

V2

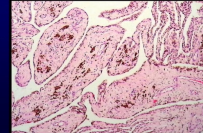
-In slide no. 40:

- T(1;2)(p13q;37); affecting type **VI** collagen α - 3.

** (type **6** collagen, not type **4**)

TENOSYNOVIAL GIANT CELL TUMOR:

- Benign neoplasm of synovium
- Diffuse (pigmented villonodular synovitis, PVNS, large joints) or localized small hands tendons
- T(1;2)(p13q;37); affecting type **VI** collagen α -
3



Lecture

6

GIANT CELL TUMOR OF BONE:

- Locally aggressive neoplasm of adults.
- Epiphyses of long bones
- Osteoclast-like giant cells
- Rare malignant behavior
- Cells contain high levels of RANKL
- Trx: curetting

Giant cell tumors often destroy the overlying cortex, producing a bulging soft tissue mass delineated by a thin shell of reactive bone (Fig. 21.25). Grossly, they are red-brown masses that frequently undergo cystic degeneration. Microscopically, the tumor conspicuously lacks bone or cartilage, consisting of numerous osteoclast-type giant cells with 100 or more nuclei with uniform, oval mononuclear tumor cells in between (Fig. 21.26).



FIG. 21.25 Radiographically, giant cell tumor of the proximal fibula is predomi...

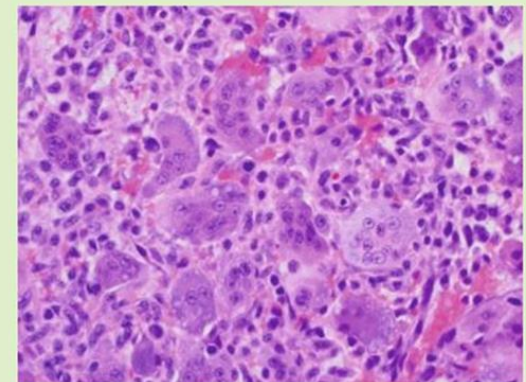
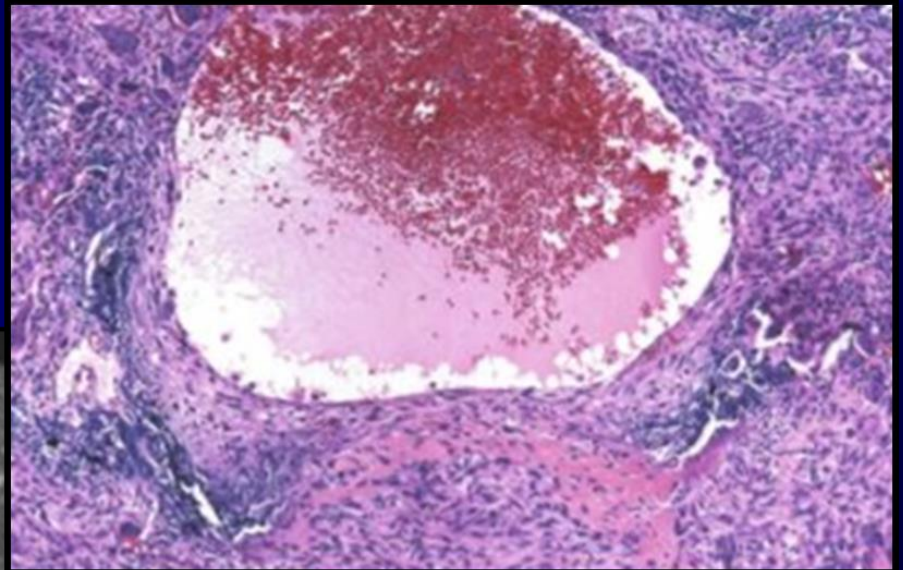
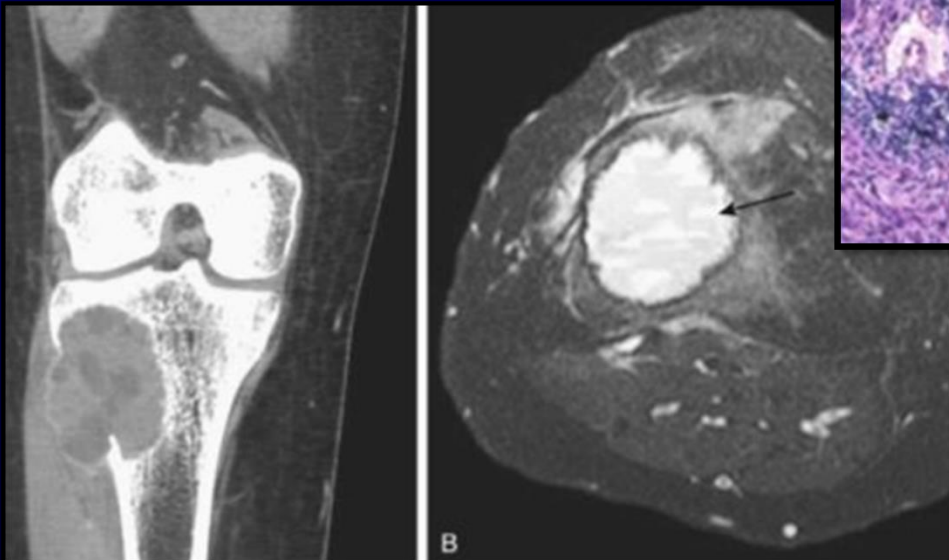


FIG. 21.26 Giant cell tumor illustrating an abundance of multinucleated giant c...

ANEURYSMAL BONE CYST:

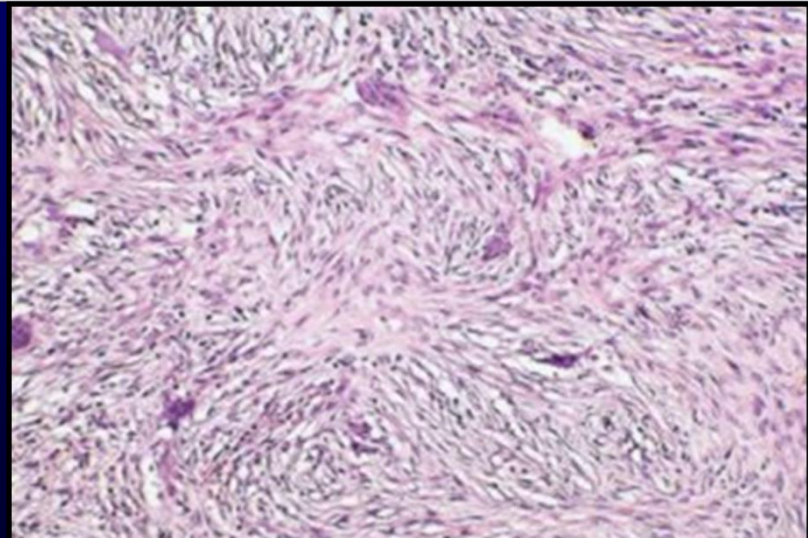
CYST:

- Benign tumor
- Blood filled cyst
- Metaphysis of long bones; adults



NONOSSIFYING FIBROMA:

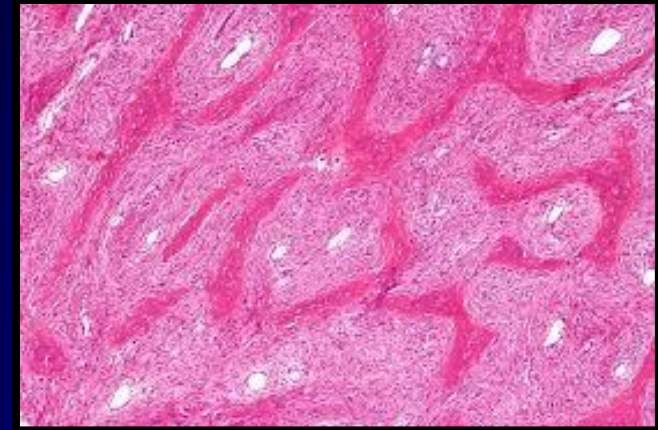
- **Benign lesion, maybe reactive not a true neoplasm (other names: FCD, MFD)**
- **Metaphysis**
- **Histology: bland fibroblastic proliferation**
- **May resolve spontaneously**



FIBROUS DYSPLASIA (FD):

- **Not a real tumor; rather a developmental abnormality of bone genesis due to mutations in GNAS1 gene (cAMP mediated osteoblast differentiation).**
- **Forms of FD:**
 - **Monostotic: affecting one bone**
 - **Polystotic: multiple bones**
 - **Mazabraud syndrome: FD + soft tissue myxoma**
 - **McCune-Albright syndrome: polystotic FD + café-au-lait skin pigmentation + endocrine abnormalities (precocious puberty)**

McCUNE-ALBRIGHT SYNDROME:



METASTATIC TUMORS TO BONE:

- **Much more common than primary bone tumors**
- **In adults: most are carcinomas; lung, prostate, breast, kidney, thyroid & liver**
- **In children: Neuroblastoma, Wilms tumor and rhabdomyosarcoma**
- **Usually multiple and axial; mostly hematogenous spread.**
- **Lytic, blastic or mixed (via mediators secretions)**

BLASTIC METASTASIS



LYTIC METASTASIS





Summary

Bone Tumors and Tumorlike Lesions

Primary bone tumors are classified according to the cell of origin or the matrix that they produce. The remainder is grouped according to clinicopathologic features. Most primary bone tumors are benign. Metastases, especially from lung, prostate, kidneys, and breast, are far more common than primary bone neoplasms.

Major categories of primary bone tumors include

- **Bone forming:** Osteblastoma and osteoid osteoma consist of benign osteoblasts that synthesize osteoid. Osteosarcoma is an aggressive tumor of malignant osteoblasts, predominantly occurring in adolescents.
- **Cartilage forming:** Osteochondroma is an exostosis with a cartilage cap. Sporadic and syndromic forms arise from mutations in the *EXT* genes. Chondromas are benign tumors producing hyaline cartilage, usually arising in the digits. Chondrosarcomas are malignant tumors of chondroid cells that involve the axial skeleton in adults.
- **Ewing sarcomas** are aggressive, malignant, small round cell tumors most often associated with t(11;22).
- **Fibrous dysplasia** is an example of a disorder caused by gain-of-function mutations that occur during development.

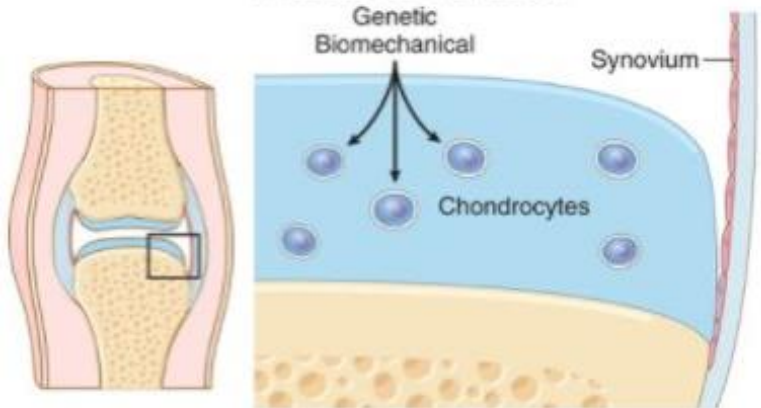
JOINTS (BASIC KNOWLEDGE):

- **Provide motion & stability to our skeleton**
- **Synovial (cavitated): synovial joints, wide motion (knee, elbow...)**
- **Non synovial (solid): synarthrosis, minimal movement (skull, sternum...)**
- **Synovial joints covered by hyaline cartilage (70% water, 10% type II collagen, 8% proteoglycans + chondrocytes)**
- **Synovial membrane contains: A synoviocytes (diff. macrophages), and B synoviocytes fibroblast-like**
- **Synov membrane lacks basement membrane**
- **Hyaline cartilage: no blood supply, no nerves, no lymphatics (shock absorber)**

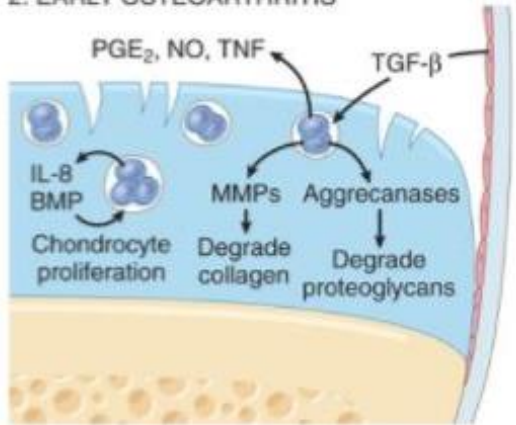
OSTEOARTHRITIS (DJD):

- **Degeneration of cartilage, not true – *ITIS***
- **Primary or idiopathic: aging process; few joints**
- **Secondary: due to pre existing diseases**
- **Insidious; increase with age (>50 yr); 40% of people > 70 years are affected**
- **Degeneration of cartilage >> repair and proliferation**

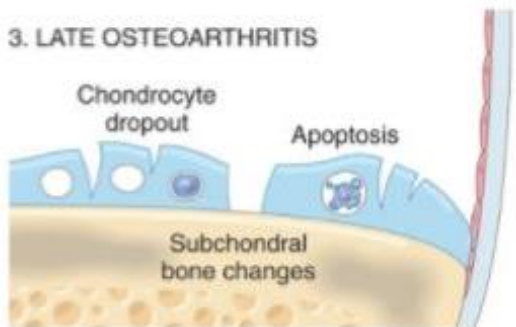
1. CHONDROCYTE INJURY



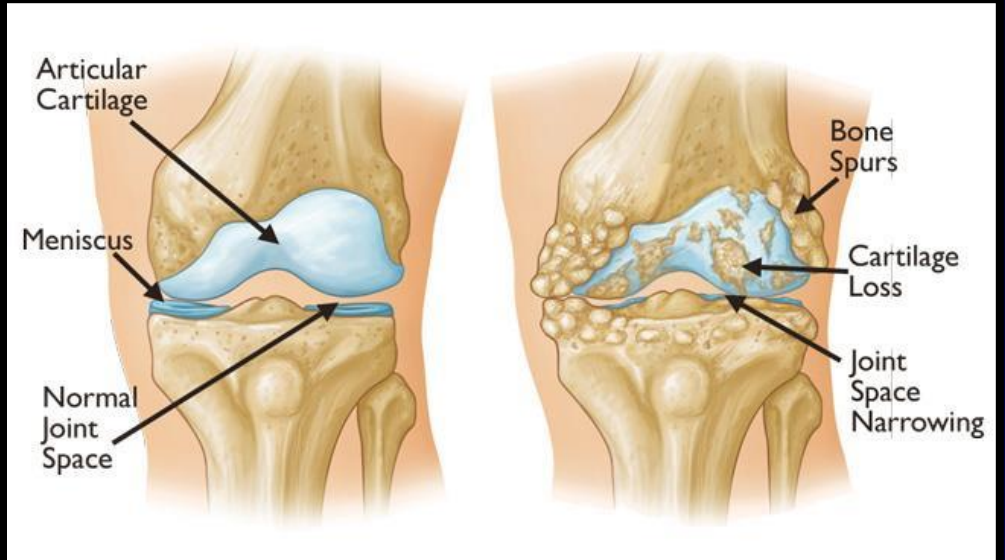
2. EARLY OSTEOARTHRITIS



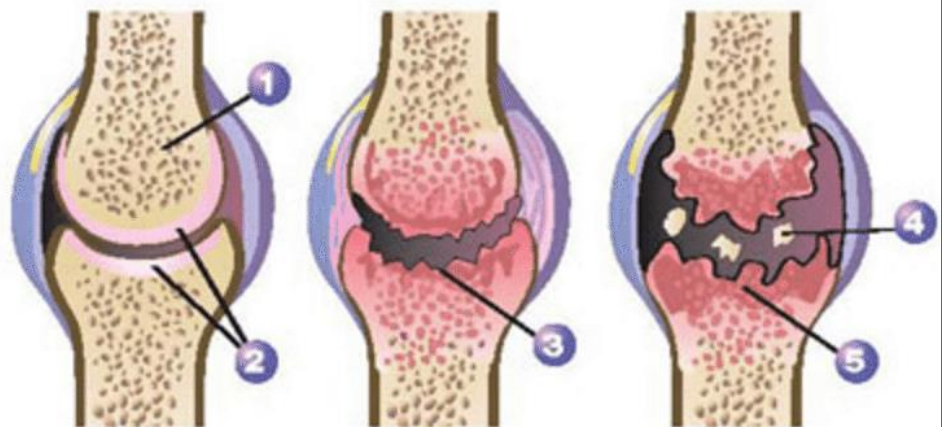
3. LATE OSTEOARTHRITIS



Schematic view of osteoarthritis (OA). OA is thought to be initiated



Evolution of Osteoarthritis



1. Bone

2. Cartilage

3. Thinning of cartilage

4. Cartilage remnants

5. Destruction of cartilage

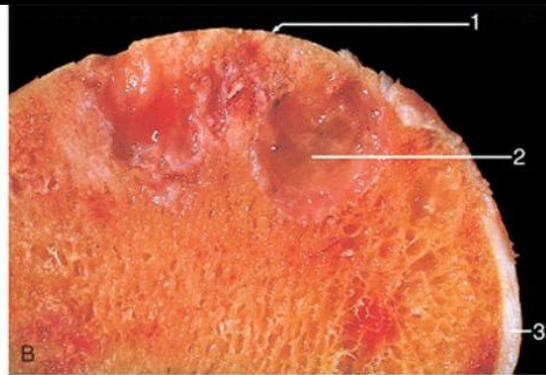
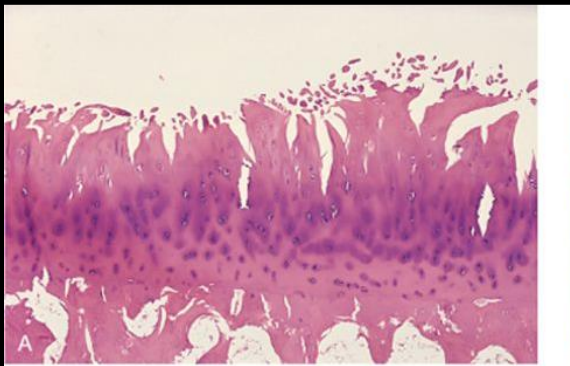
Normal Knee



Advanced Osteoarthritis (Grade III)



Very Advanced Osteoarthritis (Grade IV)



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- Osteoarthritis. **A**, Histologic demonstration of the characteristic fibrillation of the articular cartilage. **B**, Severe osteoarthritis with 1, Eburnated articular surface exposing subchondral bone. 2, Subchondral cyst. 3, Residual articular cartilage

OA (DJD)

CLINICALLY:

- **Joint pain worsens with use, morning stiffness, crepitus & range limitation, radicular pain, osteophytes impingement on vertebrae, muscle spasm & atrophy**
- **No magic preventive strategies (wt loss?)**
- **Trx: pain control, decrease inflammation (NSAIDs), intra-articular steroids, or joint replacement for severe cases**
- **Large health cost on countries**

Lecture

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RHEUMATOID ARTHRITIS:

- **Chronic inflammatory disease; autoimmune in nature; attacks joints with nonsuppurative proliferative and inflammatory synovitis; leading to destruction of joints and adhesions (ankylosis); systemic disease (skin, heart, vessels & lungs).**
- **1% prevalence in USA; F:M = 3:1; 4th-5th decade**
- **Genetic predisposition + environmental factors plays a role in the development, progression and chronicity of the disease**

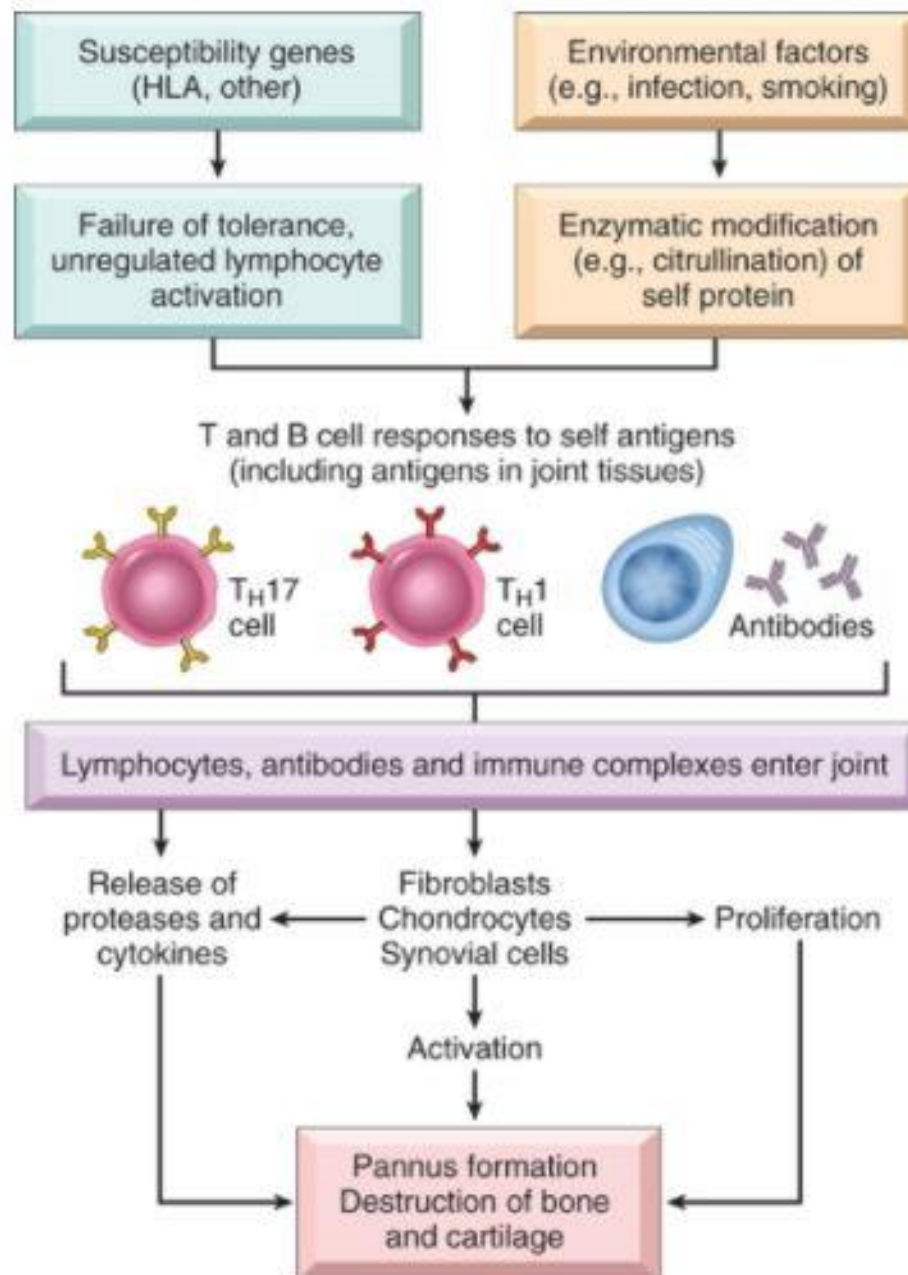


FIG. 21.36 Major processes involved in the pathogenesis of rheumatoid arthritis.

PATHOGENESIS:

IFN-γ from T _H 1	Activates macrophages & synovial cells
IL-17 from T _H 17	Recruits neutrophils and monocytes
RANKL from T cells	Stimulates osteoclasts & bone resorption
<u>TNF</u> & IL-1 from macrophages	Stimulates residents synoviocytes to secrete proteases that destroy hyaline cartilage

80% of patients with RA have autoantibodies IgG & IgM against the Fc portion of their own IgG [Rheumatoid factor]

70% of patients with RA have Anti-Citrullinated Protein Antibodies (ACPA)

OSTEOARTHRITIS

RHEUMATOID ARTHRITIS

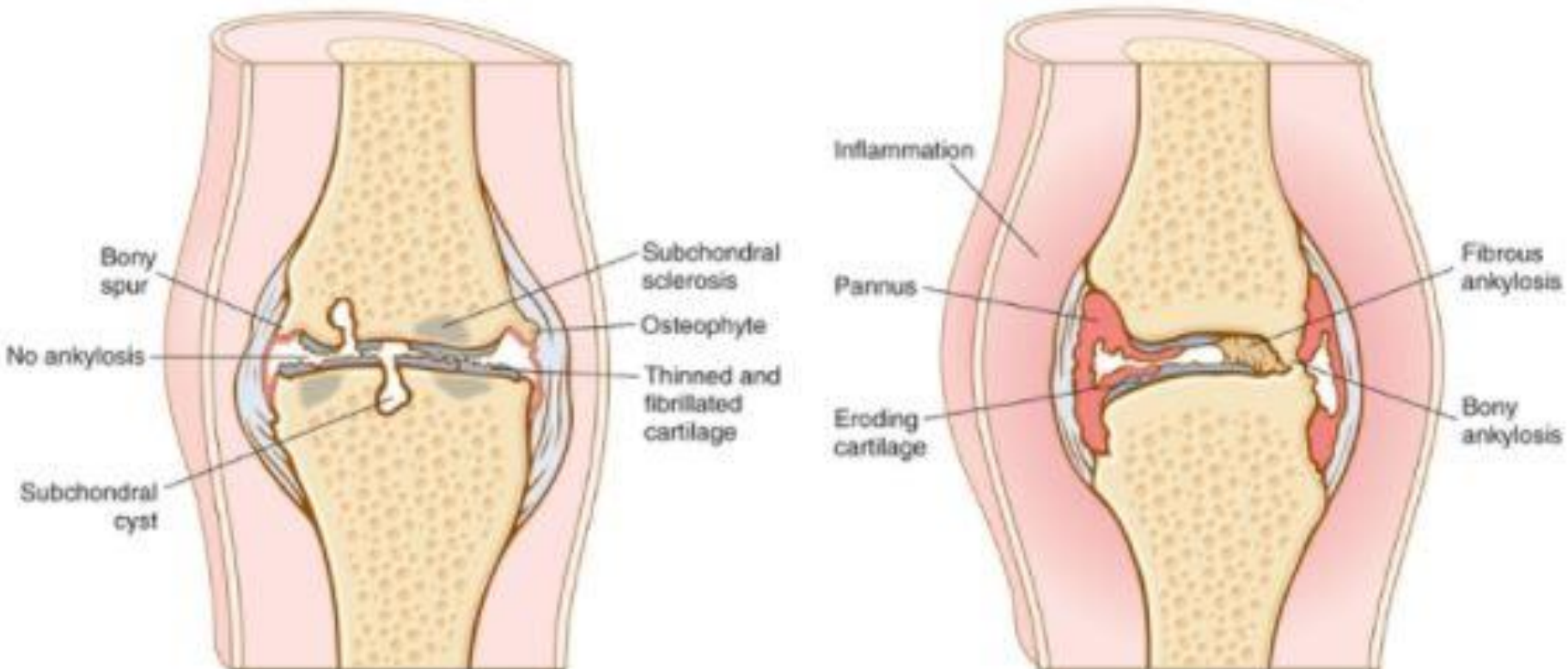
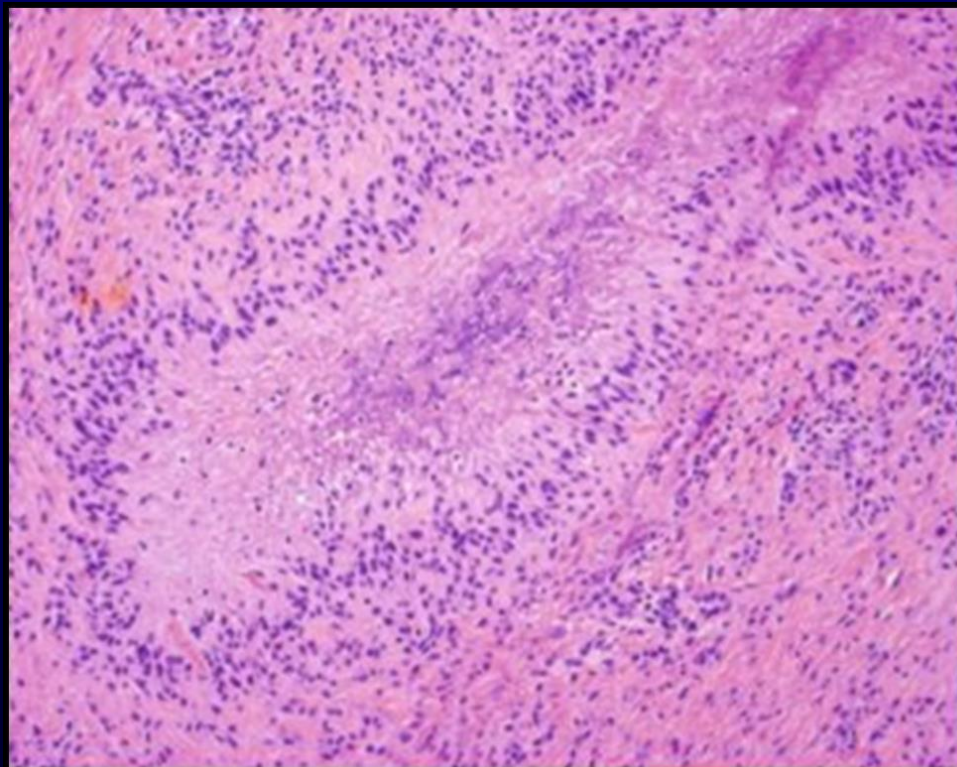
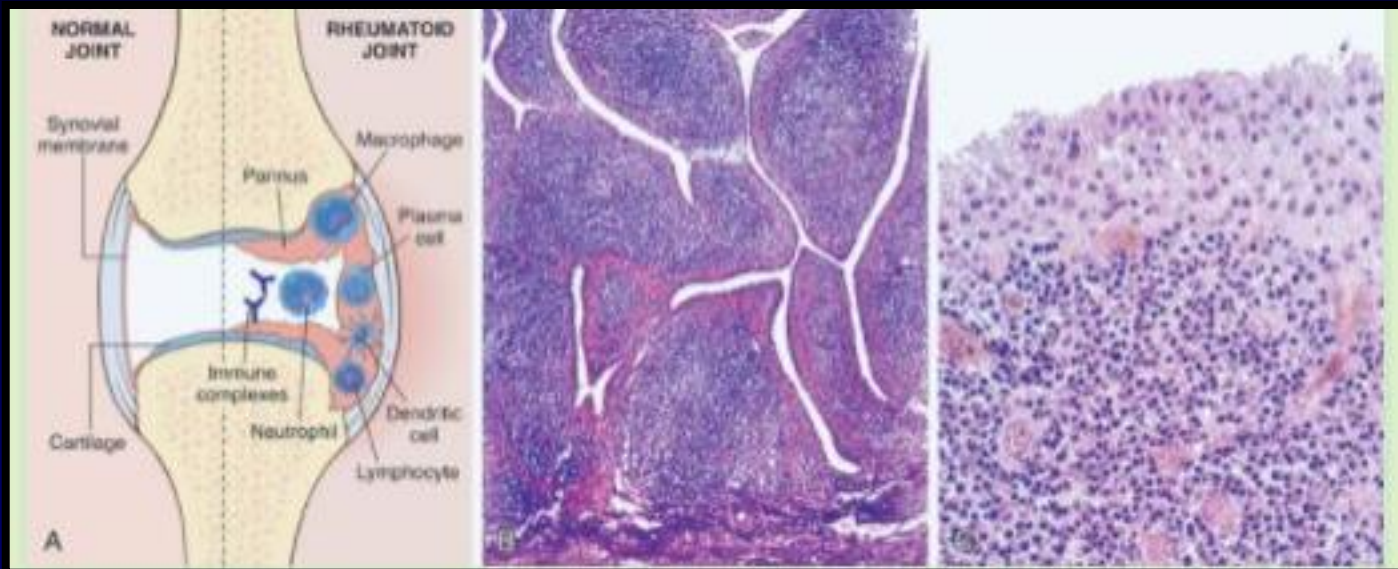


FIG. 21.35 Comparison of the morphologic features of rheumatoid arthritis and osteoa...



CLINICAL COURSE OF RA:

- **Begins slowly and insidiously, polyarthrititis**
- **Symmetrical joints: hands, feet, wrists, ankle, MCP and proximal IPJ are commonly affected**
- **Joints: warm, swollen & painful**
- **Stiffness when inactive and in the morning**
- **Waxing and waning chronic**
- **Ulnar deviation**
- **Trx: Steroids, MTX, Anti-TNF**



Rheumatoid arthritis
(late stage)

Boutonniere
deformity
of thumb

Ulnar deviation of
metacarpophalangeal
joints

Swan-neck deformity
of fingers



ADAM.



JUVENILE IDIOPATHIC ARTHRITIS (JIA):

- **Heterogeneous group; arthritis of unknown cause ; <16 years for at least 6 weeks**
- **Pathogenesis is similar to adult RA**
- **Prognosis variable; only 10% will have serious functional disability**

IN CONTRAST TO ADULTS RA; JIA IS CHARACTERIZED BY:
Oligoarthritis is more common
Systemic disease is more common
Large joints are affected more than small joints
Rheumatoid nodules and Rheum Factor are usually absent
Anti Nuclear Antibody seropositivity is common

SERONEGATIVE

Autoimmune T cell response to unidentified antigen (possibly infectious agent) that cross react with self musculoskeletal antigens

HETEROGENOUS GROUP THAT SHARE THE FOLLOWING FEATURES:

Absence of rheumatoid factor

Ligaments pathology rather than synovium

Sacroiliac joints mainly

Association with HLA-B27

Bony ankylosis (fusion)

- **Ankylosing spondylitis: most common prototype.**
- **Destructive arthritis and bony damage and ankylosis of sacroiliac joint, main joint involved.**
- **90% HLA-B27**
- **Anti IL-17 has shown some efficacy as treatment**

SERONEGATIVE SPONDYLOARTHRITIS:

● **Ankylosing Spondylitis:**

- Adolescent boys, HLA B27, axial joints (sacroiliac)

● **Reiter Syndrome:**

- Triad of arthritis, urethritis/cervicitis & conjunctivitis
- Autoimmune but initiated by bacterial infection.

● **Enteropathic Arthritis:**

- Secondary to bowel infections (salmonella, shigella)
- HLA B27 positive

● **Psoriatic Arthritis:**

- 5% of patients, starts in DIP joints, similar to RA.

Spondyloarthropathies: Subtype Classification

Ankylosing Spondylitis	Psoriatic Arthritis	Enteropathic (IBD-associated)	Reactive Arthritis	Undifferentiated SpA
<p>Most common subtype along with uSpA</p> <p>2.5:1 male:female</p> <p>Gradual onset of IBP</p> <p>Acute anterior uveitis most common extra-articular manifestation</p> <p>Can lead to sacroiliac fusion and spinal syndesmophyte formation</p>	<p>Between 10% and 40% of patients with psoriasis develop PsA, depending on study population and psoriasis severity</p> <p>Most phenotypically diverse SpA with 5 subtypes</p> <p>Skin disease precedes joint disease in approximately 70% of cases</p>	<p>5% to 29% of patients with IBD develop arthritis</p> <p>Peripheral arthritis (not axial) can parallel bowel inflammation and can occur in up to 20% of patients</p> <p>Spondylitis occurs in 3% to 6%</p>	<p>Typical acute asymmetric oligoarticular (<4 joints) arthritis 1-3 months after gastrointestinal and genitourinary infection</p> <p>Characteristic triad of urethritis, conjunctivitis, and arthritis seen in < 35% of patients</p> <p>Keratoderma blennorrhagica and circinate balanitis</p>	<p>Most common subtype along with AS</p> <p>Typically used to describe patients not fulfilling criteria of any one SpA but presenting with IBP and other extra-articular SpA manifestations</p> <p>Up to 50% of uSpA will develop into AS</p>

uSpA = undifferentiated SpA; IBP = inflammatory back pain; PsA = psoriatic arthritis; IBD = inflammatory bowel disease; AS = ankylosing spondylitis

SUPPURATIVE ARTHRITIS:

- **Bacterial infection**
- **Hematogenous spread**
- **< 2 years: *H. influenza*; older children & adults
S. aureus; gonococcus young adults**
- **Sickle cell disease: salmonella**
- **Clinically: sudden acute pain, swollen and warm joints, mainly knee with systemic manifestation (fever, leukocytosis, elevated ESR)**
- **Dx & Rx: aspiration of joint; antibiotics**

LYME ARTHRITIS

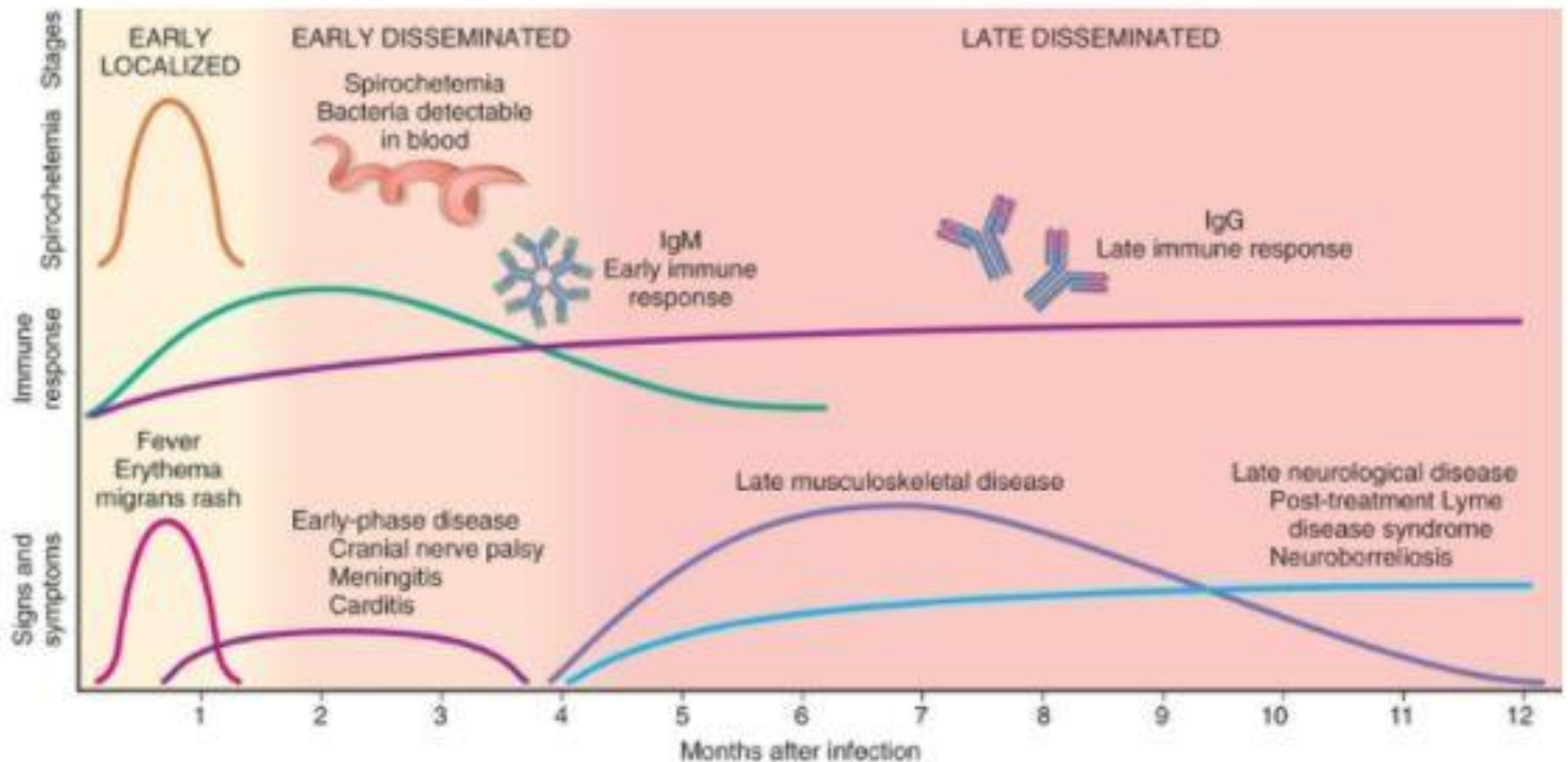



FIG. 21.40  Lyme disease progresses through three clinically recognizable phases: early...

CRYSTAL-INDUCED ARTHRITIS:

- **Crystals deposited in joints causing disease**
- **Crystals triggers inflammatory reaction that destroys cartilage**
- **Endogenous crystals:**
 - **Monosodium urate, MSU (GOUT)**
 - **Calcium pyrophosphate dehydrogenase, CPPD (PSEUDOGOUT)**

Lecture

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GOUT: النقرس

- **Transient attacks of arthritis, mainly big toe, triggered by deposition of MSU crystals**
- **Uric acid: purine metabolite; increased production or decreased excretion from kidney**
- **With hyperuricemia, risk increases with: 20-30 years of age, obesity, alcohol, genetic predisposition, drugs (thiazides)**

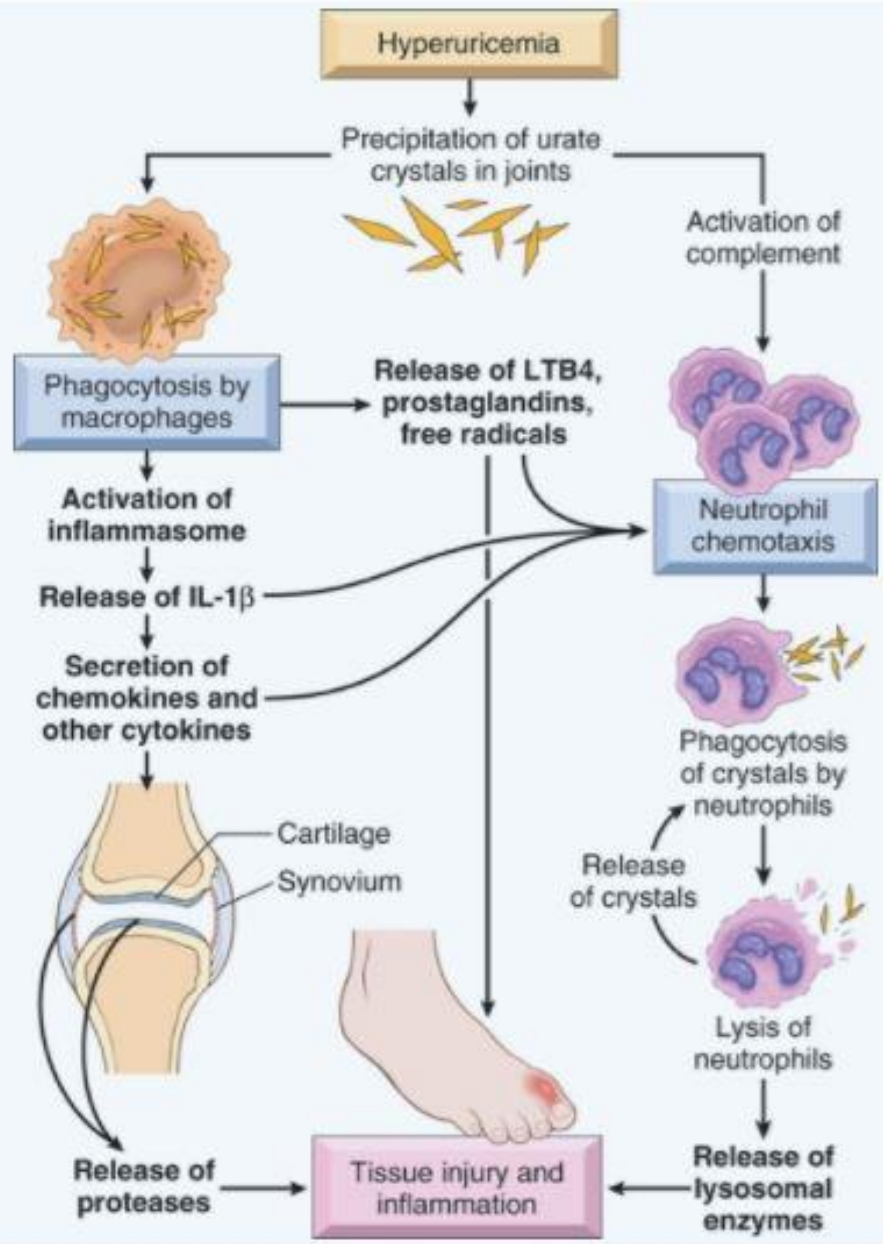
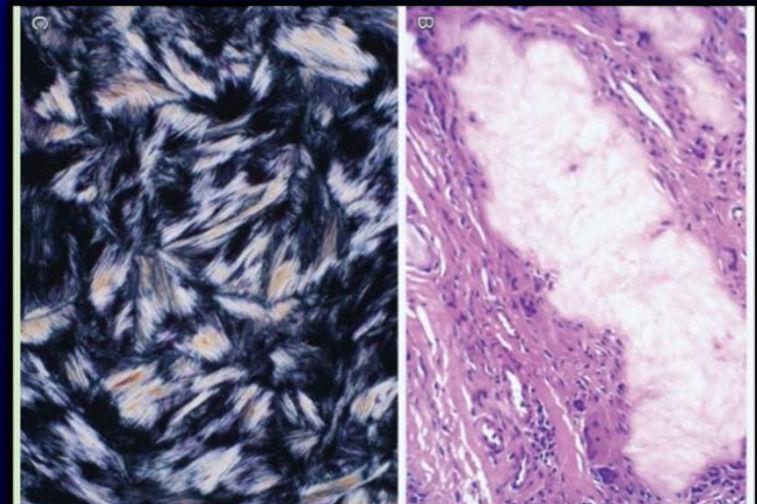


FIG. 21.41 Pathogenesis of acute gouty arthritis. Urate crystals are phagocytosed by m...

MORPHOLOGIC CHANGES OF GOUT:

Acute arthritis	Dense inflammation of synovium, MSU crystals in neutrophils, -ve birefringent
Chronic tophaceous arthritis	Repetitive attacks & crystals deposition in the joint; thick synovium, pannus
Tophi in various sites	Cartilage, ligaments, bursae and tendons
Gouty nephropathy	MSU crystals deposition in kidney; nephrolithiasis & pyelonephritis

Trx: life style modifications, NSAIDS & Colchicine in acute gout, Xanthine oxidase inhibitors (Allupurinol) in chronic and prevention

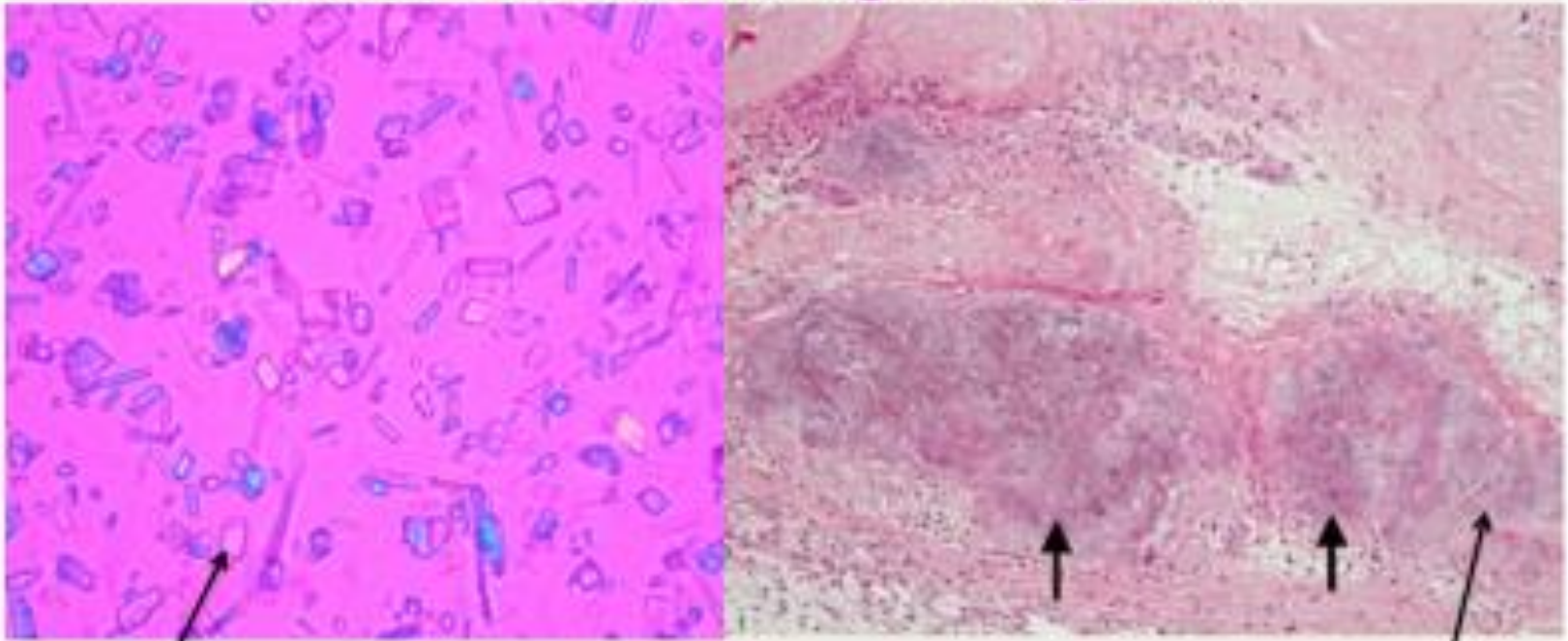


PSEUDOGOUT:

- **> 50 years; increase with age**
- **Idiopathic (genetic) or secondary**
- **CPPD crystal induced arthritis via triggering inflammatory reaction**
- **Secondary: DM, previous joint damage, HPTH, hemochromatosis**
- **Acute, subacute and chronic forms**
- **Trx: supportive, no preventive measures so far**

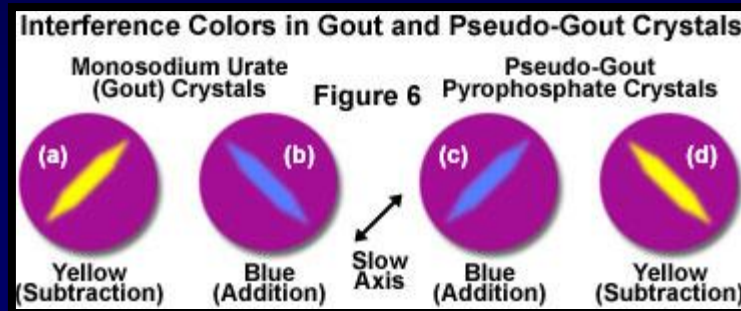
PSEUDOGOUT:

IIIb. CPPD: Pathologic Diagnosis

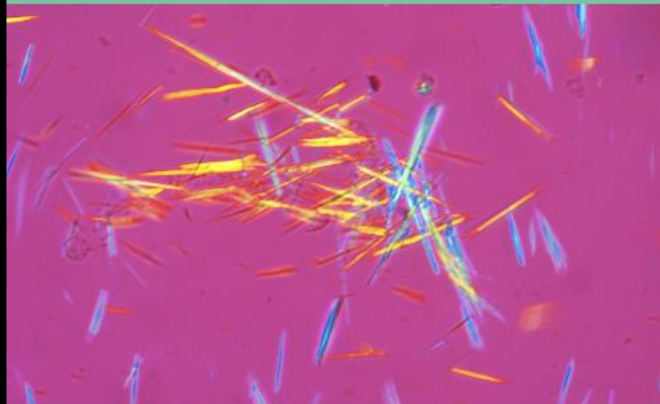


- Synovial Fluid: geometric or rhomboid-shaped crystals, weakly positively birefringent under polarized light
- Histopathology: amorphous purple deposits on H&E with *little inflammatory response*.

NEGATIVE VS POSITIVE BIREFRINGENCE

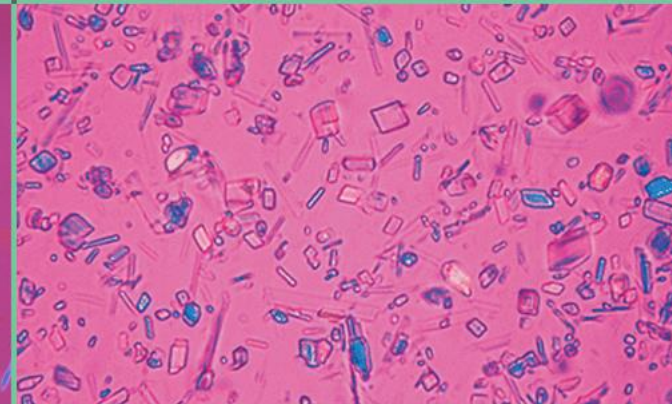


Monosodium Urate (MSU) Crystals



Needle shaped, strong negative birefringence
Yellow when parallel to compensator ray

Calcium Pyrophosphate Dihydrate (CPPD) Crystals



Rod or rhomboid, weak positive birefringence
Blue when parallel to compensator ray



Summary

Arthritis

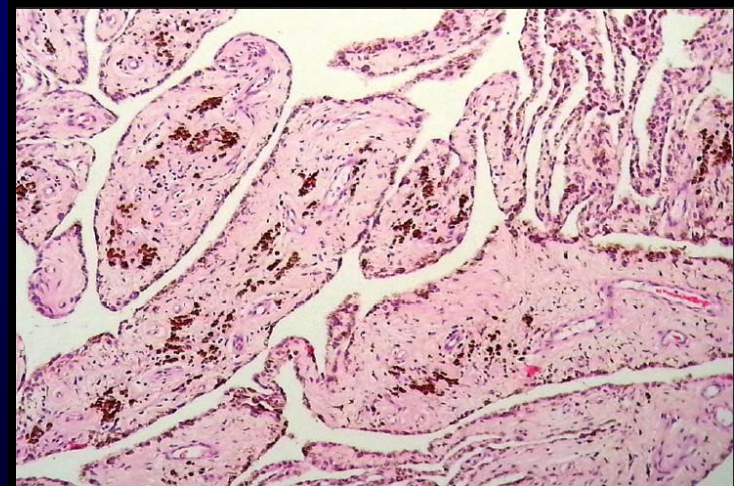
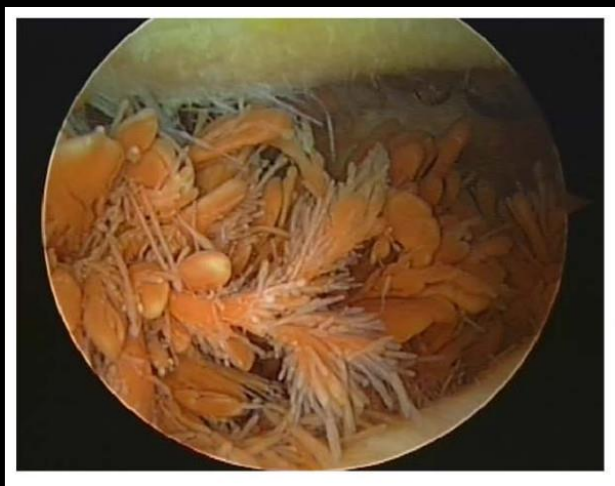
- **Osteoarthritis (OA, degenerative joint disease)**, the most common disease of joints, is a degenerative process of articular cartilage in which matrix breakdown exceeds synthesis. Inflammation is minimal and typically secondary. Local production of inflammatory cytokines may contribute to the progression of joint degeneration.
- **Rheumatoid arthritis (RA)** is a chronic autoimmune inflammatory disease that affects mainly small joints, but can be systemic. RA is caused by a cellular and humoral immune response against self-antigens, particularly citrullinated proteins. TNF plays a central role and antagonists against TNF are of clinical benefit.
- **Seronegative spondyloarthropathies** are a heterogeneous group of likely autoimmune arthritides that preferentially involve the sacroiliac and vertebral joints and are associated with HLA-B27.
- **Suppurative arthritis** describes direct infection of a joint space by bacterial organisms.
- **Lyme disease** is a systemic infection by *Borrelia burgdorferi*, which manifests, in part, as an infectious arthritis, possibly with an autoimmune component in chronic stages.
- **Gout and pseudogout** result from inflammatory responses triggered by precipitation of urate or calcium pyrophosphate, respectively.

JOINT TUMORS & TUMORLIKE CONDITIONS:

- **Joint tumors are rare**
- **Ganglion cyst and tenosynovial giant cell tumor are the most frequent**
- **Ganglion cyst: common condition; close to a joint, dorsum of wrist; not true cyst, no communication with synovial joint; may cause pressure pain; treated by surgical removal**
- **True synovial cyst (Baker cyst around the knee): herniation process**

TENOSYNOVIAL GIANT CELL TUMOR:

- Benign neoplasm of synovium
- Diffuse (pigmented villonodular synovitis, PVNS, large joints) or localized small hands tendons
- T(1;2)(p13q;37); affecting **type VI collagen α -3**

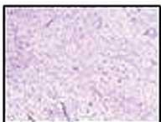

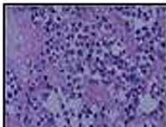
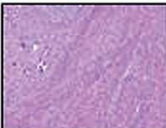
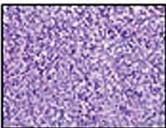


SOFT TISSUE TUMORS:

- **Benign >>>>> malignant**
- **Incidence: 1% and cause 2% cancer death**
- **Sarcomas are aggressive and metastasize mainly to lungs, hematogenous spread**
- **Most are in extremities (thigh)**
- **Most are sporadic; very few arise from tumor suppressor gene mutations (NF1, Gardner syndrome, Li-Fraumeni syndrome, Osler-Webber-Rendu Syndrome)**
- **Few occur after exposure to radiation, burns & toxins.**

SOFT TISSUE TUMORS:

- **No precursor lesions; theory that they arise from pluripotent mesenchymal stem cell which acquire somatic mutation**
- **15-20% simple karyotype, single signature mutation (Ewing and synovial sarcoma)**
- **80-85% complex karyotype (genomic instability), LMS and pleomor. Sarcoma**
- **Wide range (benign-highly malignant)**
- **Diagnosis, grade and stage are all important**

	DIFFERENTIATION	Subtypes	Chromosomal traslocations	Fusion trascripts
	ADIPOCYTIC TUMORS	<i>Lipoblastoma:</i> <i>Myxoid liposarcoma</i>	t(7;8)(q31;q13); t(8;8)(q24;q13) t(12;16)(q13;p11); t(12;22)(q13;q12)	PLAG1-COL1A2; PLAG1-HAS2 CHOP-TLS; CHOP-EWS
	FIBROBLASTIC/ MYOFIBROBL. TUMORS	<i>Inflammatory myofibroblastic tumor</i> <i>Infantile fibrosarcoma</i> <i>Dermatofibrosarcoma protuberans/ Giant cell fibroblastoma</i>	t(1;2)(q25;p23); t(2;19)(p23;q13); t(2;17)(p23;q23) t(12;15)(p13;q25) t(17;22)(q22;q13)	TPM3-ALK; ALK-TPM4; ALK-CLTC ETV6-NTRK3 COL1A1-PDGFB
	SKELETAL MUSCLE TUMORS	<i>Alveolar rhabdomyosarcoma</i>	t(2;13)(q35;q14); t(1;13)(p36;q14)	PAX3-FKHR; PAX7-FKHR
	TUMORS OF UNCERTAIN DIFFERENTIATION	<i>Angiomatoid fibrous histiocytoma</i> <i>Synovial sarcoma</i> <i>Alveolar soft part sarcoma</i> <i>Clear cell sarcoma</i> <i>Extraskeletal myxoid chondrosarcoma</i> <i>Desmoplastic small round cell tumor</i>	t(12;22)(q13;q12); t(12;16)(q13;p11) t(X;18)(p11.2;q11.2) t(X;17)(p11;q25) t(12;22)(q13;q12) t(9;22)(q22;q12); t(9;15)(q22;q21) t(11;22)(p13;q12)	SYT-SSX1/2/4 TFE3/ASPL EWS-ATF1 EWS-TEC; CHN-TFC12 EWS-WT1
	EWING SARCOMA		t(11;22)(q24;q12); t(21;22)(q22;q12); t(17;22)(q12;q12); t(7;22)(p22;q12);	FLI1-EWS; ERG-EWS E1AF-EWS; ETV1-EWS

ADIPOSE TISSUE TUMORS:

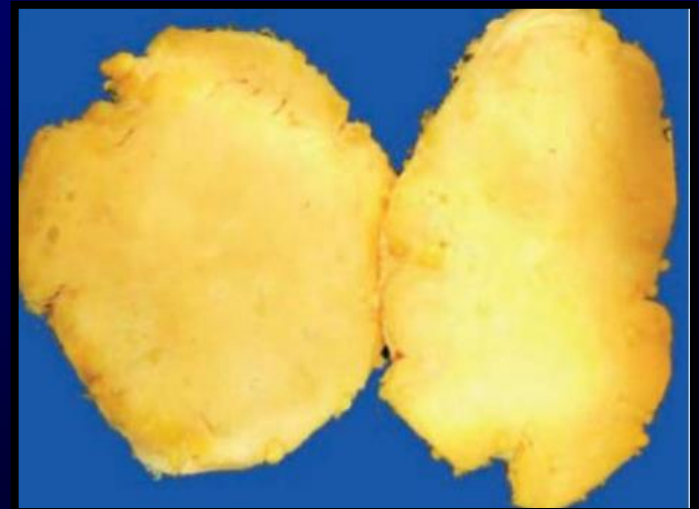
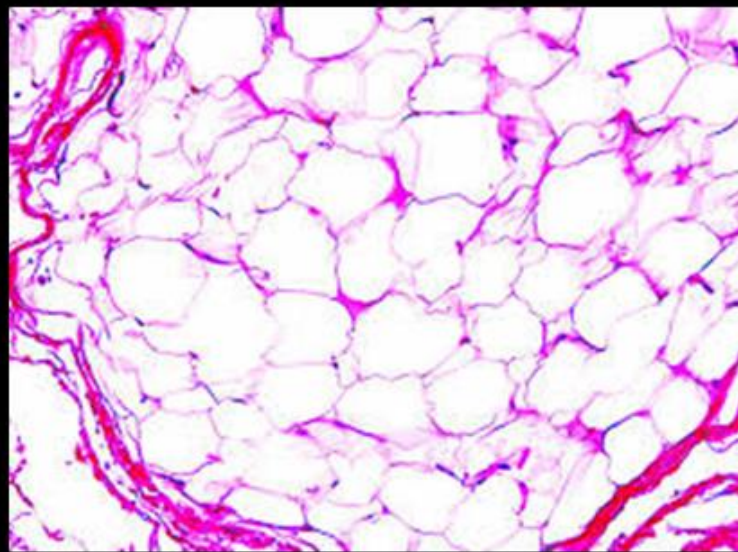
LIPOMA

- **Most common soft T tumor**
- **Well-encapsulated, subcutis**
- **Mature fat cells**
- **Trx: excision**

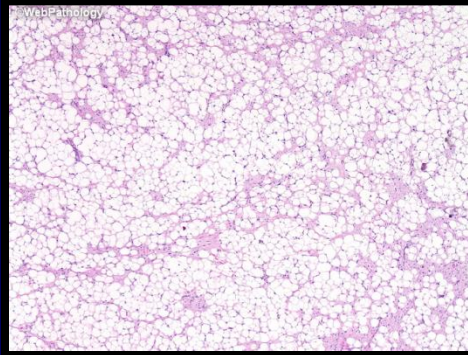
LIPOSARCOMA

- **Most common sarcomas in adults. >50 years**
- **Extremities and retroperitoneum**
- **3 types:**
 - **WD (MDM2 gene chr 12)**
 - **Myxoid, t(12,16)**
 - **Pleomorphic (aggressive)**

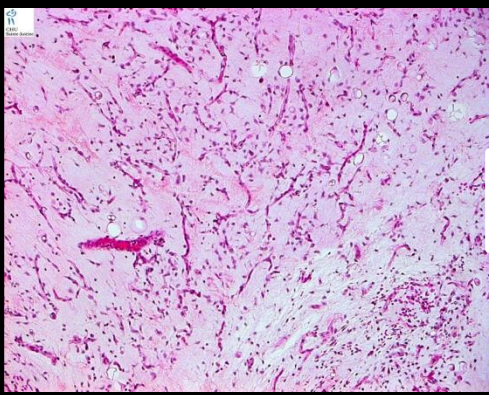
LIPOMA PATHOLOGIC FEATURES:



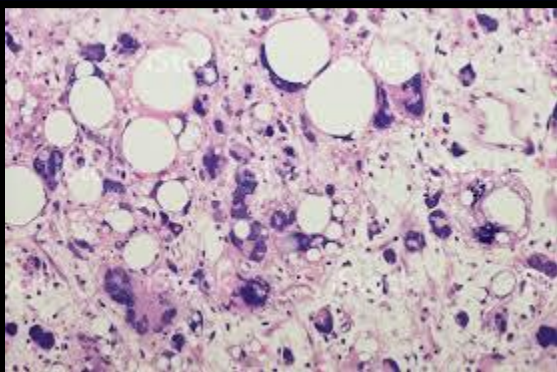
LIPOSARCOMA FEATURES:



**Well-
differentiated**



Myxoid



Pleomorphic



Lecture

9

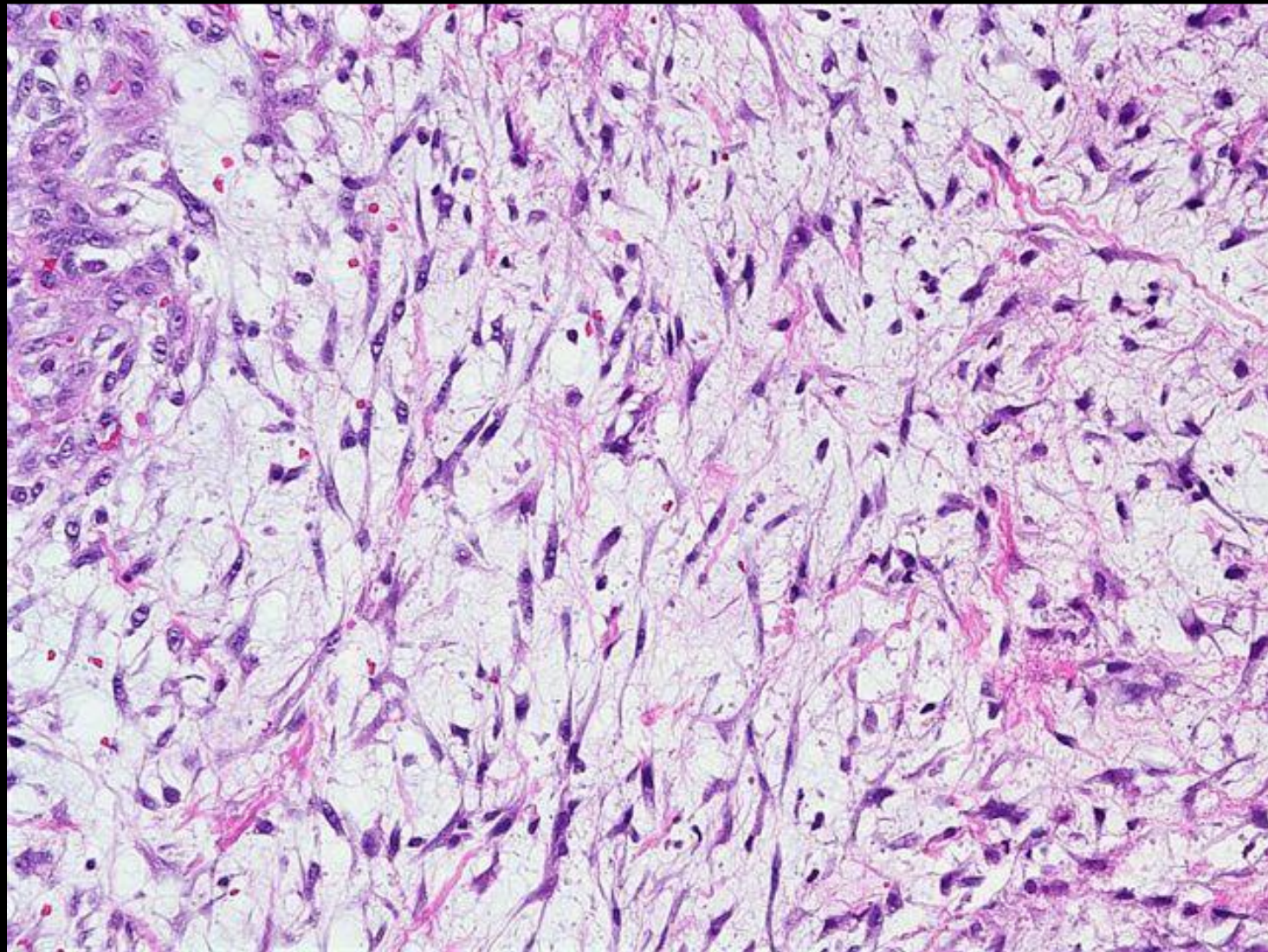
FIBROUS TUMORS:

- **Nodular fasciitis**
- **Fibromas and Fibrosarcoma**
- **Fibromatoses:**
 - **Superficial**
 - **Deep (Desmoid tumor)**

NODULAR FASCIITIS:

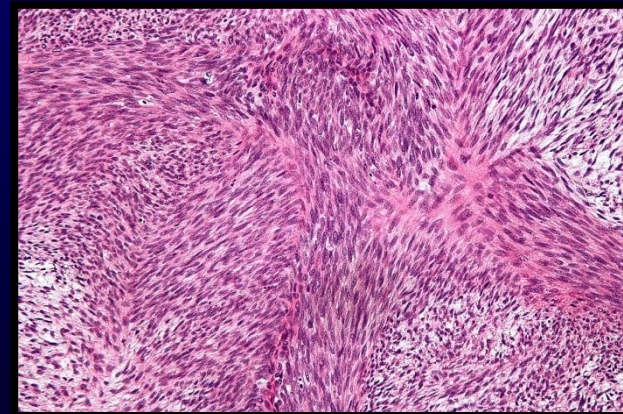
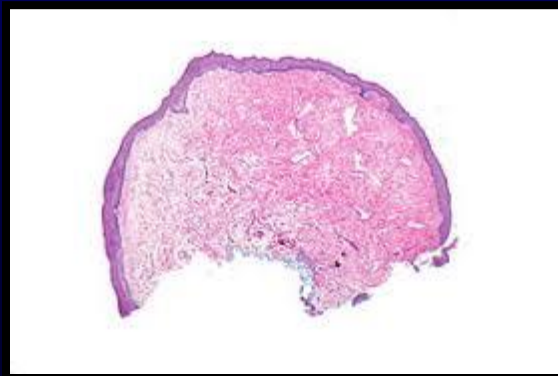
- **Nodular fasciitis: thought to be reactive process**
- **Now, clonal, t(17;22) producing *MYH9-USP6* fusion gene**
- **Trauma history, recent rapid size increase**
- **Maybe self-limiting**
- **IMPORTANT: not to diagnose it malignant**
- **Culture-like histology**

NODULAR FASCIITIS:





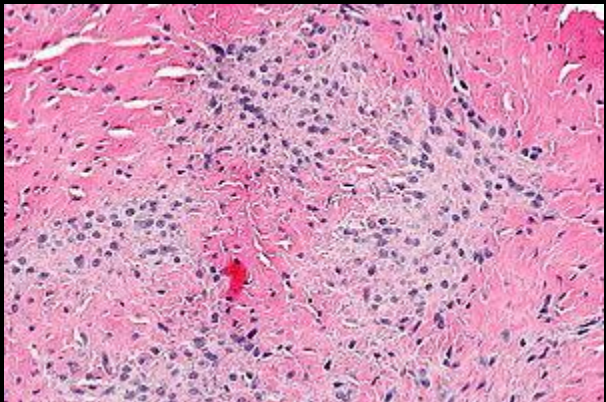
FIBROMAS AND FIBROSARCOMAS:

- **Fibromas: benign proliferation of fibroblasts, very common, skin and subcutaneous tissue**
- **Fibrosarcoma: malignant counterpart; usually superficial cutaneous tumors of fibroblasts, cellular, storiform pattern with increased mitosis**



SUPERFICIAL FIBROMATOSES:

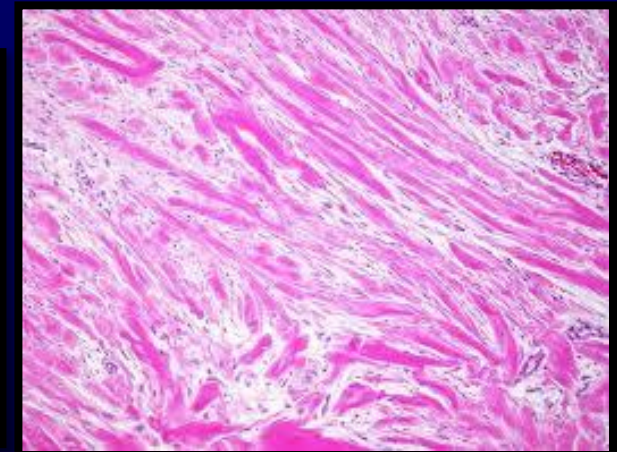
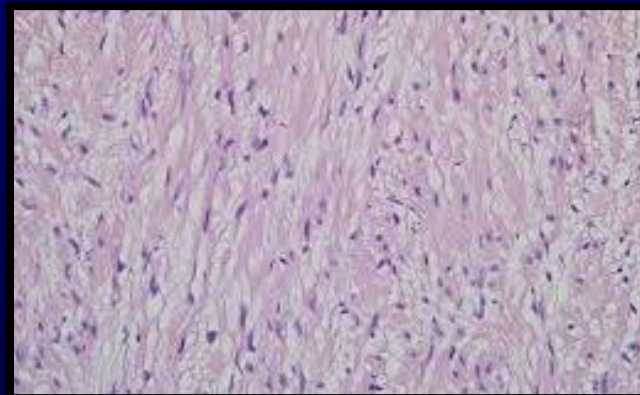
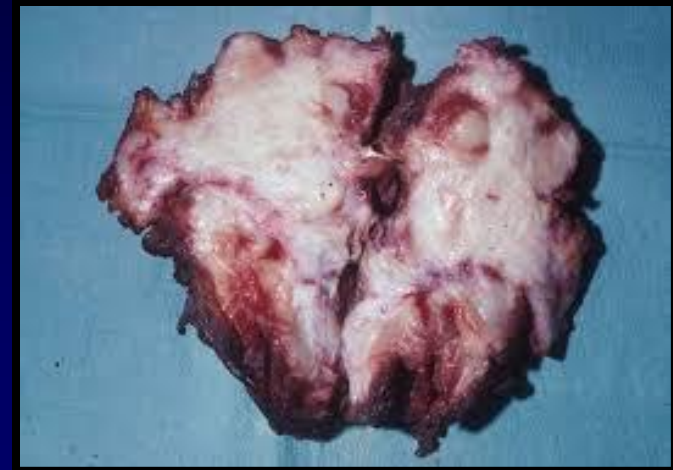
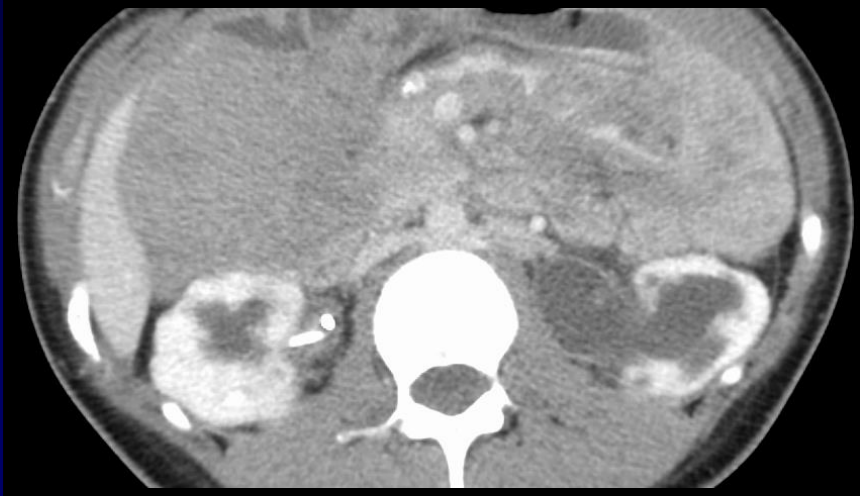
- Infiltrative benign fibroblastic proliferation
- May run in families; may impact function

PALMAR (DUPUYTREN CONTRACTURE)	PLANTAR FIBROMATOSES	PENILE (PEYRONIE DISEASE)
Palmar fascia	Sole of foot	Dorsolateral aspect of the penis
		

DEEP FIBROMATOSSES (DESMOID TUMOR):

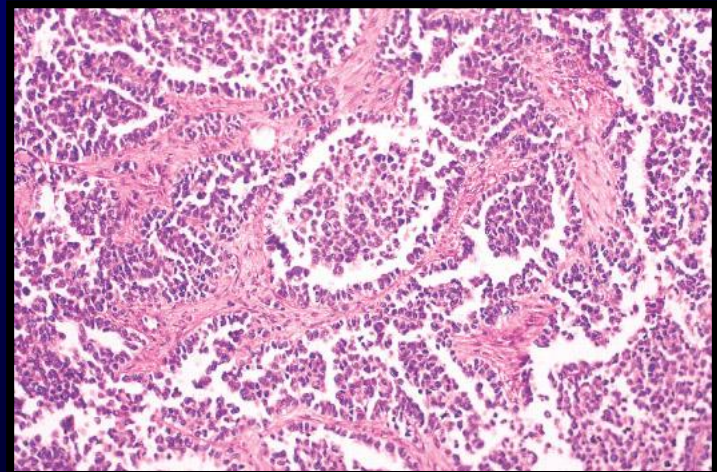
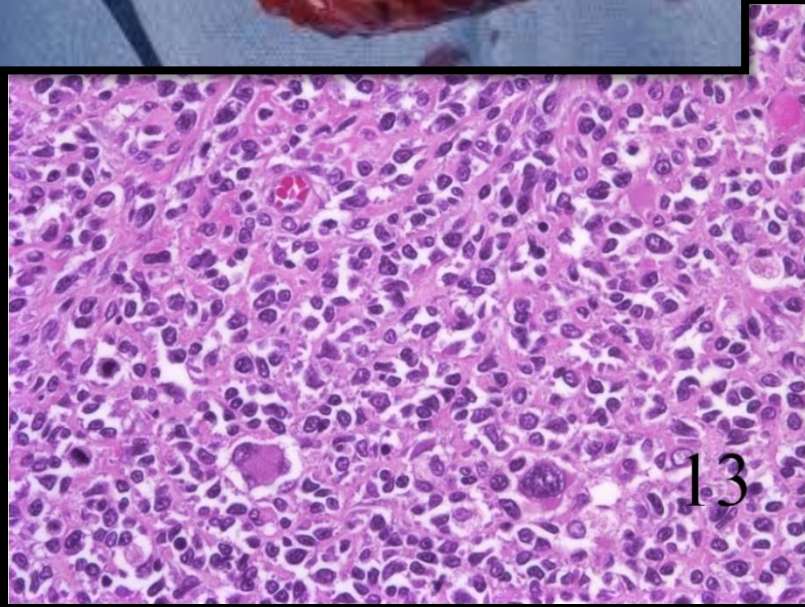
- Deep infiltrative but bland fibroblastic proliferation; doesn't metastasize but recur
- 20-30years, females more common
- Abdominal wall, mesentery and limbs
- Mutations in *CTNNB1* (β -catenin) or *APC* genes leading to increased Wnt signaling
- Mostly are sporadic; but patients with Gardner (FAP) syndrome are susceptible
- Complete excision is needed to prevent recurrence which is very common
- These tumors kill by local infiltration NOT metastasis

DEEP FIBROMATOSSES (DESMOID TUMOR):



SKELETAL MUSCLE TUMORS:

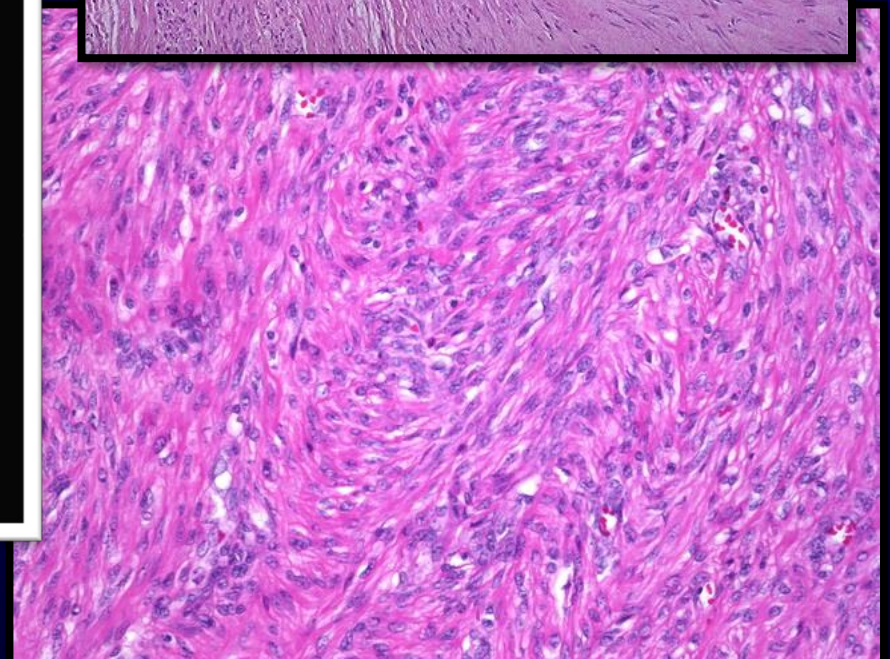
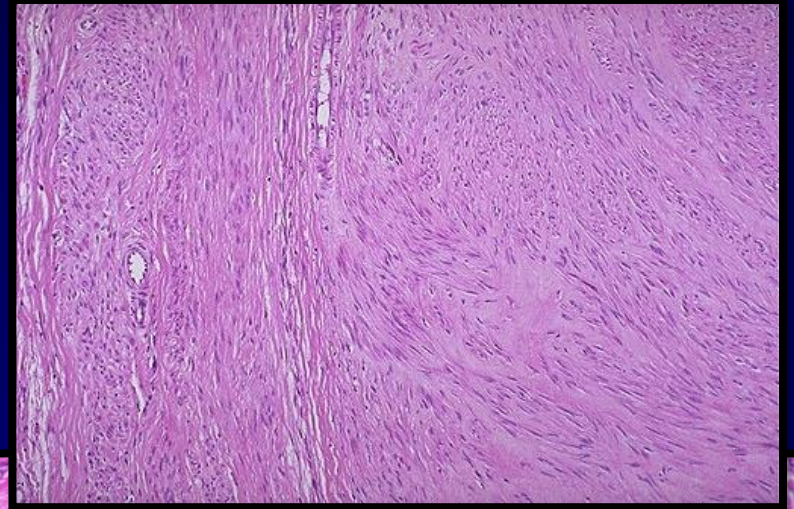
- **Almost all malignant; except rhabdomyoma which is benign, rare, occurs with tuberous sclerosis**
- **Rhabdomyosarcoma (RMS) is the malignant prototype; most common child sarcoma**
- **3 types (embryonal 60%; alveolar 20%; pleomorphic 20%)**
- **Specific mutations are common**
- **Aggressive tumors; treated by surgery, CT +/- RT**



SMOOTH MUSCLE TUMORS:

- **Leiomyoma (benign) and leiomyosarcoma (malignant)**
- **Leiomyoma (LYM): very common; any site but mostly uterus (fibroid)...menorrhagia and infertility**
- **LYM vary in size and location**
- **Few can have specific mutations (Fumarate hydratase on chromosome 1q42.3)**

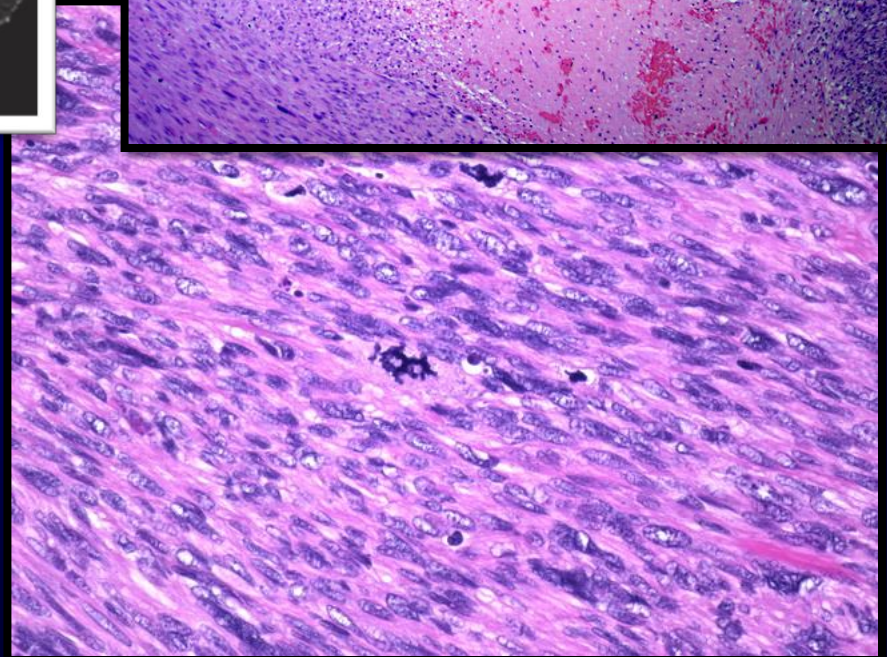
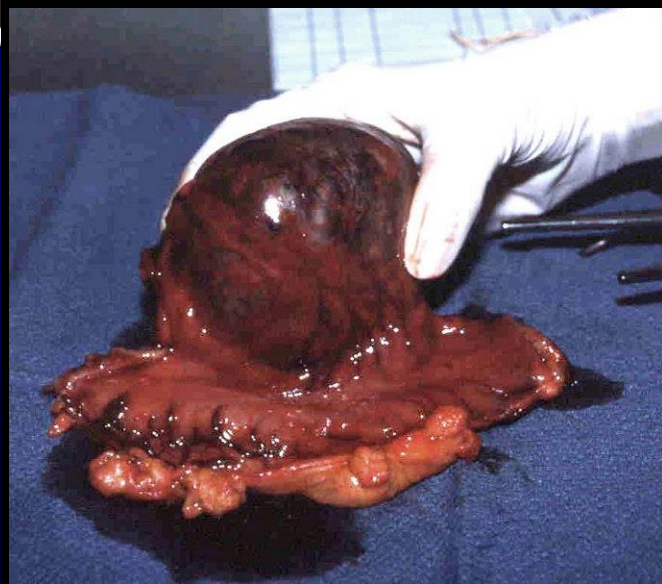
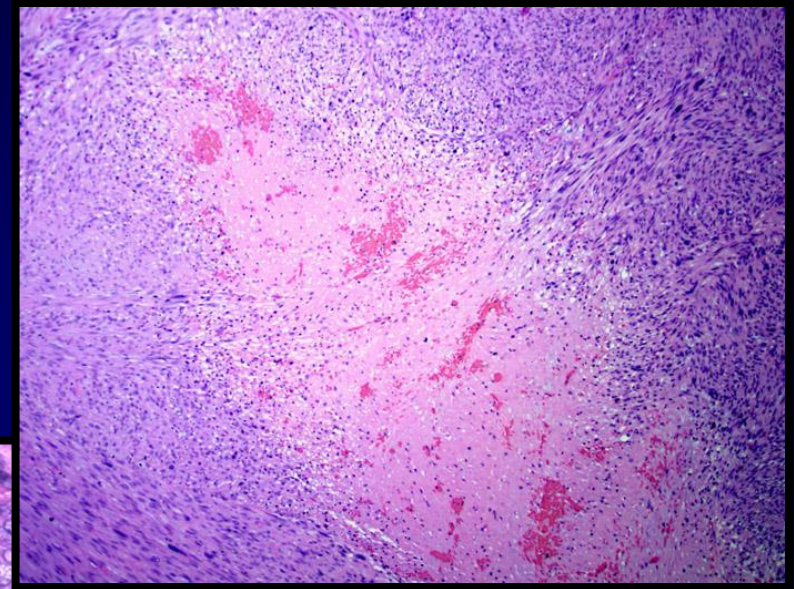
LEIOMYOMA FEATURES:



LEIOMYOSARCOMA:

- **10-20% of soft tissue sarcomas**
- **Adults; more in females**
- **Deep soft tissue, extremities and retroperitoneum or from great vessels**
- **Complex genotypes**
- **Hemorrhage, necrosis, increased mitosis and infiltration of surrounding tissue**
- **Trx: depends on location, size and grade**


LEIOMYOSARCOMA FEATYURES:



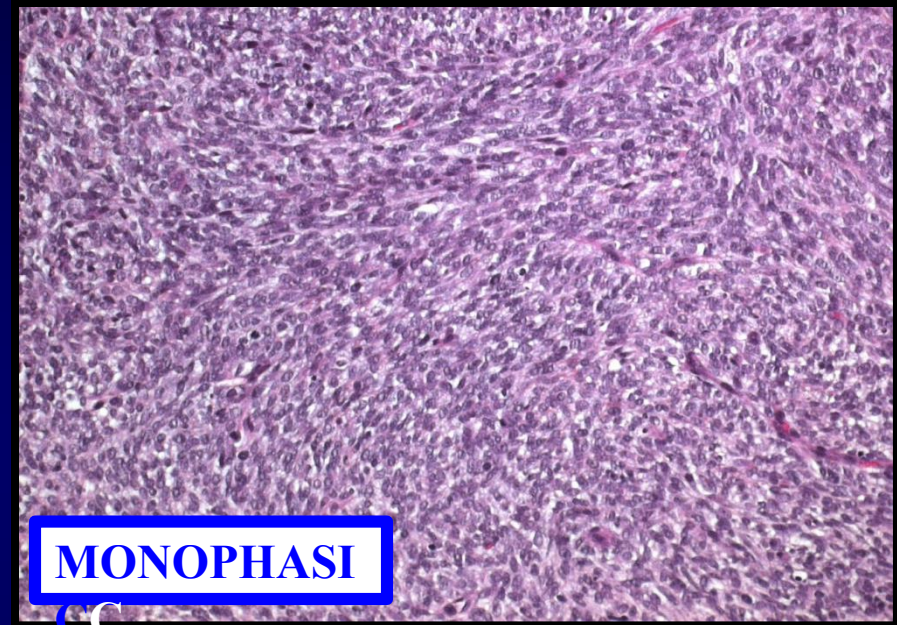
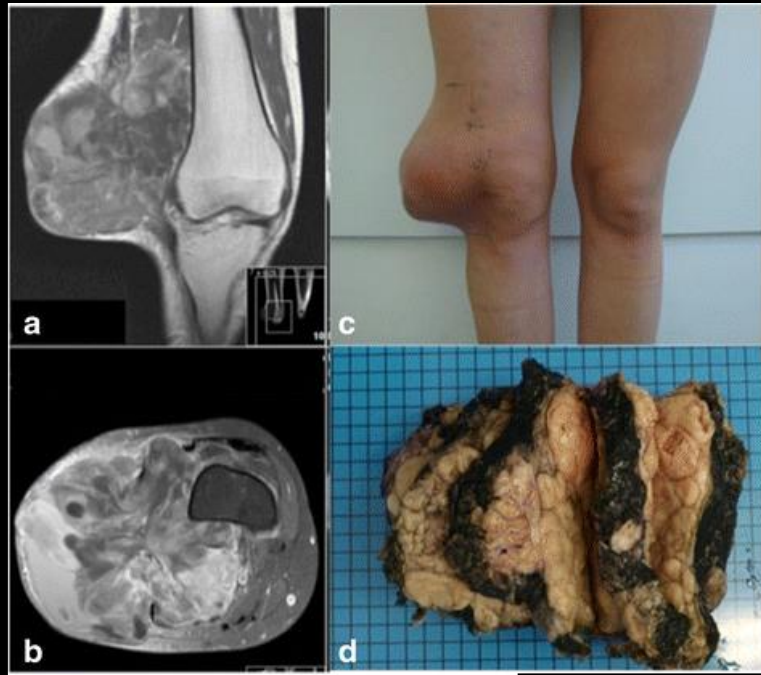
TUMORS OF UNCERTAIN ORIGIN:

- **Uncertain mesenchymal lineage**
- **Synovial sarcoma**
- **Undifferentiated pleomorphic sarcoma**

SYNOVIAL SARCOMA:

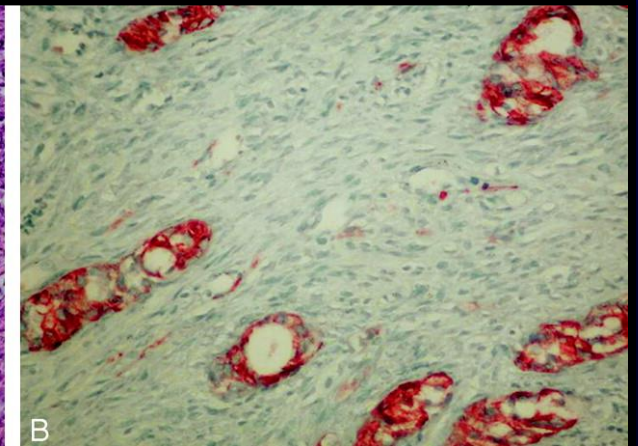
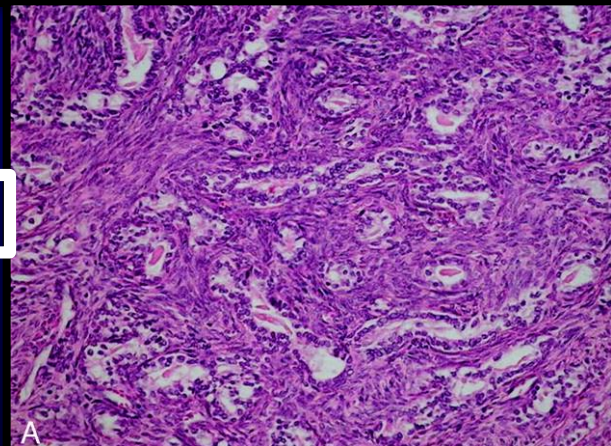
- Name is misnomer
- 10% of all soft tissue sarcomas; 20-40s age
- Deep seated mass of long history
- $T(X;18)(p11;q11)$  fusion genes *SS18...*
- Monophasic (only spindle cells) or biphasic (spindle cells and glands)
- Trx: aggressive with limb sparing excision + CT
- 5 year survival 25-65% depending on stage
- Metastasis: lung and lymph nodes

SYN. SA. FEATURES:



CC

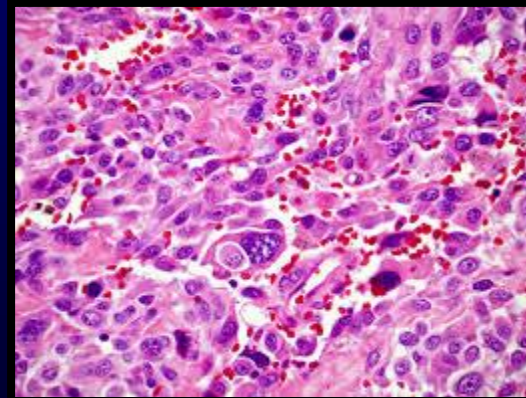
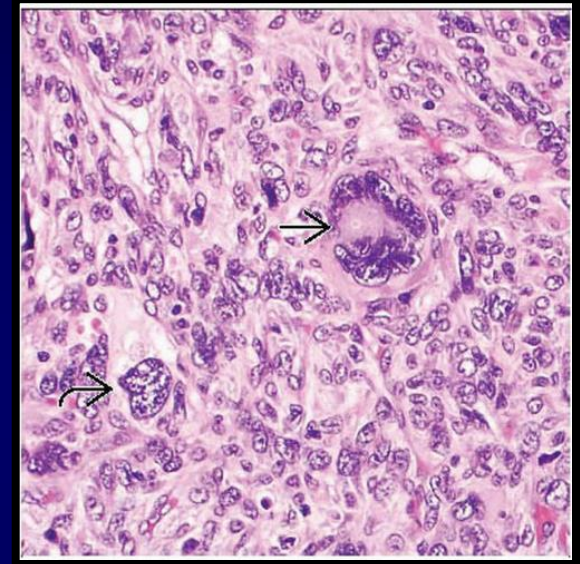
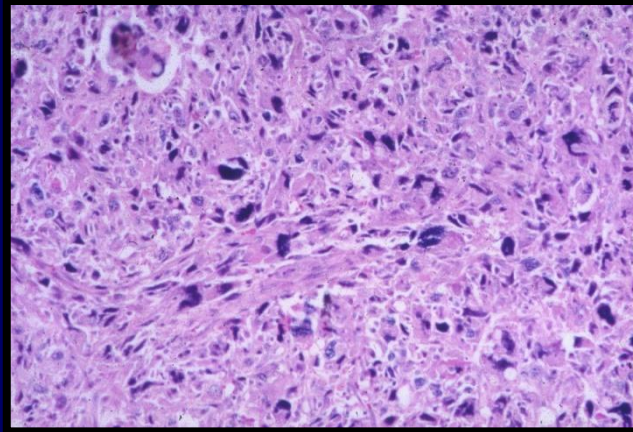
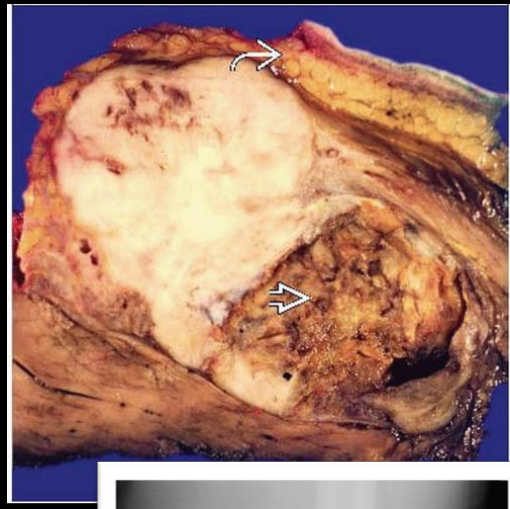
BIPHASIC



UNDIFFERENTIATED PLEOMORPHIC SARCOMA (UPS):

- **High grade mesenchymal sarcomas of pleomorphic cells that lack cell lineage**
- **Deep soft tissue and extremities**
- **Old terminology: malignant fibrous histiocytoma (MFH)...not anymore**
- **Aneuploid and complex genetic abnormalities**
- **Large tumors; anaplastic and pleomorphic cells, abnormal mitoses, necrosis**
- **Trx: aggressive with surgery and adjuvant CT +/- RT; poor prognosis**

UPS FEATURES:





Summary

Soft Tissue Tumors

- The category of soft tissue neoplasia describes tumors that arise from non-epithelial tissues, excluding the skeleton, joints, central nervous system, and hematopoietic and lymphoid tissues. A sarcoma is a malignant mesenchymal tumor.
- Although all soft tissue tumors probably arise from pluripotent mesenchymal stem cells, rather than mature cells, they can be classified as
 - Tumors that recapitulate a mature mesenchymal tissue (e.g., fat). These can be further subdivided into benign and malignant forms.
 - Tumors composed of cells for which there is no normal counterpart (e.g., synovial sarcoma, UPS).
- Sarcomas with simple karyotypes demonstrate reproducible, chromosomal, and molecular abnormalities that contribute to pathogenesis and are sufficiently specific to have diagnostic use.
- Most adult sarcomas have complex karyotypes, tend to be pleomorphic, and are genetically heterogeneous with a poor prognosis.

Lecture

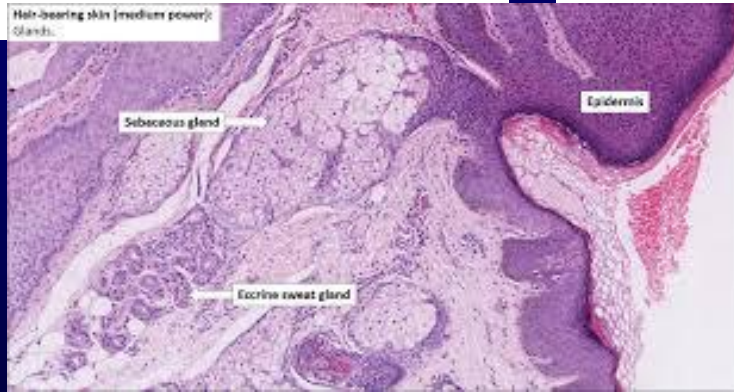
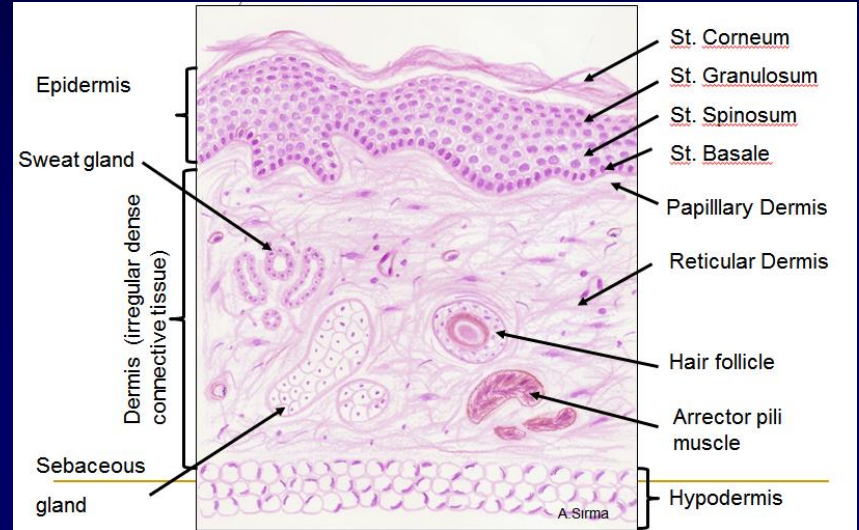
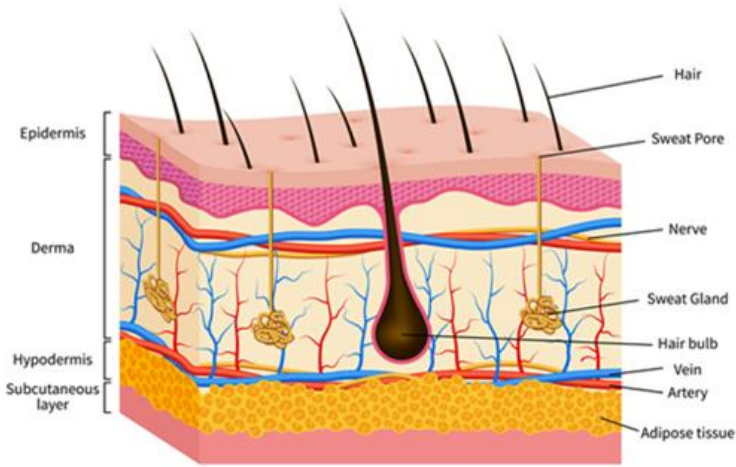
10

Skin Pathology: cysts and (neoplasms)

- **Inflammatory and infectious dermatosis (dermatology rotation)**
- **Very common lesions**
- **Increase with increasing age**
- **Rarely fatal (except melanomas)**
- **More common in sun exposed areas**
- **Associated with sun damage (solar elastosis)**



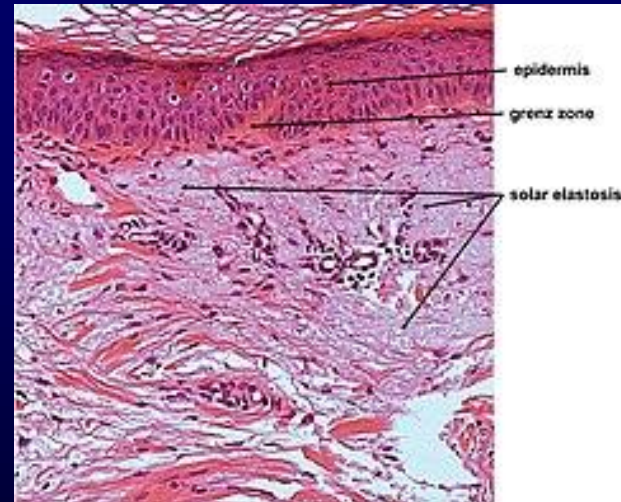
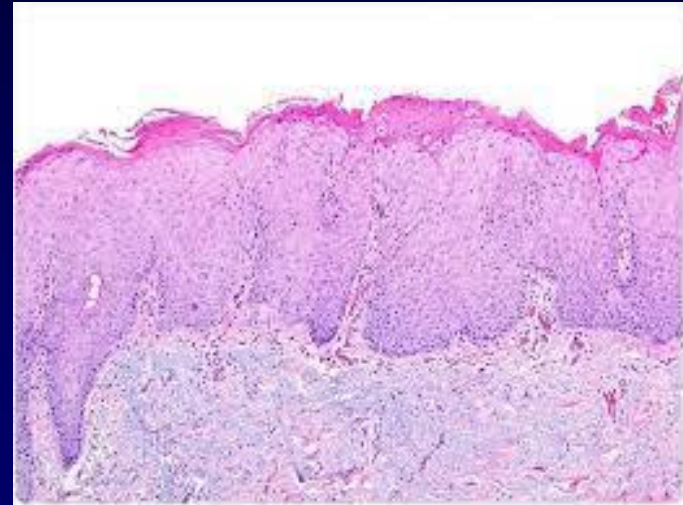
SKIN ANATOMY



Solar (actinic) elastosis

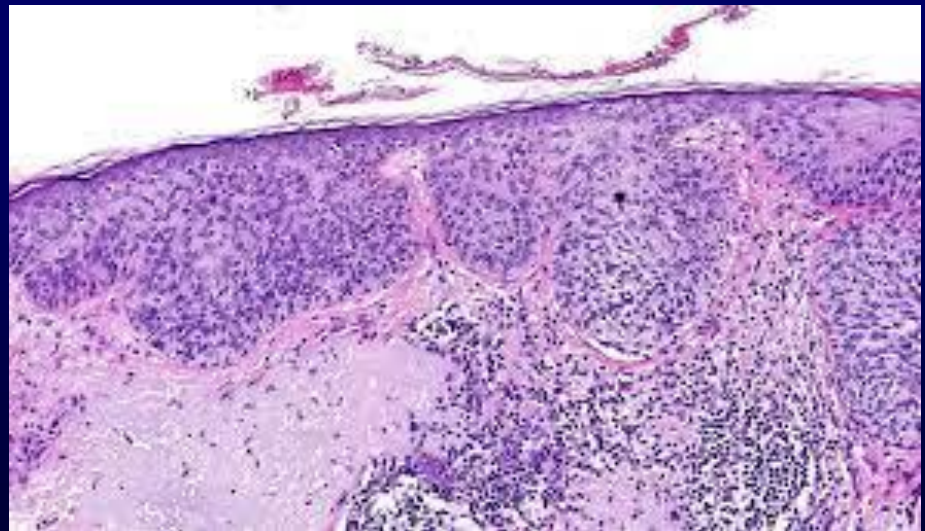
- **Chronic sun damage leading to: thickened and yellow skin**
- **“Damage to skin elasticity from sun exposure”**
- **Preventable disease**
- **UV rays damage collagen and elastic fibers of the skin**
- **This will increase the risk of many skin pre-malignancies (Actinic keratosis) and malignancies (melanomas, squamous cell carcinomas, basal cell carcinomas)**

Morphology:



Actinic keratosis:

- Premalignant skin disease due to sun damage
- UV light damage DNA via mutations in *TP53*
- They progress to squamous cell carcinoma (rate: 1-3%)



Seborrheic keratosis:

- **Very common pigmented neoplasms**
- **Middle age- older patients; anywhere but mainly trunk**
- **FGFR3 mutations**
- **Clinically insignificant (removed to R/O malignancy)**
- **Coin-like lesions, usually pigmented, elevated “Stuck-on”**

Seborrheic keratosis:

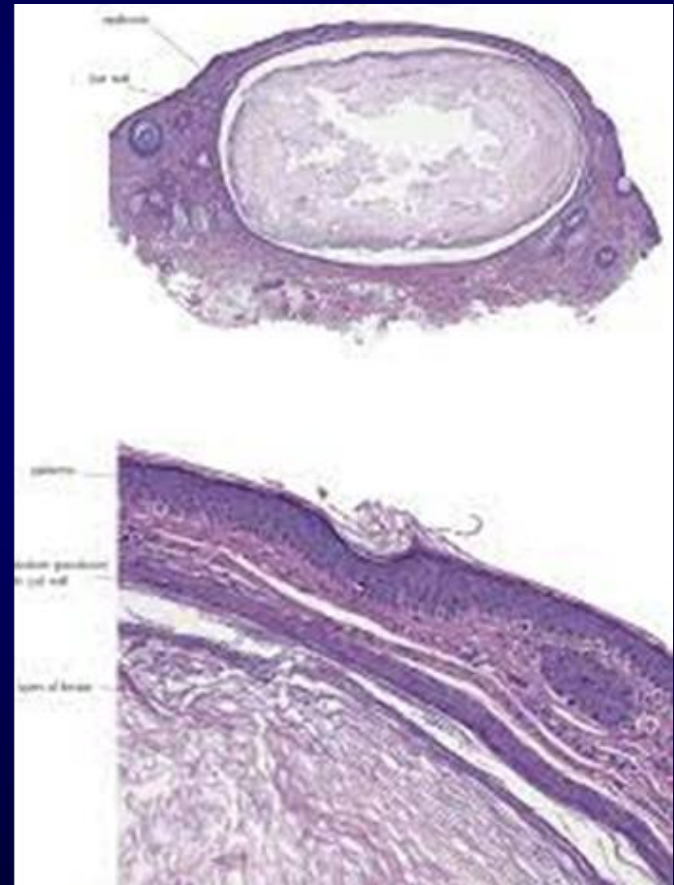


Kumar et al: Robbins Basic Pathology, 9e.
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Cysts:

- **Very common**
- **Almost all are benign (Skin bumps)**
- **Clinically: the surgeon call them “Sebaceous cyst”**
- **Malignant transformation is extremely rare**
- **Many types:**
 - **Epidermal inclusion cyst**
 - **Dermoid cyst**
 - **Trichilemmal cyst**

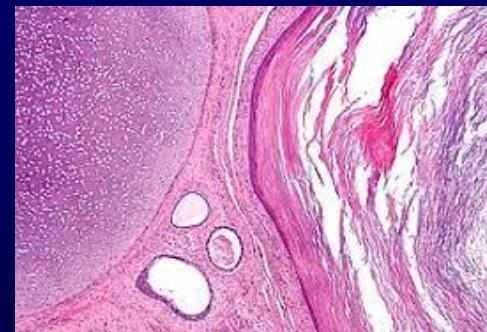
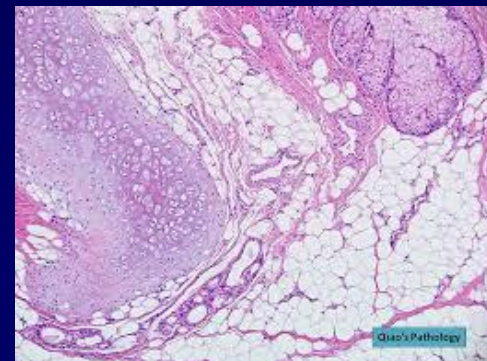
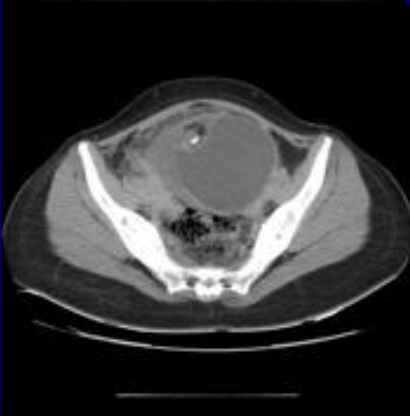
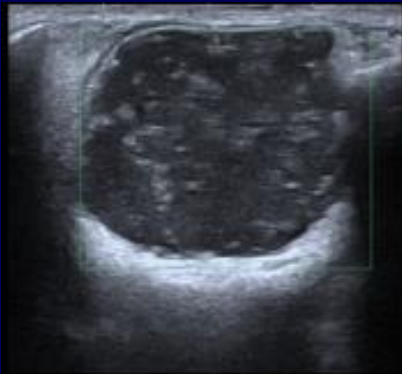
Epidermal (epithelial) inclusion cyst:



Dermoid cyst:

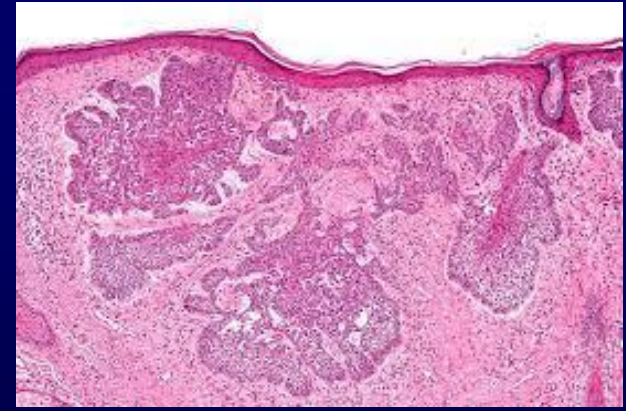
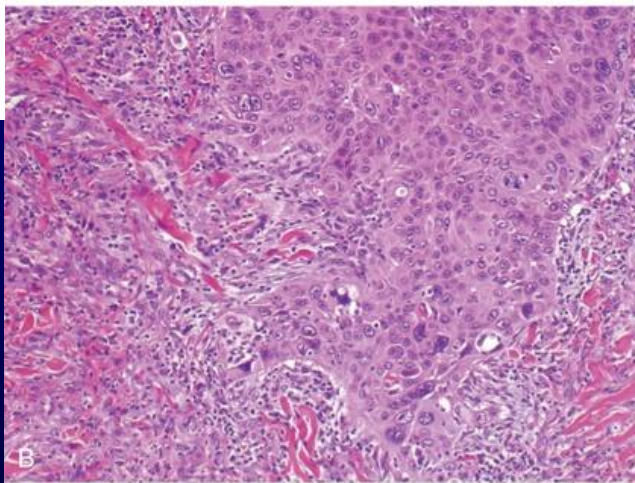
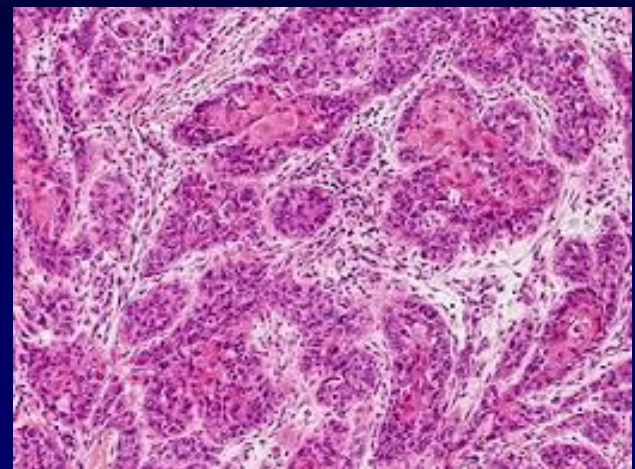
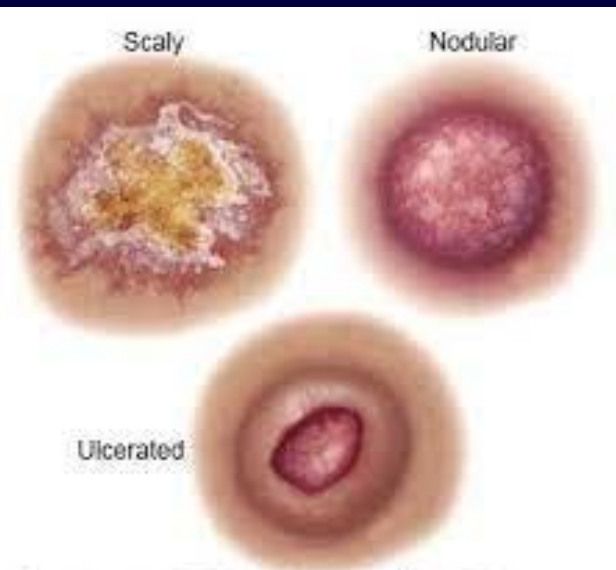
- **A dermoid cyst is a growth of normal tissue enclosed in a pocket of cells called a sac. This tissue grows in or under your skin in an unexpected location.**
- **A cyst is a lump or bump that may contain fluid or other material. Most often, dermoid cysts contain a greasy yellow material, but they may contain: mature tissues (bone, hair, muscle, teeth...etc)**
- **Dermoid cysts can be anywhere on your body.**
- **Rarely they can have immature or malignant elements (malignant dermoid cysts or teratoma)**
- **Peri-orbital, ovarian, spinal...etc**

Dermoid cyst:



Squamous cell carcinoma:

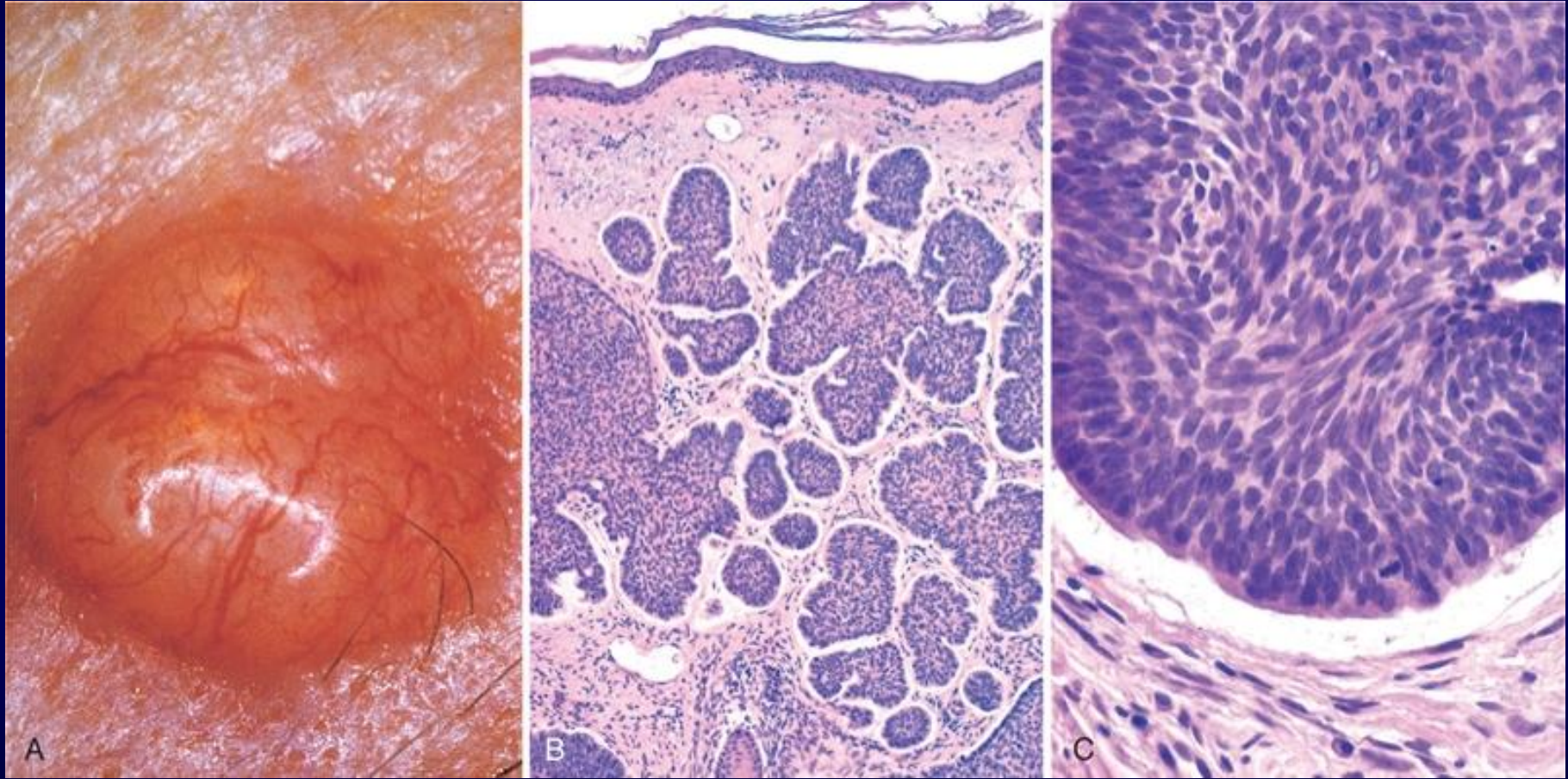
- **Common neoplasms**
- **Sun damage (sun exposed areas)**
- **Most commonly localized with rare deep infiltration or metastasis.**
- **Invasive, usually keratinizing squamous cell carcinoma**
- **Risk increases: immunosuppression (HPV), prolonged sun exposure, tars & oils, old burns, ionizing radiation**



Basal cell carcinoma:

- Arise from basal cells of epidermis
- Sun exposure
- Can be multiple
- Papules, slightly pigmented
- Localized, deep infiltration and metastasis are extremely rare
- *PTCH1* mutations and *TP53* mutations
- Gorlin syndrome: multiple basal cell carcinoma (Basal cell nevus syndrome)

Basal cell carcinoma:



Melanocytic neoplasms:

- **Nevus: benign congenital melanocytic neoplasm**
- **Melanocytic nevus: any melanocytic neoplasm (congenital or acquired)**

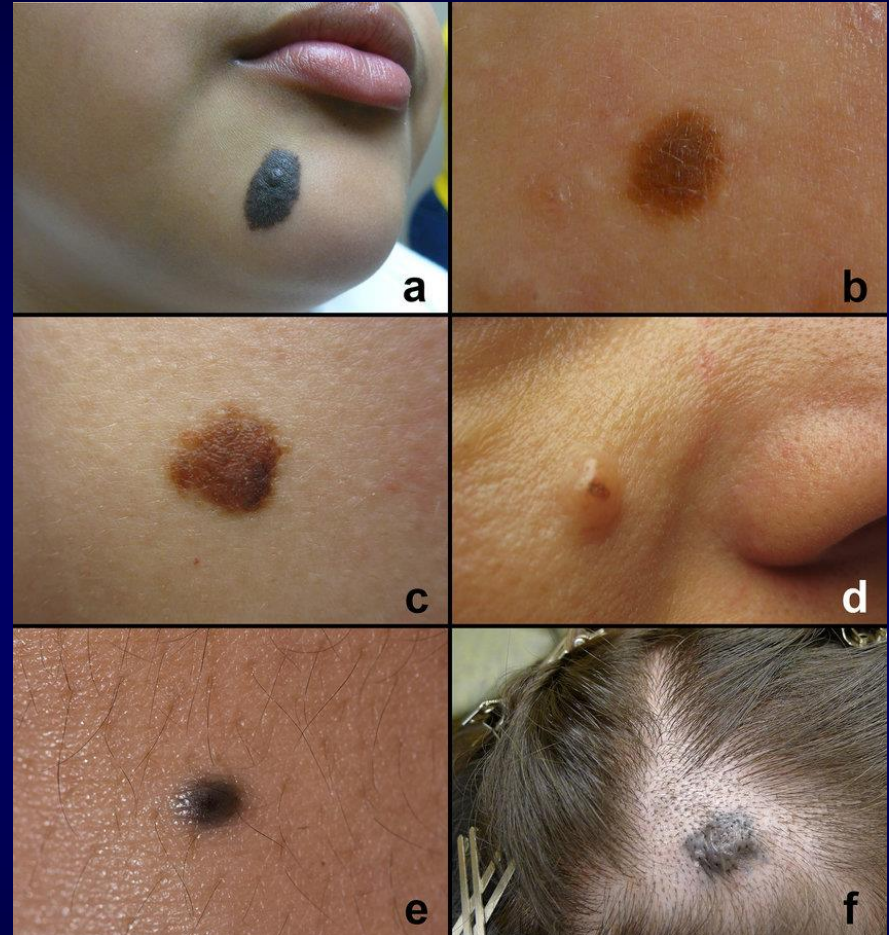


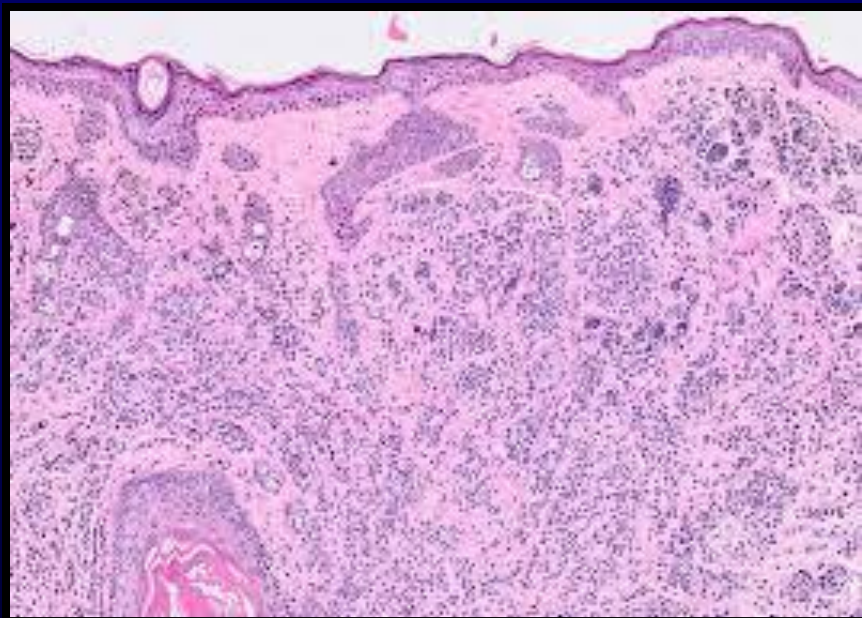
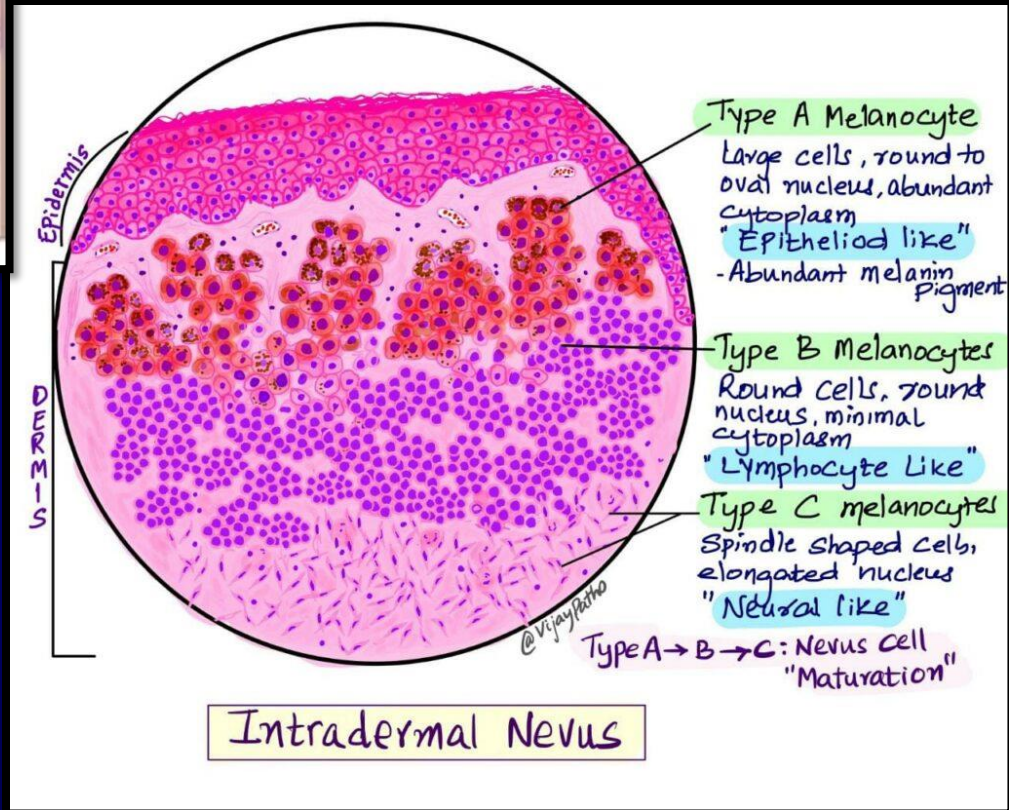
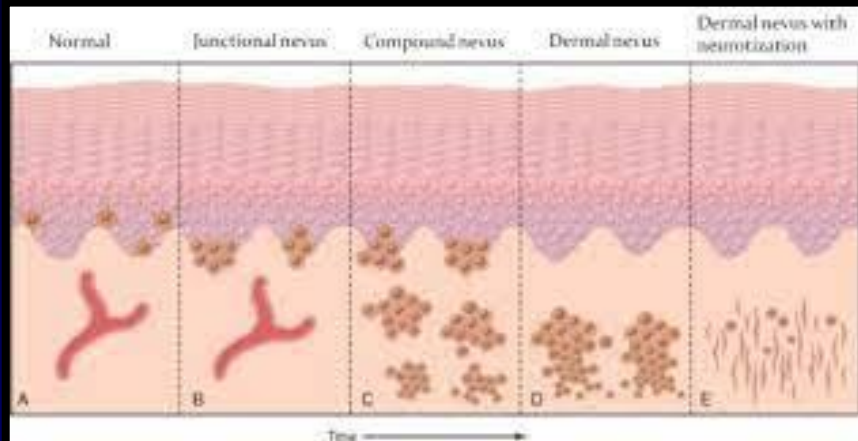
NEVUS

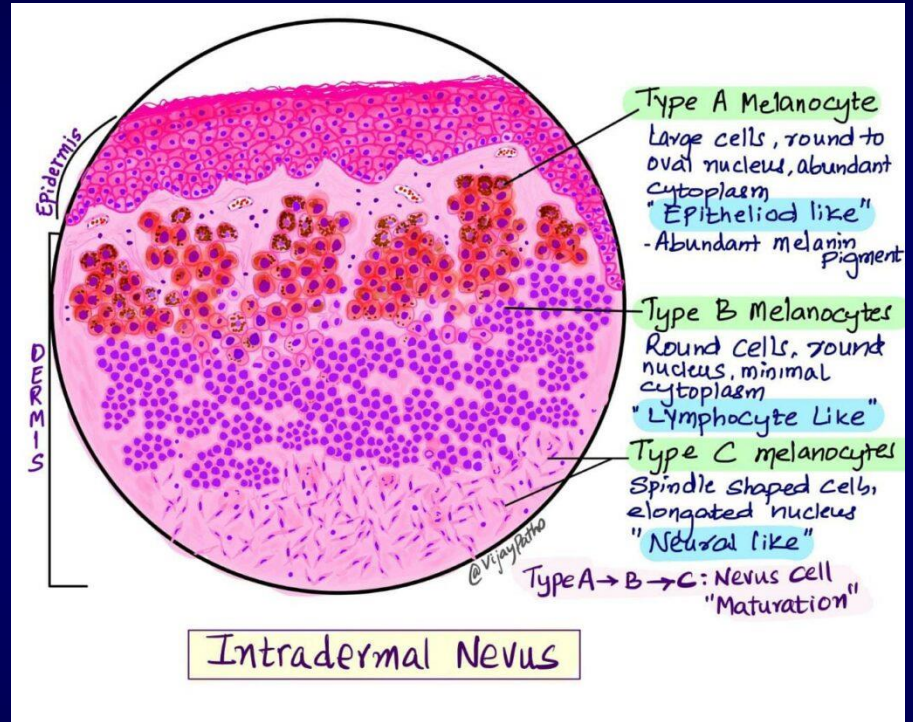
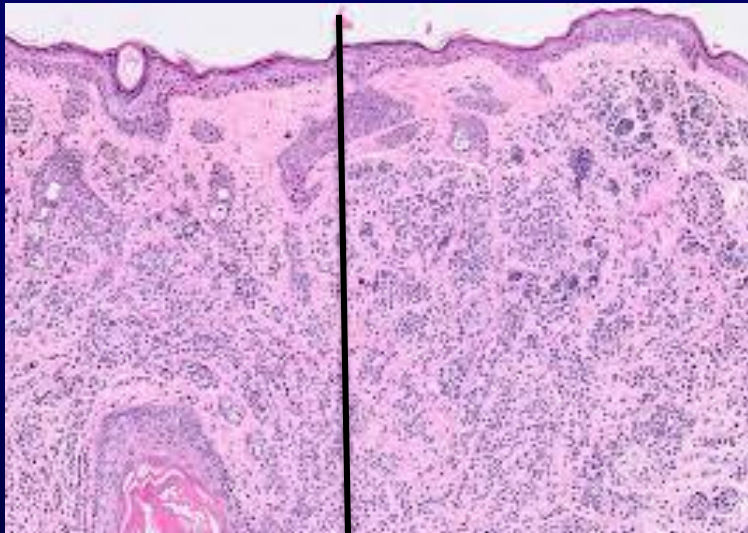
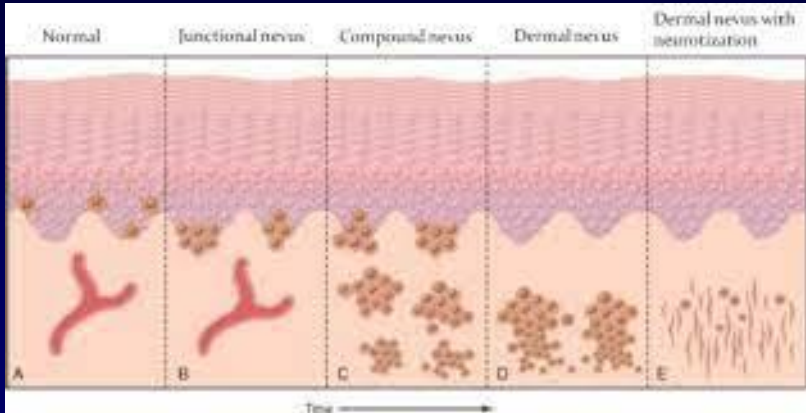
- **Benign pigmented melanocytic proliferation**
- **Caused by somatic gain of function mutation *BRAF* or *RAS***
- **This is followed by inactivity “Senescence”**
- **Clinically: sharply demarcated, elevated and pigmented.**
- **Removed surgically for cosmetic reasons, irritation and to rule out dysplasia or melanoma**
- **Junctional N. → Compound N. → Intradermal N**

Benign features:

- Well-demarcated
- Sharp borders
- No significant change over time
- Histology: symmetry, absence of atypia (cellular enlargement, nuclear enlargement, nuclear chromatin abnormalities, prominent nucleoli, mitosis, maturation as you move deep into dermis).





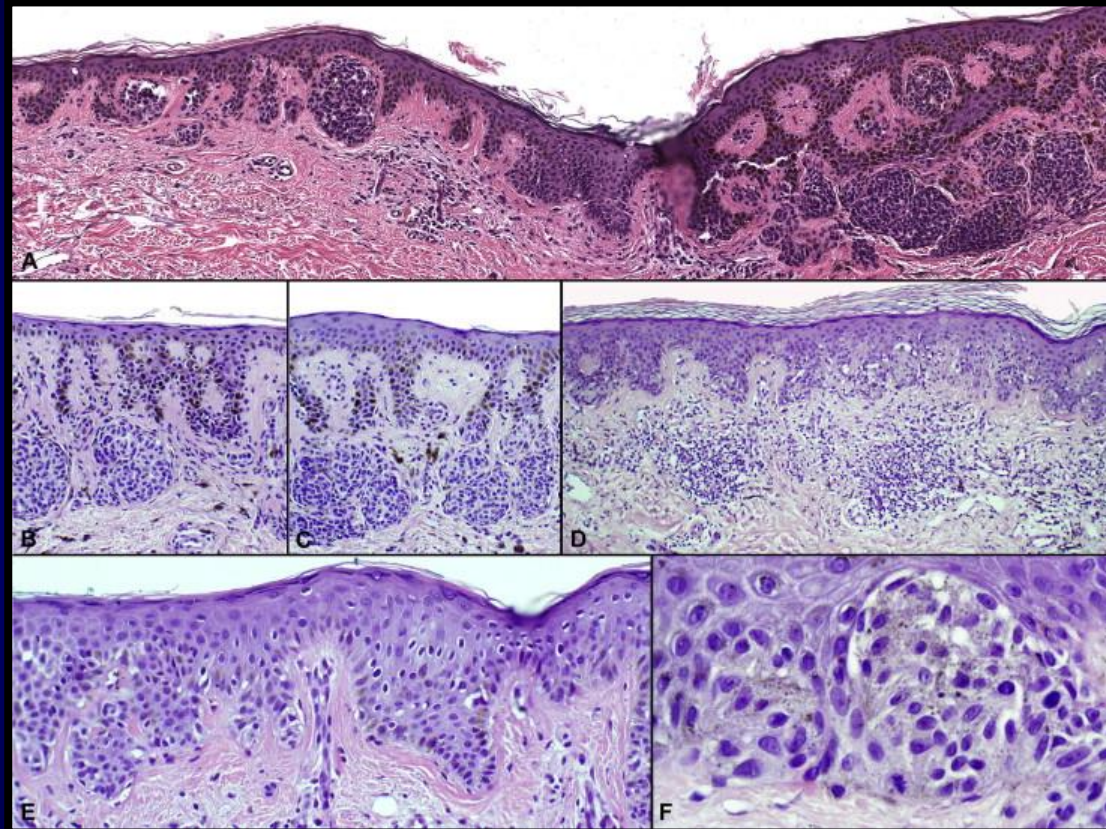


DYSPLASTIC NEVUS:

- Nevi with atypical features, usually larger (>5 mm)
- Sporadic or familial
- Occur on both sun exposed as well non sun exposed
- Can be multiple (specially familial type)
- Risk of melanoma is higher than non dysplastic
- However: risk is low and most melanomas occur “de novo”
- ***Familial dysplastic nevus syndrome***: high life-time risk

Histopathological features:

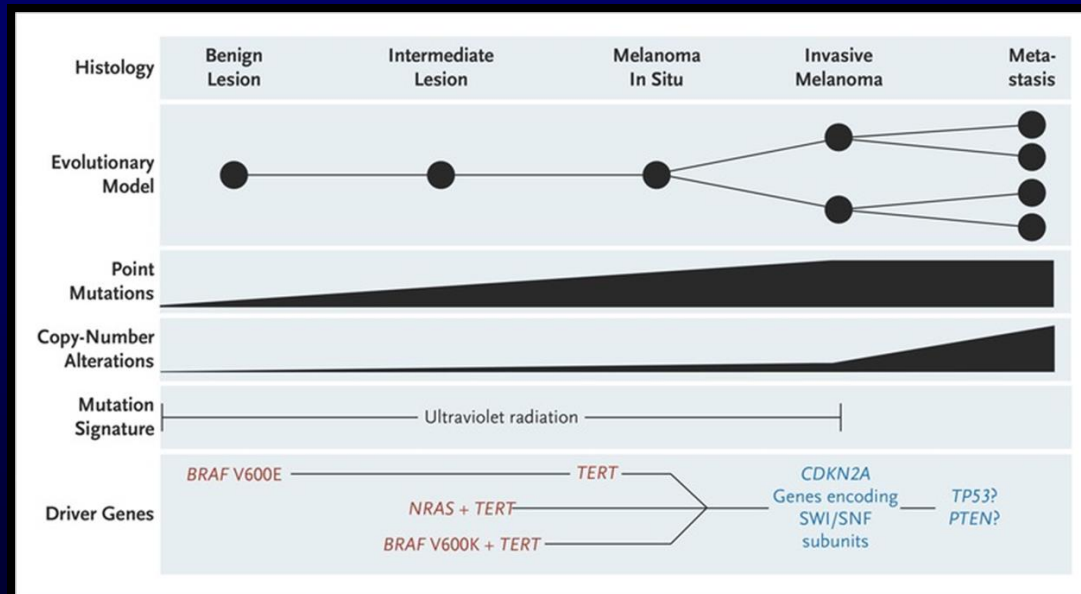
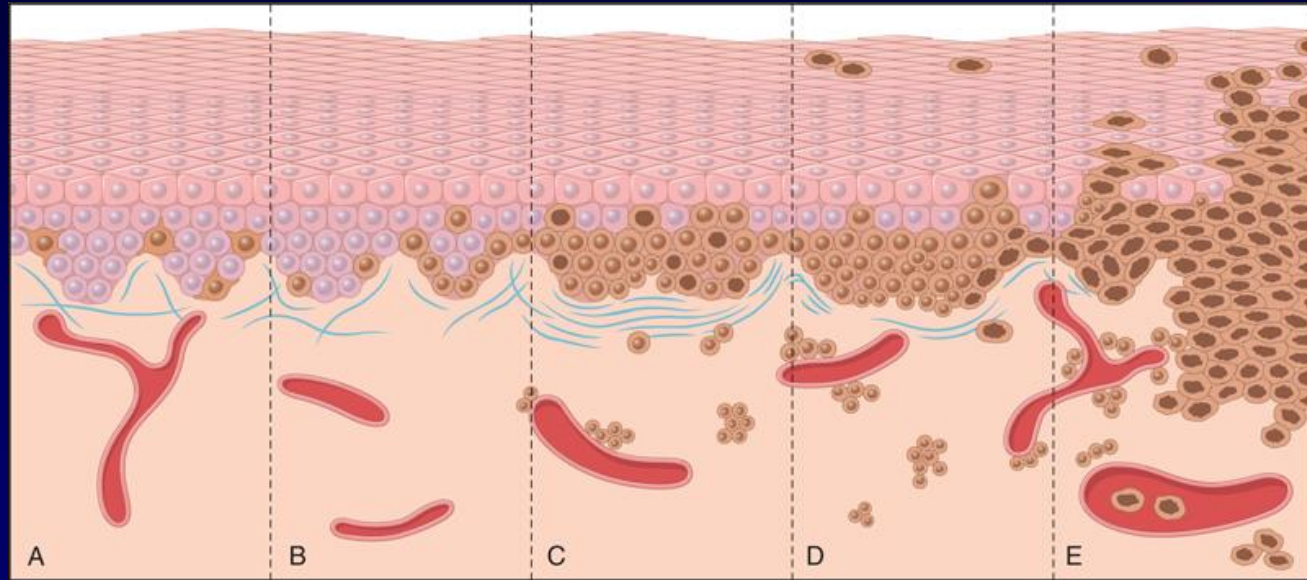
- Loss of symmetry
- Fusion of junctional nests
- Cellular and nuclear atypia
- Superficial dermal fibrosis
- Lymphocytic infiltration
- Melanin incontinence

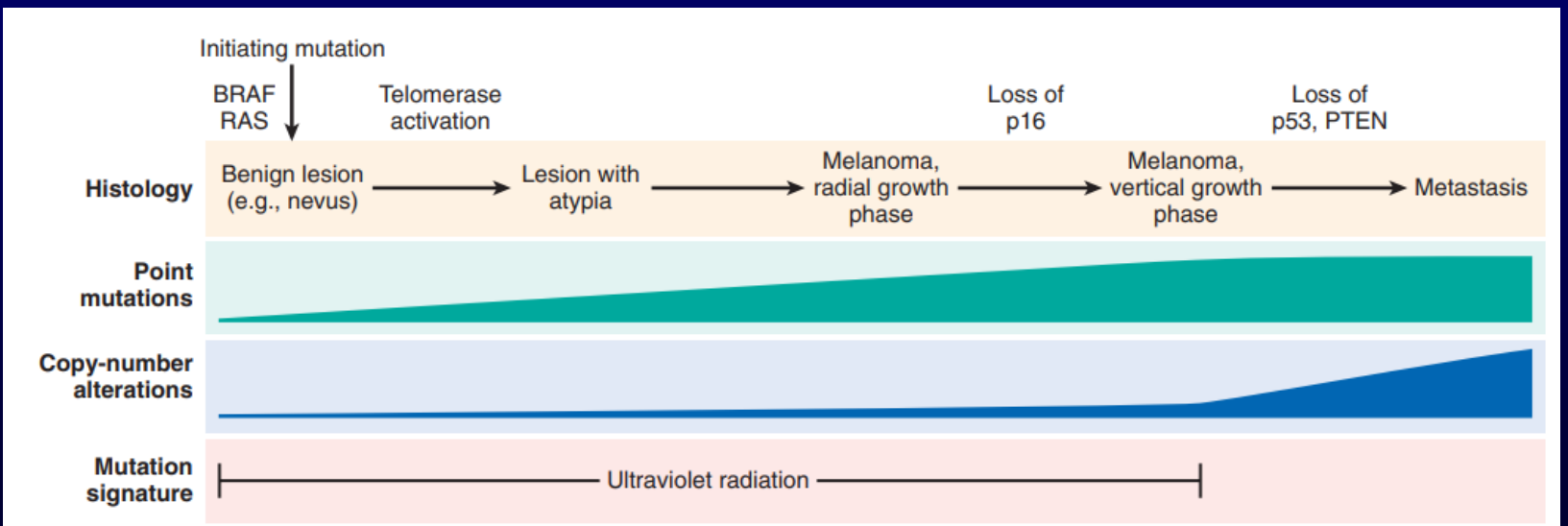
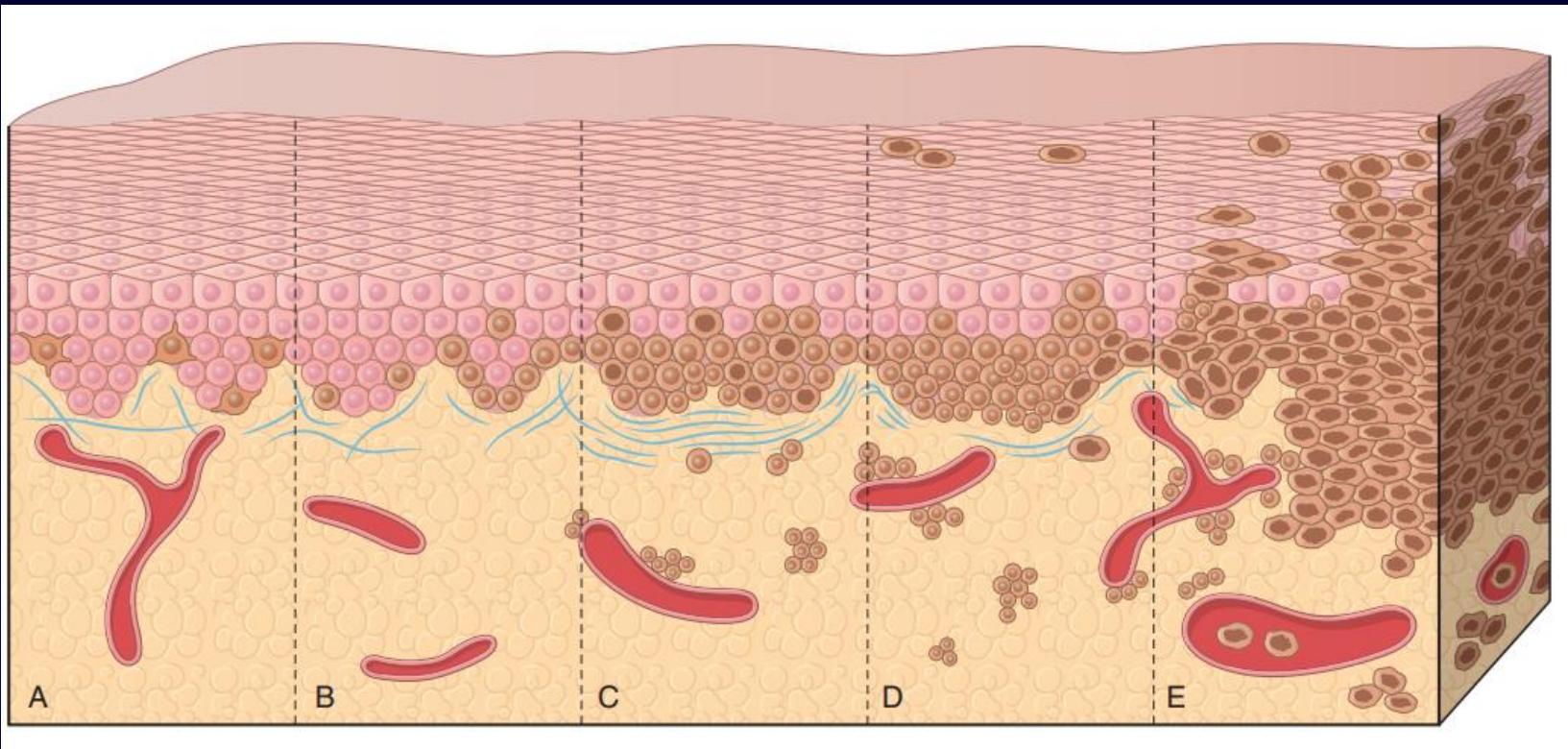


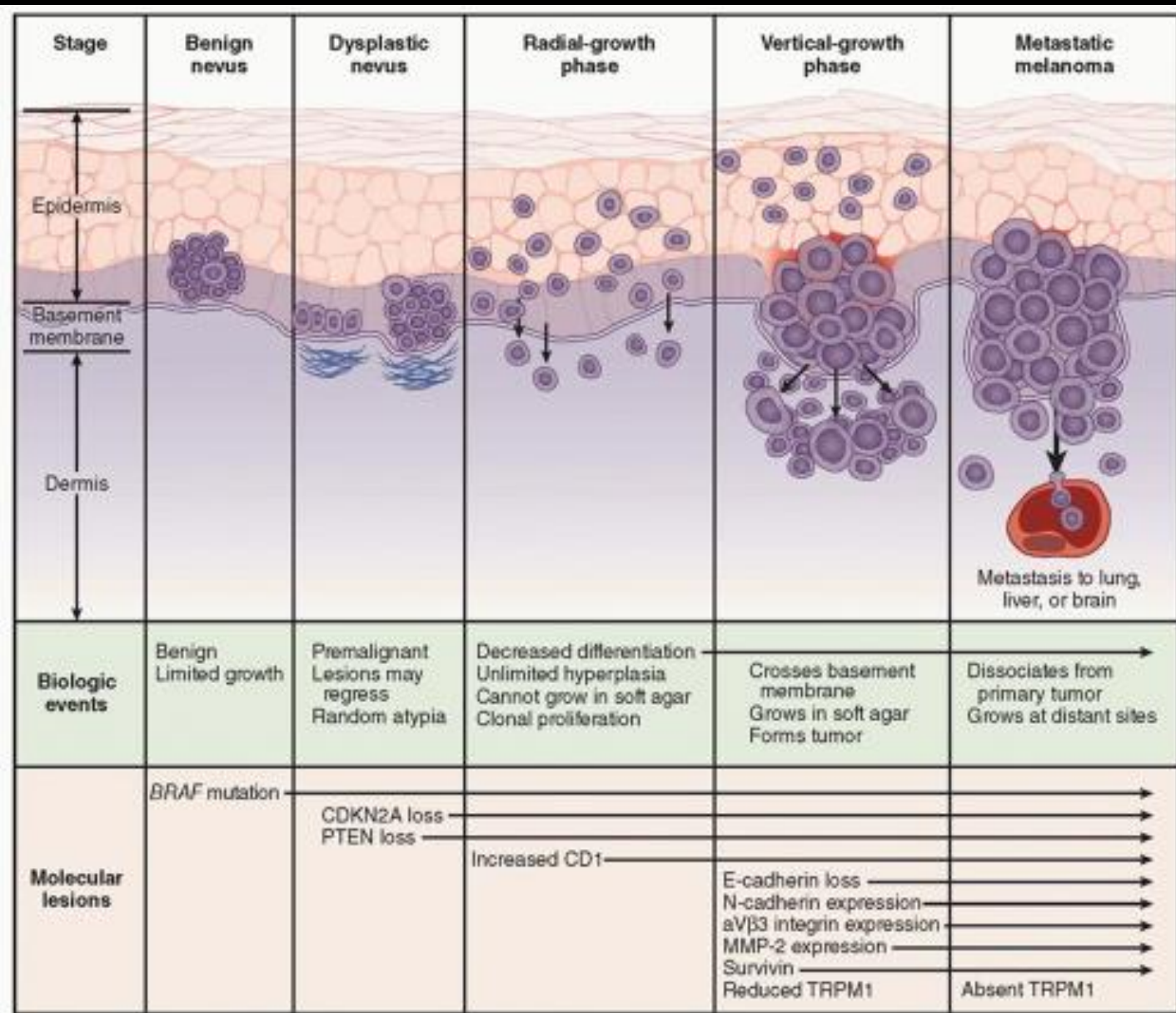
MELANOMA

- **Malignant neoplasm of melanocytes and can be fatal**
- **Less common than Sq. CCa, Basal CCa and nevi**
- **Currently: most melanomas are cured surgically**
- **The incidence is on the rise:**
 - **More sun exposure**
 - **More surveillance**
 - **More public awareness**

MELANOMA EVOLUTION

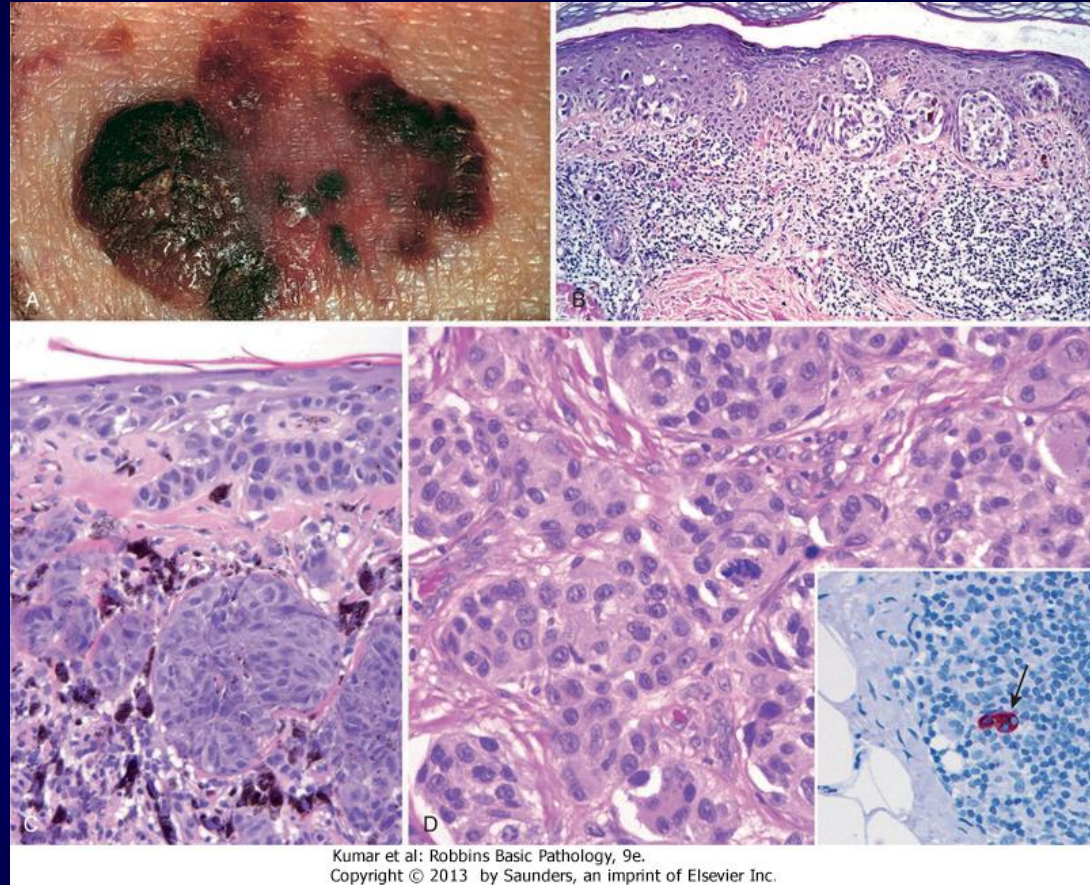






Pathological features:

- Irregular borders and pigmentation
- Irregular nesting with increased numbers of single cells
- Radial and vertical growth
- Increased thickness (Breslow thickness)
- Deeper invasion
- Larger atypical cells
- Atypical larger nuclei with prominent cherry-red nucleoli



WARNING SIGNS OF MELANOMA:



- **Rapid enlargement of a preexisting nevus**
- **Itching or pain**
- **New pigmented lesions development**
- **Irregular borders of a pigmented lesion**
- **Variiegation of color within a pigmented lesion**

CLINICAL FEATURES AND PROGNOSIS:

- Most can be cured surgically
- Stage is critical (depth of invasion)
- Metastatic disease exhibits poor prognosis
- “Sentinel node” evaluation may help in stage determination
- Recent evolution in treatment options (targeted therapy):
 - Anti *BRAF* and *KIT* agents
 - Immune check point inhibitors (T-cell mediated immunotherapy)

GOOD

LUCK