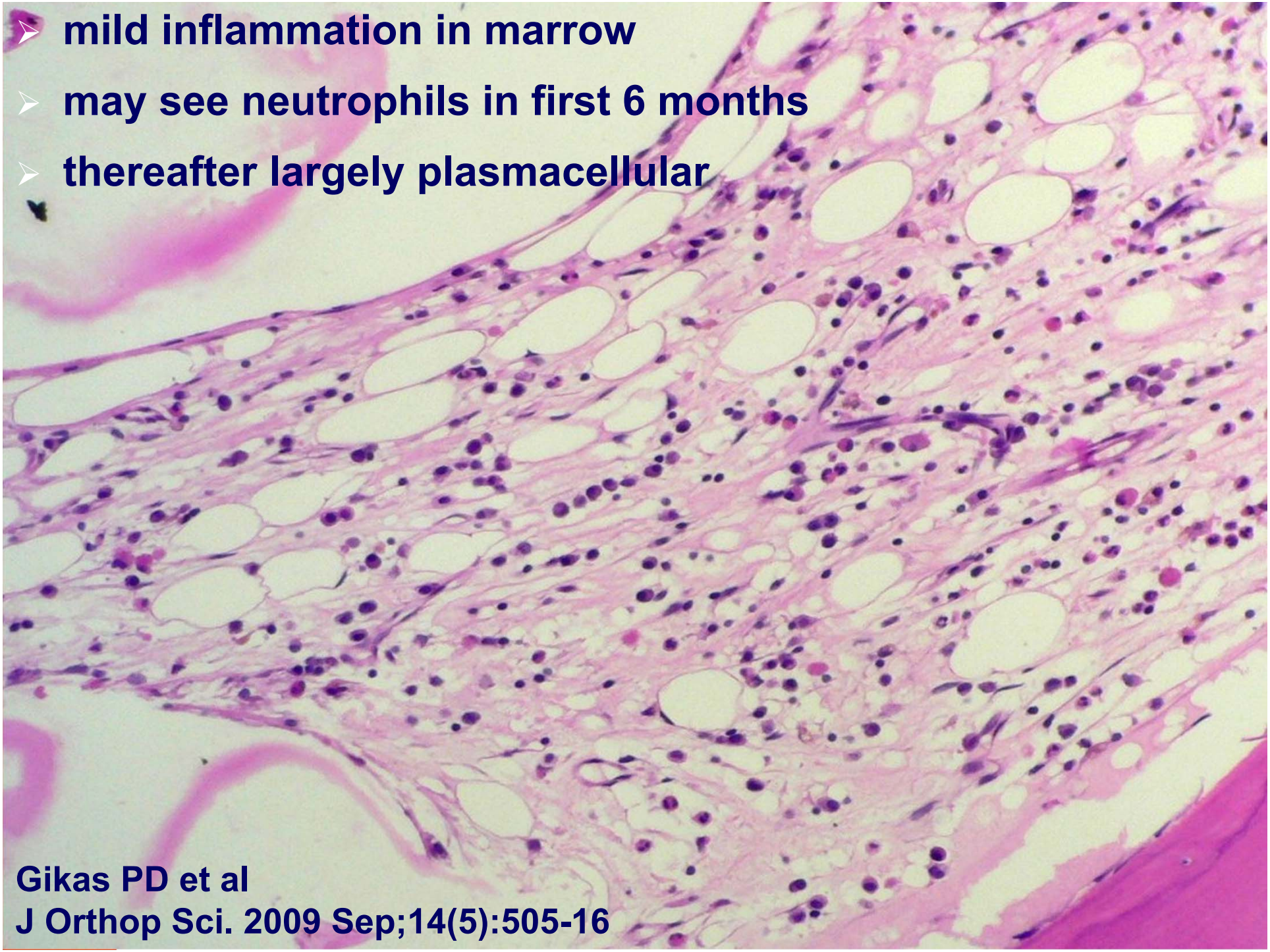
Earwaker J, Cotton A: Skeletal Radiology 2003 32: 311-327

- **reactive bone sclerosis and periostitis**



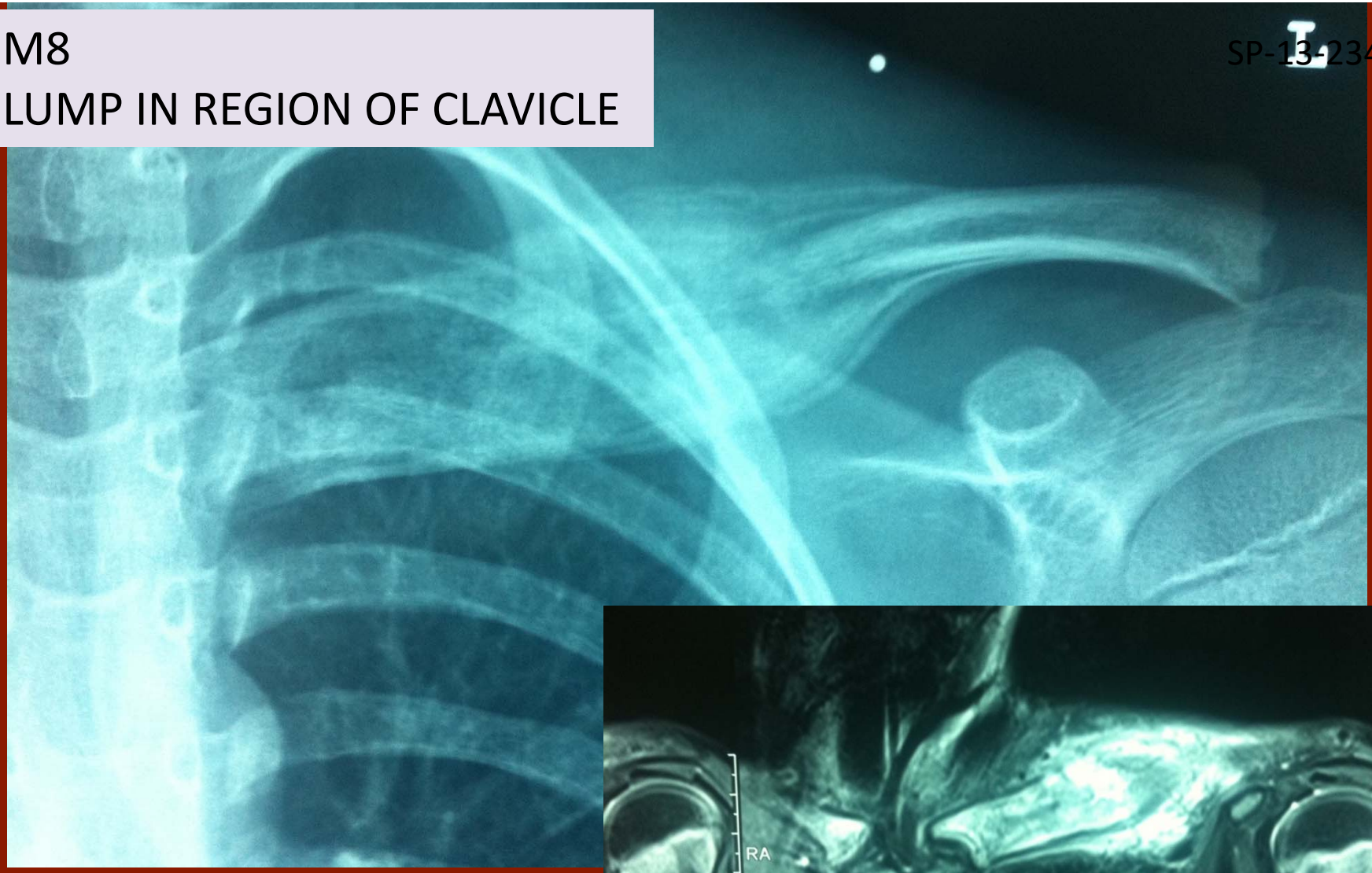
- reactive bone sclerosis and periostitis

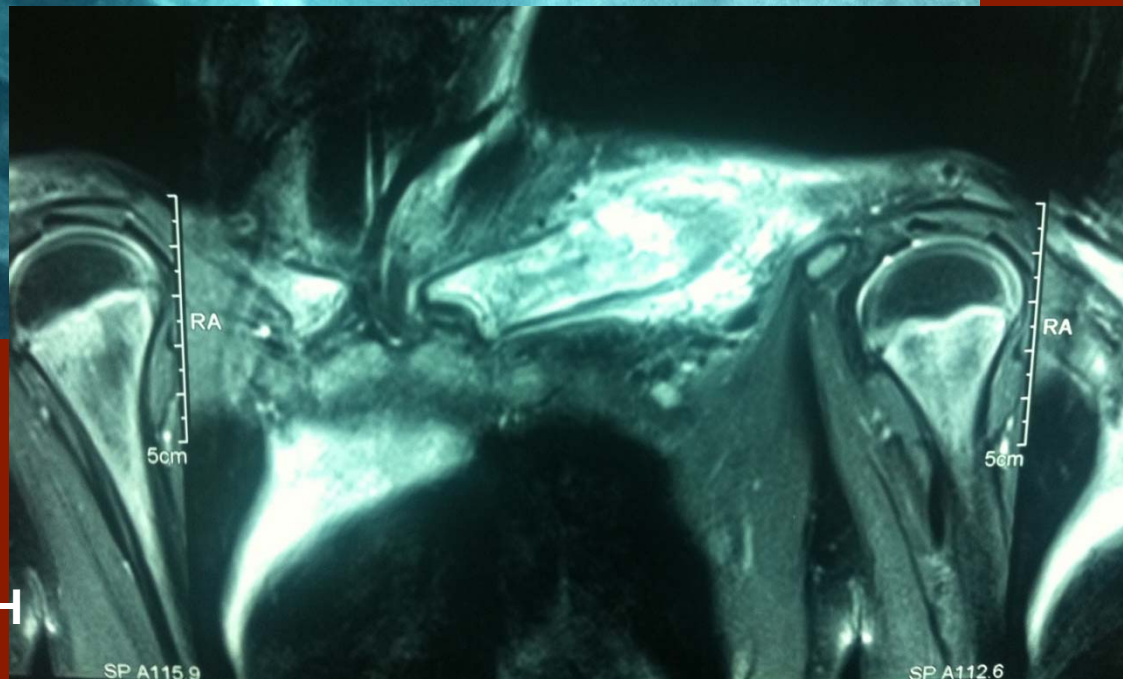



mild inflammation in marrow
may see neutrophils in first 6 months
thereafter largely plasmacellular
Gikas PD et al
J Orthop Sci. 2009 Sep;14(5):505-16

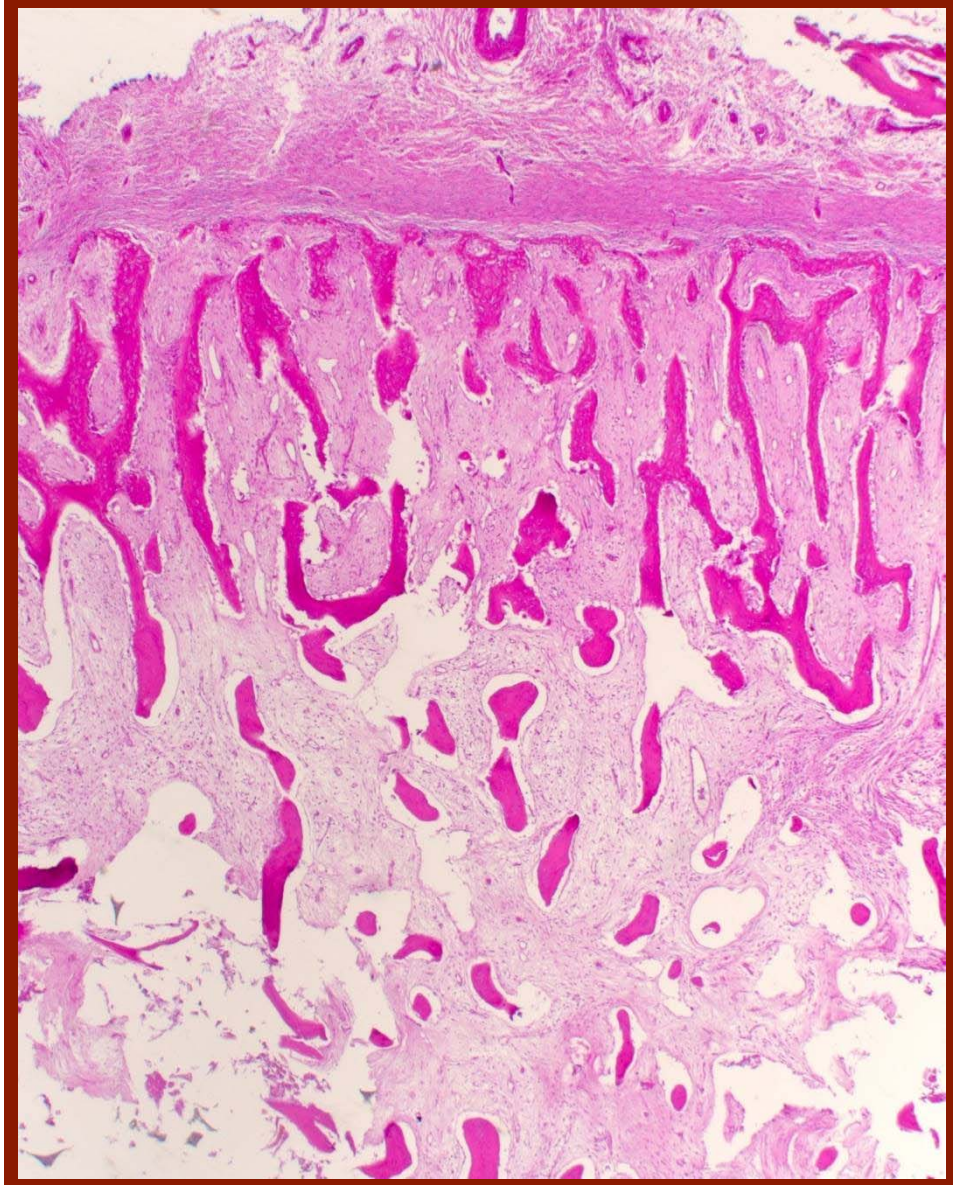
M8
LUMP IN REGION OF CLAVICLE

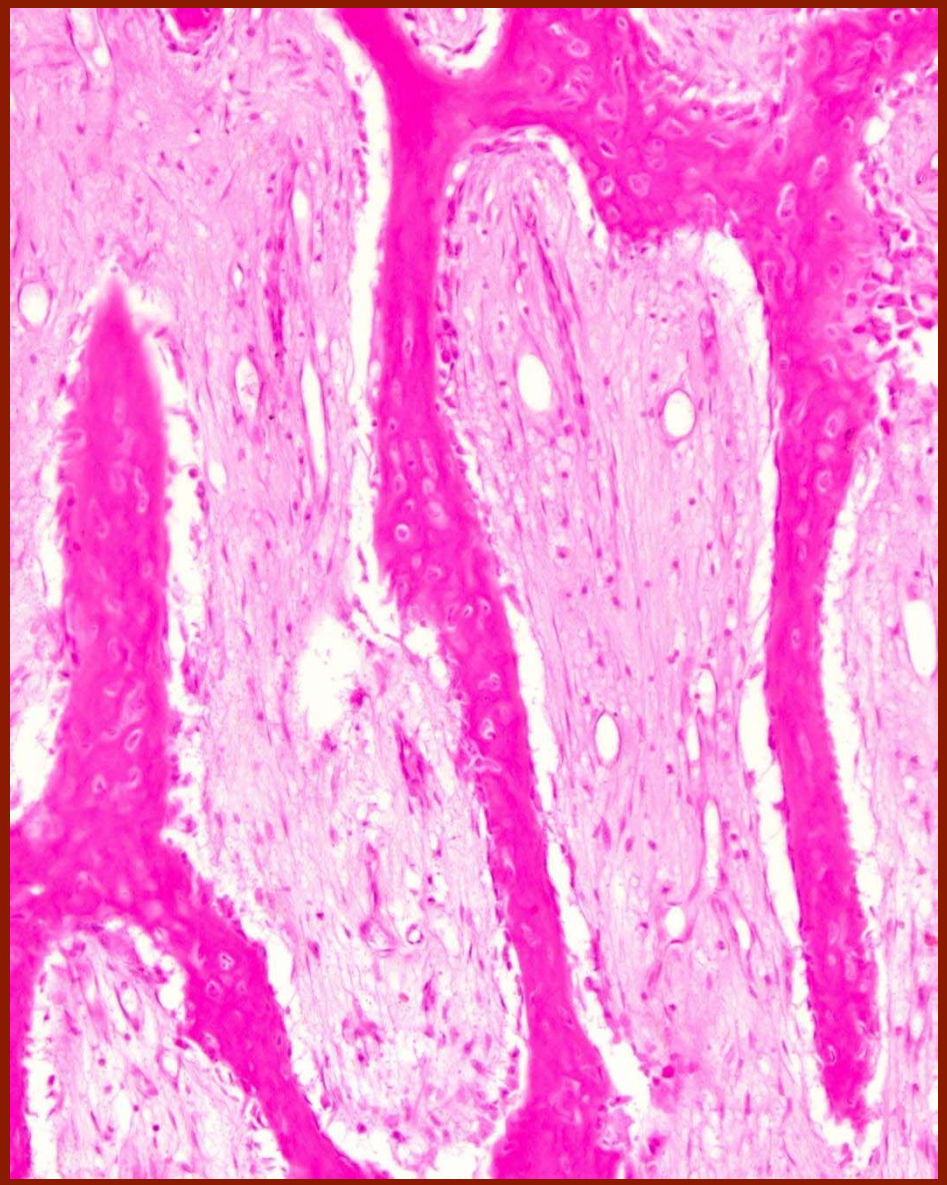
SP-13-23440





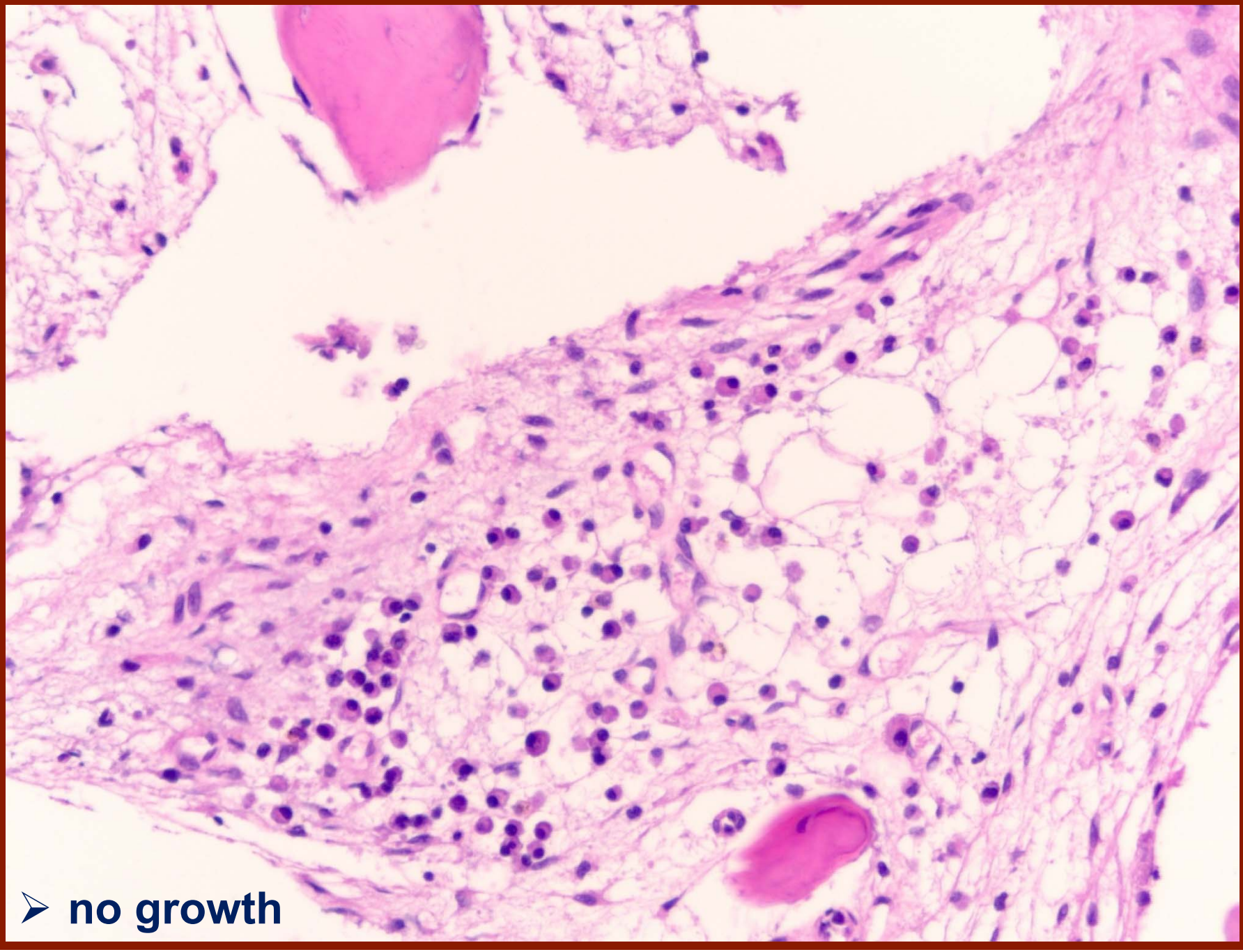
from Drs Annabelle Mahar, RPAH





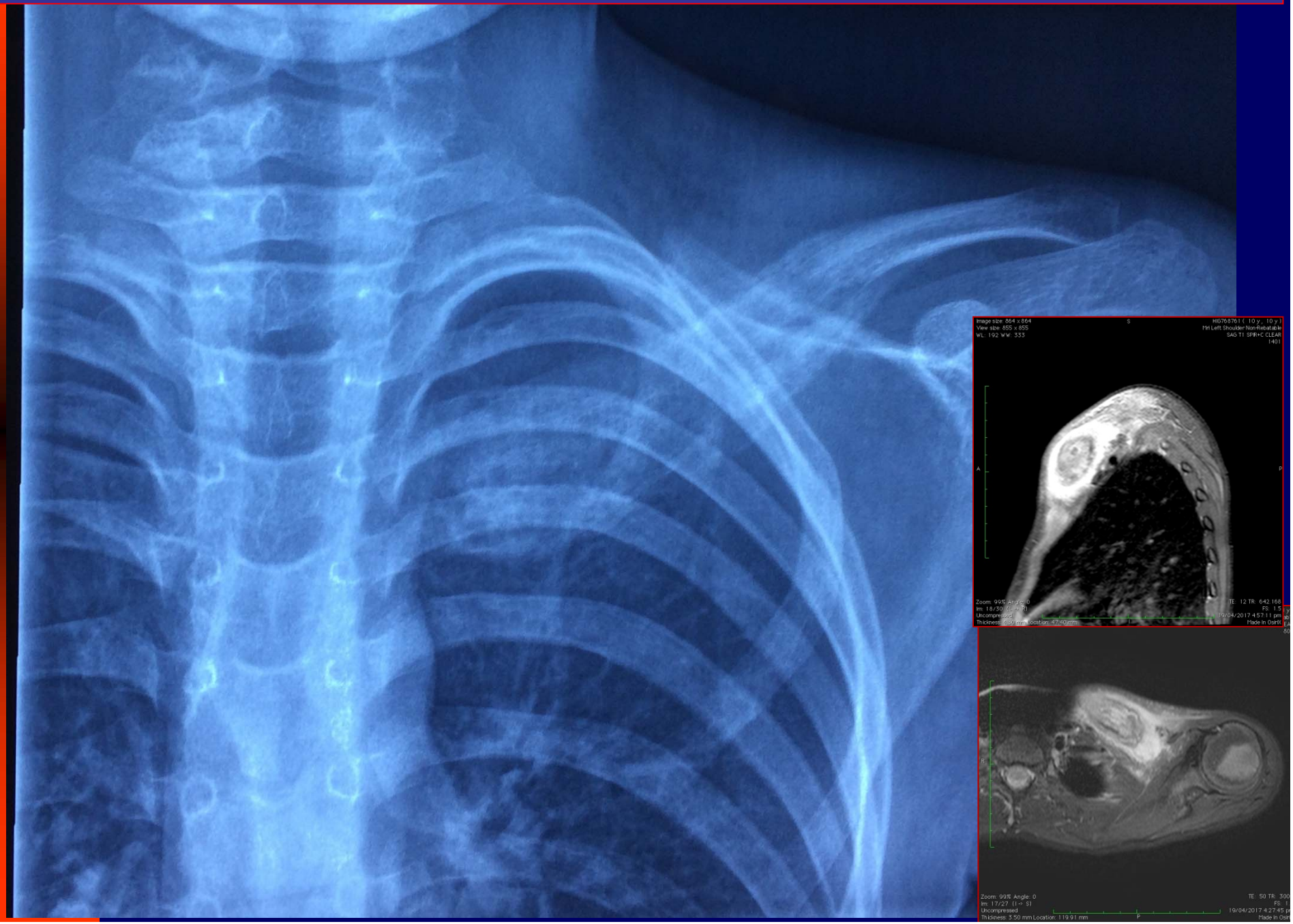
periosteal reaction++

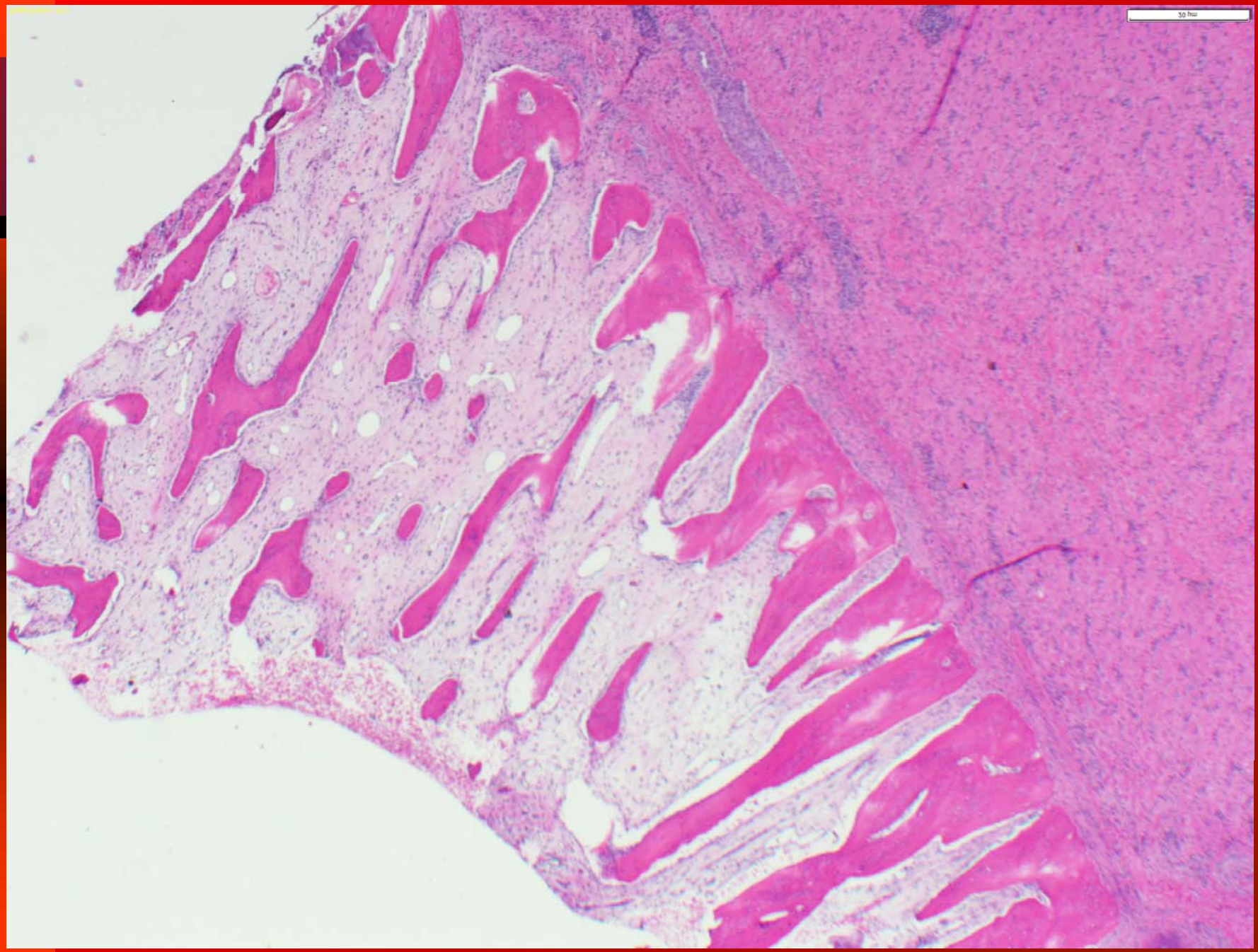
medullary sampling: chronic inflammatory cells: plasma cells



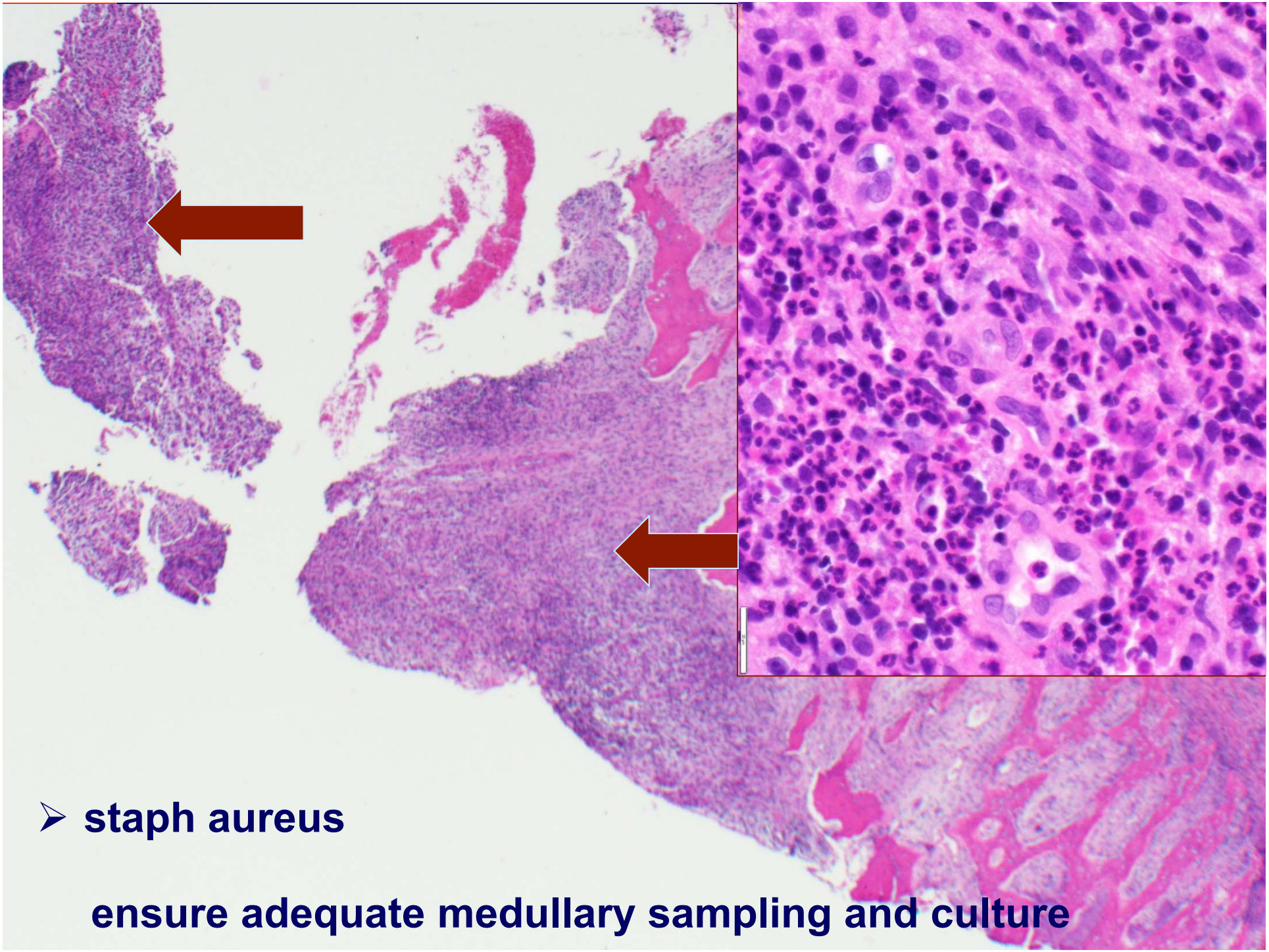
- no growth

◆ boy aged 10





periosteal reaction++



- staph aureus

ensure adequate medullary sampling and culture

Chronic non bacterial osteomyelitis

Ultimately

DIAGNOSIS OF EXCLUSION

- clinical
- imaging
- biopsy

- no infection
- no neoplasia

Chronic non bacterial osteomyelitis

Pathogenesis

poorly understood

Chronic non bacterial osteomyelitis

- "autoinflammatory"
  - recurrent systemic inflammation
  - protean sites
    - joints
    - eyes
    - skin
    - gut
  - no pathogens
  - no autoantibodies
  - no antigen specific T cells

?genetic susceptibility

locus18q21.3-18q22 not confirmed

- ? variant spondyloarthropathy
  - 10 – 30% HLA B27

- rare cases grew propionibacterium acnes: prob contaminant
- bacterial ribosomal DNA PCR negative

★ autoinflammatory:
- primary dysfunction innate immune system
- yet to be defined

Chronic non bacterial osteomyelitis

- abnormal regulation NLRP3 inflammosome
- disrupted innate immune system
- imbalance of pro, anti inflammatory cytokines
- mediated via impaired gene expression IL10
- exact mechanism not clear

IL-1β: critical cytokine in CNO

◆ Ferguson PJ, Laxer RM. Seminar Immunopathol 2015;37:407-412

NALP3 Inflammosome

- binds to procaspase
- active caspase 1
- activation Interleukin Iβ
  Interleukin 18

regulated by pyrin

- mutations affecting pyrin
  - loss of inhibition of this pathway

- mouse model with pyrin mutations (ptspip1)
  - pustular skin disorders and osteitis

◆Lukens JR et al 2014 Nature;516: 246-249

Dietary modulation of the microbiome affects autoinflammatory disease

- **pstpip-deficient cno mouse**
  - **High fat diet protective from CNO**
  - **Low fat diet developed CNO**
    - enrichment of inflammation associated microbes
    - ↑ Prevotella spp
    - ↓ Lactobacillus spp…pro IL1β levels
  - Faecal transplant
    - HFD to LFD improved
    - LFD to HFD deteriorated!

diet - gut bacterial population - affect inflammasome

gut	neutrophil	bone
Diet induced intestinal dysbiosis	Increased active IL-1β	IL-1β mediated inflammation

severe genetic diseases

Autoinflammatory: PAPA syndrome

- destructive arthritis
- neutrophilic infiltrates
- acne / abscess /pyoderma
- infancy

- **PSTPIP1 gene mutations**
- **regulating pyrin**

- **pyrin regulates the NALP3 inflammosome**

➢ **mouse model with pyrin mutations (ptspip1)**

Syndromic CRMO

Majeed syndrome, DIRA syndrome

- LPIN2, IL1RN mutations
- abnormal regulation NLRP3 inflammosome

- LPIN2 has a major role in fat metabolism
- mutation results in increased IL-1β production
- imbalance of pro, anti inflammatory cytokines
- exact mechanism not clear

IL-1β: critical cytokine in CNO

- Ferguson PJ, Laxer RM. Seminar Immunopathol 2015;37:407-412
- Cox AJ, Ferguson PJ Curr Opin Rheumatol 2018; 30: March

Syndromic CRMO

- FBLIM1 mutations
- encodes FBLP-I: Filamin Binding LIM Protein 1

- important in bone remodelling
- regulator of cytoskeleton
- anchor for extracellular matrix,
- involved in intergrin activation
- regulated by STAT 3
- anti-inflammatory properties

deficient mice have overexpression RANK-L

- Cox AJ et al PLOS one March 2017
- Cox AJ, Ferguson PJ Curr Opin Rheumatol 2018

Chronic non bacterial osteomyelitis
(CNO and CRMO)

- abnormal regulation NLRP3 inflammosome

specific mutations in less severely affected children and adults are rare

- Cox AJ, Ferguson PJ Curr Opin Rheumatol 2018

Chronic non bacterial osteomyelitis
(CNO and CRMO)

- **therapy: variably successful**
- **antibiotics….(usually given)….**

- **NSAIDS**
- **steroids**
- **bisphosphonates**
- **TNF alpha blockers**
  - **anakinra (anti interleukin 1)**

suppression inflammatory cytokines

- Clincal setting of non specific symptoms
  - sclerosis/lysis
  - ? infection… no growth
- mild chronic inflammation, sclerosis

Consider and suggest

Chronic non bacterial osteomyelitis (CNO and CRMO)

Possible ‘SAPHO’ syndrome

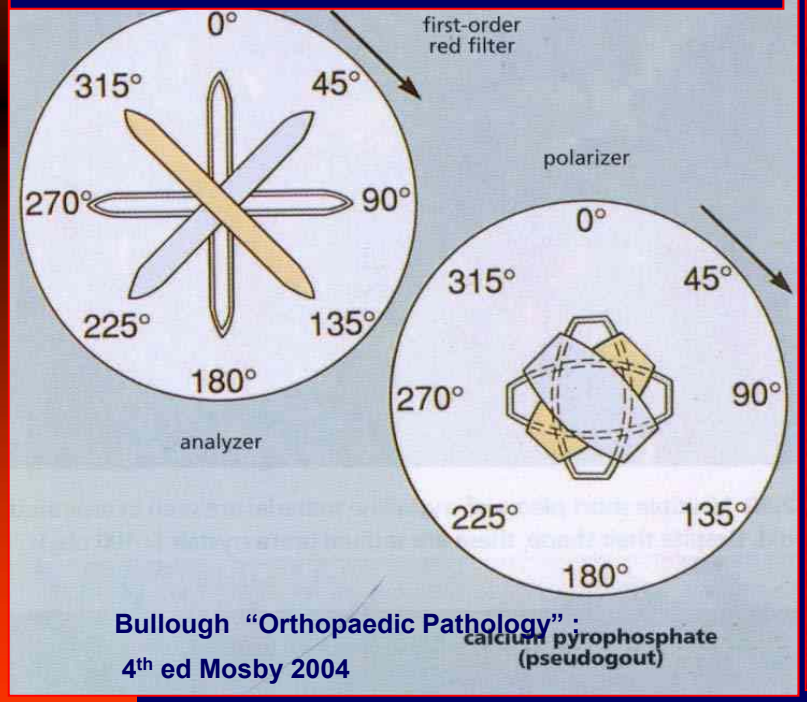
Chronic non bacterial osteomyelitis
(CNO and CRMO)

- prevent unnecessary antibiotic rx
- protect gut bacterial population
- increasing relevance in recent years
- in a variety of clinical settings…

Crystal deposition disease

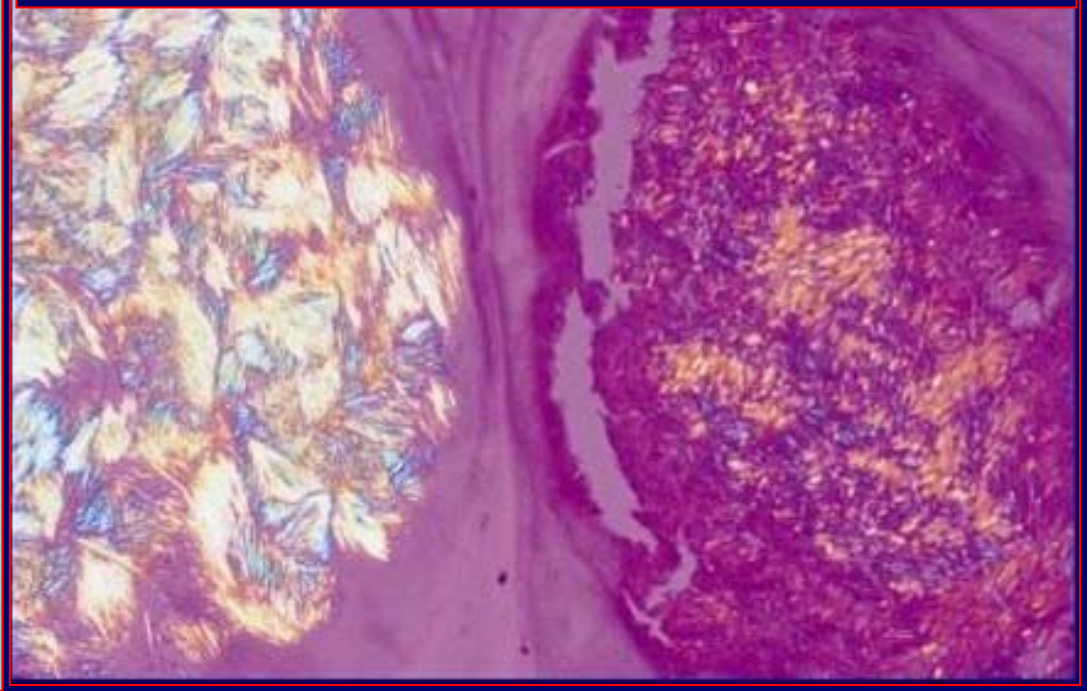
Gout: arthritis; tophi in soft tissue
CPPD: degenerative joint disease

uric acid **CPPD**

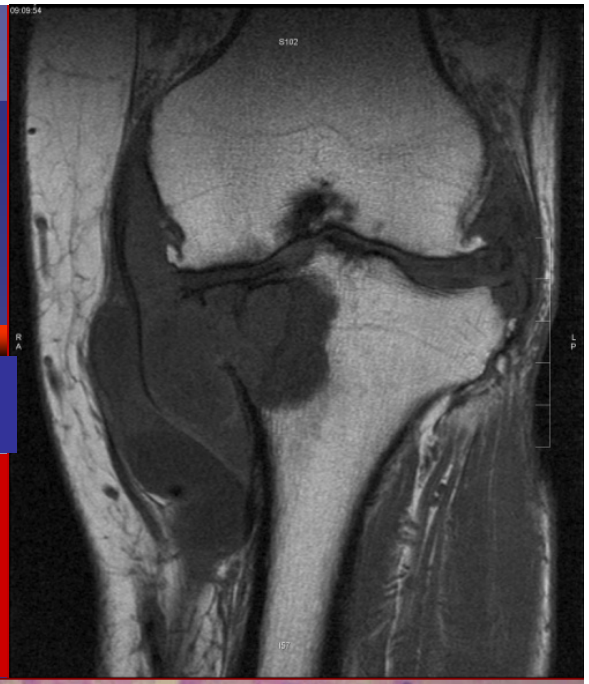


Bullough "Orthopaedic Pathology" : 4th ed Mosby 2004

uric acid **CPPD**



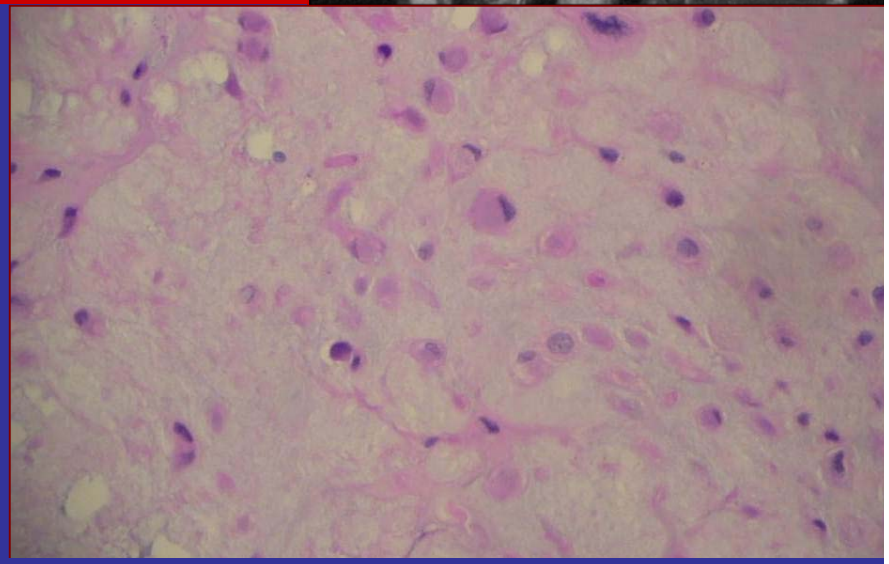
Tumoral C.P.P.D
(Tophaceous Pseudogout)



calcium pyrophosphate crystal deposition

Rare, often mimicking tumours on imaging and histology

- **Temporomandibular joint**
- **Hands and feet**
- **Hips**
- **Spine**

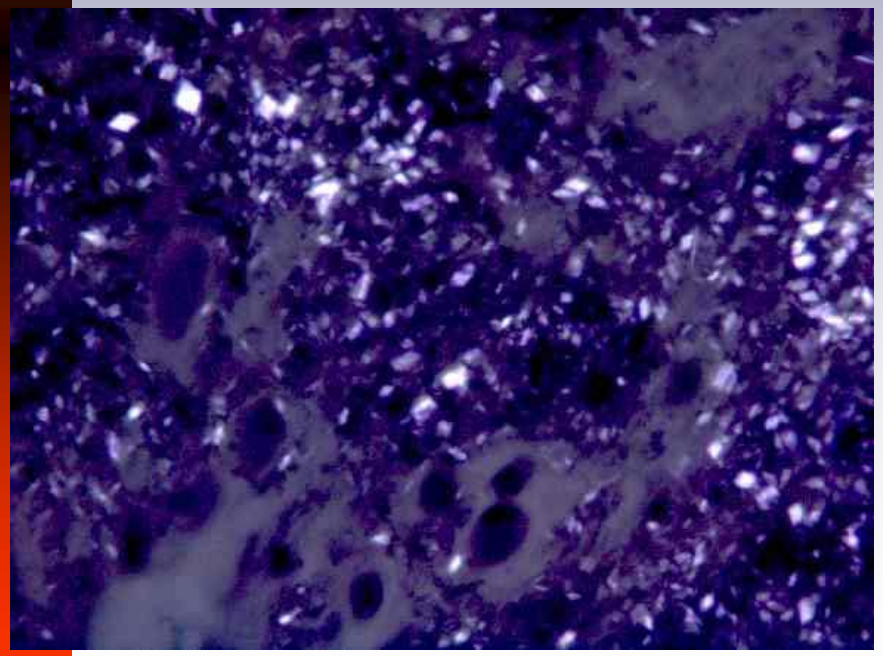


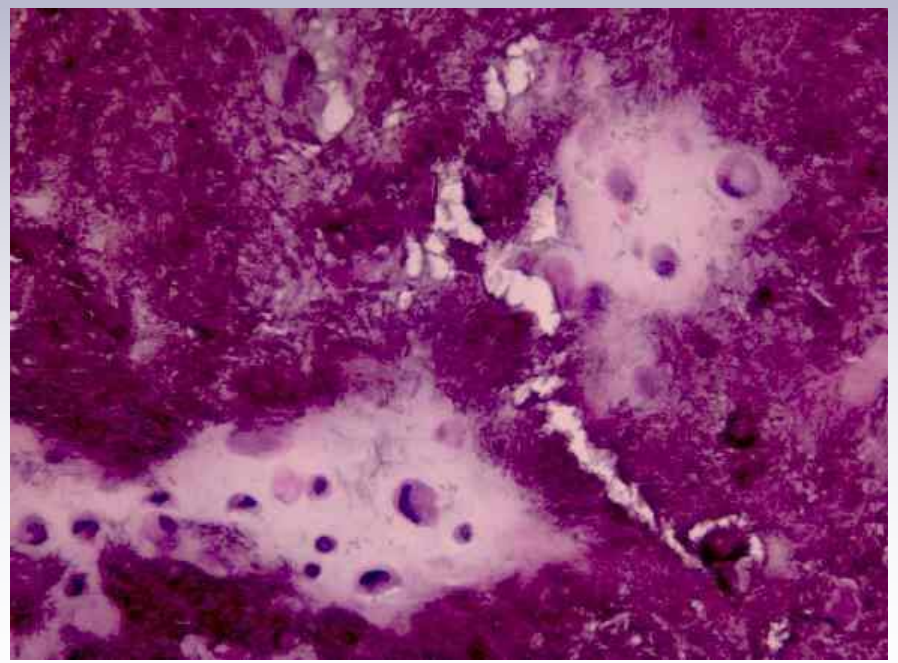
hypertrophic chondrocytic cells

- **sarcoma…?.....chondrosarcoma?**

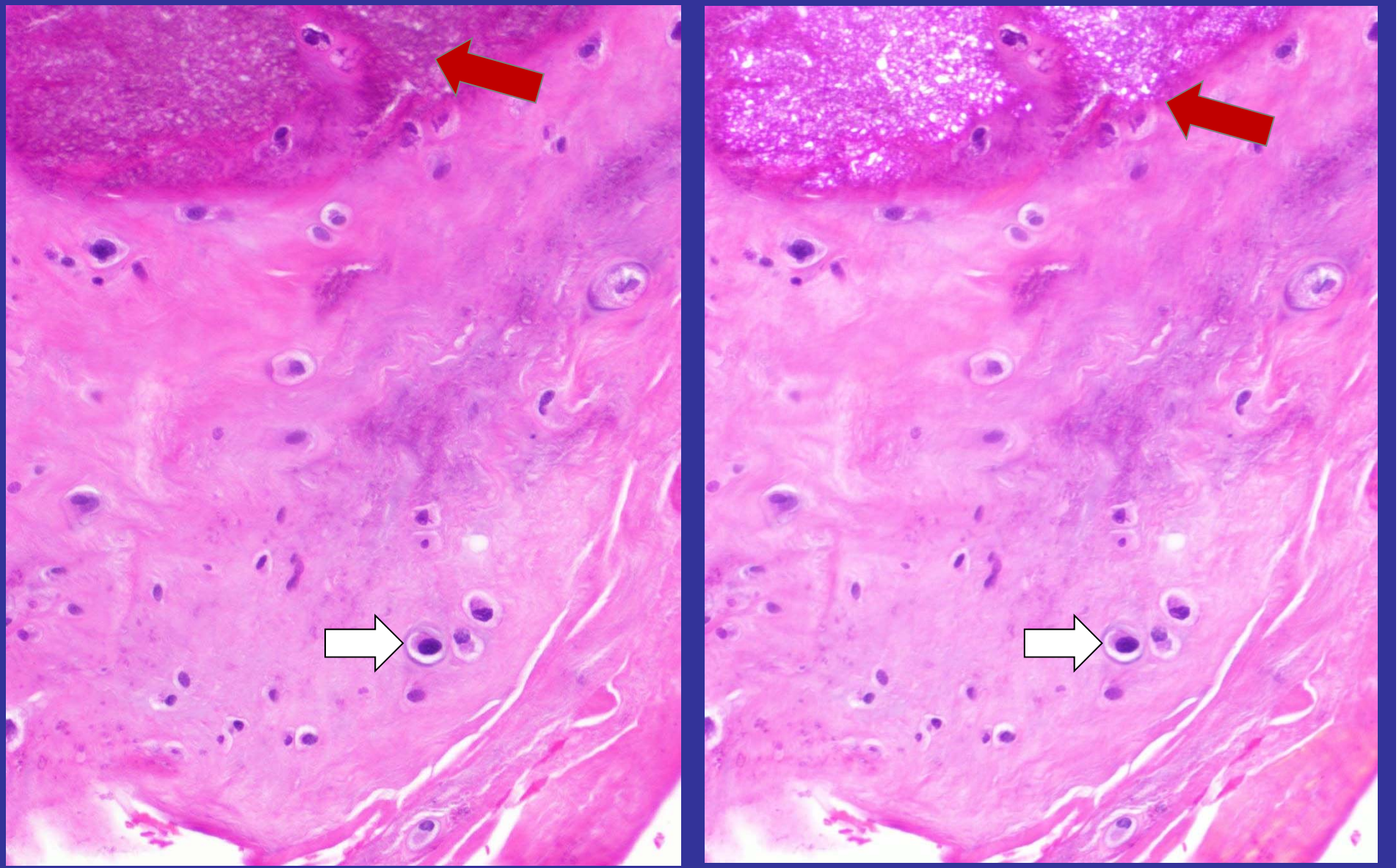
degenerative change in soft tissue

chondrometaplasia

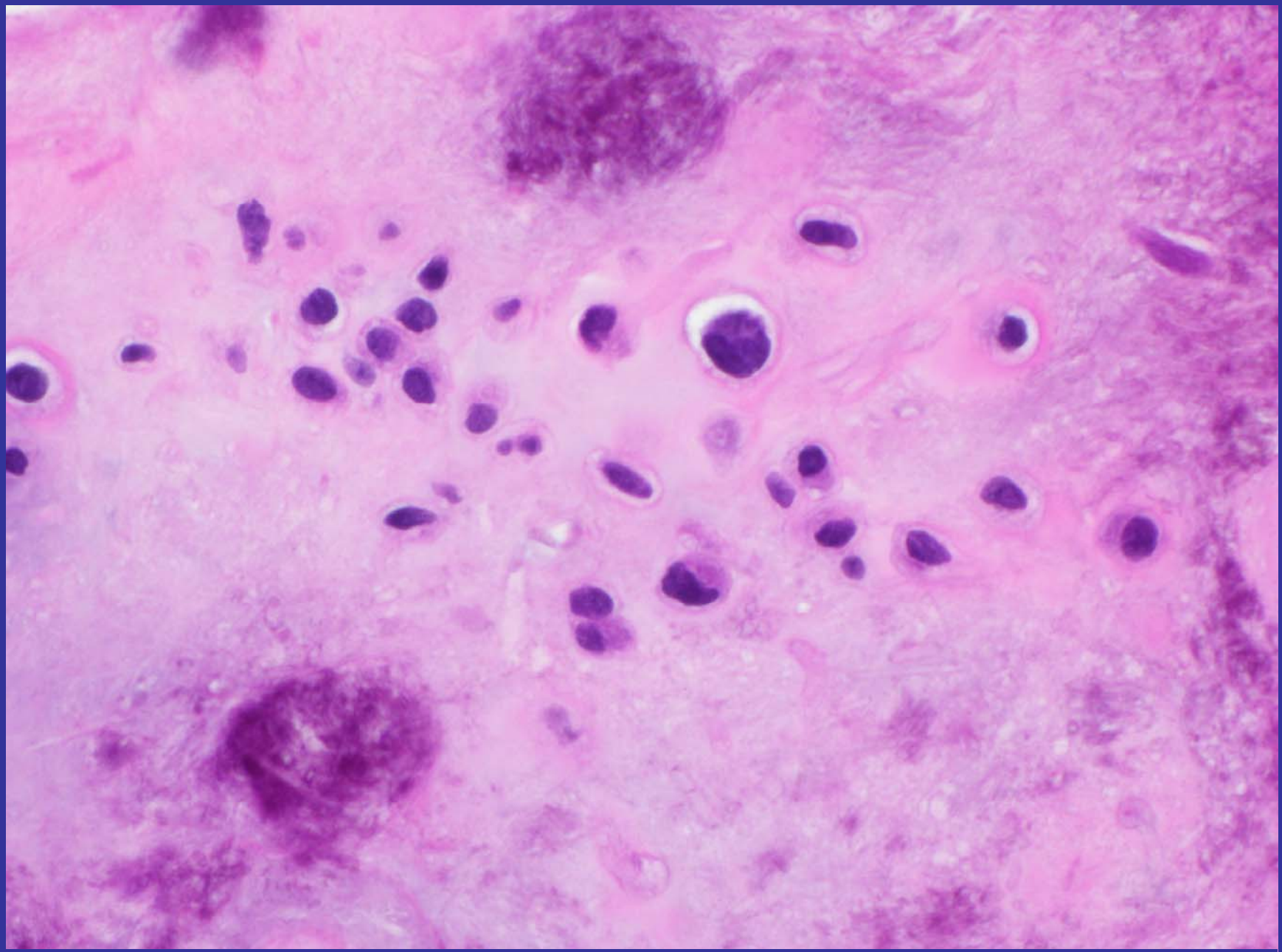




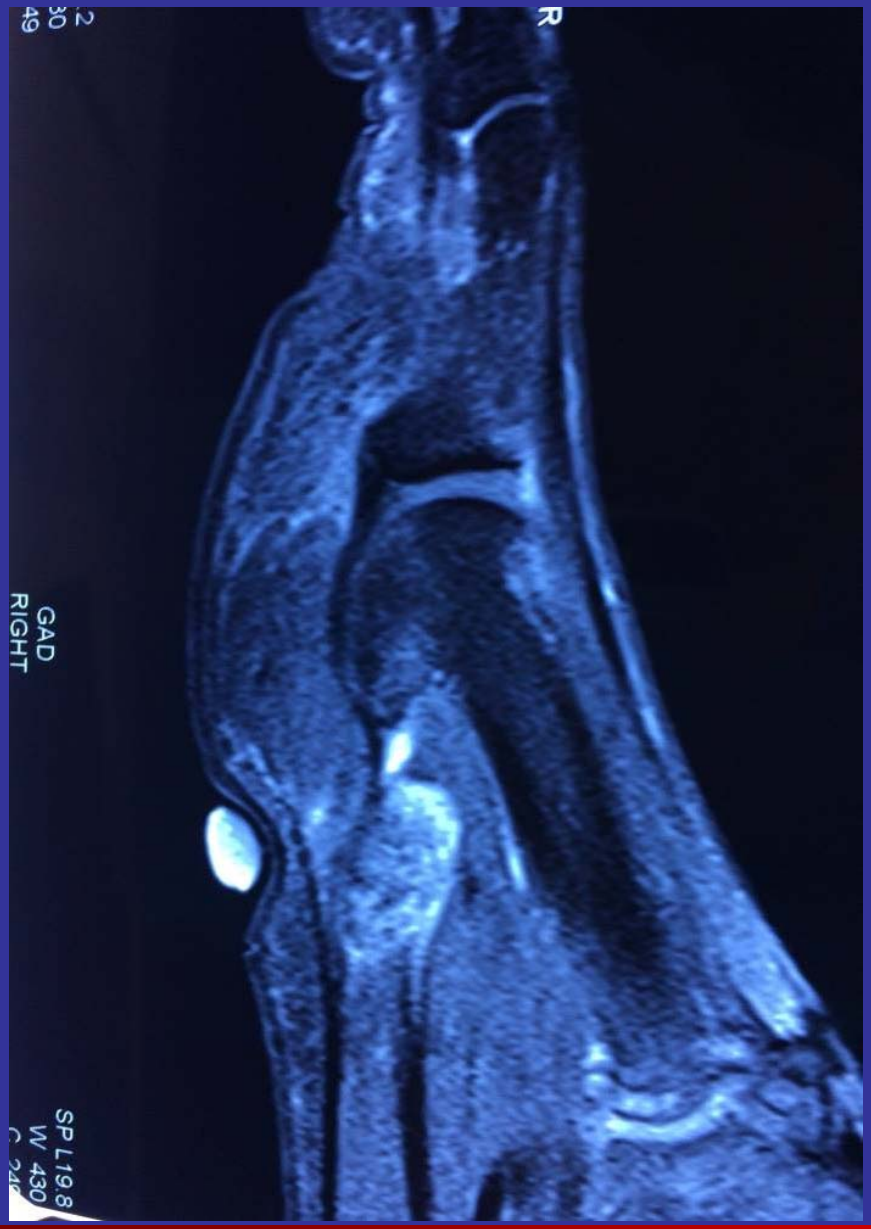
calcium pyrophosphate crystal deposition

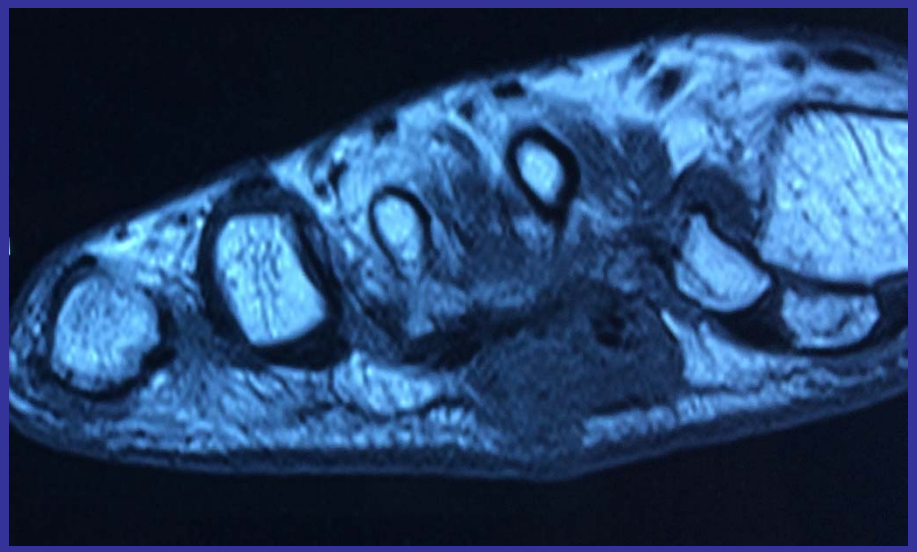


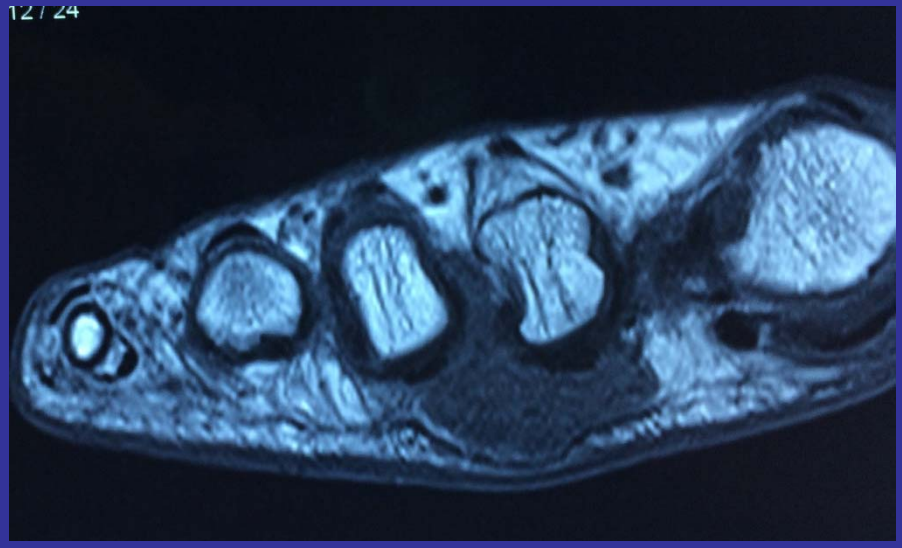
hypertrophic chondrocytic cells



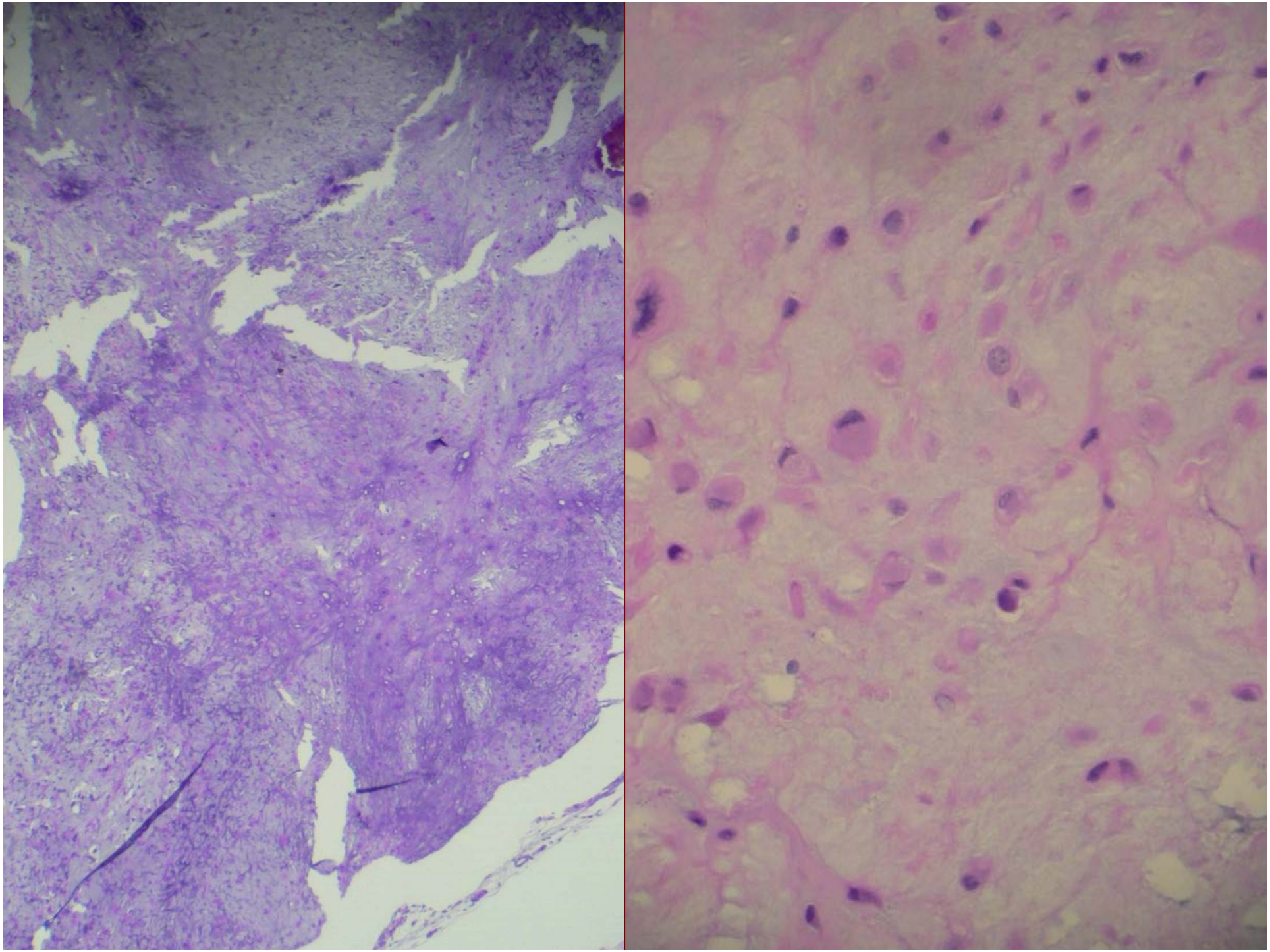
hypertrophic chondrocytic cells

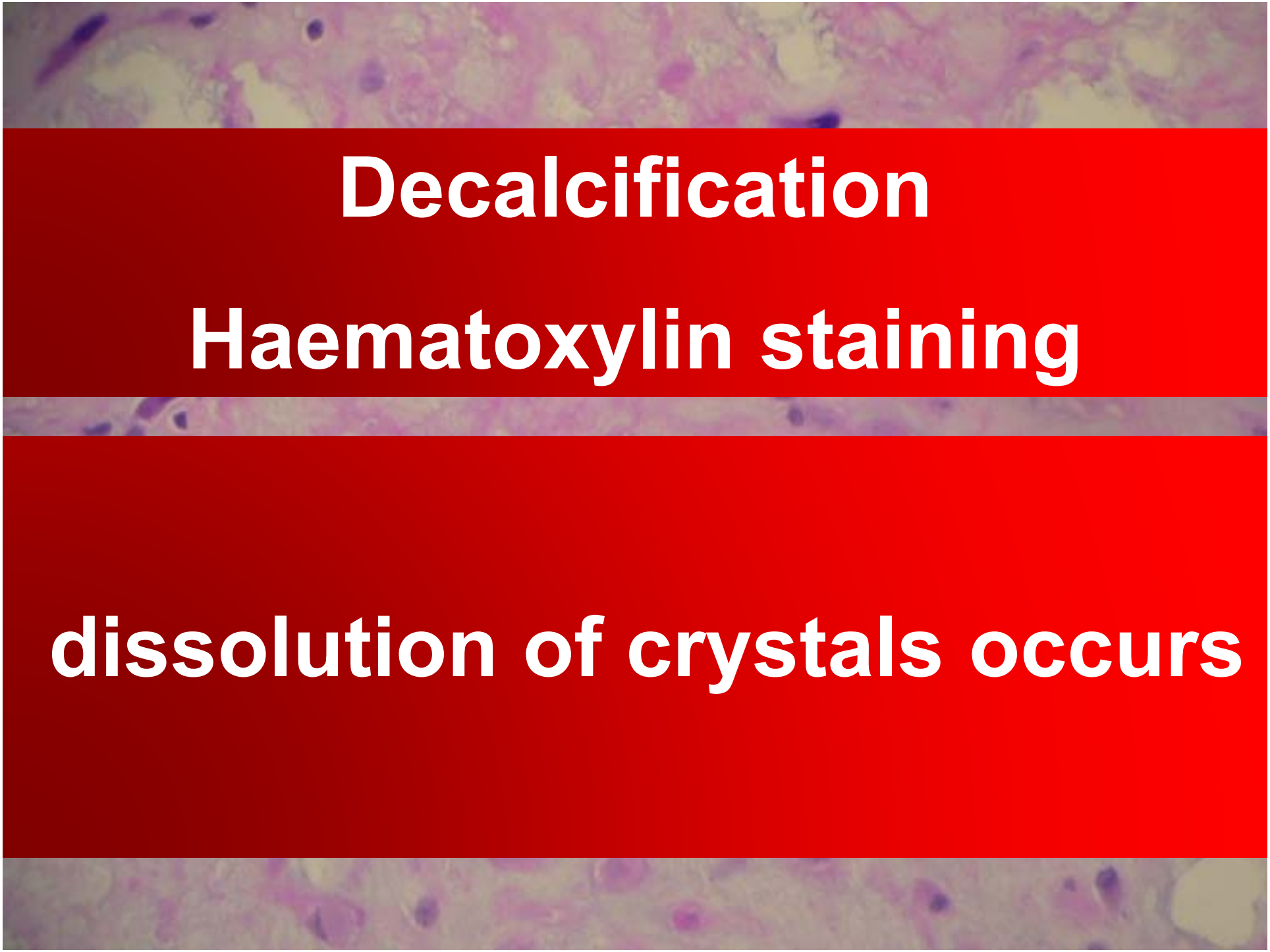




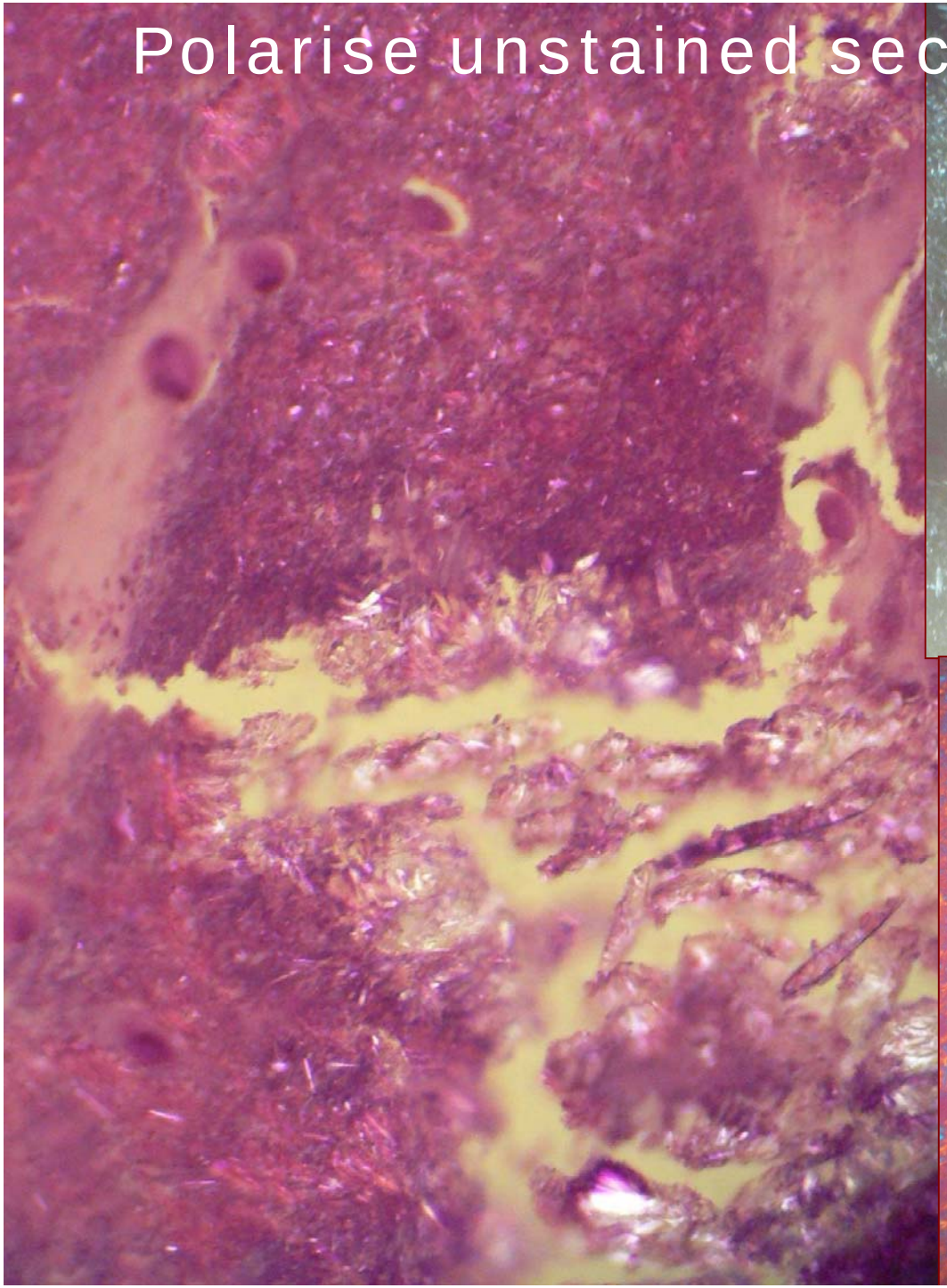


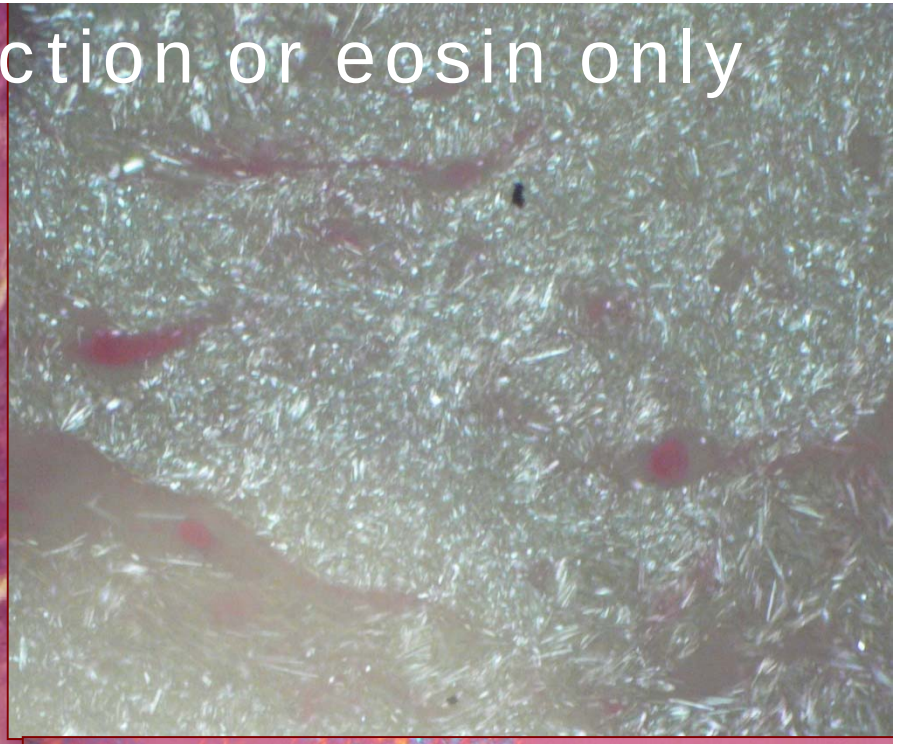
May 2018
F/71 – Mass right foot

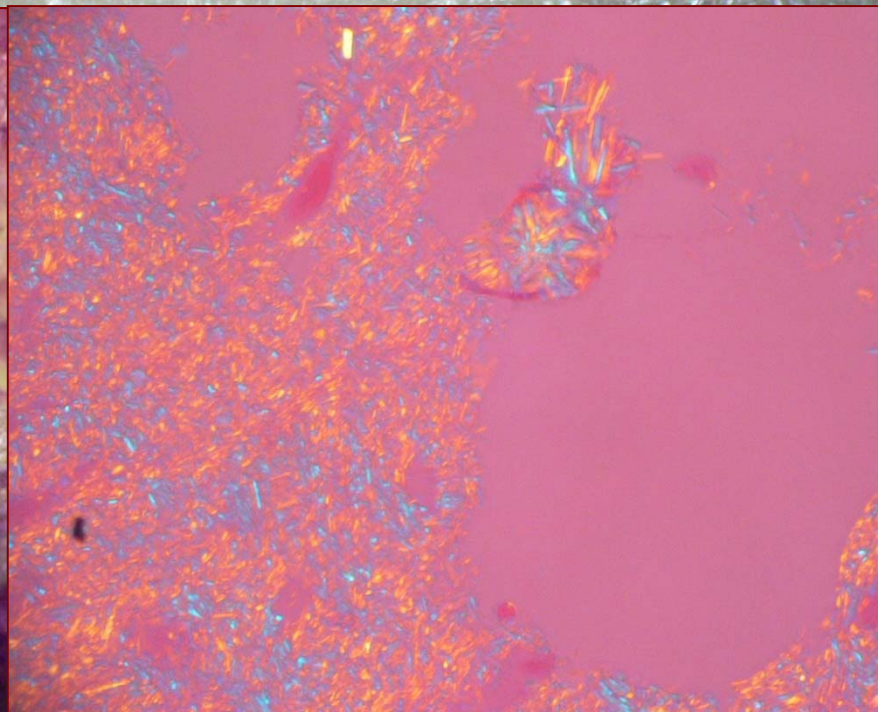



Decalcification
Haematoxylin staining
dissolution of crystals occurs

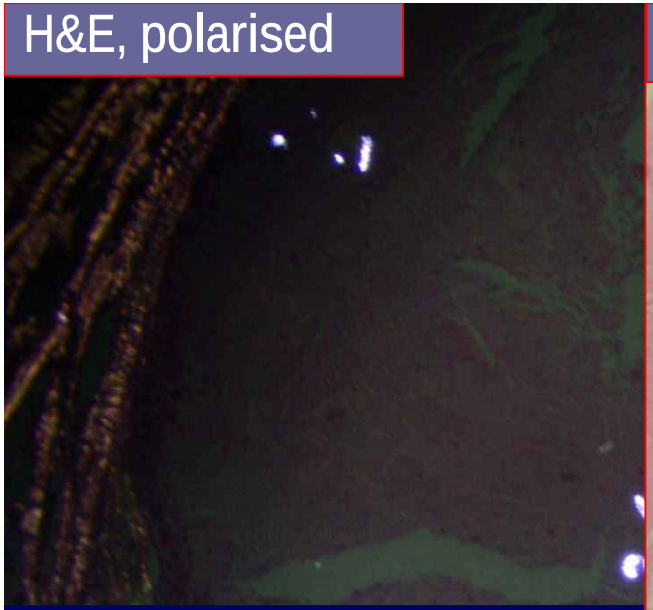
Polarise unstained section or eosin only



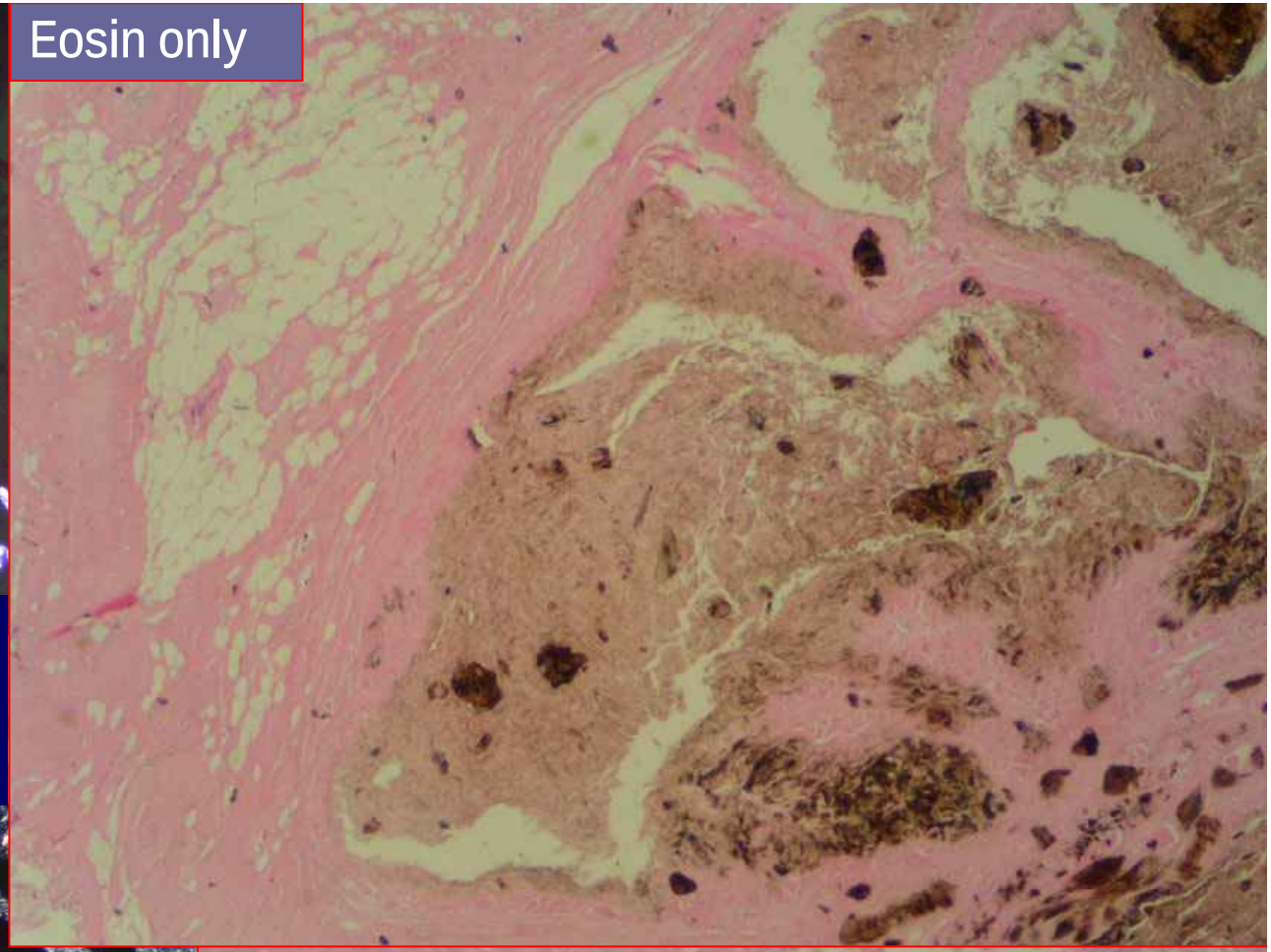




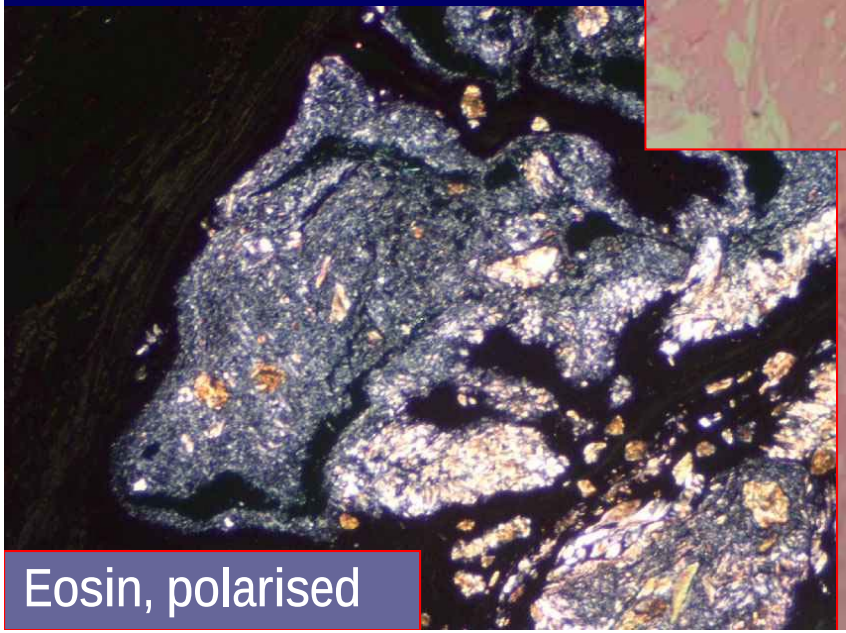
H&E, polarised



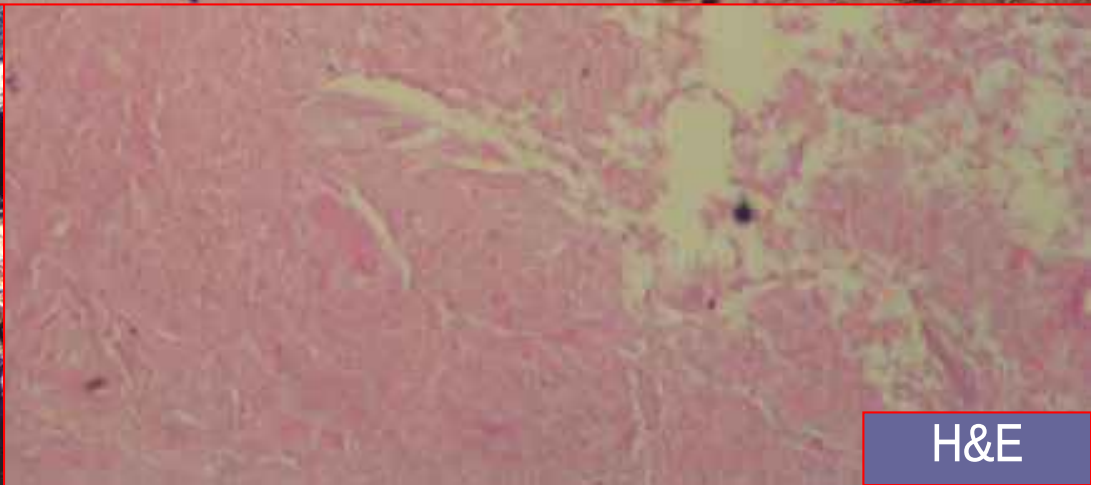
Eosin only



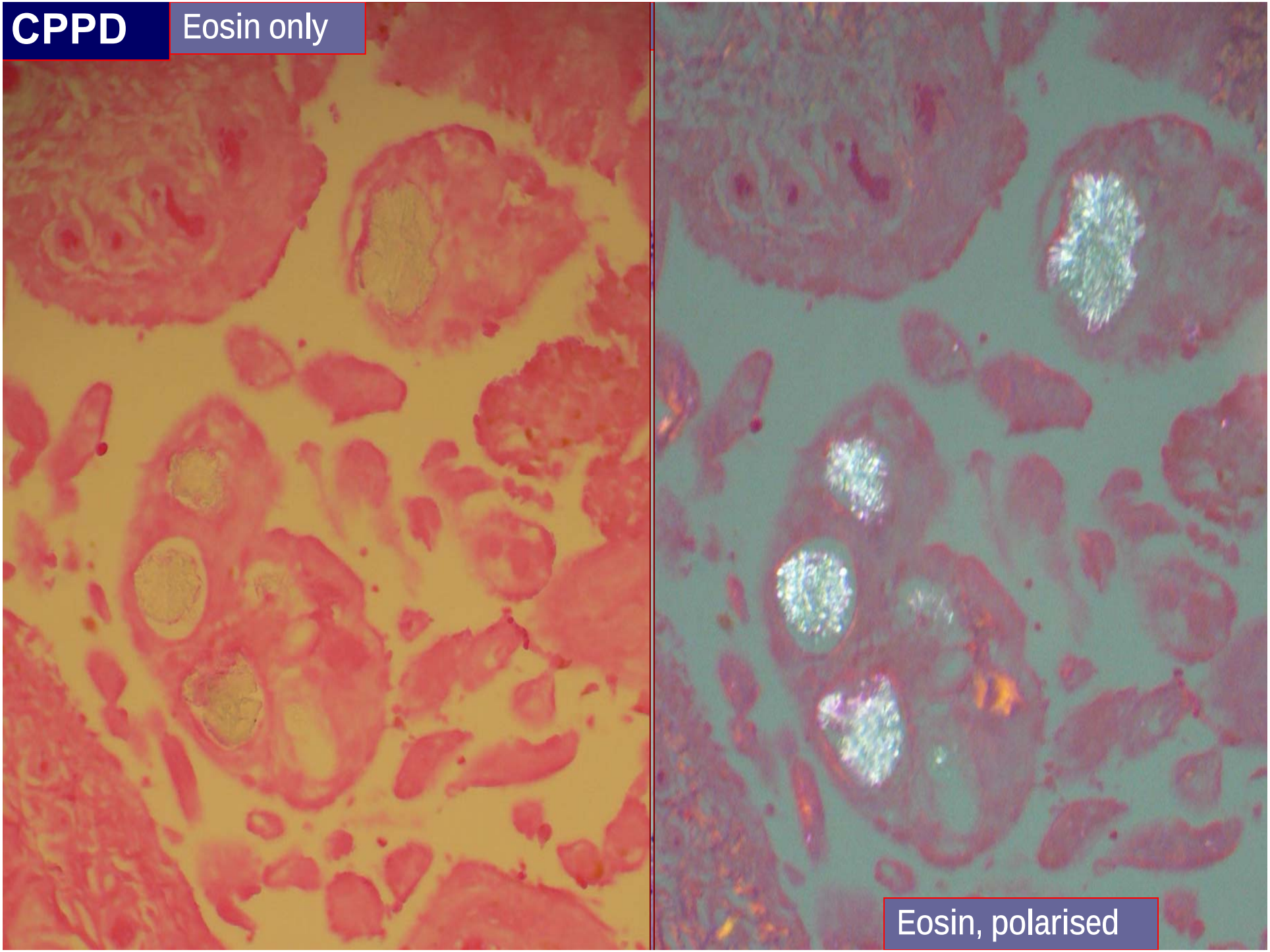
- **gouty tophus**
- **uric acid**



Eosin, polarised



H&E


CPPD
Eosin only
Eosin, polarised

Sir James Paget 1877

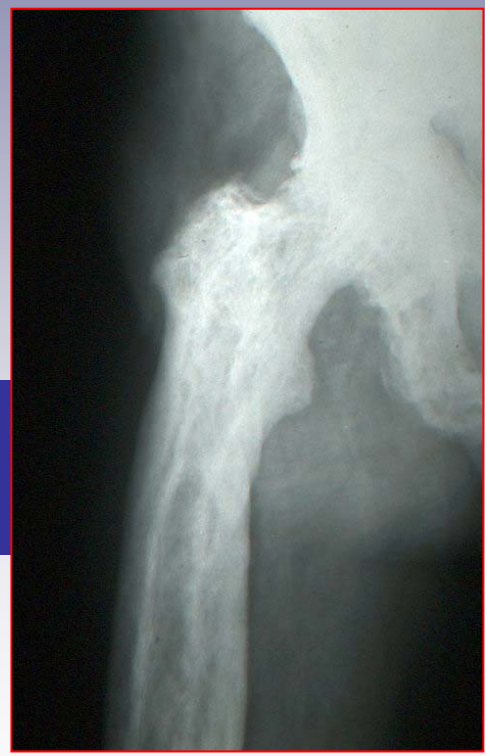
Paget disease:

- lucent lesion
- sclerotic lesion

disordered bone remodelling

- lumbar spine
- pelvis
- skull
- femur
- tibia

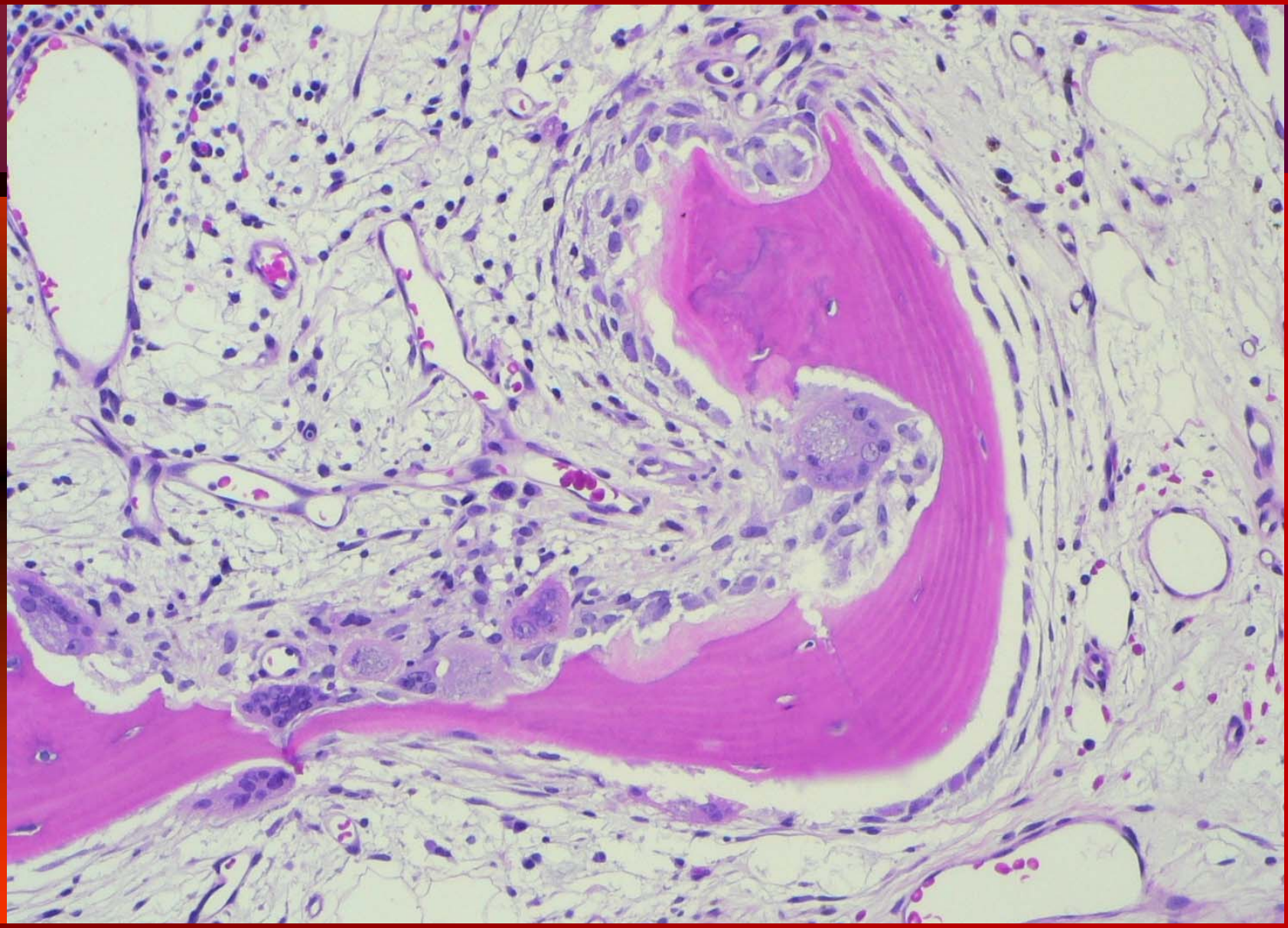
  - localised (commonest)
  - extensive/ generalised



- early: may be lucent
- later: usually sclerotic

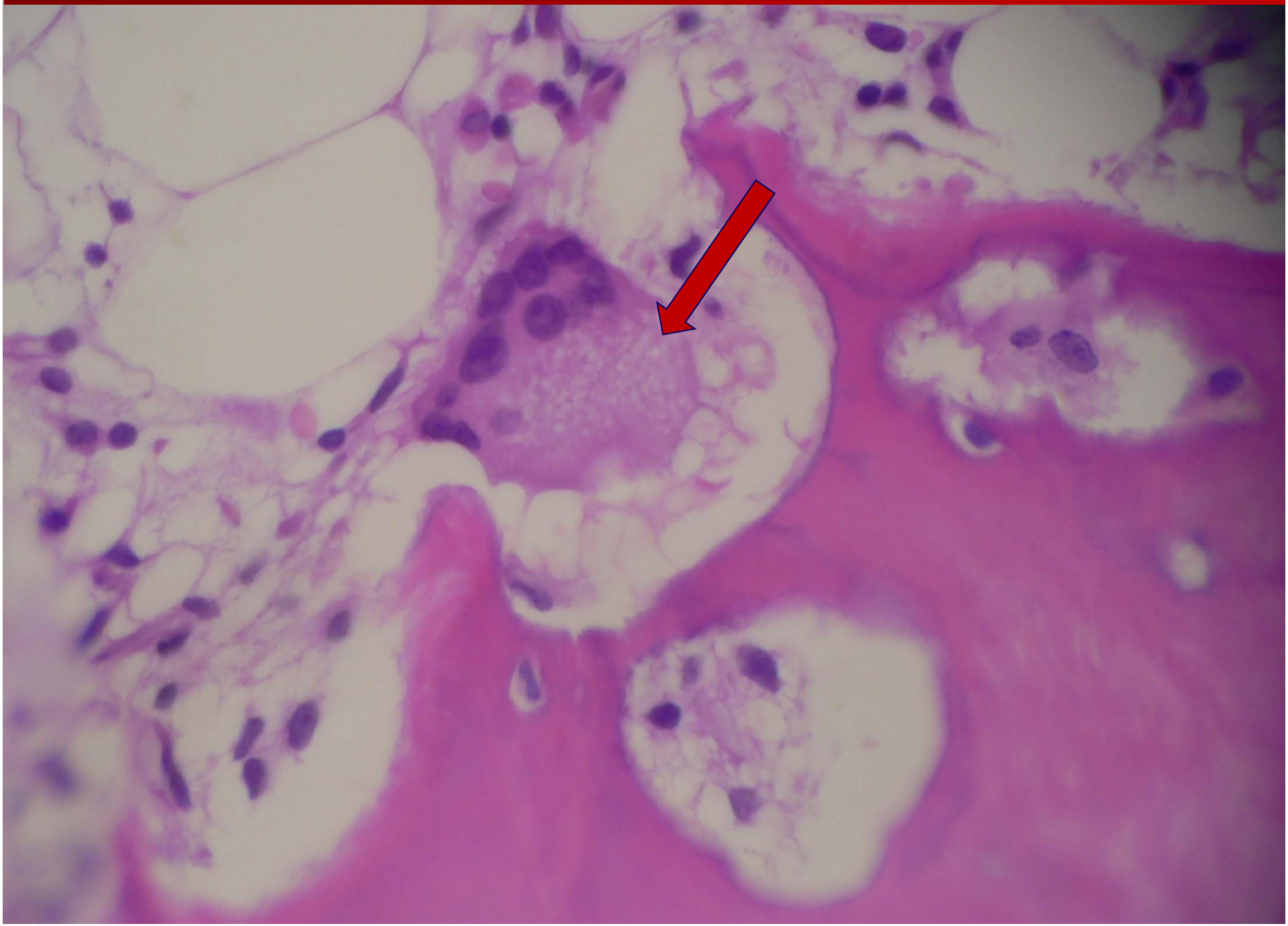
localised form often biopsied: alk phos may be normal

localised form often biopsied: alk phos may be normal

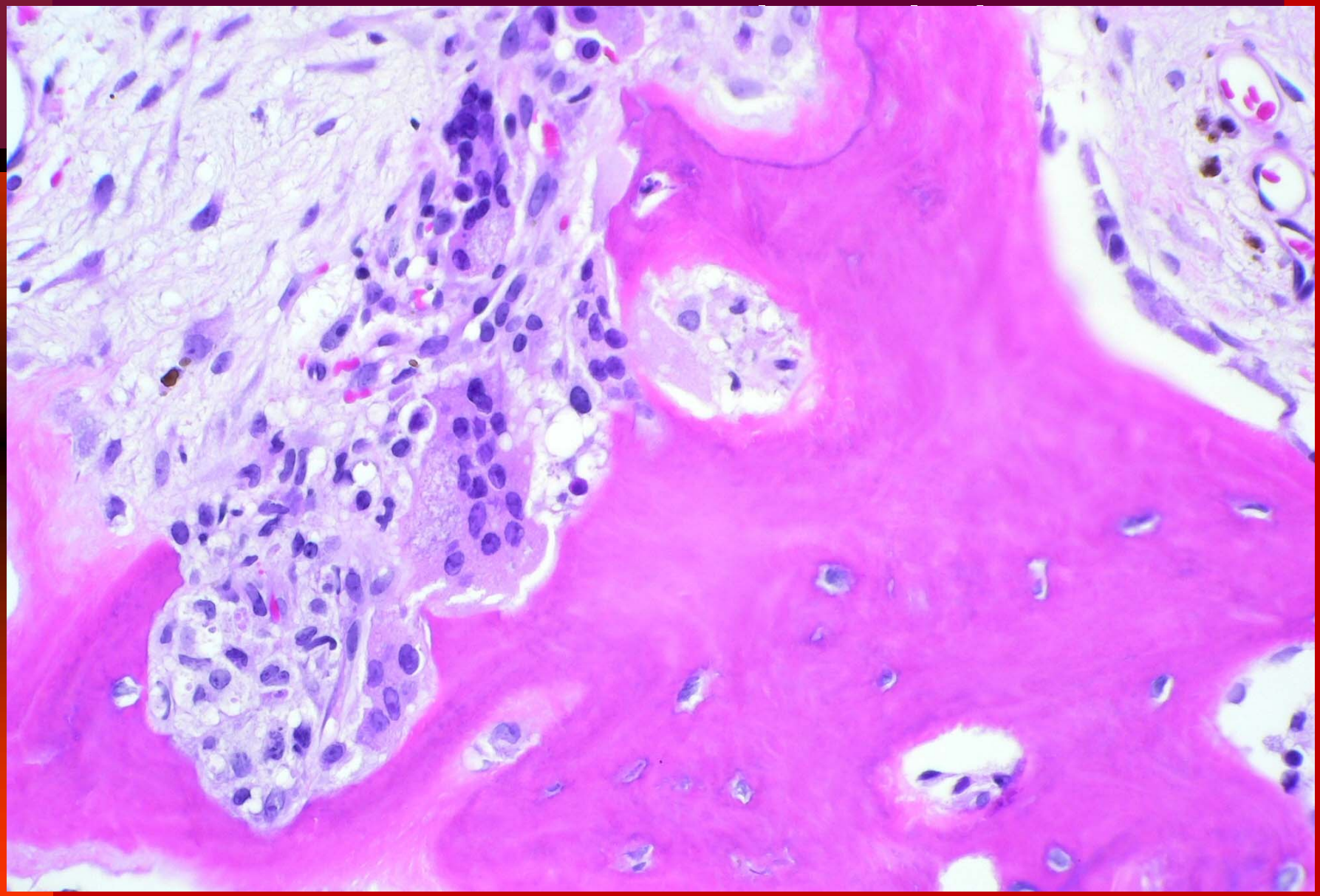


early phase: normal sized trabeculae of lamellar bone, loose fibrous vascularised stroma, vigorous osteoclastic resorption, accompanying osteoblastic activity

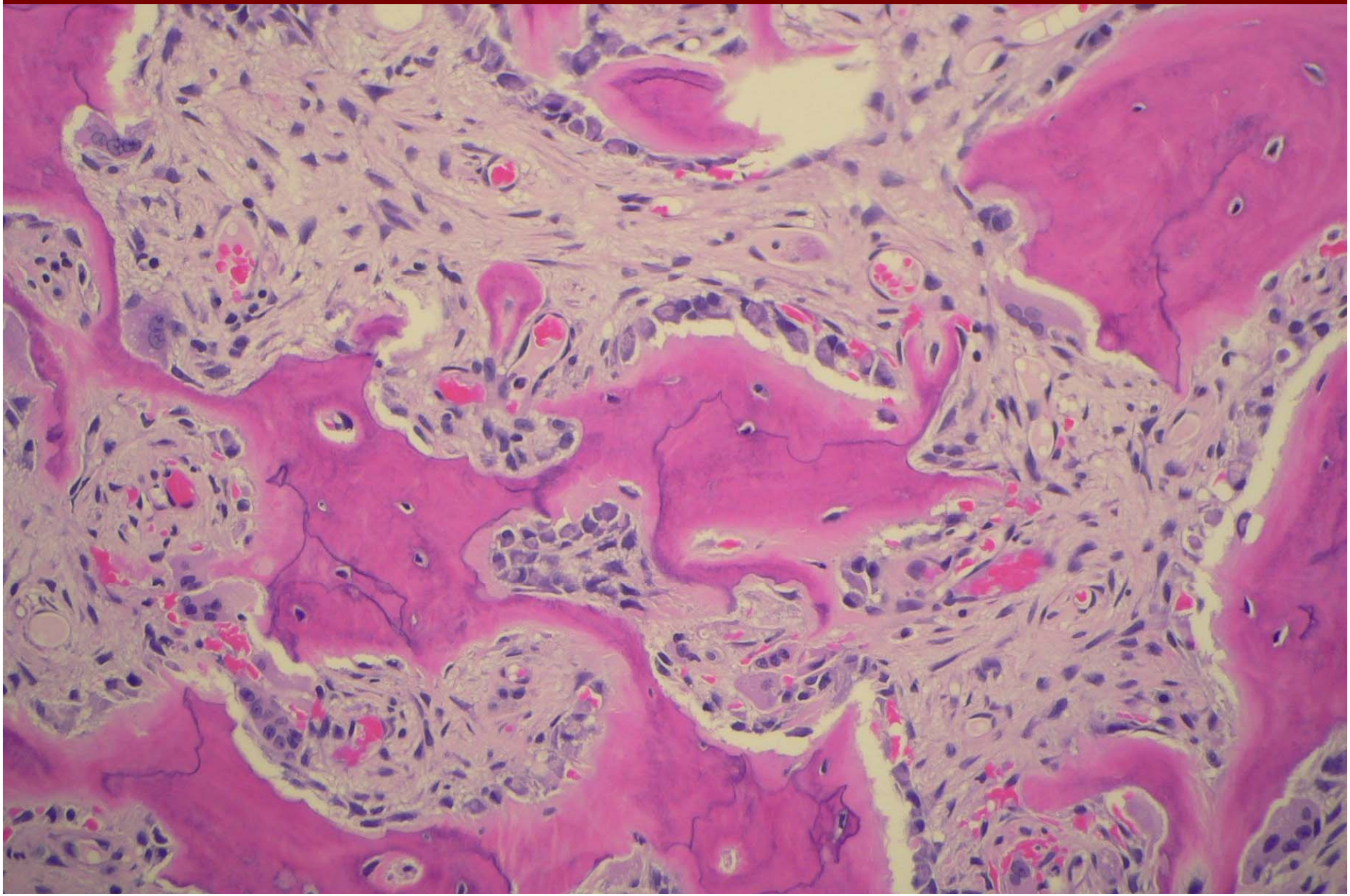
large osteoclasts, multiple nuclei, commonly vacuolated cytoplasm



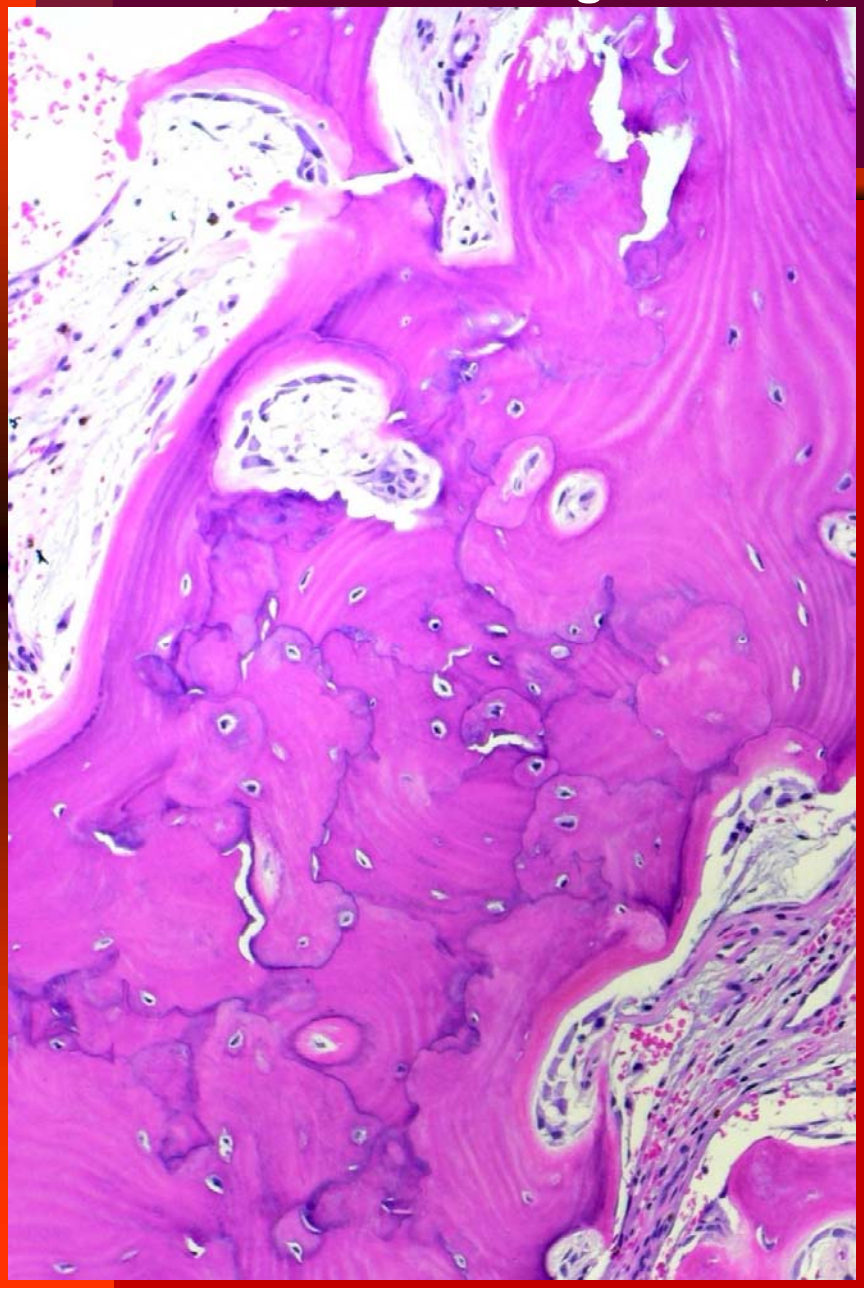
irregular variably sized resorption pits

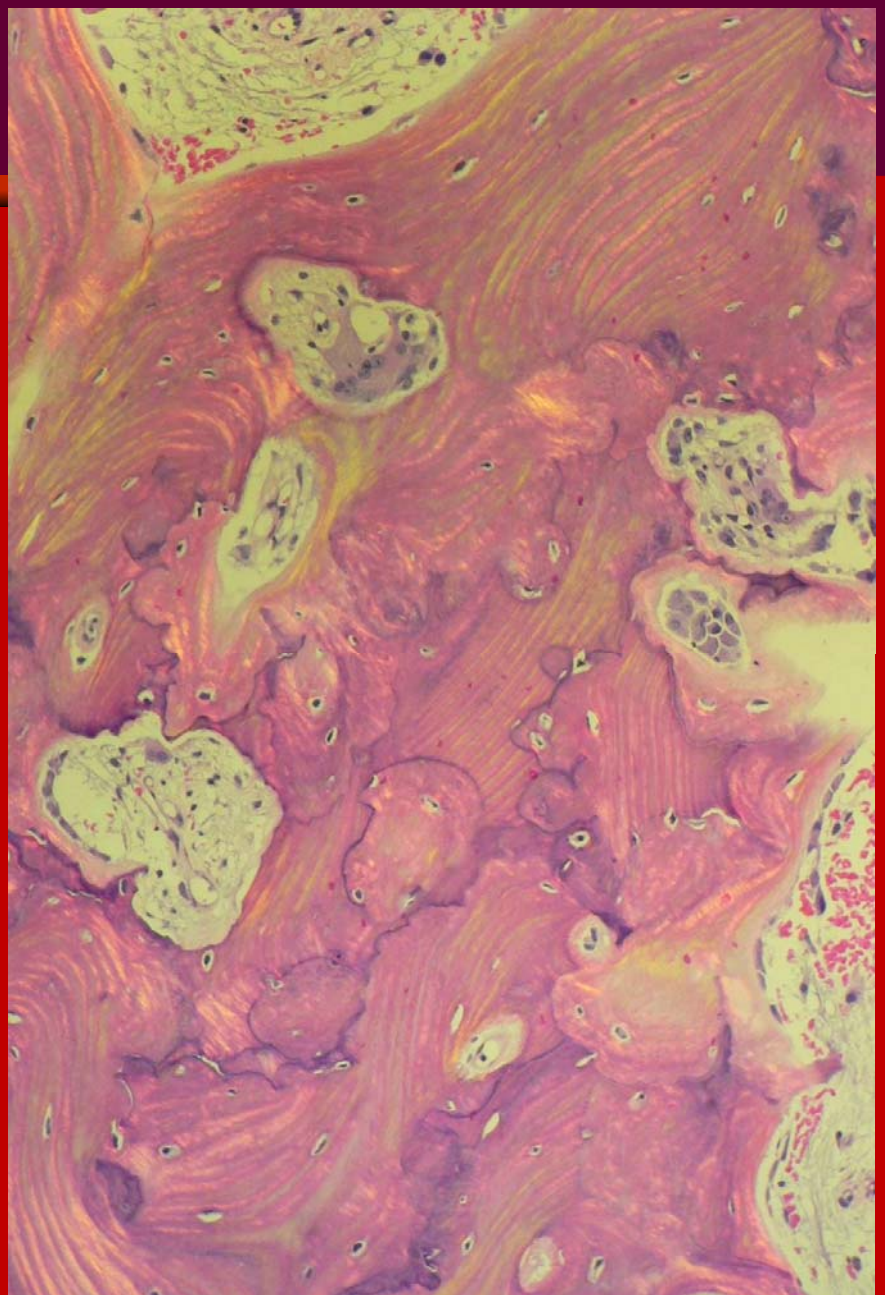


Loose fibrous stroma with osteoid deposition by abundant osteoblasts..producing the mosaic pattern of cement lines

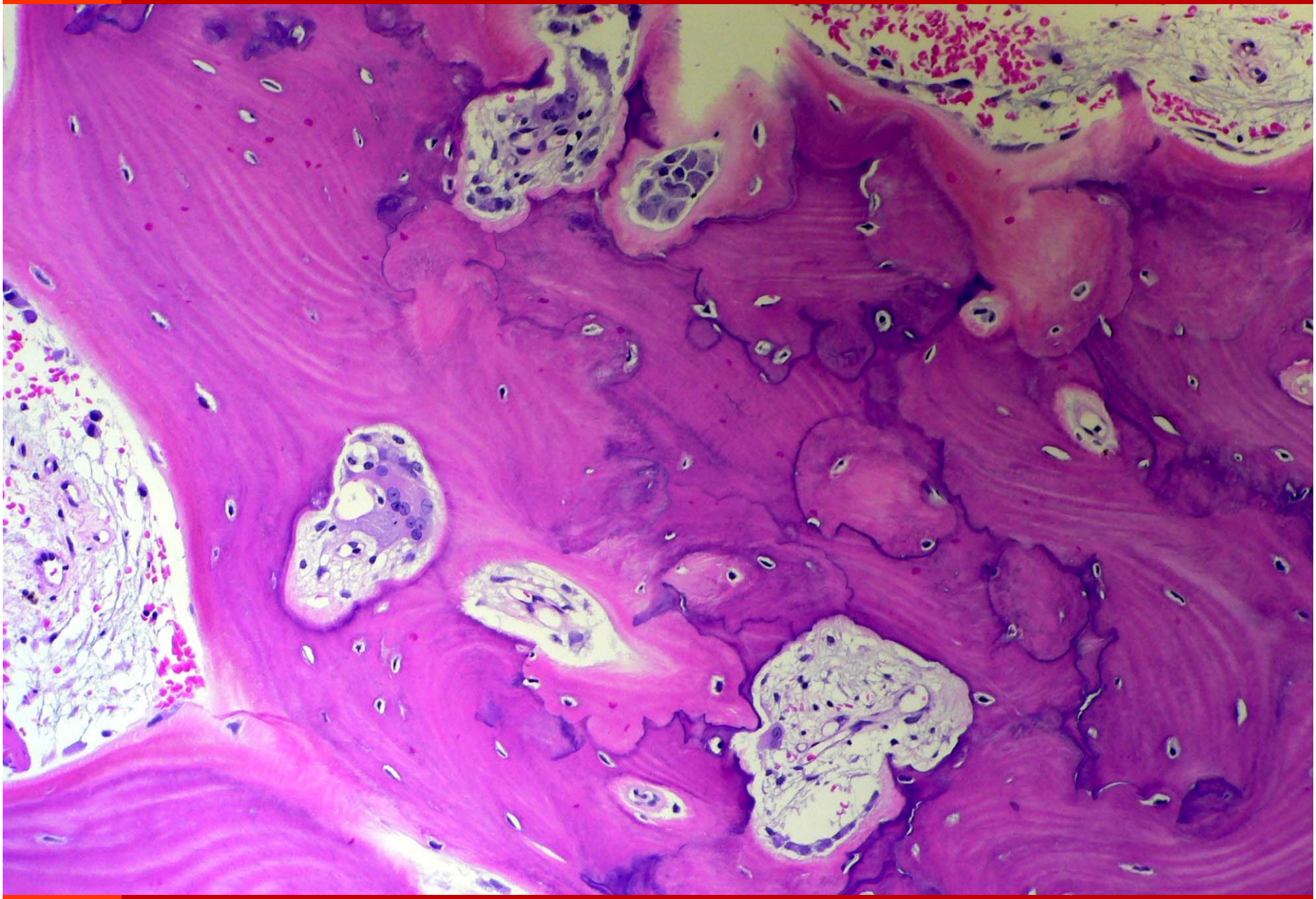


- thicker sclerotic trabeculae with disordered apposition
- woven bone becoming lamellar, vascular stroma

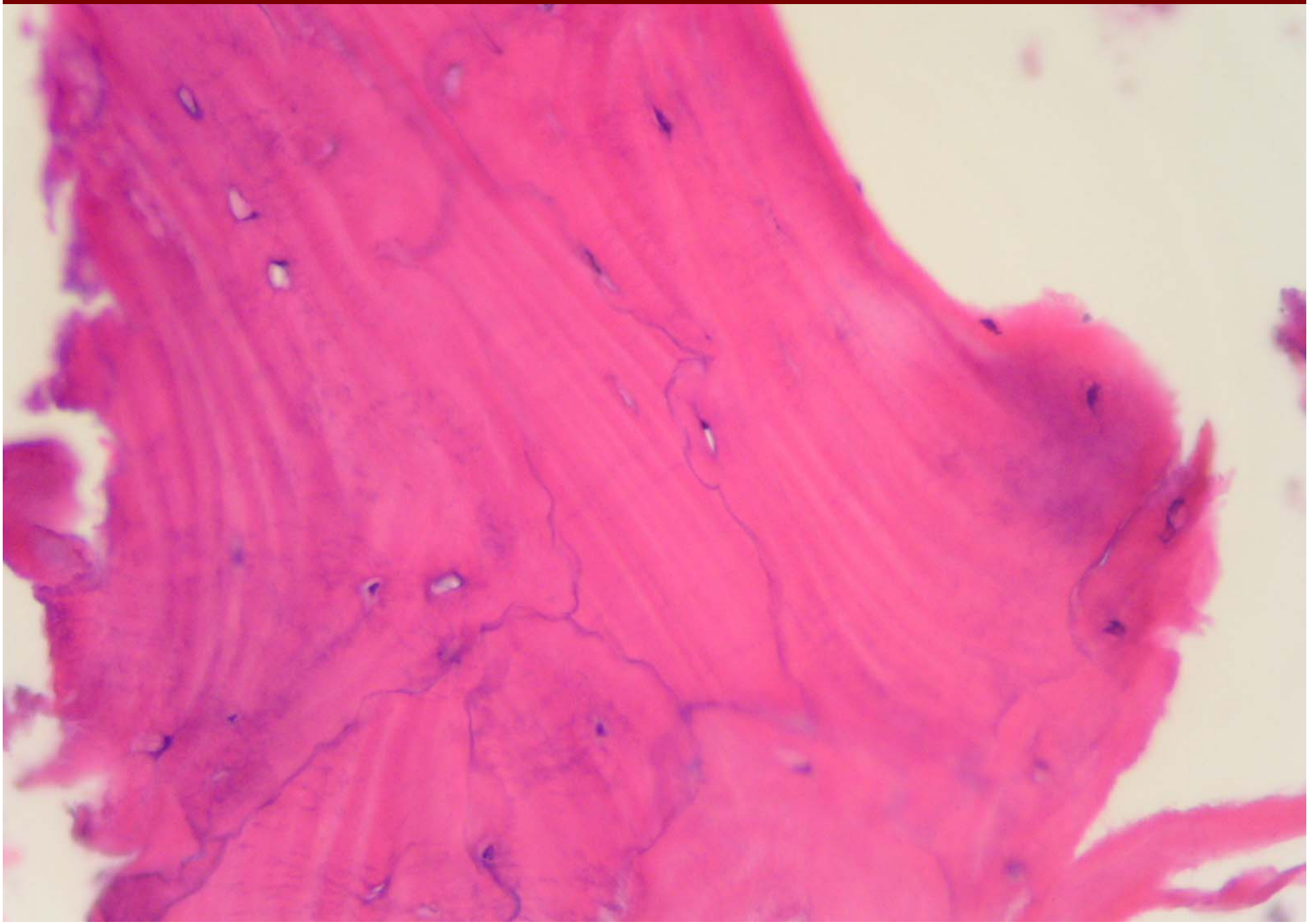




➢ characteristic diagnostic features

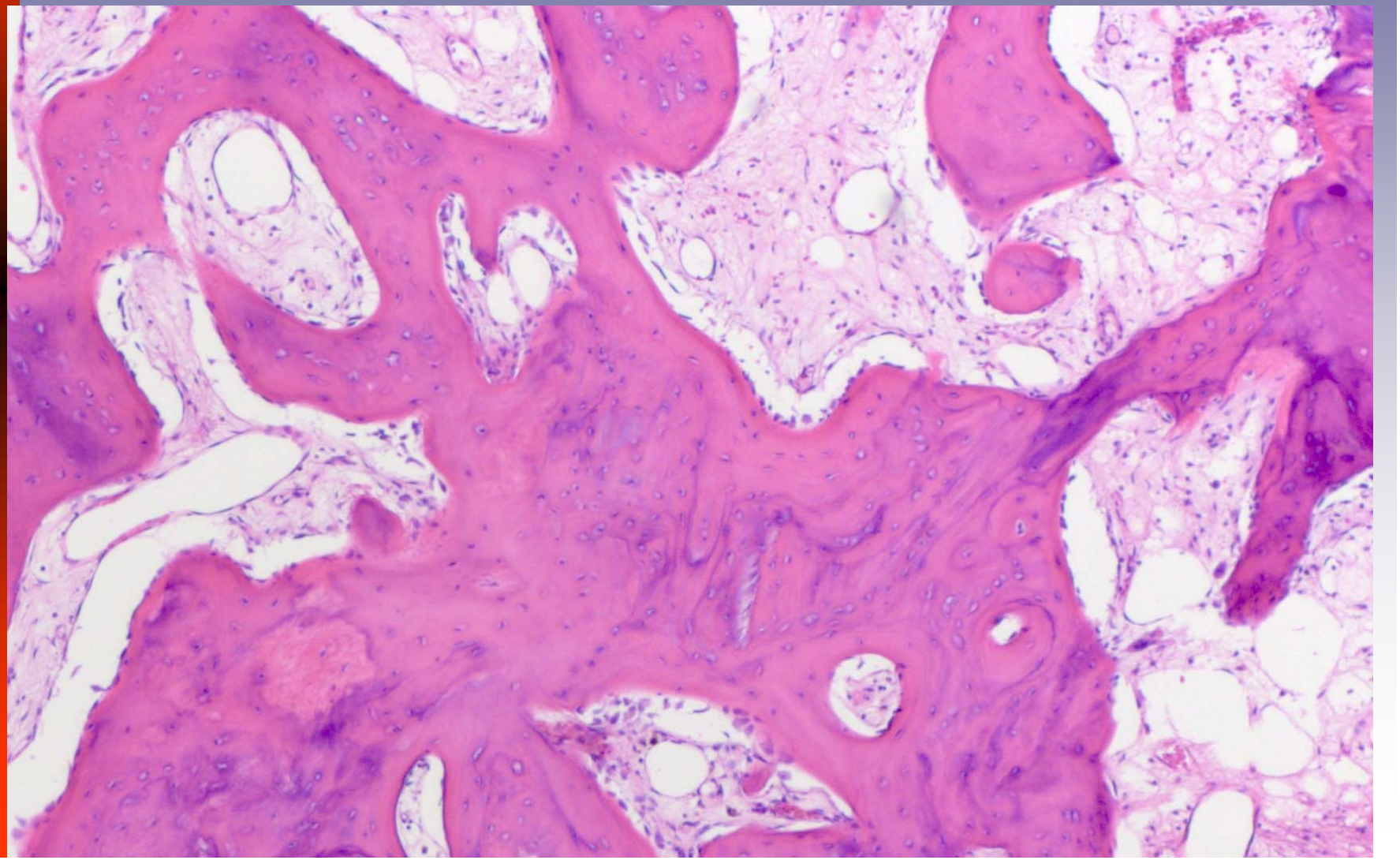


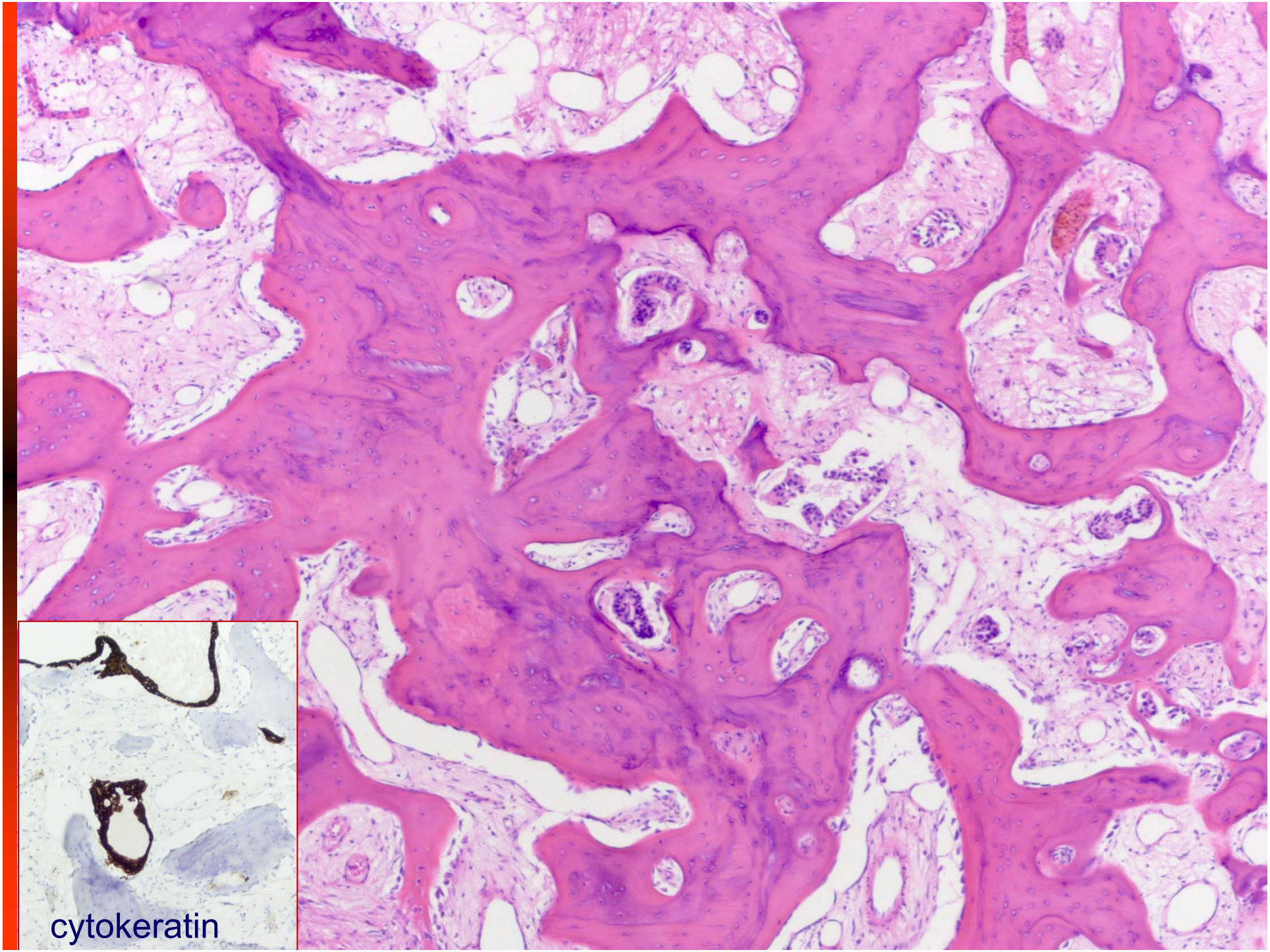
inactive Paget…mosaic pattern may be the only clue



➢ differential diagnosis in biopsies

- metastatic carcinoma (breast, prostate)



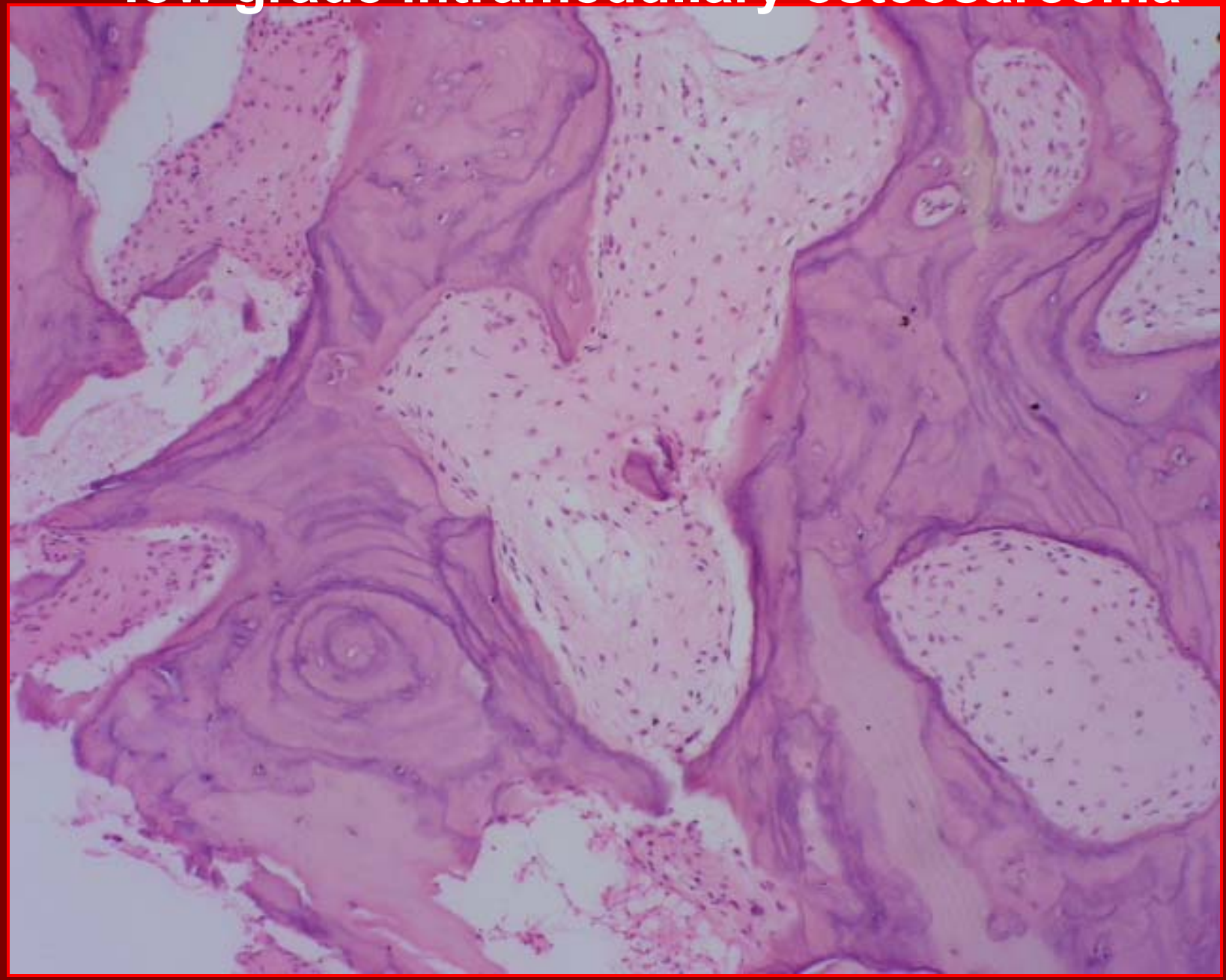

cytokeratin

Paget disease

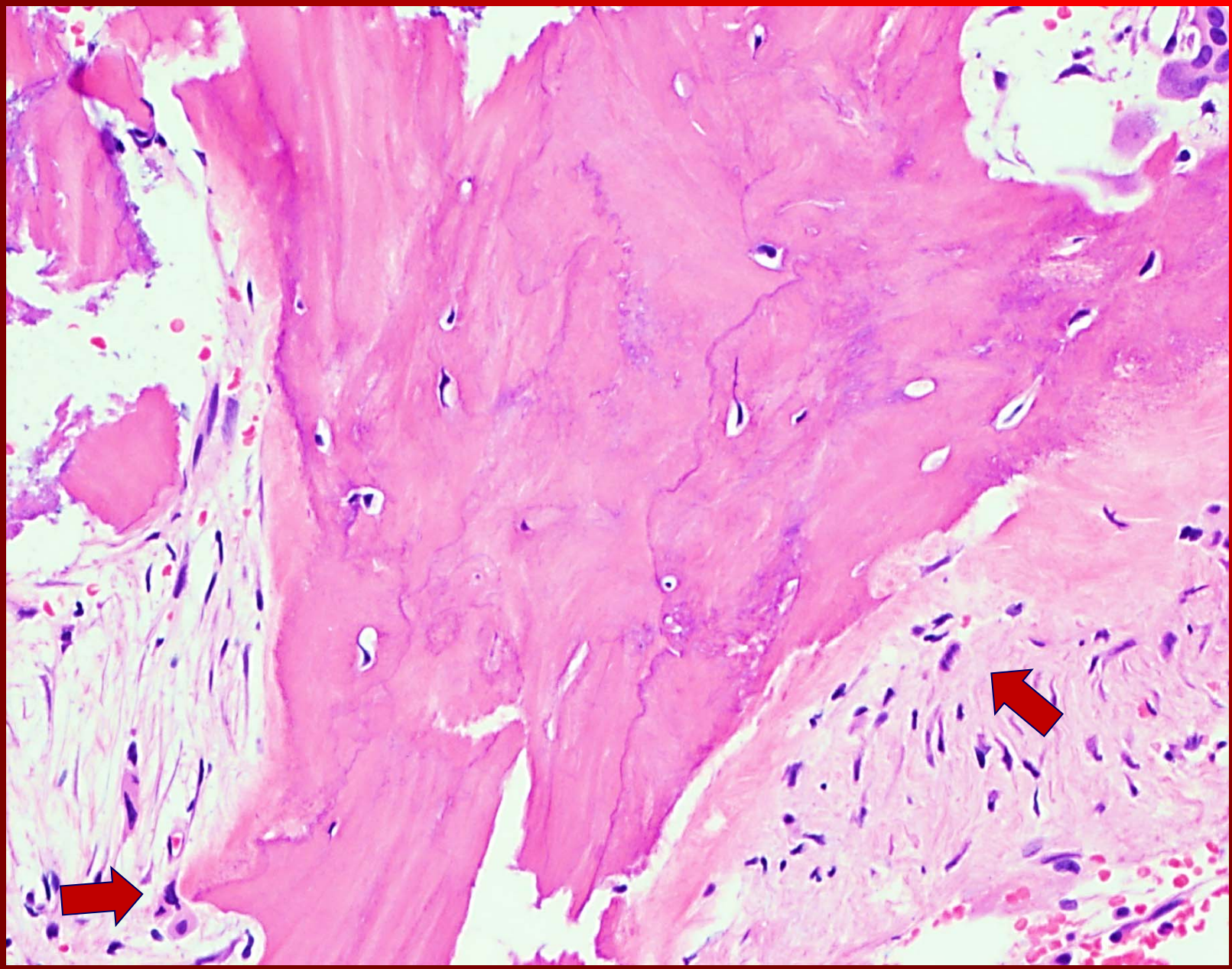
differential diagnosis in biopsies

- **metastases (carcinoma, melanoma)**
- **angiomatous lesions (common in spine)**
- **myelofibrosis…CD61**
- **mastocytosis…MCT**
  - **sclerosis in BNCT (in spine)**
  - **intraosseous hibernoma (axial skeleton)**
  - **bisphosphonate associated lesions (jaw)**
  - **low grade intramedullary osteosarcoma (any)**
- **hyperparathyroidism**

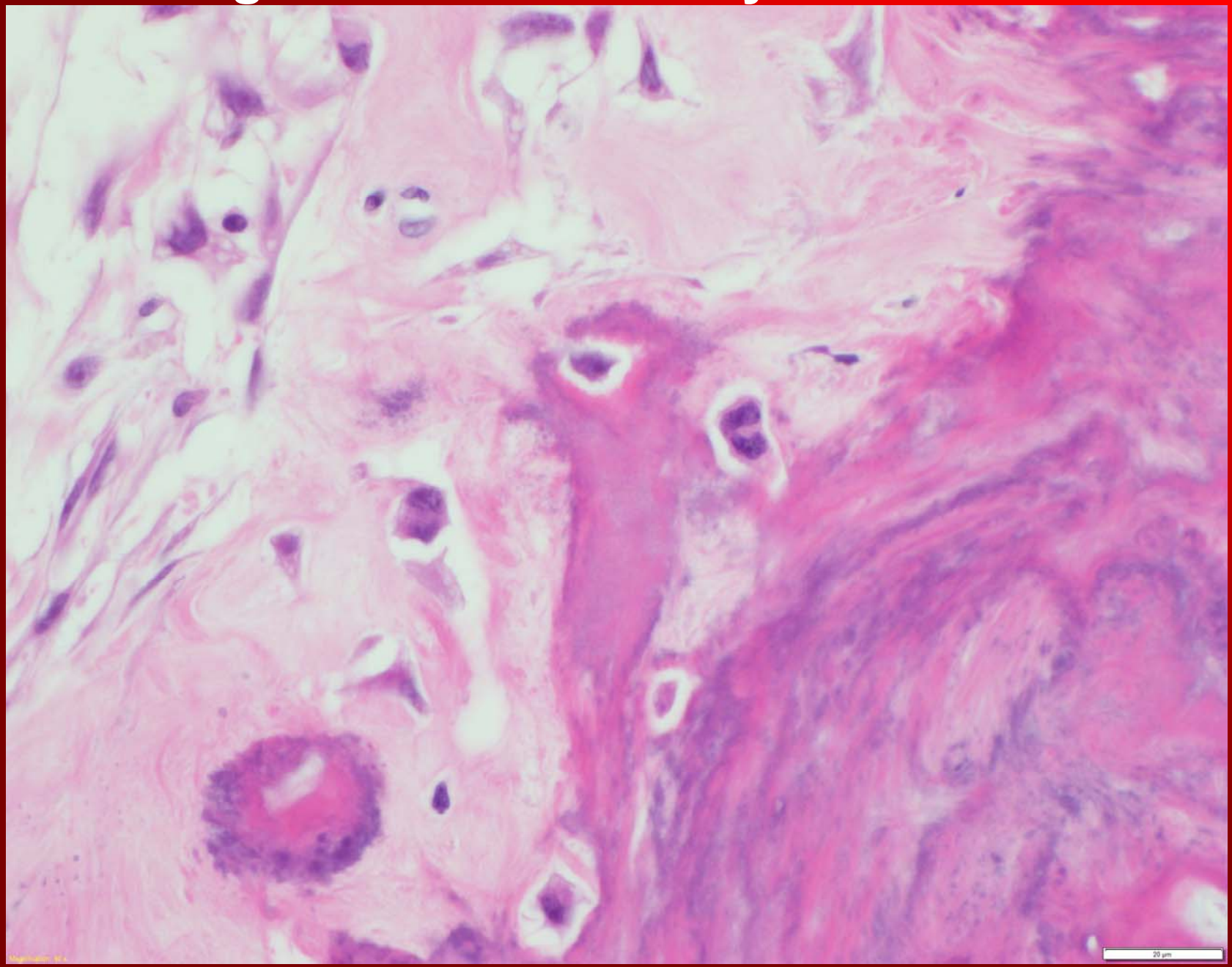
low grade intramedullary osteosarcoma



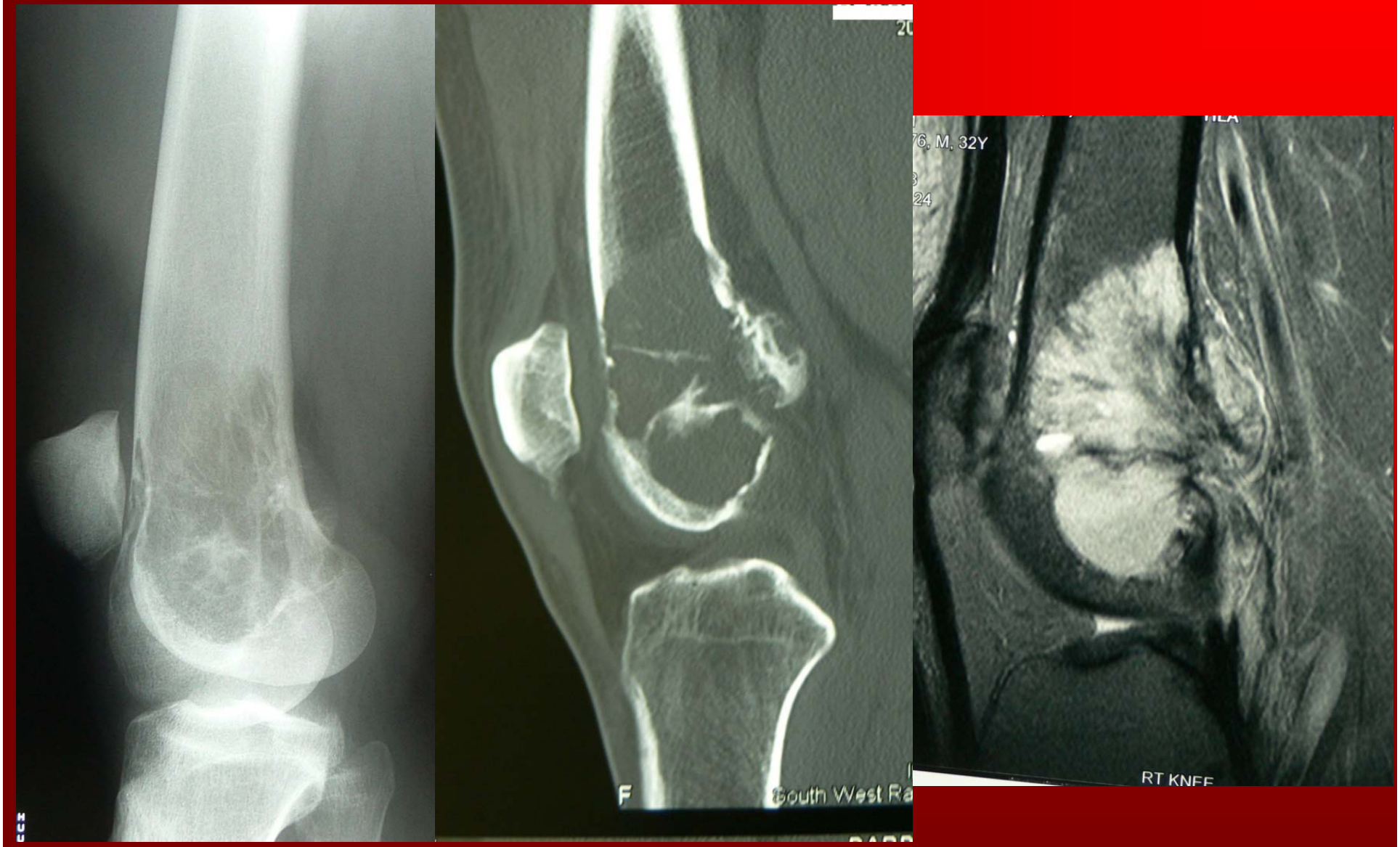
low grade intramedullary osteosarcoma



low grade intramedullary osteosarcoma

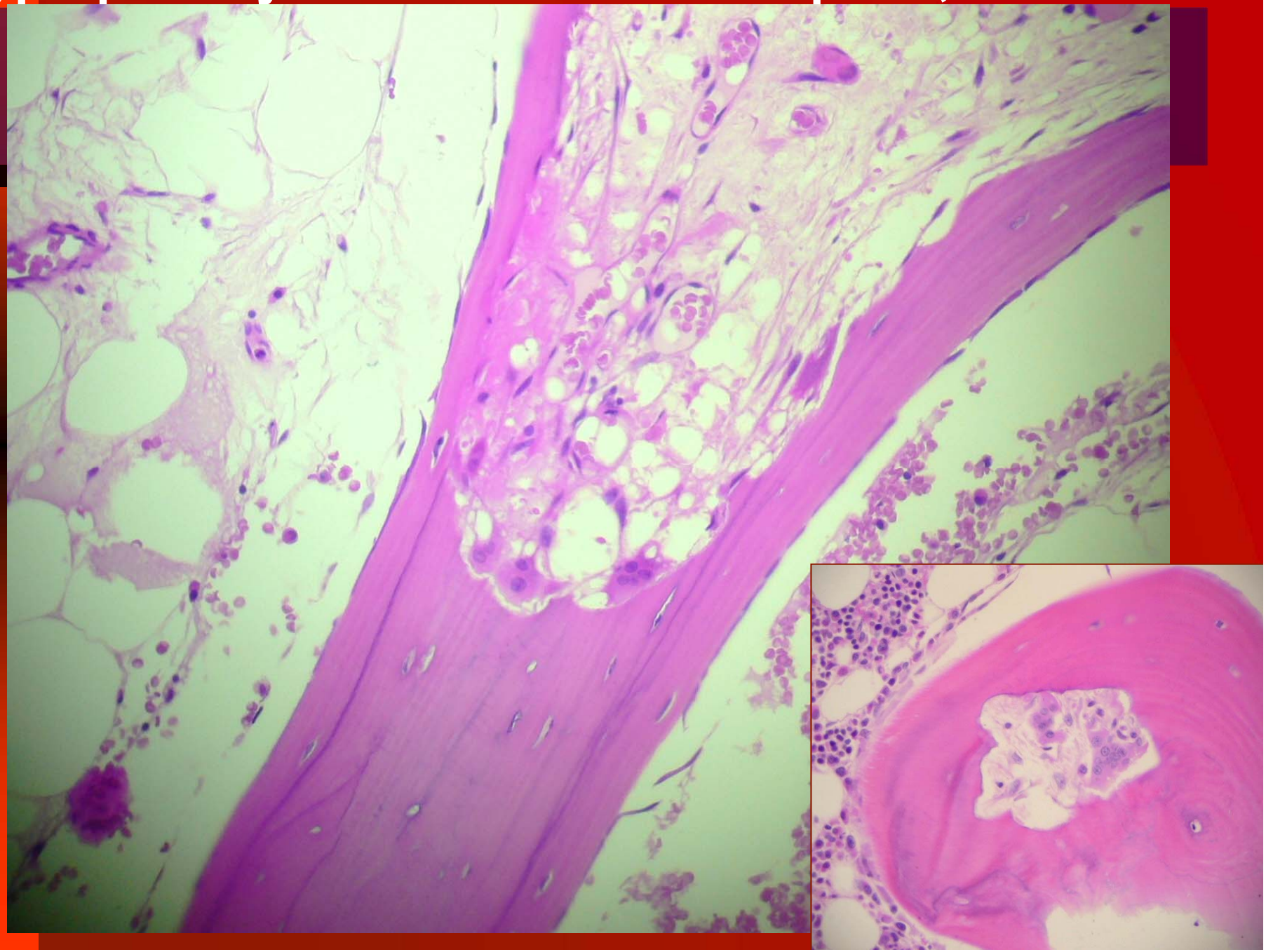


low grade intramedullary osteosarcoma

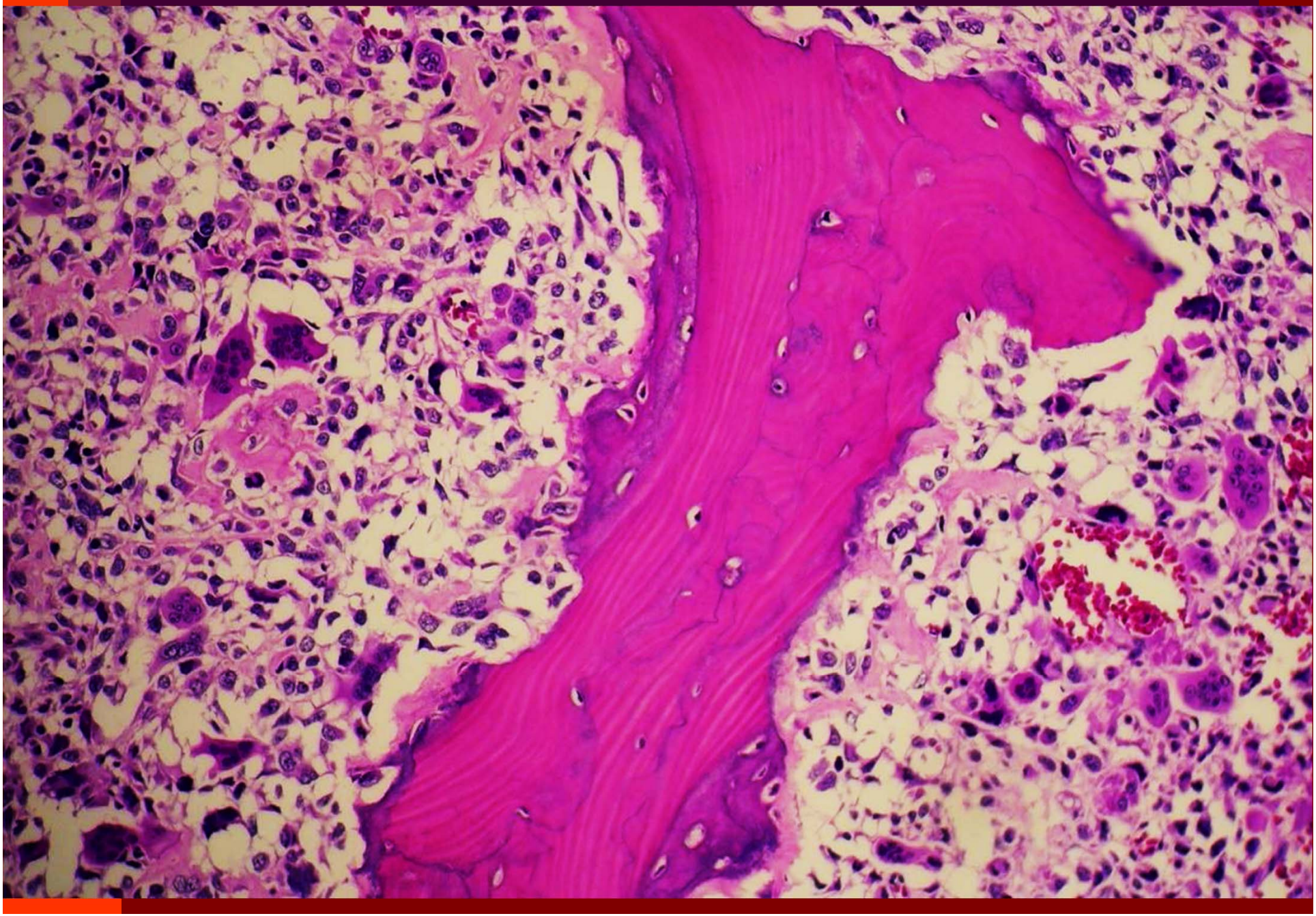


imaging features favouring a tumour

Hyperparathyroidism: tunnel resorption, fibrosis



Paget sarcoma : consider in all bone sarcomas over age 40



Osteoclasts ➢ bone resorption

derived from monocytes/macrophages

Monocyte ← Transcription factors PUI

↓ CSF 1*

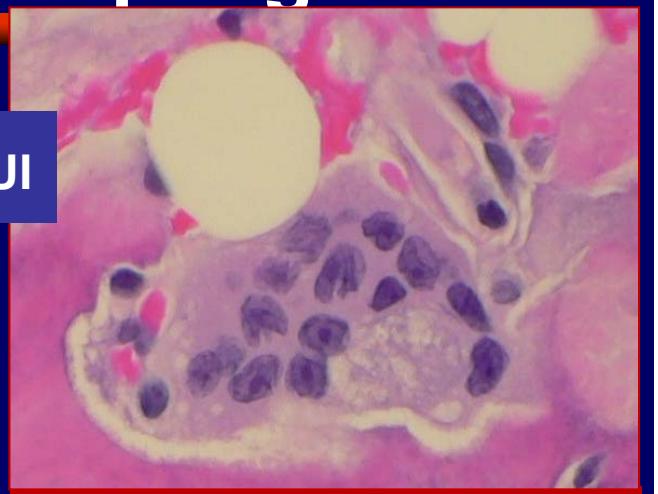
Preosteoclast ← Differentiation

↓

- RANK L* ← NFATc1
- cfos
- NFκB

↓

Osteoclast



SQSTM1
(Sequestrome 1 / P62)
important protein in this axis

Paget disease: pathogenesis

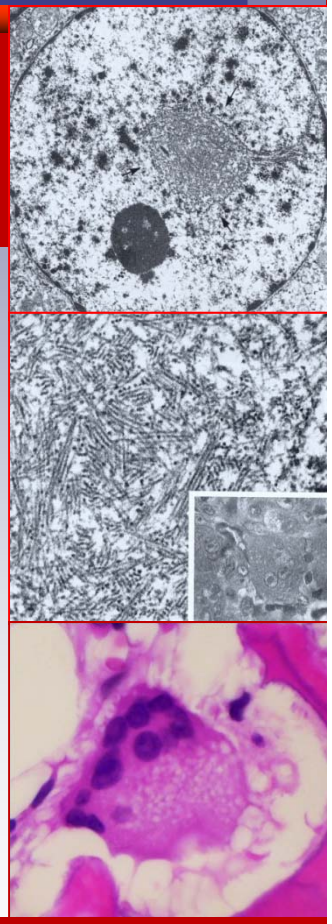
- genetic associations
  - family history : autosomal dominant incomplete penetrance
  - SQSTM1 gene mutations: most ubiquitin binding domain
    - 50% familial Paget disease
  - protein product P62 (sequestrome 1)
    - affects regulation of RANKL mediated activation of NF κB
  - some genotype phenotype relationship
  - severity diminishing despite mutations
- not all people with mutations get Paget disease

Paget's disease: pathogenesis

Roodman GD Ann NYAcad Sci 2010 1192"176-180
Ralston SH Calcif Tissue Int 2012;91:97-113
Ralston SH NEJM 2013;368:644-50
Vallet M, Ralston SH J Cell Biochem 2016;117:289-299

intracytoplasmic inclusions ....postulating a viral cause : evidence conflicting and controversial:

- **likely reflect dysfunctional osteoclasts**
- **similar inclusions in**
  - **osteopetrosis**
  - **hereditary oxalosis**
  - **familial expansile osteolysis (RANKL mutations)**
  - **mice with SQSTM1 mutations**



? due to undegraded protein aggregates

? due to dysregulation of protein autophagy (p62)

Paget's disease: pathogenesis

? genetics
? environment
? both

Environmental associations: factors suggested

- low dietary calcium
- vitamin D deficiency
- environmental toxins (wood fired heating, mining)
- ★ rural vs urban living
  - exposure to cattle
  - dog ownership
    - canine distemper virus
- ★ trauma –repetitive mechanical loading of bones

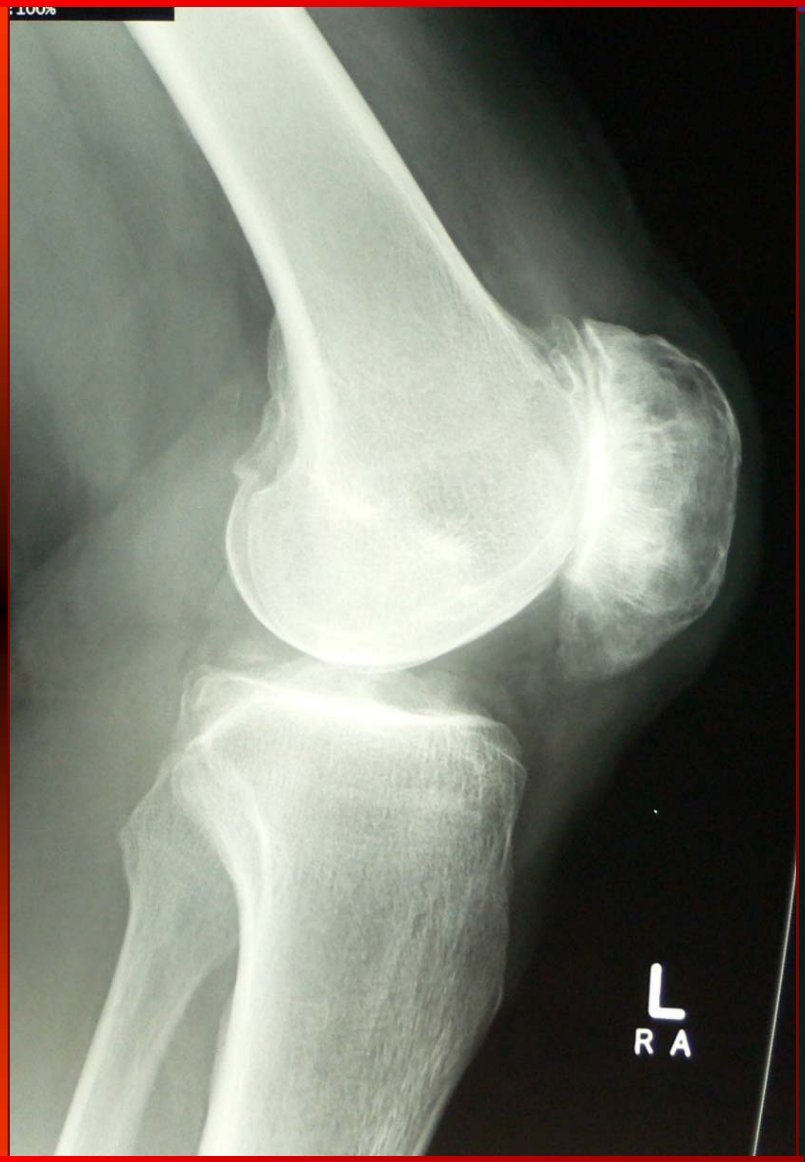
Paget disease: pathogenesis

- relationship to trauma often mooted
- never clarified……

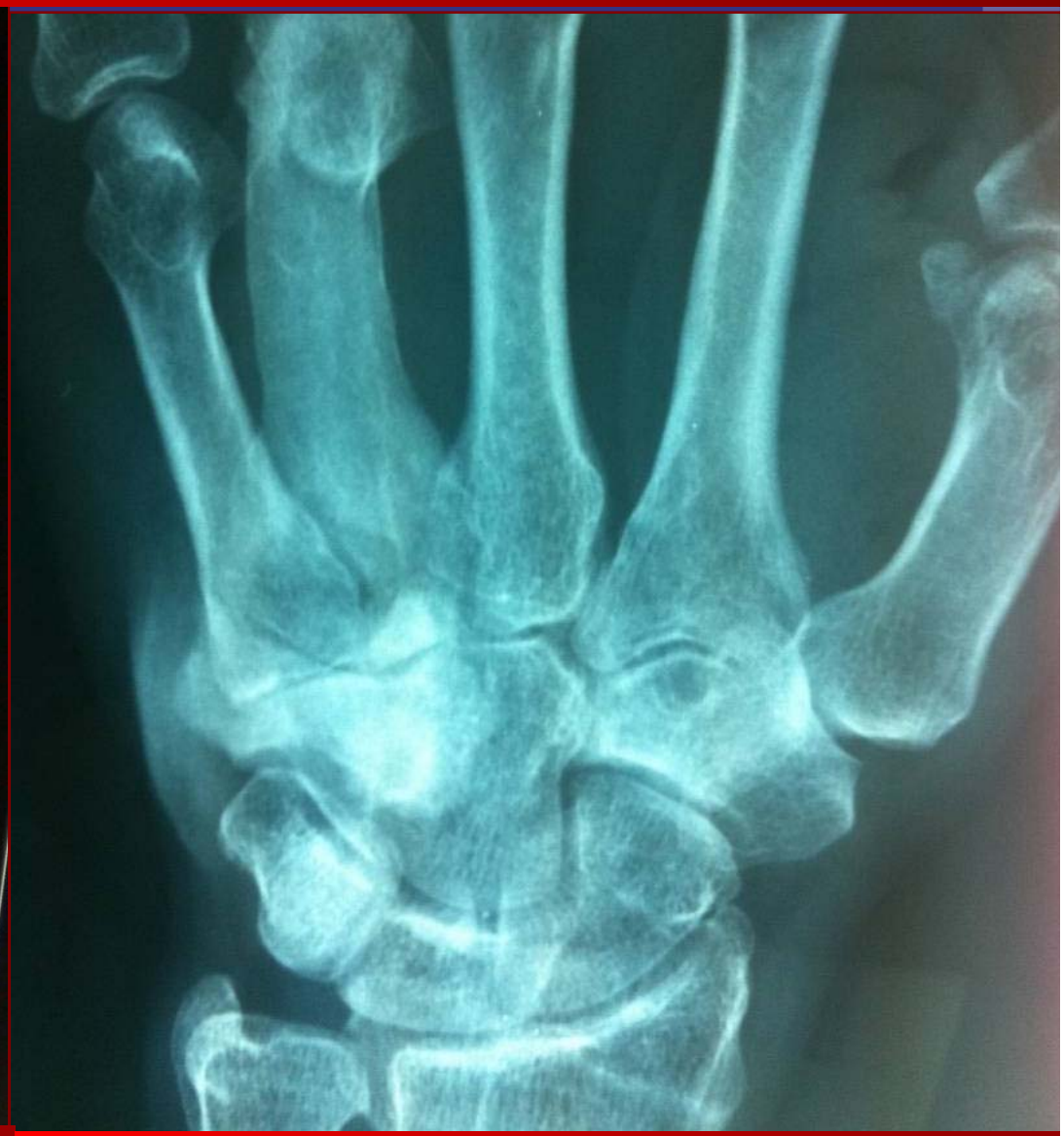
- Billiard players fingers: an unusual case of Paget disease of bone"
  - Solomon LR BMJ 1979 4:931
    - lower right radius
    - upper halves both humeri
    - 1st metacarpal right hand
    - proximal phalanges 2nd and 4th fingers left side
- Paget disease in a treadle machine operator
  - paddled with right foot from during first world war to early 1950"s
  - Gasper TM BMJ 1979 5:1217-8
    - right ilium
    - lower right femur
    - upper right tibia
  - Barry HC 1969: MJA
    - male patient with generalised Paget disease
    - spared a limb afflicted by polio!

- distribution disease correlated with the severity of mechanical forces applied in a repetitive manner

Exceedingly rare sites

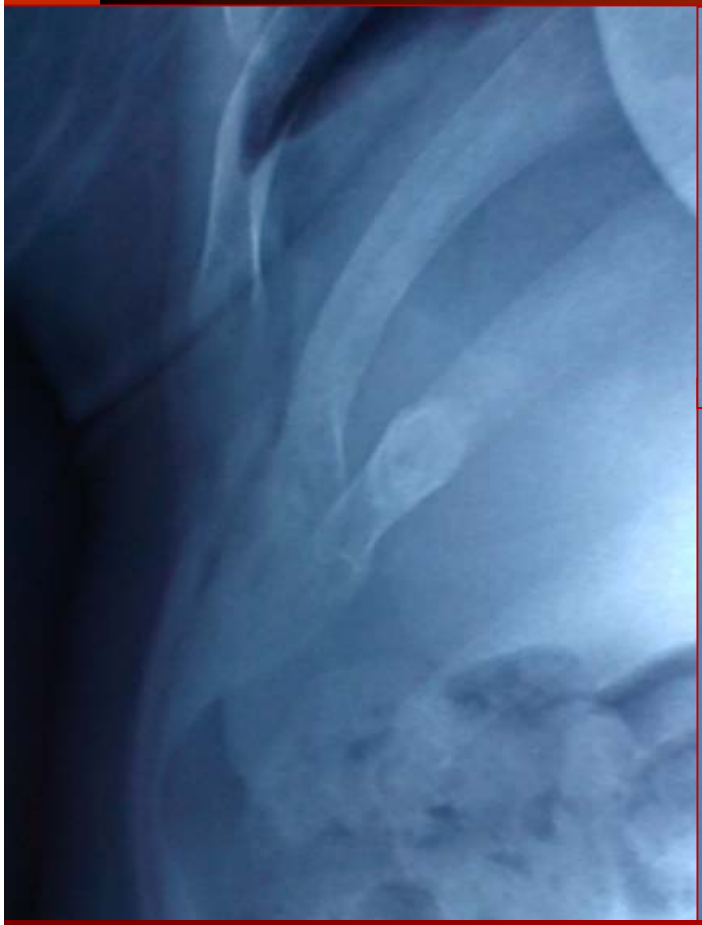


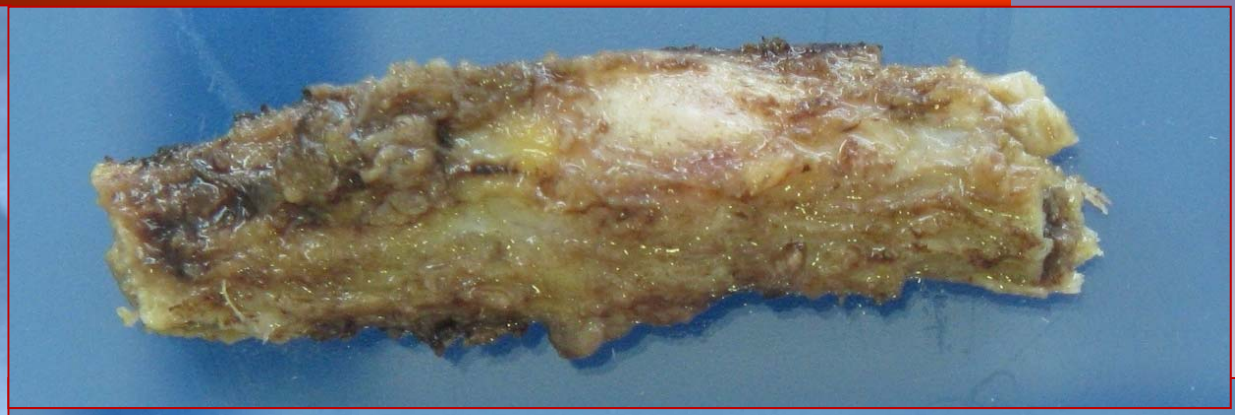
Patella
fracture 40 years prior



Metacarpal, hamate, trapezoid in saxophone player

Exceedingly rare sites



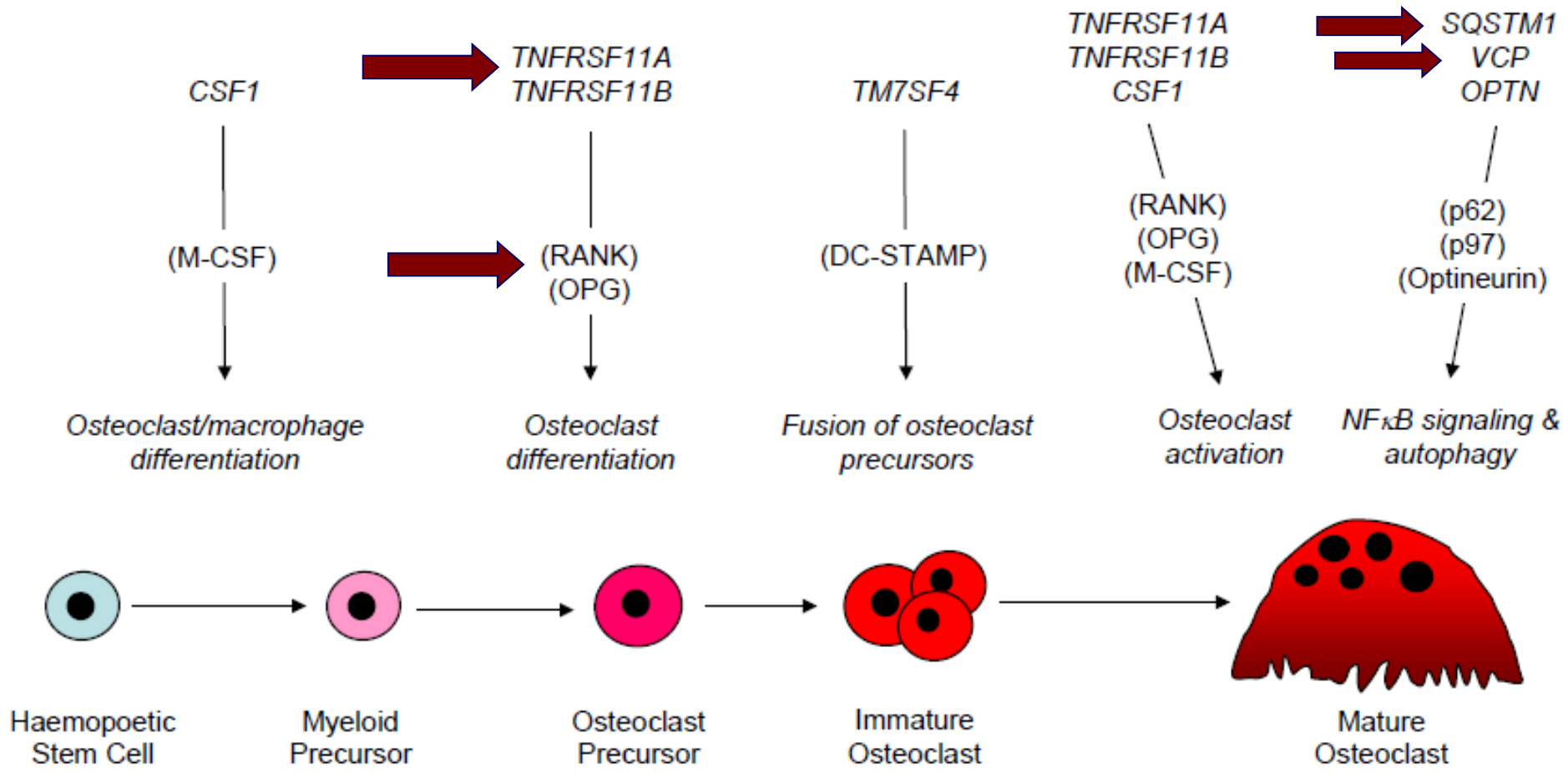


Female 63, chinese origin, fracture 8 years previously

Familial forms of PDB

Ralston SH. Paget's disease of bone. N Engl J Med 2013;368:644-50. DOI: 10.1056/NEJMcp1204713

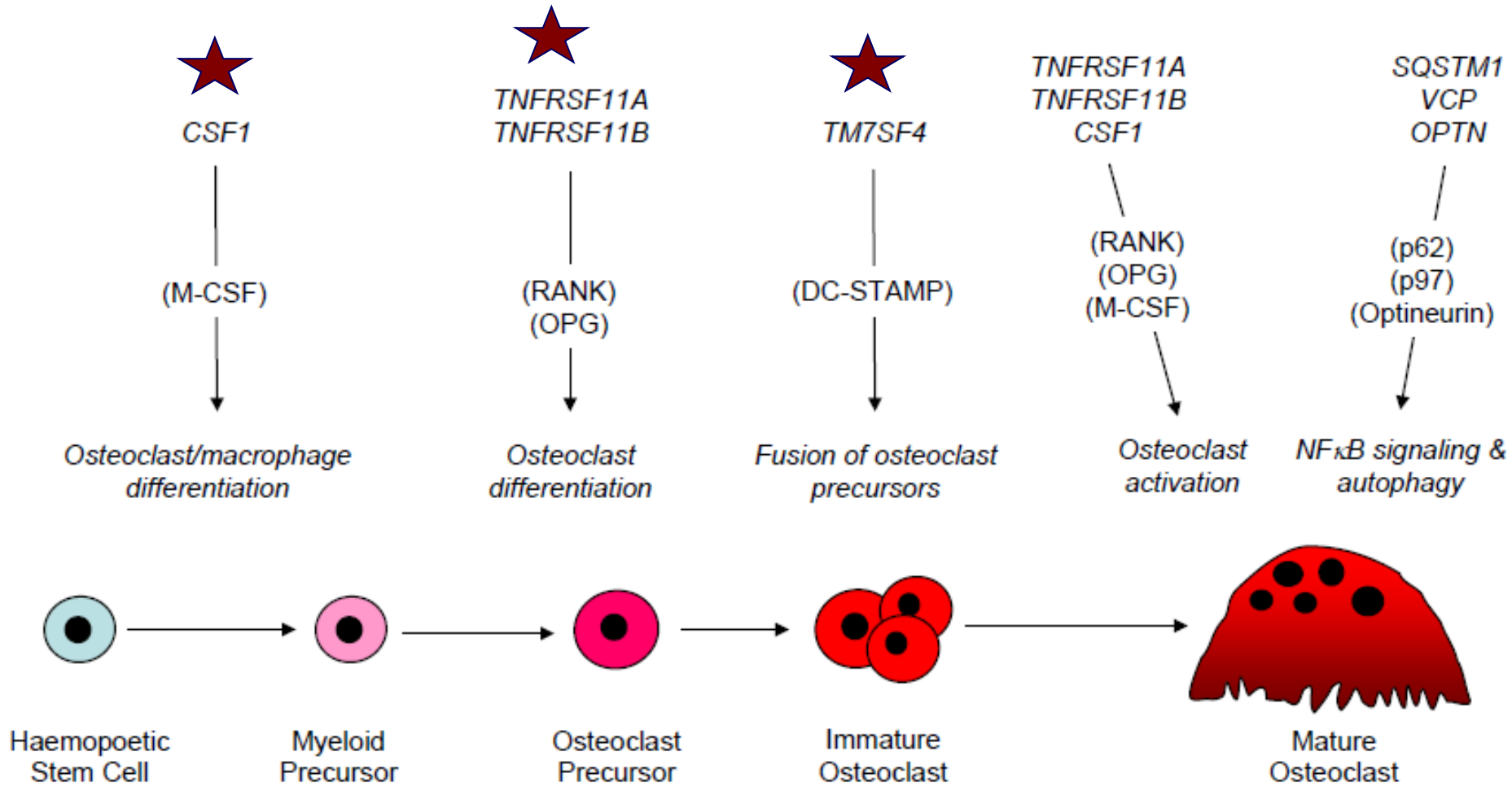
- **Familial expansile osteolysis (A,RANK)**
- **Juvenile Paget disease (B,OPG)**
- **Classical Paget (SQSTM1)**
- **Inclusion body myopathy (VCP)**



mutations in major transcription factors in osteoclast evolution and differentiation

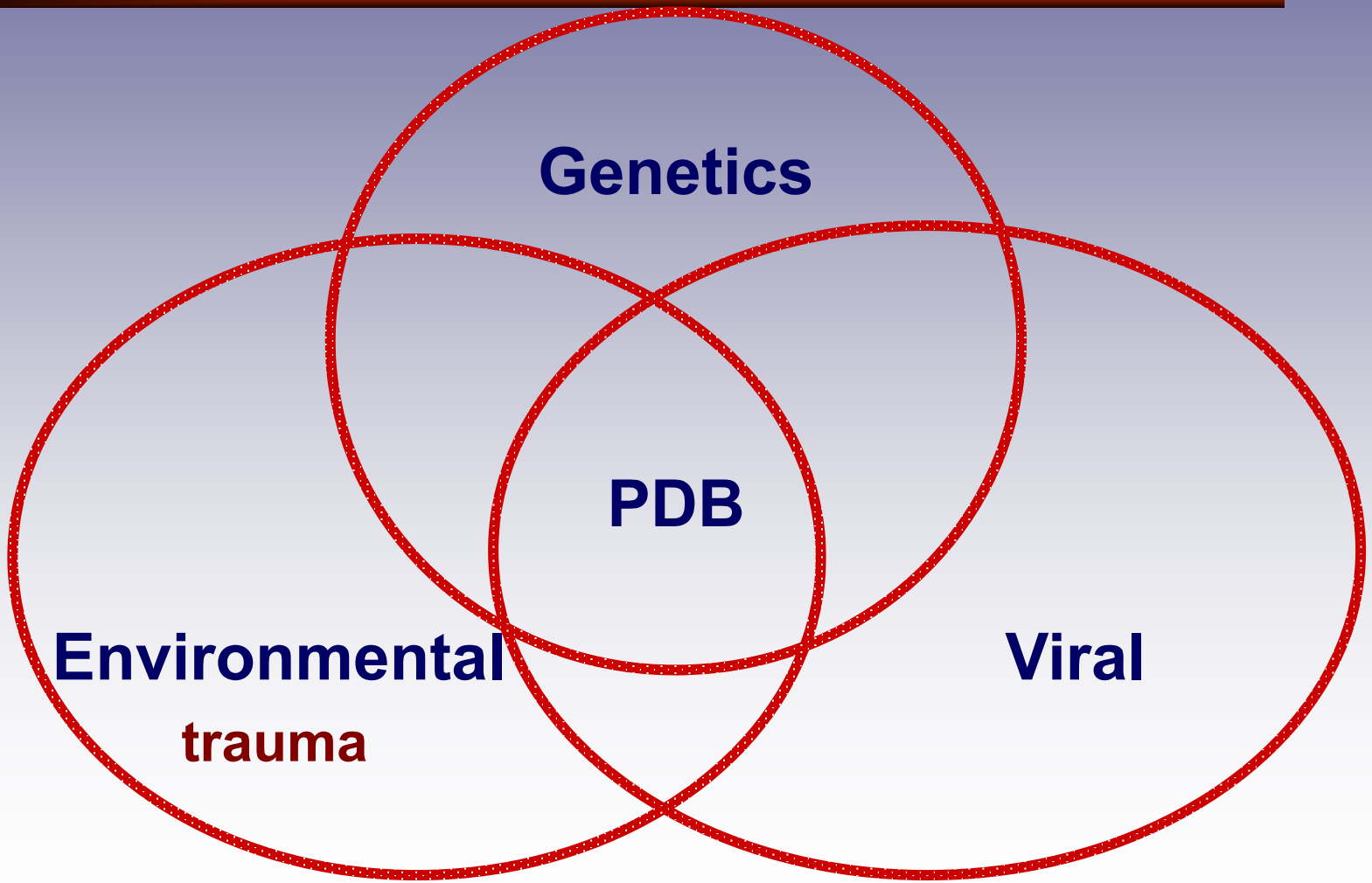
- variant mutations of these genes in adults
- individually no disease

↑ combinations cause increased risk PDB : dysregulation osteoclasts

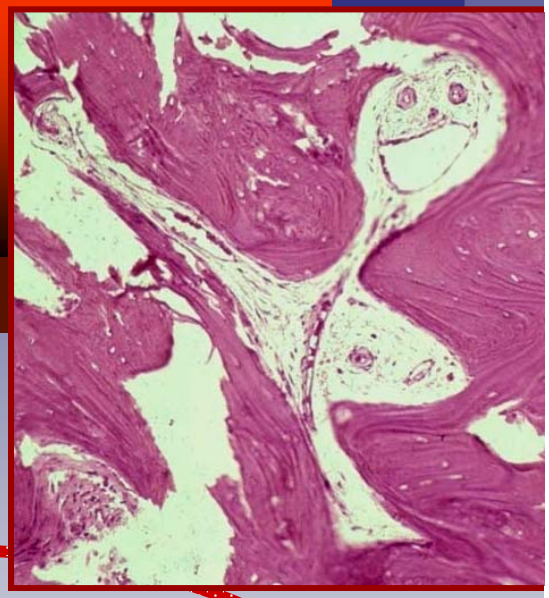


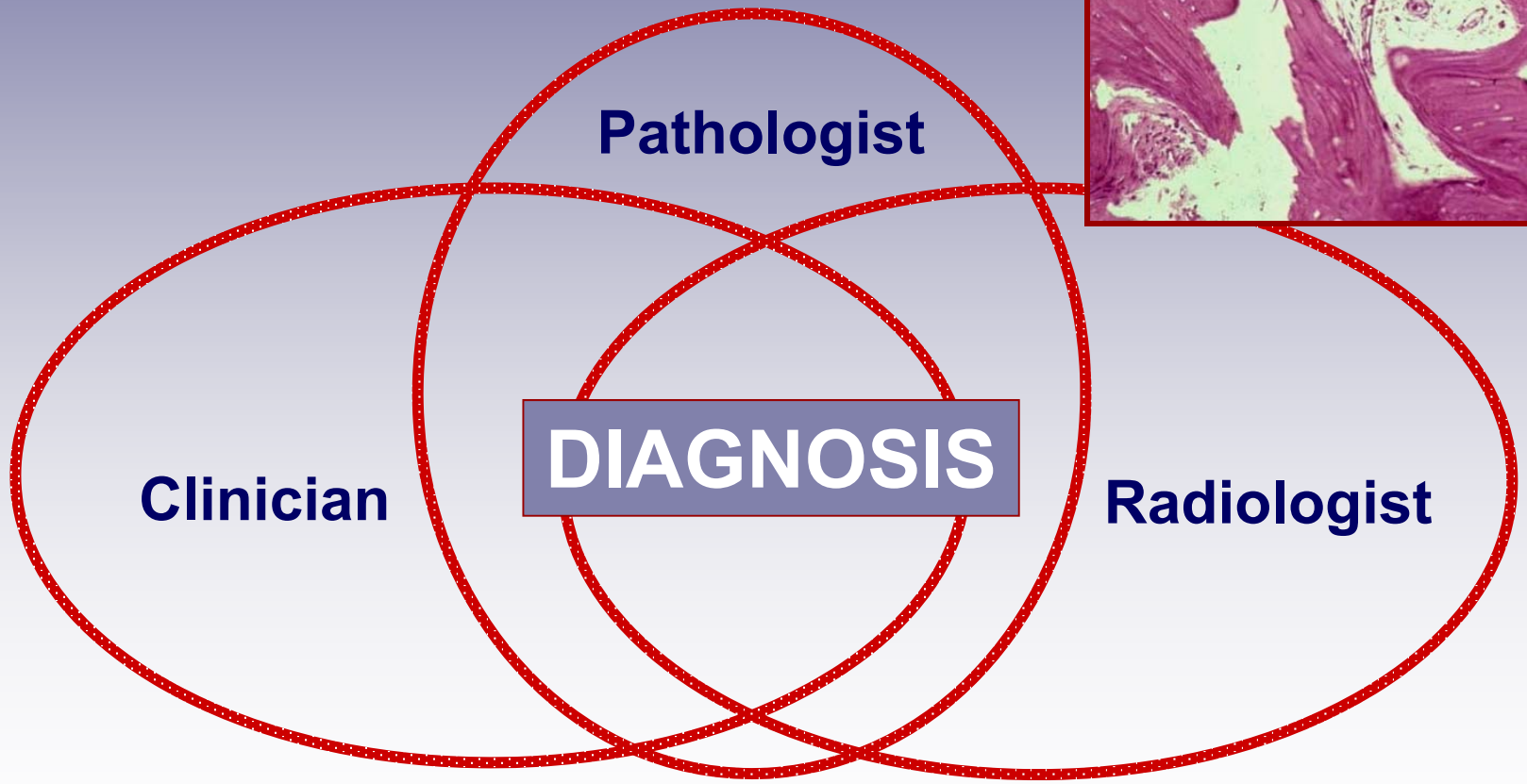
Ralston SH. Paget's disease of bone. N Engl J Med 2013;368:644-50. DOI: 10.1056/NEJMcp1204713

Pathogenesis



Disorders of Bone





- collaboration is essential

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- J Soper, W Brown, J Schatz (radiologists)