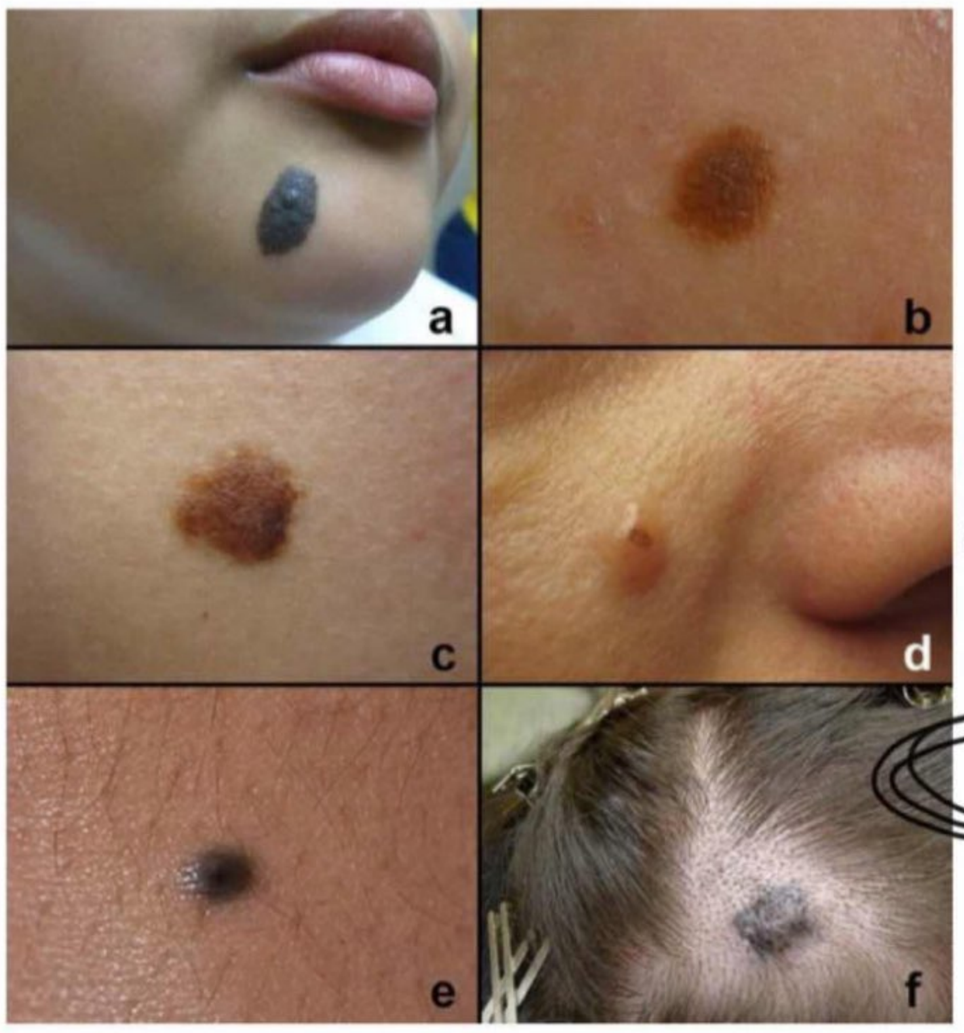
(مراجعة)

BENIGN FEATURES OF NEVUS

مهمة!



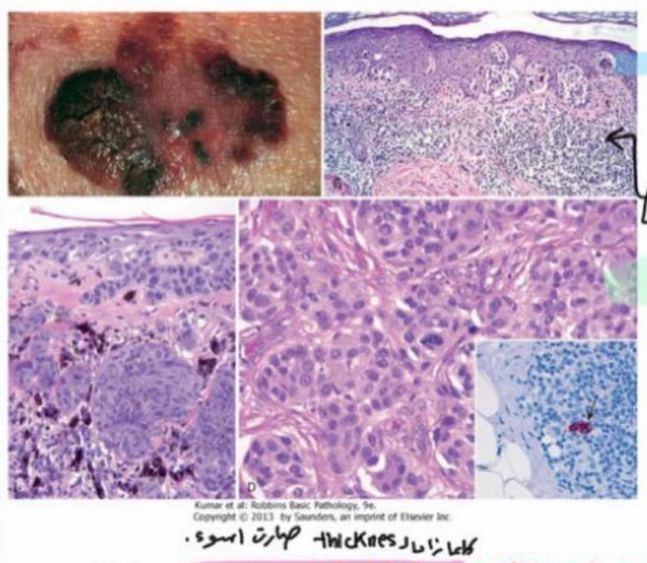
- It is characterized by **well-demarcated and sharp borders**.
- It usually **does not change** significantly over time. ← ① نقول ثابتة من أول ما اتخلقت
- Histologically, it **exhibits symmetry and absence of atypia**, (including cellular enlargement, nuclear enlargement, nuclear chromatin abnormalities, prominent nucleoli, mitosis), and **maturation as you move deep into dermis which is a feature.**

→ No mitosis
→ No atypia

These are the initial heads (early changes): BRAF & RAS (Extremely Important!)

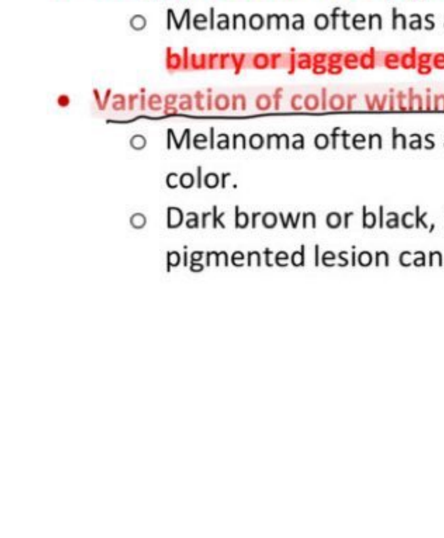
PATHOLOGICAL FEATURES OF MELANOMA (IMPORTANT!)

أهم سلايد



- Melanoma has irregular borders and pigmentation (not always present).
- It shows irregular nesting with increased numbers of single cells.
- Melanoma exhibits radial and vertical growth. (علامة الخطورة) (deeper)
- The Deeper and thicker it is, the worse (prognosis) it is because it can metastasis.
- The more superficial and thinner it is, the better (prognosis) it is. (thickness علامة خطورة اسوء)
- It has increased thickness (Breslow thickness)!
- Deeper invasion and larger atypical cells are also common.
- The nuclei in melanoma cells are larger and atypical with prominent cherry-red nucleoli. (النيوبلازم اكتر)
- Nucleus and cytoplasm are both enlarged; the ratio of nucleus to cytoplasm will not be high, as both components are similarly enlarged

EVOLUTION OF MELANOMA (IMPORTANT!)



- So we have multiple heads:
  - the Initial head: BRAF and RAS.
  - The Middle head: TERT
  - The Later Heads: TP53 and PTEN which mainly involve the Tumor Suppressor Genes!
  - These Heads are the target of treatment.
- First is Rapidly growth (radial growth) and then vertical growth.

WARNING SIGNS OF MELANOMA

كتير مهمة

1. **Rapid enlargement of a preexisting nevus**
   - A nevus is a mole or pigmented lesion on the skin.
   - If the size of the nevus increases rapidly, it can be a warning sign of melanoma.
- **Itching or pain**
- **New pigmented lesions development**
  - The development of new pigmented lesions on the skin, **especially in adulthood**.
- **Irregular borders of a pigmented lesion**
  - Melanoma often has an irregular or **asymmetrical shape with blurry or jagged edges**.
- **Variegation of color within a pigmented lesion** (ال Color بتختلف من مكان لمكان)
  - Melanoma often has a mix of colors or an uneven distribution of color.
  - Dark brown or black, red, white, or blue shades within a pigmented lesion can be warning signs of melanoma.

Answer: D) The evolution of melanoma can occur in two ways: either progressing from a benign nevus to a dysplastic nevus and then to melanoma or arising de novo without arising from a pre-existing nevus

*Important notes:

→ The doctor said that the main differentiator between Solar elastosis and actinic keratosis is the presence of CELLULAR ATYPIA.

* Solar elastosis = NO ATYPIA. [thickened + yellow skin + deep wrinkles lines]
* Actinic keratosis: ATYPIA must be present. [it's a pre-malignant] [mutation in gene +p53]

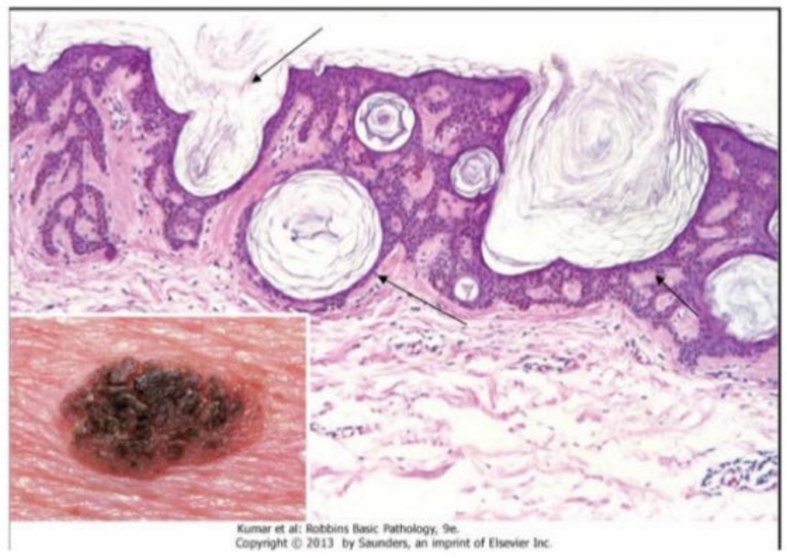
Scanned with CamScanner

Seborrheic Keratosis:

→ Coin-like lesions with intra-epidermal keratin filled cysts. They appear "Stuck on" to the skin.

→ The most common mutation occurs in the FGFR3 gene.

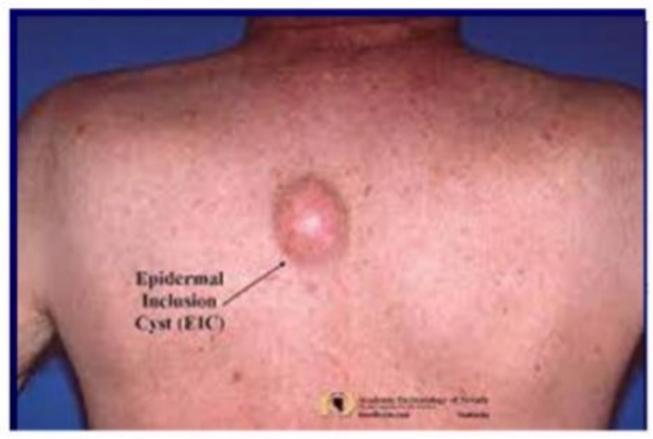
→ They can present anywhere on the body, but the trunk is the most common site of presentation.

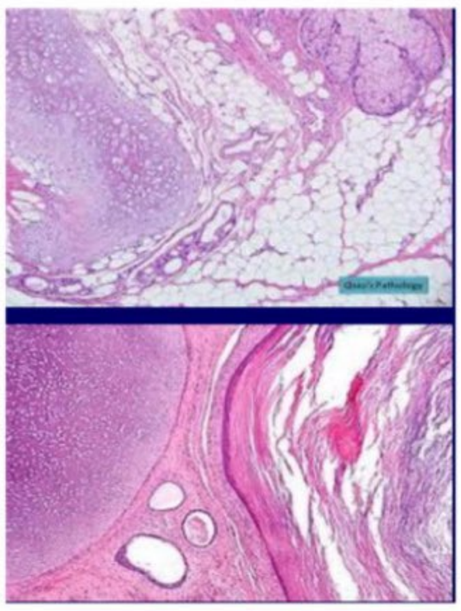


Skin cyst:

① → Epidermal (Epithelial) Inclusion cysts: Keratin filled cysts inside fully mature squamous epithelium with granular cell layer (Granulosum layer).

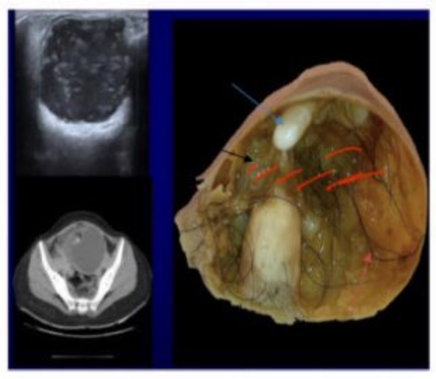
→ They are abnormally located sacs filled with a greasy yellow material and other MATURE mesenchymal tissue such as: Bone, hair, muscle, teeth, cartilage, etc. (Dermoid cyst)





Perfect representation of how one dermoid cyst can have multiple types of fully mature mesenchymal tissue.

We can see cartilage, skin, adipocytes, and other tissue in one histological sample



→ Ovarian teratomas (dermoid cysts) are 90-95% benign,

→ ALL teratomas found in the testes are malignant.

Squamous cell carcinoma:

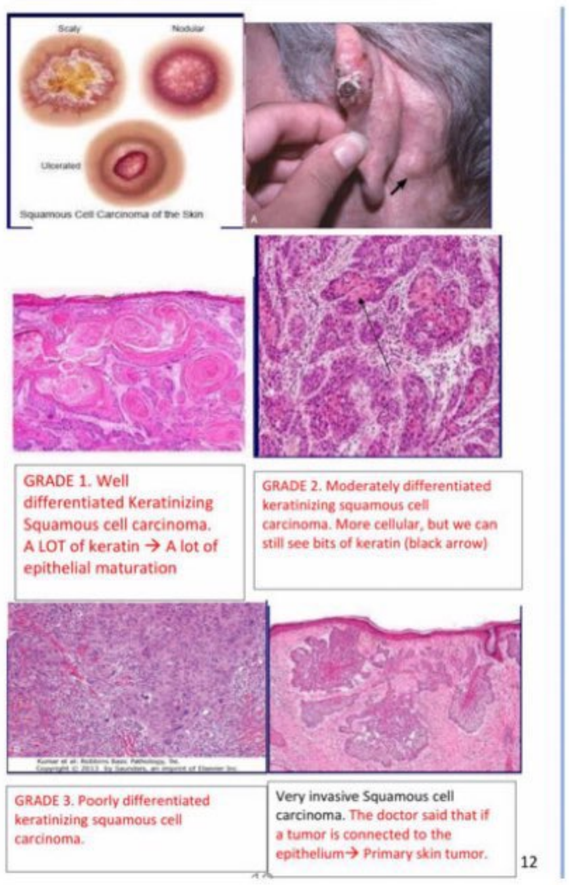
Risk factors:

① → Immunosuppression (HPV in cervical cancer cases), prolonged sun exposure, tars and oils, Old Burns (Squamous cell carcinoma that develops on top of old burns is called a Marjolin Ulcer), and Ionizing radiation.

→ They are common neoplasms that happen due to sun damage.

→ They are commonly localized to the epidermis and dermis. Very rarely do they ever metastasize or infiltrate deep tissue layers.

→ They are however invasive.



two types:

① -Keratinizing squamous cell carcinoma

② -Non-keratinizing Squamous cell carcinoma: More dangerous than its keratinizing counterpart.

Basal cell carcinoma:

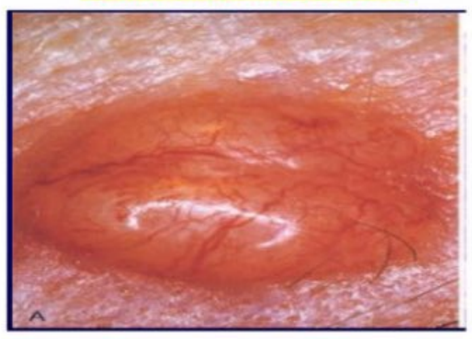
→ Prolonged sun exposure that causes loss of function in tumor suppressor genes such as PTCH1 and TP53 that regulate cell division.

→ Basal cell carcinoma arises from mutated Basal cells of the epidermis.

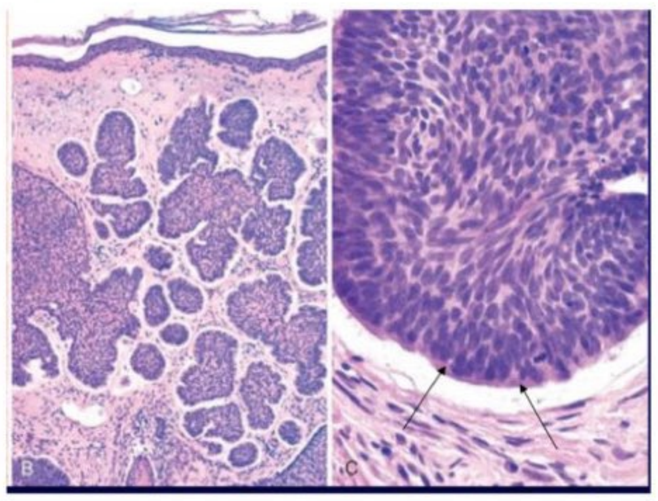
→ Most common tumor of the skin.

→ It is less aggressive than squamous cell carcinoma.

→ The cell mutated in both squamous cell carcinoma and basal cell carcinoma is the keratinocyte. The only difference is where the mutated cell is found.



Pearly papule with prominent, dilated subepidermal blood vessels.



Picture on the left shows multiple basal cell tumors invading the underlying dermis. They show cellular atypia and a more bluish color.

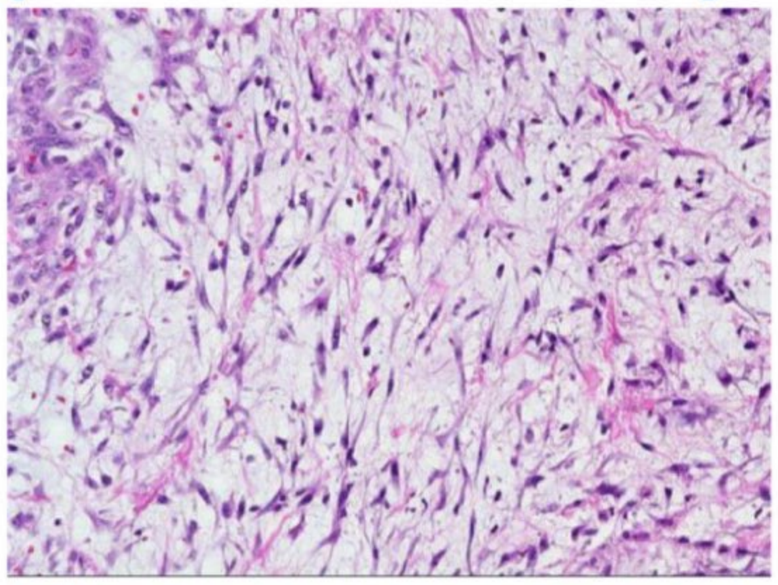
The black arrows on the right show the palisading pattern of basal cell carcinoma. Look at how the nuclei is forming a line that separates the tumor from the stroma.

Scanned with CamScanner

FIBROUS TUMORS:

1. Nodular Fasciitis: benign disease.

of culture-like histology.



- Nodular fasciitis: thought to be reactive process.
- Now, clonal, t(17;22) producing MYH9-USP6 fusion gene.

Nodular fasciitis is a tumor **not** an inflammatory proliferative reaction .

- Maybe self-limiting

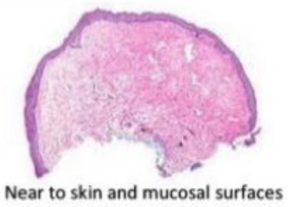
Nodular fasciitis maybe **self-limiting**, and this is the excuse of the people who believe that nodular fasciitis is not a true tumor even though it has a clonal signature change.

- Trauma history, recent rapid size increase

A Case: 35 or 45 years old patient, who had a chest trauma, after couple of weeks, he came with a mass nodular fasciitis. (recent trauma history).

Spindle cells + Inflammatory cell
Fregent mitosis + + lymphocytes.

2. Fibromas and Fibrosarcoma:

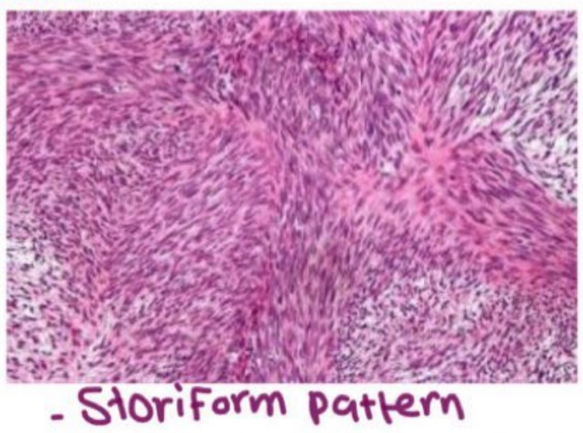


Near to skin and mucosal surfaces (oral mucosal surface, vagina... etc)

① • Fibromas: benign proliferation of fibroblasts, very common, skin and subcutaneous tissue.

② • Fibrosarcoma: malignant counterpart. usually, superficial cutaneous tumors of fibroblasts, cellular, storiform pattern with increased mitosis. →

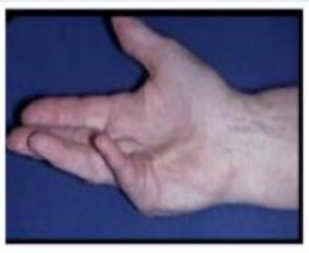
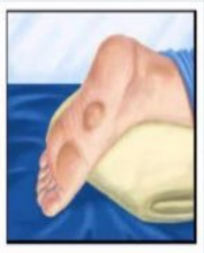
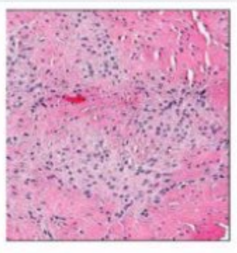
Low grade sarcomas, t



- Storiform pattern
- herring Bone appearance.

3 A. Superficial fibromatoses:

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

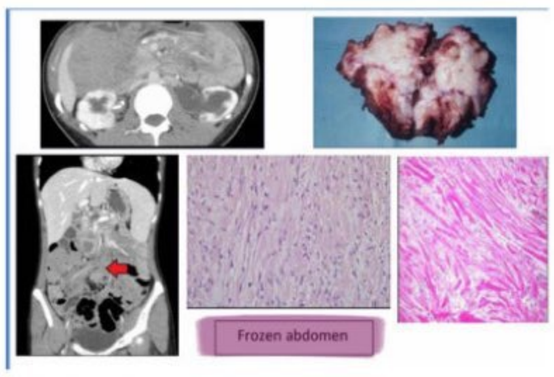
Palmer (DUPUYTREN CONTRACTURE)	PLANTAR FIBROMATOSES	PENILE (PEYRONIE DISEASE)
Palmar fascia	Sole of foot	Dorsolateral aspect of the penis
		
Palmer contraction, flexion of finger and you cant open it, so interfers with the function.	they are painful.	Very painful especially in erections and very difficult to treat.

B. Deep fibromatoses (Desmoid tumor):

→ 20- 30 years. Females are common
→ mostly Common in Intra-abdominal wall + thigh.

- Mutations in CTNNB1 (β-catenin) or APC genes leading to increased Wnt signaling. • Mostly are sporadic; but patients with Gardner (FAP) syndrome are susceptible.

→ Infiltrative but not metastasis
→ They can Kill you by local Infiltrative Not metastasis.

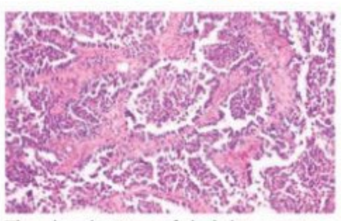


FROZEN abdomen.

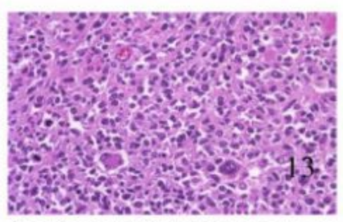
SKELETAL MUSCLE TUMORS

① • Almost all malignant; except rhabdomyoma which is benign, rare, occurs with tuberous sclerosis 3

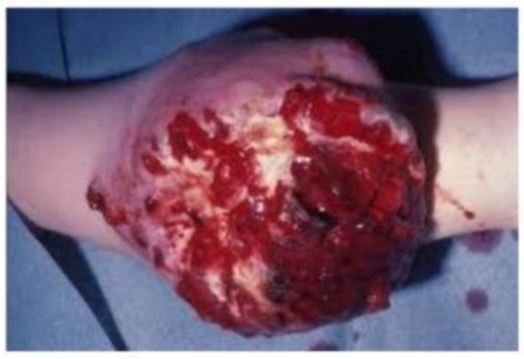
② • Rhabdomyosarcoma (RMS) is the malignant prototype; most common child sarcoma <15 yr. more common than rhabdomyoma.



The alveolar type of rhabdomyosarcoma, because it looks like the alveoli of the lung.



The pleomorphic rhabdomyosarcoma (Embryonal type).

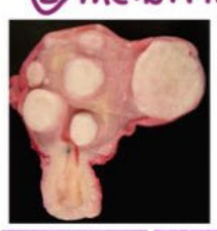


Rhabdomyosarcoma
→ bulky + necrosis + hemorrhage

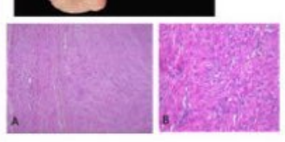
SMOOTH MUSCLE TUMORS

leiomyoma (Benign)
*very common
*any site but mostly uterus. (Fibroid)

①Infertility
②menorrhagie



·ball-like masses
·No necrosis + No hemorrage +

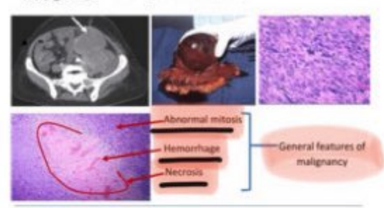


No increased mitosis.
No inFiltration.

leiomyosarcoma (malignant)

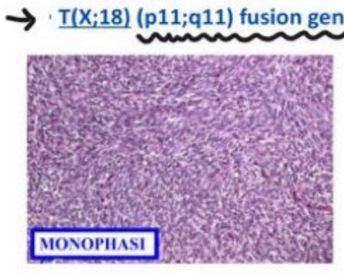
• Hemorrhage, necrosis, increased mitosis and infiltration of surrounding tissue.

·more in female

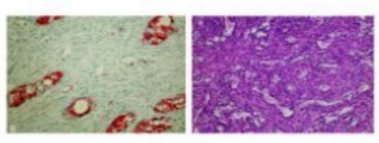


→Synovial Sarcoma: it can be anywhere but commonly around joint

→ T(X;18) (p11;q11) fusion genes SS18...



monophasic: only spindle cells.



• Metastasis: lung and lymph nodes.

biphasic (spindle cells + glands)

2. Undifferentiated pleomorphic sarcoma

Occur in abdominal, thigh

* No origin + anaplastic cells + pleomorphic appearance (ugly + necrosis + hemorrhage

• Large tumors; anaplastic and pleomorphic cells, abnormal mitoses, necrosis

Scanned with CamScanner

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).

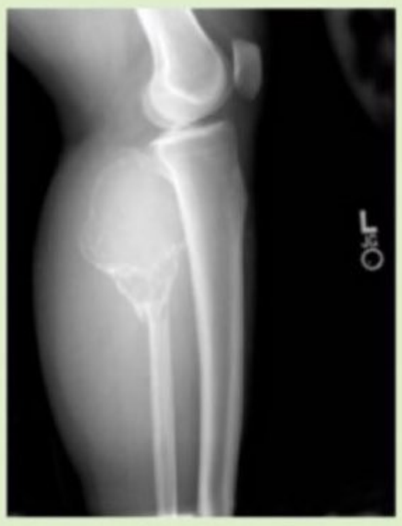


FIG. 21.25 Radiographically, giant cell tumor of the proximal fibula is predomi...

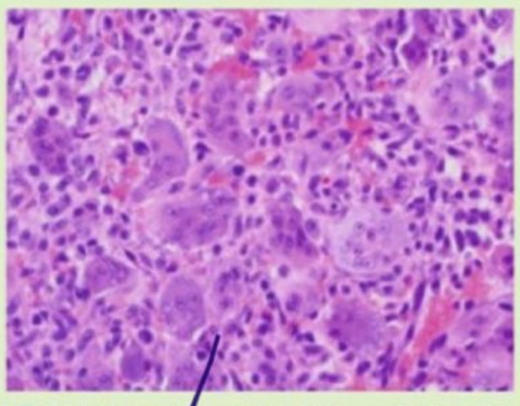


FIG. 21.26 Giant cell tumor illustrating an abundance of multinucleated giant c...

giant cell tumor:

① 90% - 95% (benign)

② potentially malignant

③ destroying vertebral bodies

④ locally aggressive neoplasm of adult

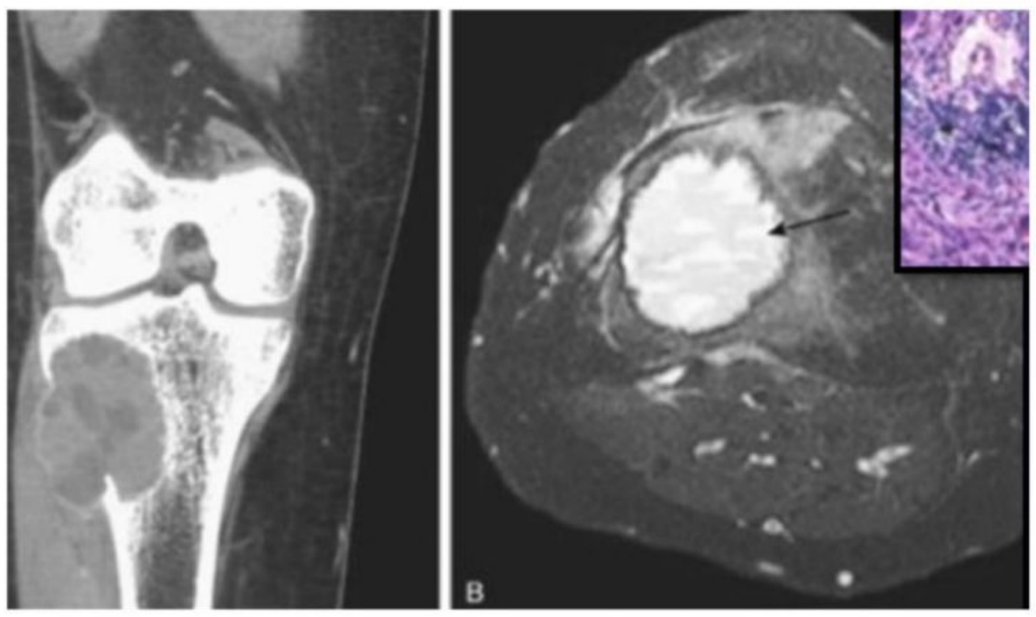
⑤ it's located in Epiphyseis of long Bone.

⑥ it's called osteoclastoma

⑦ cells Contain high level of RANKL

it's mononuclear cell and multi-nucleated giant cell

ANEURYSMAL BONE CYST:

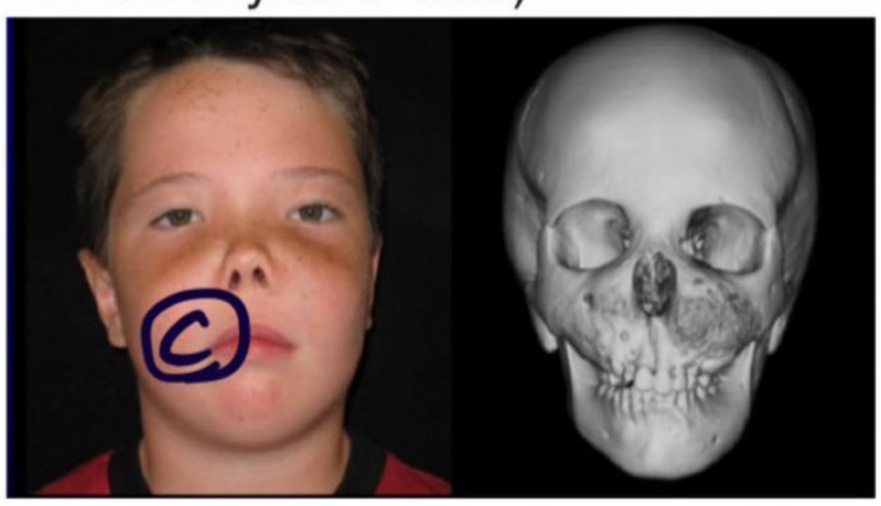


*benign tumor
* cyst Filled with blood
* it's located in metaphysis of long Bone.
* it occur to old (adult but not children
* No codman tringle No Filtration.

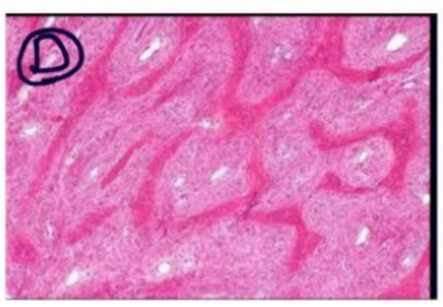
FIBROUS DYSPLASIA (FD):

something Wrong happen during osteoblast differentiation and maturation. not a real tumor [due to mutation in GNAS 1 gene (CAMP)

– Mazabraud syndrome: FD(fibrous dysplasia)+ soft tissue myxoma(benign tumor of the myxoid cells)



Common locations:face and jaws



abnormal Bone Formation + abnormal marrow (Chienese letter)

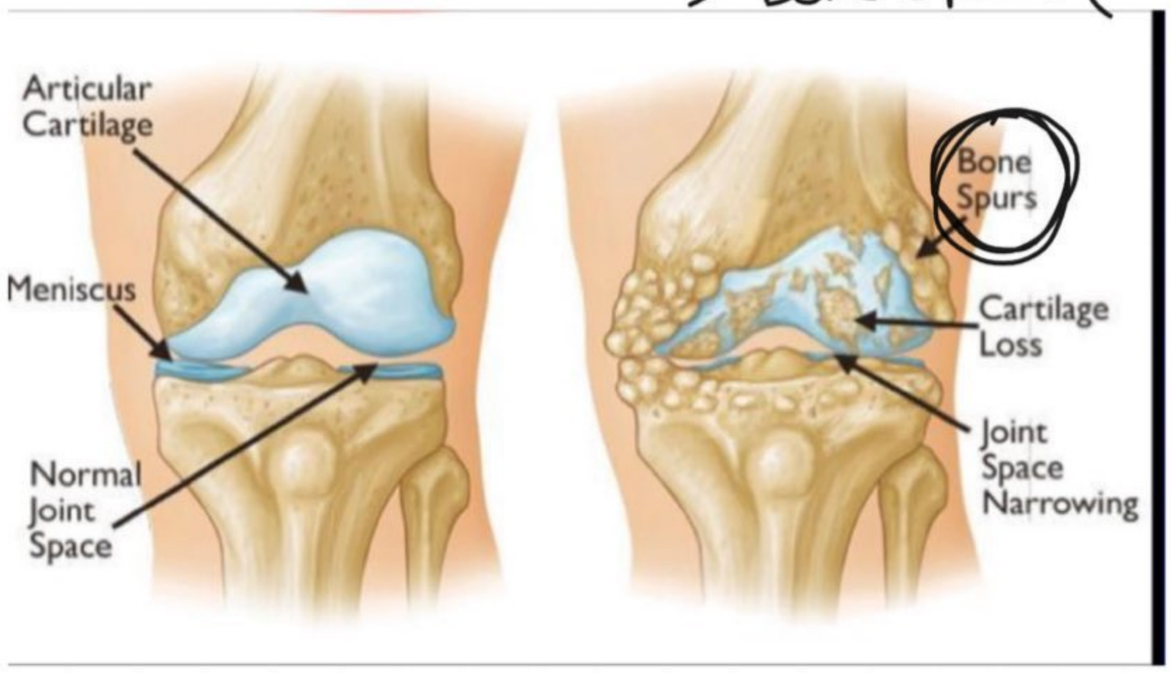
maccune-albright Syndrom

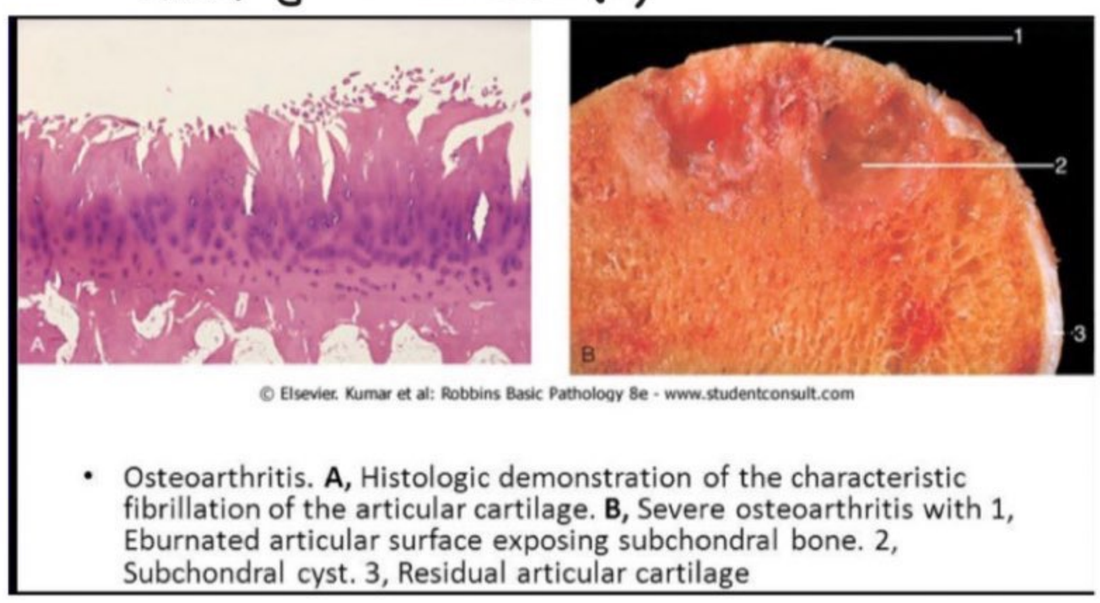
① Polystotic Fibrous dysplaica
② abnormality in Bone of Jaws, Pelvis
③ Café-au-lait skin Pigmentation
④ endocrine abnormality (hyperthyrodisim) + precocious puberty

Scanned with CamScanner

-In children: Neuroblastoma, Wilms tumor (these the top two most common causes of abdominal masses in children(under 6 years)and rhabdomyosarcoma(sarcoma of the skeletal muscles)

* osteoarthritis → ① it's not itis, it's ajoint cartilage disease (not in the bone) more
→ ② degenerative of cartilage due to → ① aging process (common)
→ ② pre-existing disease.
↓
→ ③ Injury → repair
→ subcondral cyst may happen also
→ Bone spurs (some of the Bone will leave the Bone and go to cartilage)





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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

- HLA-B27 + sacroiliac joint pain+ RF negative→ seronegative.
  - **Ankylosing Spondylitis:**

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

Reiter sondrom

  - **Reiter Syndrome:**

    Triad of arthritis, urethritis (males)/ cervicitis (females) and conjunctivitis, usually induced by bacterial infections (mainly STD; sexually transmitted diseases) such as gonococcal infections.

    Good prognosis.

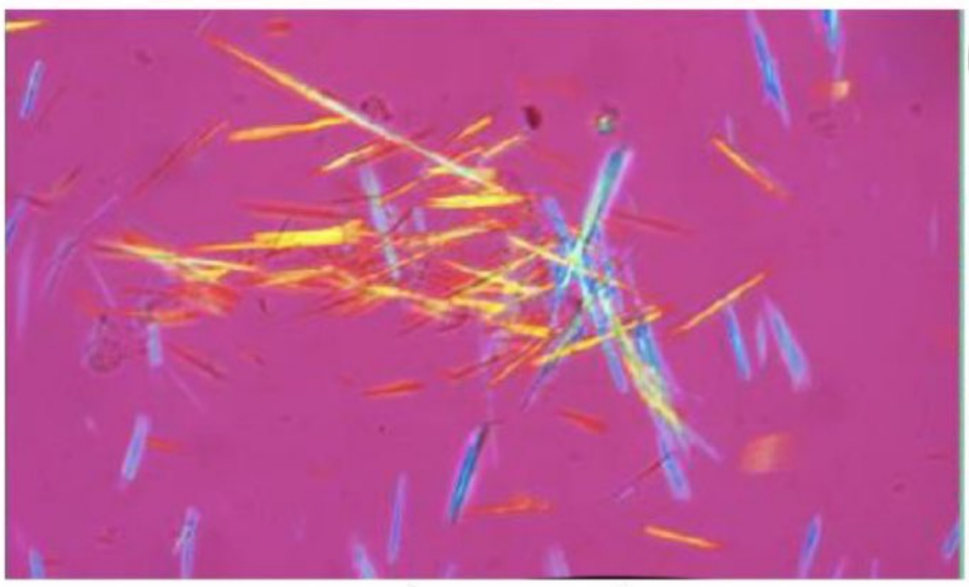
  - **Enteropathic Arthritis:**

    Secondary to bowel infection (salmonella, shigella).

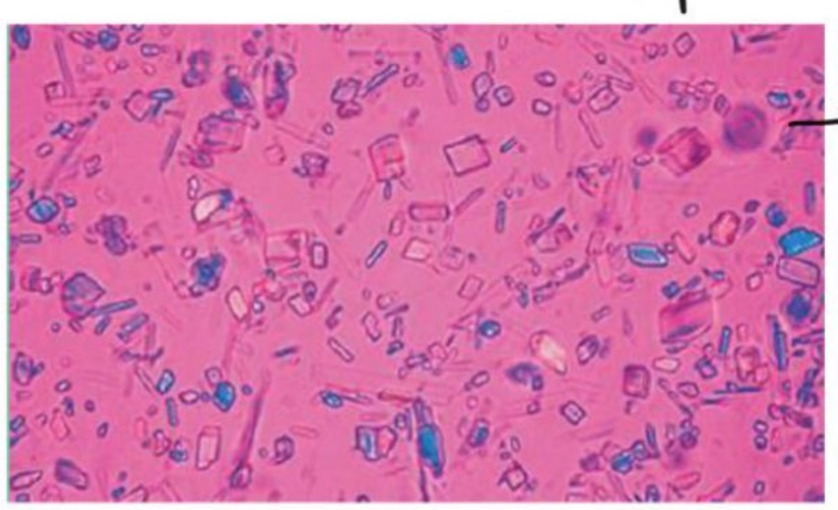
    HLA B27 positive.

  - **Psoriatic Arthritis:**

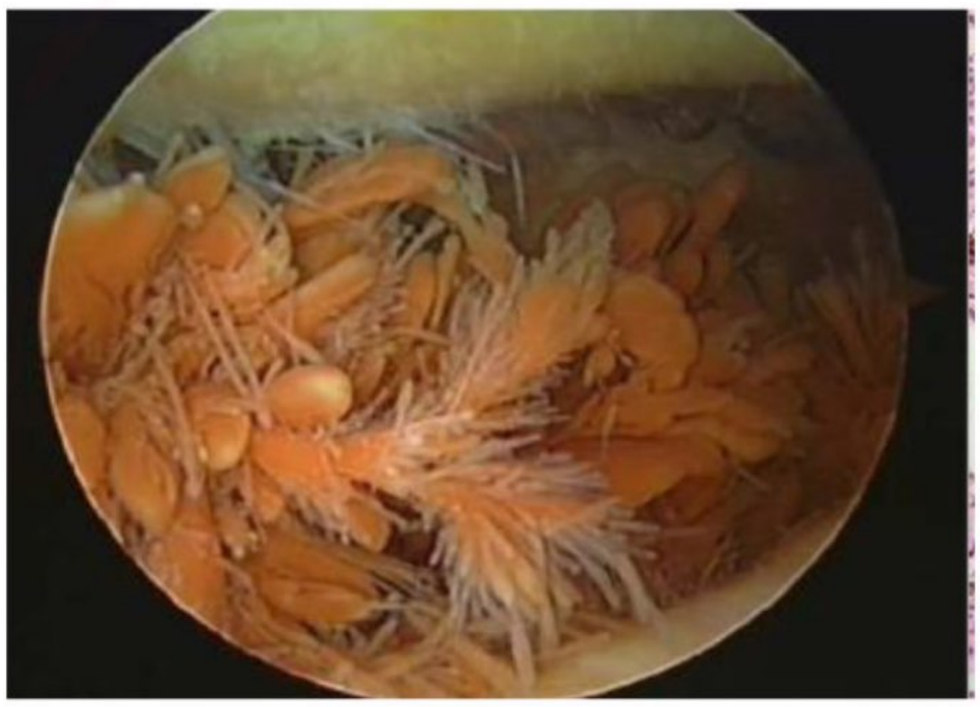
    5% of patients, starts in DIP (distal interphalangeal) joints, similar to RA (arthritis+ psoriasis).


(Gout)

① Parallel + needle shape +
② birefringence −
② Yellow + Monosodium urate deposition.


→ pseudoGout
Blue rod cell or rhomboid + parallel
(positive birefringence) +

Scanned with CamScanner



tenosynovial gaint cell

① Benign neoplasm OF Synovium
② affectig large joint (Knee)
③ Cause sever pain + lock OF joint
④ pigmented villonoduar synovitis
(vinger like shape)

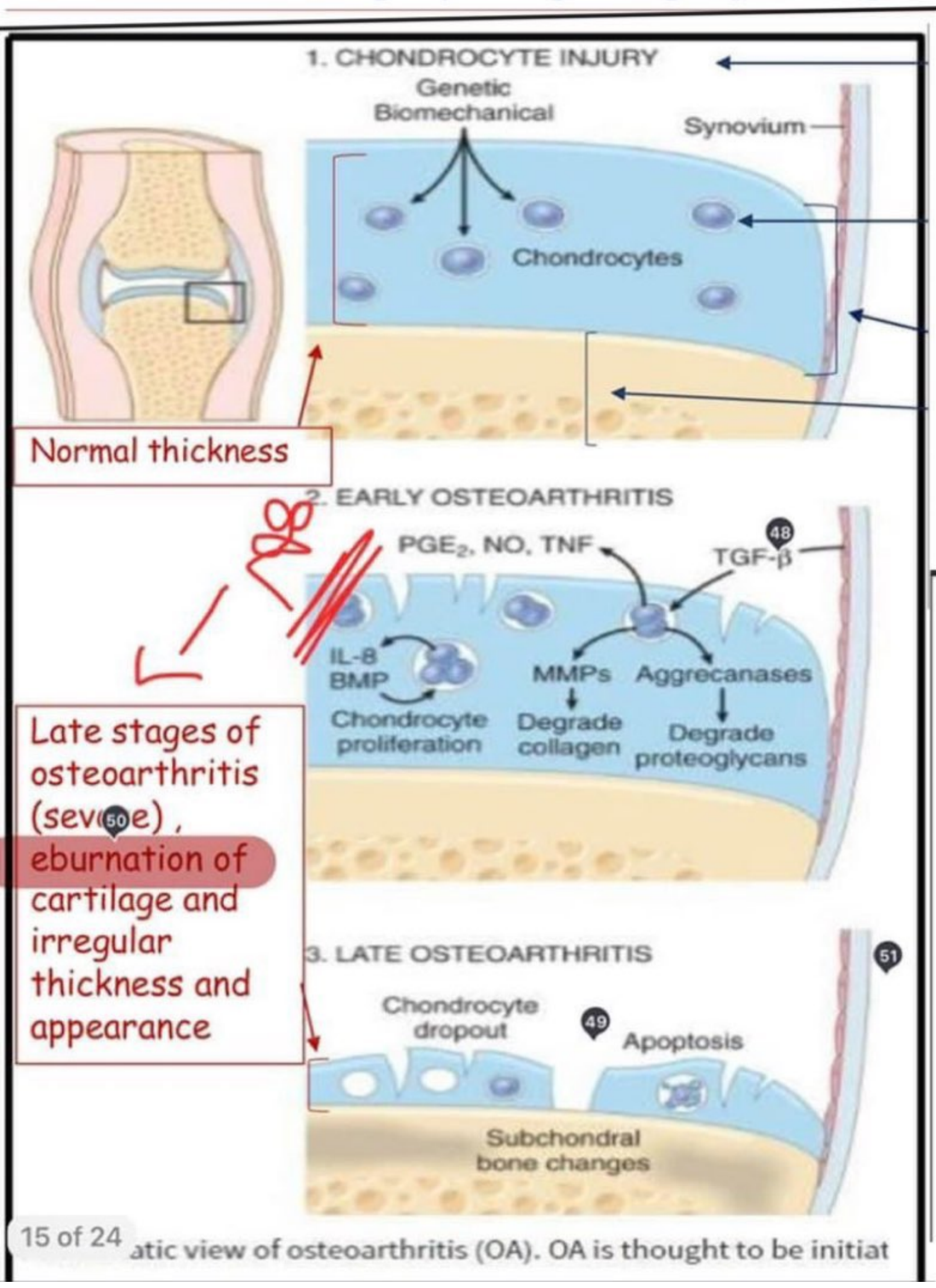
→ because OF bleeding
→ bleedig cause hemosidrin to go out and give brown color

⑤ t(1:2) (p13,q37)
⑥ affectig collage type 6

- **15-20% simple karyotype (single mutation or single translocation which makes it easy to diagnose by FISH or next-generation sequencing), single signature mutation (Ewing and synovial sarcoma)**

- in certain situations in sarcoma we need to do molecular test and check the mutation

- **80-85% complex karyotype (genomic instability), LMS (leiomyosarcoma), and pleomorphic Sarcoma**
- **Wide range (benign-highly malignant)**



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atic view of osteoarthritis (OA). OA is thought to be initiat

SOFT TISSUE TUMORS:

They are much more common than joint tumors.

- Benign is MUCH more common than malignant
- Incidence: 1% and cause 2% cancer death (compared to breast, lung, colon cancer, etc)
- Sarcomas are aggressive and metastasize mainly to lungs, hematogenous spread
- Most common sites are in extremities (thigh), followed by retroperitoneum.
- 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. → These are called Secondary Sarcomas; they are becoming more common nowadays due to the heavy use of radiation in treatments

JUVENILE IDIOPATHIC ARTHRITIS (JIA):

Another form of RA which affects children

- Heterogeneous group; arthritis of unknown cause ; <16 years for at least 6 weeks → You can't diagnose a patient with JIA if he didn't have the symptoms for at least 6 weeks !
- Pathogenesis is similar to adult RA
- Prognosis variable; only 10% will have serious functional disability → better, short term complications

IN CONTRAST TO ADULTS RA; JIA IS CHARACTERIZED BY:	
Oligoarthritis is more common	•Asymmetrical pattern •Large, weight-bearing joints (knee ,elbow and ankle) are usually affected.
Systemic disease is more common	Can have heart problems, skin issues, ophthalmologic abnormalities , both adults RA and JIA can have systemic diseases but in JIA it's more common
Large joints are affected more than small joints	knee ,elbow ,ankle
Rheumatoid nodules and Rheum Factor are usually absent	
Anti Nuclear Antibody seropositivity is common	Simple screening test → ANA

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RHEUMATOID ARTHRITIS:

True inflammatory joint arthritis , but less common than osteoarthritis

- True and strong **Chronic inflammatory disease; autoimmune in nature; attacks joints with nonsuppurative** (no pus ,non pyogenic no bacteria) **,proliferative** (proliferation of fibroblasts) **and inflammatory synovitis** (the major target is the synovium and the surrounding ligaments not the articular cartilage)**; leading to destruction of joints and adhesions (ankylosis** (fusion of the joint)**);**
- **systemic disease (skin, heart, vessels & lungs)** (it is a multi Oorgan disease, that can affect several regions rather than the knees only "as the osteoarthritis". In this disease, the major factor of mortality is the involvement of other organs such as lung, heart and kidney involvement)
- **1% prevalence in USA; F:M = 3:1**(more common in females)**; 4th-5th decade**

"Important ratio"

- **Genetic predisposition** (some families have a higher RA rate than other) + **environmental factors plays a role in the development, progression and chronocity of the disease**

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PATHOGENESIS:

Involvement of multiple mediators in the inflammatory process

IFN-γ from TH1	**Activates macrophages & synovial cells**
IL-17 from TH 17	**Recruits neutrophils and monocytes**
RANKL from T cells	**Stimulates osteoclasts & bone resorption**
TNF & IL-1 from macrophages	**Stimulates residents synoviocytes to secrete proteases that destroy hyaline cartilage**

The changes in chondrocytes and cartilage are secondary to the nonsuppurative chronic inflammatory cells

TNF is the major player in the pathogenesis of RA

2 tests to confirm the Dx of RA

- **80% of patients with RA have autoantibodies IgG & IgM against the Fc portion of their own IgG** we test this by **[Rheumatoid factor]** which is the basic serum test
- **70% of patients with RA have Anti-Citrulliniated Protein Antibodies (ACPA)**

Negative rheumatoid factor **doesn't roll out** RA because 20% of the patients with definitive RA have negative RF

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SERONEGATIVE SPONDYLOARTHROPATHIES:

- **Ankylosing Spondylitis:**
  - Adolescent boys, HLA B27, axial joints (sacroiliac)
- **Reiter Syndrome:**
  - Triad of arthritis, urethritis/cervicits & conjuctivitis
  - 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.

specially Sexually induced infection

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Pathology notes for final:

LECTURE 6:

GNAS1 GENE abnormality causes fibrous dysplasia (FD)

Mazabraud syndrome => FD+ soft tissue myxoma حسيت الدكتور نبه عليها

McCune-albright syndrome: هيذي مهم جدا جدا وهي غالبا اهم من اللي فوق

*café au lait pigmentation اهم مميز لهاذ المرض

*polystatic FD + endocrine abnormalities (hair before puberty)....

****histologic feature of FD => Chinese letters like

DJD (osteoarthritis) worsen with use / morning stiffness

Articular cartilage

LECTURE 7 :

Rheumatoid arthritis

=> **chronic , autoimmune disease , nonsuppurative , inflammatory synovitis , *systemic disease* , ankylosis joint destruction + adhesion .**

*** true arthritis *** more in females, +50 years old

Combination of both Genetic predisposition + environmental factors.##

***Most important mediator in the pathogenesis of RA is ::*

TNF +IL1 => which stimulate resident synoviocytes to secrete proteases that destroy hyaline cartilage ..

Stiffness while resting , waxing and waning (مرة كويس مرة لا)

Ulnar deviation characteristic feature of RA

Treated by : *anti-TNF , *steroids , *MTX

Juvenile idiopathic arthritis:

=> -16 years old. Children type of arthritis

Symptoms lasts for at least 6 weeks

Similar to RA

Large joints affected commonly

ANA +ve :main characteristic

Rheumatoid factor and nodules are -ve mainly

Seronegative :

- Most common prototype is **ankylosing spondylitis**
- Main joint involved is **SACROILIAC JOINT**
- 90% **HLA-B27** +ve
- Anti AL-17 effective treatment.

Reiter syndrome: triad of : arthritis ,urethritis ,conjunctivitis initiated by bacterial infection (sexually transmitted)

Suppurative arthritis:

SUDDEN acute pain, knee joint mainly affected, systemic manifestations

Bacterial infection

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LECTURE 8:

**Gout VS pseudogout ** :

- Endogenous crystals in GOUT => MSU monosodium uriate
- Endogenous crystals in PSEUDOGOUT => CPPD calcium pyrophosphate dehydrogenase.
- *Pseudogout* : weak positively birefringent under polarized light IMP.
- *Acute gout* : strong negatively birefringent under polarized light

Ganglion cyst:

Not true cyst, no communication with synovial joint ,common condition, located in the dorsum of wrist.

Baker cyst :

Common location is popliteal fossa , true synovial cyst, herniation process

Diffuse pigmented villonodular synovitis :: affecting type6 collagen a3

LECTURE 9:

About nodular fasciitis :

الدكتور حكى عن انه ضروري ما نغلط ونحددها انها malignant فا ممكن يجيب سؤال عن اعراض المرض ويحطلنا في الخيارات انه diagnosed as malignant tumor ..... 😅🧕

Deep fibromatoses (desmoid tumors):

** these tumors can kill you by local infiltration NOT metastasis VERY IMP. NOTE

Smooth muscle tumors :

Leiomyoma do not transform to leiomyosarcoma

Synovial sarcoma :

** ممكن السؤال يجي عن translocation (x;8)(p11,q11)

** وممكن يجيبلنا في السيناريو spindle cells and glands ; **biphasic**

** can go to lymph nodes ممكن يجيبلنا خيار تريكي ننتبه

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