Pathology #4

مجموعة التفريغ السريع

MSS

Subject: *Skin Tumors*

Done by: *See last page*

Doctor: *Huda Zahawi*

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EHSAN إحسان

Diseases of skeletal muscle

In this section, we will talk about skeletal muscle, and actually, it is in two sections, one is the **medical diseases of the muscle**, and the **Tumors**.

How do we diagnose diseases of muscle?

this is regarding, of course, the medical part ,it's very important to take a **Good Clinical History** , presence of *weakness* is very important, this is one of the first symptoms of muscle diseases – primary muscle disease , and the muscles involved show *irregular twitching* or what is called **Fasciculation*** , you can actually see in the – for example- the deltoid, individual muscle fibers going to change, this is for fasciculation.

There will be *muscle cramps* (تشنّج) and later on you will have *atrophy* of muscle, this is usually seen in the primary muscle diseases, and also in others, we should exclude any systemic disorder because some systemic disorders do involve muscles.

You do the **EMG (Electromyogram),** like the ECG does with the heart; EMG records electrical activity in the muscle and analyses it. The other thing, you **test for enzymes** that are released to the blood. when the muscle is destroyed – just like when someone has a myocardial infarction , which is also a muscle , you will have a rise in enzymes - , one of the enzymes involved is the **Creatine Phosphokinase** which is known as **CPK** or **CK** and it is raised in muscle disease , later on , it will become low because the muscle itself is atrophic.

You should also take a **muscle biopsy**, it is very important.

A fasciculation, or "muscle twitch", is a small, local, involuntary muscle contraction and relaxation, which may be visible under the skin or detected in deeper areas by EMG testing

This is something you should know:

Normal Skeletal Muscle & Motor Unit consists of-

- Motor neuron in brain stem or spinal cord.
- Peripheral axon.
- Neuromuscular junction.
- Skeletal muscle fiber

A disease can occur in anyone of these, which will lead to various symptoms, and if you come to the muscle itself, there are two types of muscle fiber

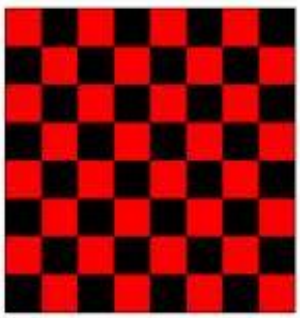
Type I (slow twitch)

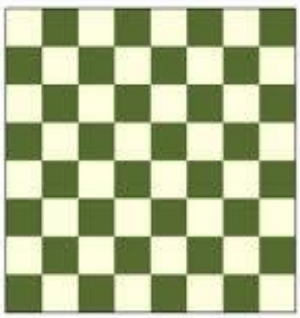
Type II (fast twitch)

MUSCLE BIOPSY

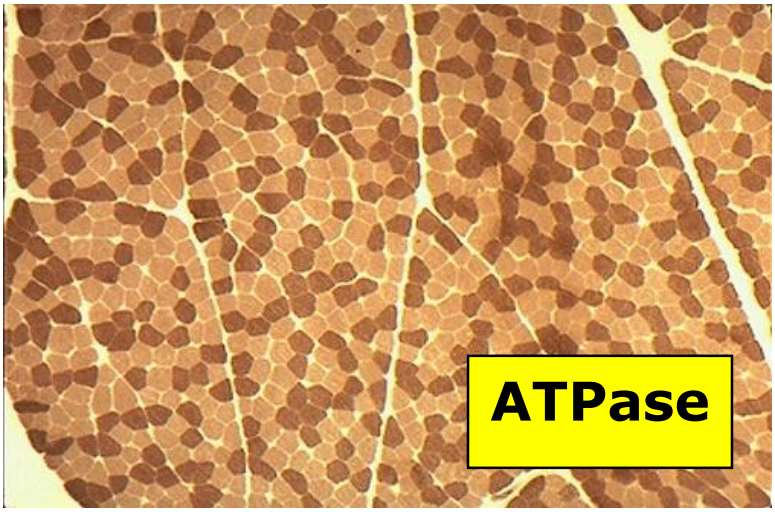
In the muscle biopsy, it should be put in Frozen Section **not** Formalin, why? Because we will be testing for enzyme activity, and the enzyme will be destroyed in formalin, so the muscle biopsy should be submitted as a frozen tissue.

According to the various enzymes, ATPase and ADH, it will show checkerboard appearance:





if you look at the normal muscle ,look at this one, it's done with ATPase , and you can see the two fibers, ***type1 is pale*** and ***type2 is dark*** , and the way it is distributed , is again like the checkerboard , irregular , but still sort of evenly distributed in number .



Now when we come to study the myopathies, and the nerve damage, this will change , the primary disease in the muscles are so many, there are many syndromes involved in many disease, if you look at your book, you'll find many names that I am not asking to you to know about , it's too much !

<u>The main disorders that we are concerned about are</u>:

- ☐ Muscular Dystrophies
- ❑ Neurogenic disorders(where the *nerve is involved, not the muscle* , the nerve and eventually the muscle)
- ☐ Inflammatory Myopathy
- ☐ Neuromuscular junction disorders

And you have:

- ☐ Metabolic e.g. glycogen storage diseases(where you have stored material in the muscle interfering its function , and it's not really a primary muscle

disease, it's a GENEALIZED disease that includes the muscles, it is well known, and it has like 6 subgroups at least)

- ☐ Endocrinopathies e.g. Cushing's Syndrome (corticosteroids lead to muscle atrophy)
- ☐ Drug induced

i. Muscular Dystrophy

Dystrophies will show the same picture, histologically, whether it is ***Duchenne*** type or any other type, but the clinical appearance, the muscle involvement and the inheritance is different.

Muscular dystrophies in general are *primary diseases*, they start in childhood or adolescence, sometimes they can delay (depending on the type), and it leads to a progressive degeneration of muscle fibers.

One of our colleague asked question, I could not hear it, but the doctor said "they differ, similar clinical in the histological feature but differ in the location and rate of progression. That means if it is this type for example, the limb girdle one differs from the Duchene type, which will be the main one.
-Which muscles are involved?
-How sever they are?
-What the age is involved?
-to lead to death or don't they?

We see the slide, whether it is of any type of dystrophy the same changes in the muscle but the *muscle is different * progression is different * inheritance is different … but histological is the same.

The individual types as I said in your book there are others not just these , but we will be concern mainly of the {**Duchene muscle dystrophy**} which is the commonest ,and next is the {**Becker muscle dystrophy**}, next is the {**girdle limb**}, {**myotonic dystrophy**} .

A. Duchene Muscle Dystrophy

Now, this one it is abbreviate by ***DMD***
it mainly affects **boys**, and it is **X-linked** inheritance disease with female carrier.
You have **very rare sporadic mutation** but the commonest are these.
It is the most **sever** type; it usually causes death by the age of 20 years.

the boy is born apparently normal, up to the age 1-2 old nothing is shown, then when he -for example- tries to get up , tries to crawl and so on ,the parents notice weakness, he can't do it, the disease starts at 1-5 years , there will be delayed walking , proximal weakness and by the age of 20 as I said he will die . ☹

First, the legs are most affected then it is goes up, involving other muscles it will be difficult for him to breath, he will be bedridden and wheel chair.

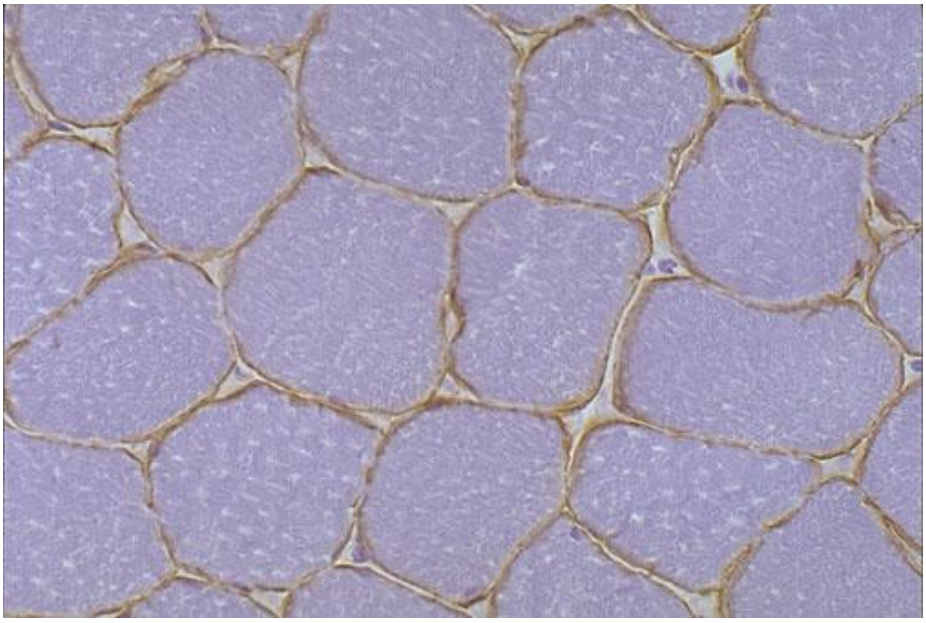
The pathogenesis is loss of function mutation which actually deletion of a gene **Dystrophin** on the **short arm of Xp21.**

Now, what is the nature of the dystrophin gene?
Dystrophin stabilizes muscle during contraction, once there is no dystrophin the sarcolemma will be very weak and this movement will induce tears (تشققات) in the sarcolemma, muscle splitting and the muscle will be destroyed.

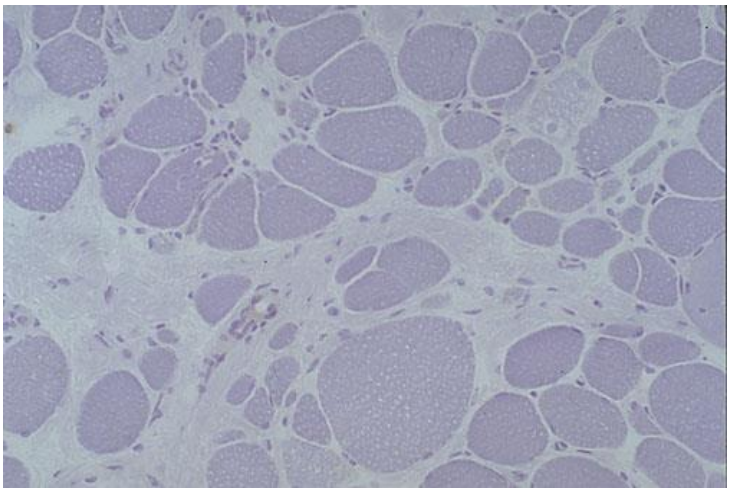
Now, in the DMD the dystrophin **is totally absent**, how do we test for dystrophin?

We do it by **immune-histochemistry**; immunohistochemistry is a procedure where a protein is linked to an antibody and it will take a stain.

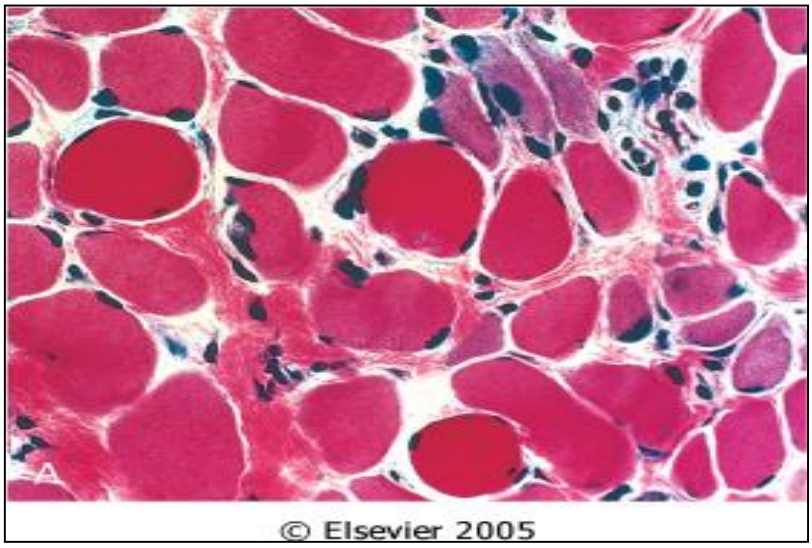
Look, this is the normal, look at the sarcolemma here. This is all dystrophin it is encircling totally the muscle fiber “protective”



And if you compare it to DMD, this is totally absent there is no dystrophin, this is the same test.



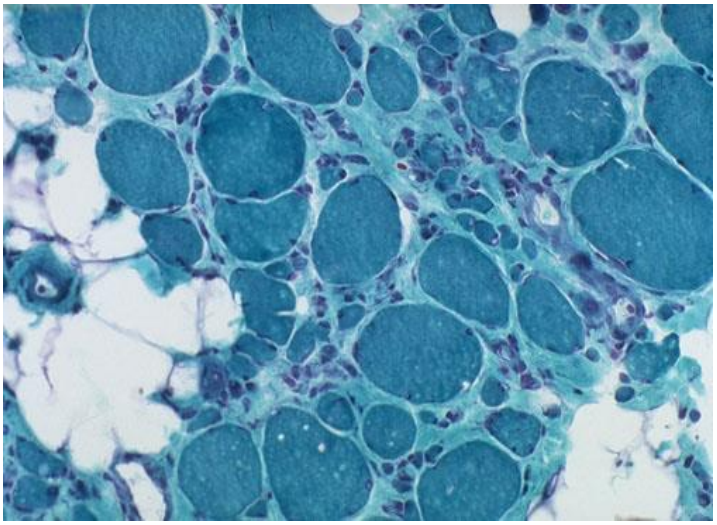
and look by time what happens to the muscle , this is very thick layer , but look there are different sizes of muscle , some are very big, and you can see how the individual fiber are **torn** , some of them are **vacuolated** .
And the whole thing ultimately shrinks, and this is close up, you can see some are huge, some are small, and some are destroyed.
Now if you look at this one, this is more basophilic, more bluish, why?



Because this is trying to regenerate, so you can see the regeneration together with destruction. And in the regenerated area, look how big is the nucleus but still it will not function very well, and here you see few inflammatory cell, so this **is typical Duchenne type**.
*Very important is loss of **striations** in muscle*.

- **Marked variation in muscle fiber size**
- **Degenerative changes in scattered fibers : fiber splitting,loss of striations, necrosis ….**
- **Regenerative changes : basophilia, nuclear enlargement, prominent nucleoli**
- **Increase in intermuscular connective tissue, few inflammatory cells**
- **Later fiber loss & infiltration by fat**
- **Abnormal dystrophin staining**

In fact, the **old name of DMD was hypertrophic muscular dystrophy**.
And the **hypertrophy** is due to the increase of fat and connective tissue and not actual hypertrophy of muscle fibers, so you see big muscles here.
And of course, you see abnormal dystrophin staining and here is a different



Stain but you can see this is all fat, this is vacuolated and it is huge, where are these small, so here if you do the ATPase, you see the same thing in different scattered (big, small).

Clinically, there will be starts approximately in the **pelvis**, later **shoulder**.
-muscle characteristic (**pseduohypertrophy**) of legs muscle
- and of course , because of destruction , the **creatine kinase** is **Raised** , and later on it will return to normal because of the atrophy
-and these patients also develop **cardiomyopathies .**

-Death from respiratory insufficiency & infection, cardiac failure**.**

B.Becker muscular dystrophy

it start in older age group its much milder, its less common, and rarely it can affect females it's the same gene defect but **dystrophin is not totally absent** it's just decreased and has **abnormal molecular weight** but is dystrophin patient may have cardiac disease but it's not as common and not as severe, the outcome is better and the patient may live adulthood with a nearly normal life span.

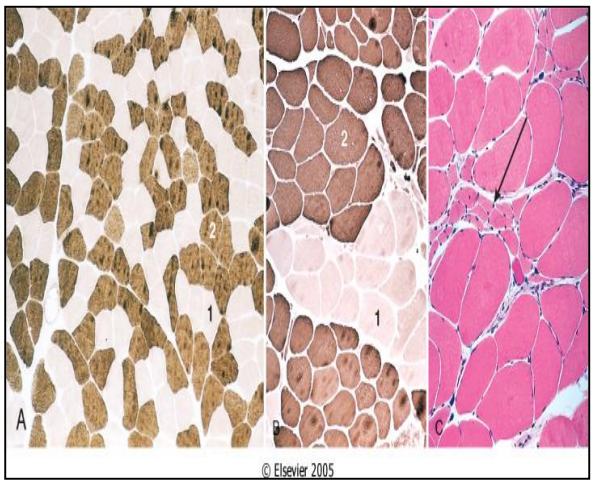
ii. Muscle Atrophy

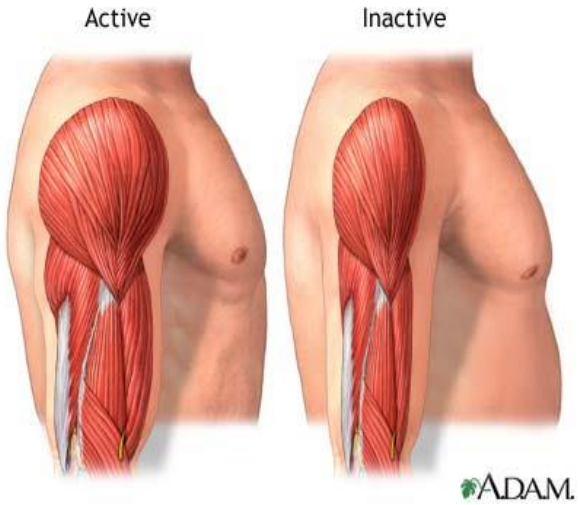
Causes:

- -motor neuron disease (ALS), polio (it is an acquired viral disease lead to atrophy of the muscle in the limbs).
- -Peripheral neuropathy.
- -Trauma.
- Patients with disuse atrophy when immobilized.
- -Patients who receive glucocorticoids.
- -Patients with hypercortisolism**.**

Now if we come to the damaged nerves it will lead to what is called (Group atrophy) why group? it's because one of the nerve is damaged the fibers: as I said they are fiber type 1 and type 2 , and this is innervated by different fibers (1,2) and initially all are affected but after that because of the regeneration there will be **sprouting** of the nerve fibers and in this case gradually type 2 overtakes type 1

so if you do the stain you will see grouping of type 2 in a bundle and the muscle involved will shrinkage secondary of deprivation of innervation and this one here as I said sprouting then type 1 and type 2 loss of the normal and there will be group atrophy and instead of the large muscle fibers the fibers are small and angulated and look at this one this is the whole group this type 2 overtaken type 1 which is damaged





iii. inflammatory myopathies :

1- Infection (myositis):

-**Bacterial**

-Viral: - Influenza, coxsackie, HIV

-Parasitic: Trichinella spiralis, Cysticercosis

And it is unusual to get it here.

2- Non-infectious immune mediated myopathies (they are group of systemic disease):

- Polymyositis

- Dermatomyositis

- Inclusion body myositis

Polymyositis & Dermatomyositis:

-Group of immunologically mediated muscle injury characterized by inflammation

-May be associated with other disease of autoimmune nature (you have to exclude other autoimmune disease)

*Pathogenesis:

Antibody mediated tissue injury in Dermatomyositis and cytotoxic T- cell injury in Polymyositis**.**

- **Clinically:-**

- Symmetric muscle weakness initially affecting large muscles of trunk, neck, limbs

- Associated skin rash of eyelids in Dermatomyositis

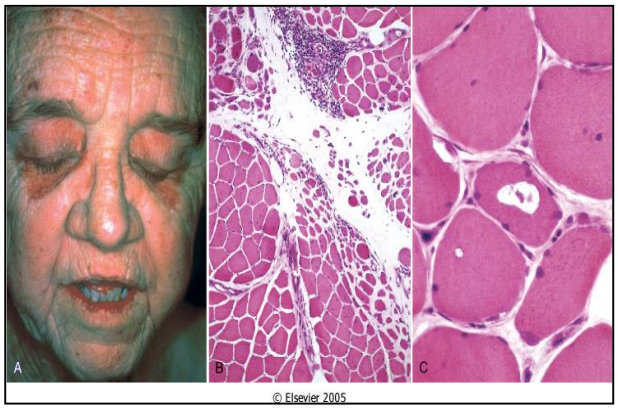
And you see here there is many inflammatory cells and these inside are atrophic, the inflammatory component is destroying the muscle.

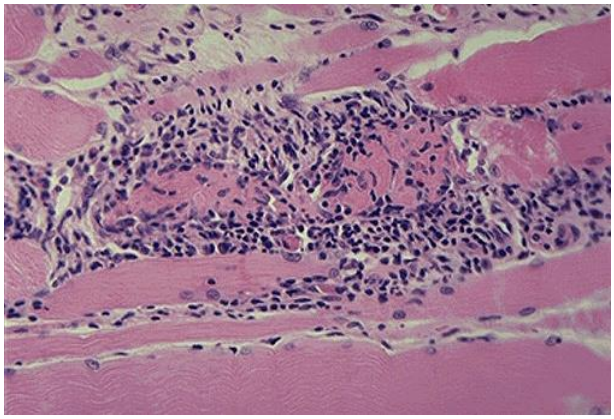
Histology:-

-**Infiltration by lymphocytes that surround muscle fibres.**

-Inflammation around blood vessels

-Degenerated and regenerated fibres.





iv. Toxic Myopathies :

-Thyrotoxic M.→ Myofiber necrosis & regeneration

-Ethanol intoxication after heavy intake → Myofiber swelling & necrosis

-Various drugs (especially those that are given for hyperlipidaemia)

v. The neuromuscular junction disorders

Are myasthenia gravis, which is not common, it is acquired autoimmune disease of neuromuscular transmission.

-Myasthenia gravis:

-Acquired autoimmune disorder of neuro-muscular transmission

-F>M, any age

-AB against postsynaptic acetylcholine receptors in 85% of cases

-Other autoimmune diseases

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Not all of them actually show abnormality in the thymus.

Abnormality in thymus:

You can get **Thymic Hyperplasia in 2/3 OR you can get an actual Thymoma in 20%, which** is a tumor of the thymus, and there are different types of Thymoma, which is benign, or malignant (usually it is benign).

The patient has **muscle weakness** and because of the weakness it also involve the muscles of the eyelids that's why the patient has **Ptosis** and its

Difficult to the patient to open there eyes easily, **fatigue** (difficulty in moving) and **dysphagia.**

- Classically diurnal variation in strength, i.e. best in morning, worse as the day progresses.

If you take a biopsy of the muscle, it would be normal and if the patient has Thymic Hyperplasia **Thymectomy** may help (but not always).

In Thymic Hyperplasia, we can see very active germinal centers in the lymphoid follicles and this patient may benefit Thymectomy.

- The other condition, which give a clinical pic much like myasthenia gravis, is Lambert-Eaton Syndrome**.**

Lambert-Eaton Syndrome:

- It also has autoantibodies that inhibit function of presynaptic channels at neuro-muscular junction.

In these patient of you continuous stimulate the muscle he may improve, however these cases usually deteriorate later and maybe become worse than those with myasthenia gravis do, why?

Because most of these patients are part of paraneupalstic syndrome, and the majority of them are those with lung cancer and that is why they die early. So although they appear to be better than the primary one (myasthenia gravis) it is actually worse.

Soft Tissue Tumors:

General Characteristics:

- *Classified according to tissue of origin, sometimes they have unknown identity, and appear in any age, present as an enlarging mass**.**

- **May be part of inherited syndromes :**

  -Neurofibromatosis, type I

  -Li Fraumeni Syndrome: it is a p53 mutation where the patient produce many type of tumors**.**

- Some of them have specific gene lesions
- Arise 'de nove' or after recurrent "Benign" tumors → SARCOMA

Soft tissue tumor according to tissue of origin:

A. -Adipose tissue.: Lipomas –Liposarcomas
B. -Fibrous tissue: Fibroma-Fibrosarcoma
C. -Skeletal muscle :
D. Rhabdomyoma ,Rhabdomyosarcoma
E. -Smooth muscle:
F. Leiomyoma , Leiomyosarcoma
G. Vasculartumors:-
H. Hemangioma,Angiosarcoma -
I. Peripheral nerve tumors.-
J. Unknown exact cell of origin

All malignant soft tissue tumors are graded according to differentiation into **I-III grades**.

Grade I is the most looking like the origin tissue, grade III will not look like the origin tissue.

Grades I & II may recur but rarely metastasize , locally they can enlarge and recur and the prognosis depend on the type of tumor , the grade of it, the stage of the tumor , and the site (why did I say the site ? because as you shall see many of the more benign side they occur most superficially than the deep **.**

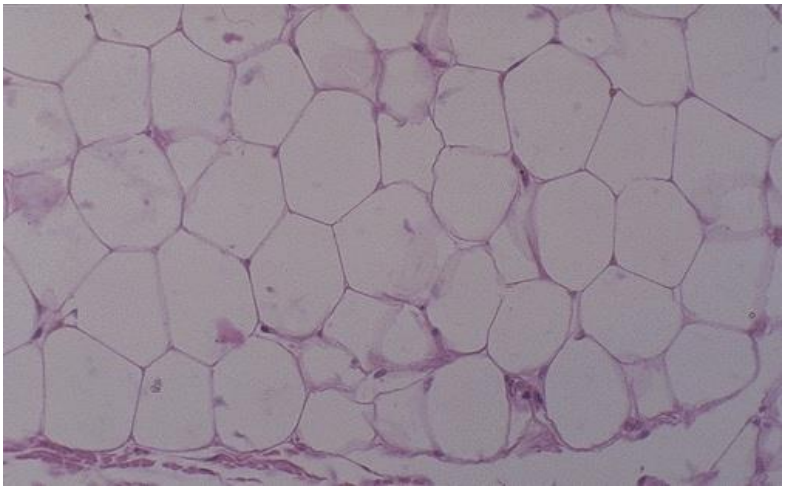
Tumors of Adipose tissue:

Lipoma:

- Commonest of soft tissue tumors most in subcutaneous tissue
- Single or multiple, may be familial , and lipomas can be small and grow slowly until the patient is sixty
- No malignant transformation
- Grossly : Circumscribed yellow mass
- **Histologically** : Mature fatty tissue
- Many histological variants but you do not have to bather yourself with it and they do not affect the prognosis.

Liposarcoma

- Occur in adults 50-60yrs not in children in the deep soft tissue & reteroperitoneum, the superficial ones very rare and they become sarcomatus, the common sites mainly in the deep tissue of the thigh and retroperitoneum.
- Grossly : Large yellow glistening mass
- Histologically :
- Low grade : Well differentiated which can be very difficult to differentiate from ordinary Lipoma , the genetic defect : (Amp.12q) & Myxoid type (t(12;16)
- High grade :Round & Pleomorphic
- Diagnosis depends on identification of lipoblasts
- Prognosis depends on type & site (the retroperitoneum is the worse site)
- Usually metastasize to the lung.



This is lipoma its look like normal fatty tissue , and this is a well differentiated liposarcoma

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And in the connective tissue and this one is a high grade *** (37:08) sarcoma... you see again u can recognize the cytoplasm and the fat cells.

Fibrous tumors and their proliferation:

Again, there are many types:

1-Nodular fasciitis:

- It is a reactive condition it is not an inflammation, and it is not an infection.
- It's a proliferation maybe very active this is misdiagnosed as sarcoma
- It is usually affects young adults as a rapidly enlarging painful mass, its self-limiting need 2 weeks to develop and then gradually it will be regress.
- It is often radiated to local trauma, it is more at the upper extremity trunk, and its proliferating fibroblastic tissue they have some mitosis but it will regress.
- Now in the muscle again related to trauma you may have similar finding only it produces bone and that's why it's called myositis because it's in muscle and ossificans from ossifying because its

actually recognize bone and because of rapid proliferation it looks so much worst with a lot of new bone formation it may be miss diagnose as osteogenic sarcoma which arise from soft tissue not in the bone so we must be very careful in diagnose these .

Morphology

- Its unincapsulated, this lesion in the myocytes and usually small than 3 cm (<3cm) in the subcutaneous tissue or fascia.
- Immature appearing fibroblast with high mitosis with no atypia with a myoxoid background.

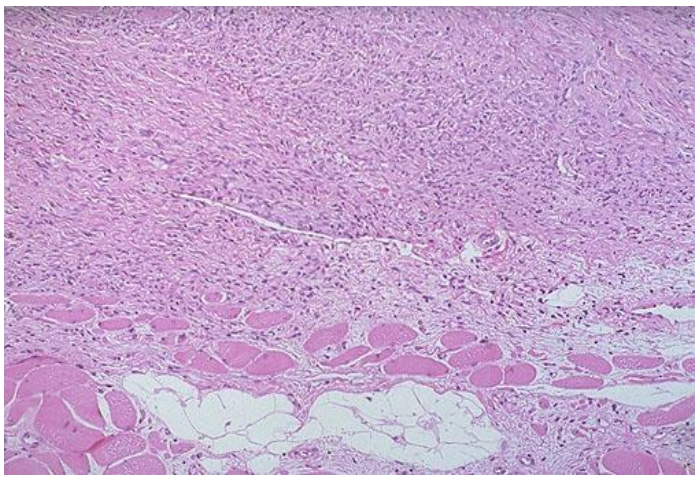
2-fibromatosis:

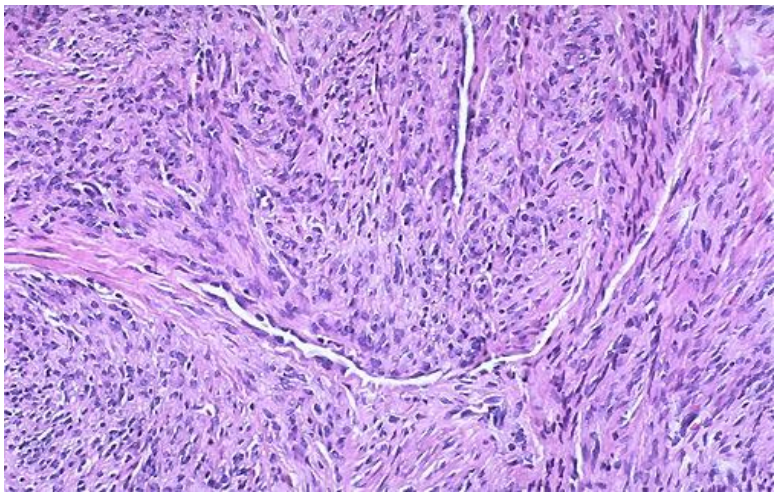
It's a fibroblastic proliferation and it has an infiltrative border it can recur after surgical excision just like that in low grade sarcoma , and it does not metastasize and it occur in various age group ,, babes ,children and sometimes in adults and each one will behave differently , the locations are different .

It has two types:

1. **Superficial** : it's called palmer , can be seen in the hand which we call it dupuytrens contracture ,, or in the penis which also produce contracture

2. **Desmoids tumors**: when its occur in the deep soft tissue, it's may look very bad and may recur and its more progressive than the one in the extremities, and often its related to trauma, many of the patients are females, how have had an operation on uterus for example ovarian session or any abdomen surgery may lead to desmoid tumor and





actually when its send to the lab they said: that it is developed after surgery.

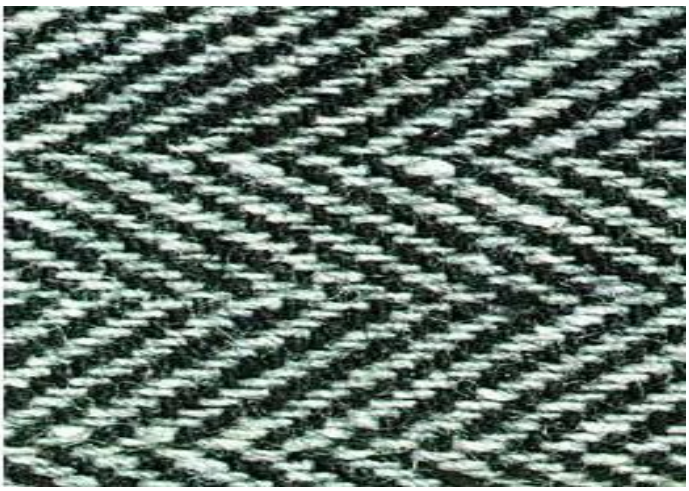
- In the pics, you can see the dismoid tumor, which is more cellular than the others are, and it is infiltrating between the muscle fibers.

3-fibrosarcoma:

Is a tumor of a fibrous tissue affecting adults usually the deep tissue of the thighs, knees, reteroperitoneum.

They tend to grow slowly, they are usually solitary, infiltrative or circumscribed, they can metastasize, actually, the low-grade ones can metastasize to lymphatics and the higher-grade ones can go to the lungs.

IN this pic, you can see the fibrosarcoma:



The fascicles of fibroblasts are arranged in herringbone appearance

. (Herring: is a fish and the fishbone is something like this in the pic)

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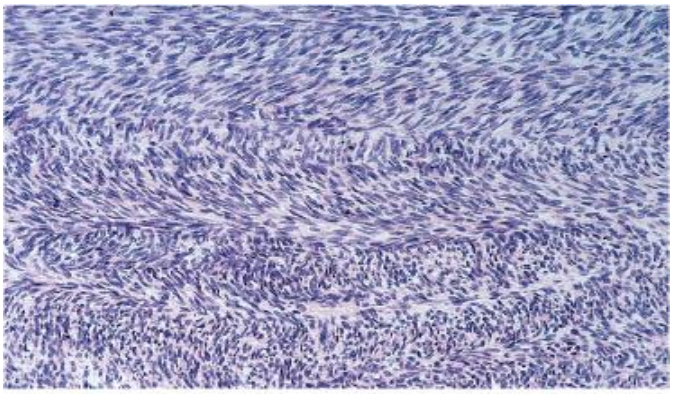


Then the Dr skipped the slides leaving small comments about some points so I will put the #of the slide with its comments

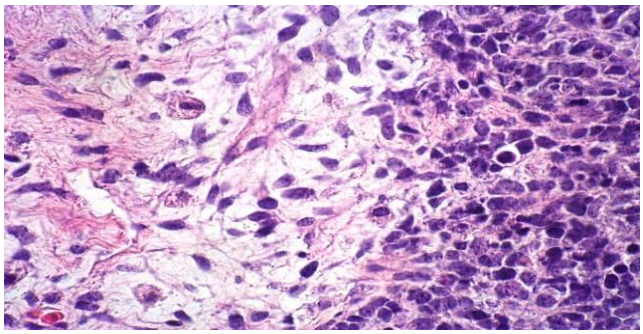
Slide #60, 61, 62, and 63 read it by your own self.

Slide #64 : **the most important** of these soft tissues tumors are those of the striated muscle which is the rhabdomyosarcoma , are basically those occurring in children ,adults(although it is rare in adults) ,there are different types of rhabdomyosarcoma :

1. Empryonal: in children are the most common mainly in the head and neck of children, genitourinary track and retroperitoneum. And this is the worst prognosis.

2. Alveolar: it is more in the extremities of adolescence.

3. Pleomorphic: in the soft tissues. This one is the worse.



And the diagnostic cell is **the tadpole or strap cell**.

(Here the dr explained the slide #67 and sorry for that but I did not understand it)

The End

Your colleagues: ☺

Mohamed Telfah

Mahmood Samara

Farah Farajat

Abdalla Abu Shaqra

Osama A. Alkhawaja