Doctor 021

PATHOLOGY

Sheet no. 15

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INTRACELLULAR ACCUMULATIONS:

accumulations of certain materials in cells.

- Four mechanisms for deposition of materials inside cells (four types of materials):

➢ 1)Inadequate removal of a normal substance (fatty change in the liver)

Fats/ Triglycerides are known to be endogenous products that are normally present in many cell types, so when there is inadequate removal of these substances, they accumulate.
Regarding triglycerides, they are normally transported outside of the cell by binding to proteins (the structure produced may be named lipoprotein, or apolipoproteins). So, if any defect happens to this transport, like for example having lack of proteins transporting lipids - and we did mention this when explaining cell injury mechanisms, one of them being decreased protein synthesis - , lipids will accumulate (figure 1 👇).

➢ 2)Accumulation of an abnormal endogenous proteins due to folding defect (α1-antitrypsin deficiency)

The gene, which encodes a1-antitrypsin enzyme, can be affected by a mutation that leads to production of abnormally folded a1-antitrypsin proteins, meaning that these proteins become non-functional, unable to be secreted outside the cell, then they accumulate in cells. In peripheral blood ortissue, a notable deficiency of this protein will be seen, because of its abnormal shape that can't be secreted outside the cell so depositing inside them , accumulation of misfolded proteins in endoplasmic reticulum (Figure2 👇).

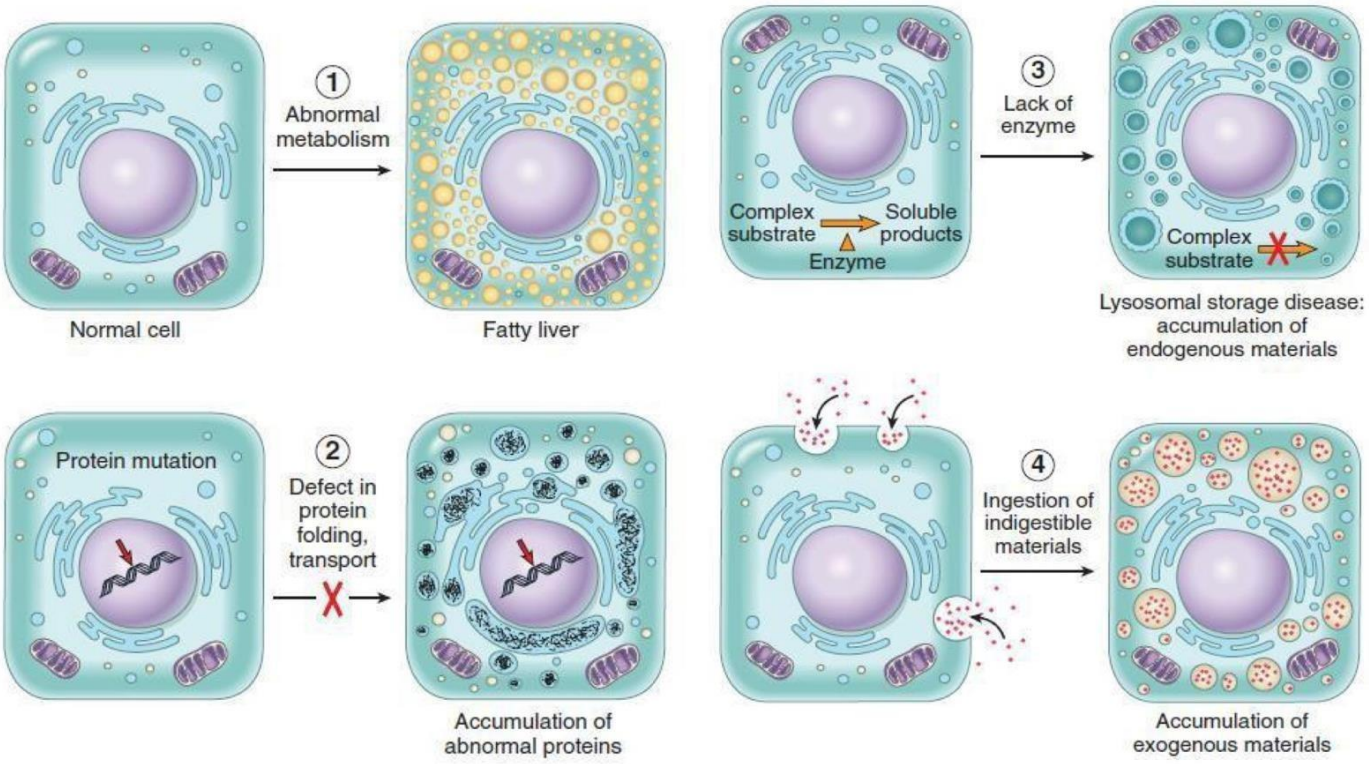
➢ 3)Failure to degrade a metabolite due to inherited enzyme deficiencies (lysosomal storage diseases)

What happens here is that we are having deficiency of lysosomal enzymes or glycogen-metabolizing enzymes due to a genetic mutation, leading to accumulation of for example glycogen or other lysosomal metabolic products that normally get degraded inside the cell (Figure3 👇).

➢ 4)Deposition and accumulation of an abnormal exogenous substance (carbon and selica)

Carbon is an exogenous substance in nature (not a natural mineral that is produced in our bodies),so it get deposited by taking it from outside, there are many ways such as smoking, it causes carbon deposition in lungs, also living in settings with polluted air may lead to carbon deposition in lungs (figure4 👇).

CLINICAL GLIMPSE: when asking for a lung biopsy then noticing heavy carbon deposition in lungs, the history of the patient will definitely include a strong cause, such as smoking.
Also Silica is an another example of accumulating exogenous materials.



This diagram above summarized all aforementioned mechanisms.

❖ **AND NOW, LET'S TALK ABOUT THE SUBSTANCES ABOVE IN MORE DETAIL!!**

FATTY CHANGE: STEATOSIS

- **Most common in liver**
- **Triglycerides**
- **Also in heart, kidney, muscle**
- **Causes: toxins, protein malnutrition, DM, obesity, anoxia**
- **Alcohol abuse and DM+obesity are the most common causes of fatty liver**

- The most common affected tissue is **LIVER** since it is the most organ evolved in fat metabolism, but also can be seen in (**HEART**, **KIDNEY**, **MUSCLES**).

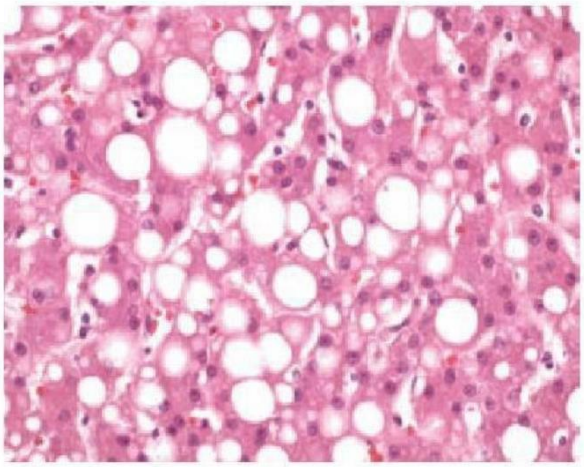
- It is due to the deposition of Triglycerides in the cells, as you see here the fatty position is manifested by white fatty droplets inside the cells which vary in their sizes (some of them are macro and others are micro).

- Alcohol abuse and DM +obesity are the most common causes of fatty liver disease in industrialized countries.

- Causes of fatty liver depend on geographic locations, for example in Western countries alcohol abuse is the most common cause, whereas in our part of the world DM+obesity is the most common cause.

- Histologically, fatty cells in a liver section appear as empty white vacuoles inside the cell, replacing the nucleus to the cell periphery.

- Degree of steatosis may vary between mild steatosis and severe steatosis, depending on the severity of for example alcohol consumption, how obese the patient is, duration of diabetes,...



A histological section of the liver illustrating the presence of fat. (triglycerides)accumulated in cells

OTHER **CAUSES** THAT SHOULD BE MENTIONED:

1. **Toxins** – carbon tetrachloride CCL4 (remember when talking about cell injury mechanisms, we mentioned toxi-mediated mechanism, and we gave an example about it, Acetaminophen, being toxic to liver-after exceeding a certain dose threshold-, causing fatty liver change).

2. **Protein malnutrition** (lipids accumulating in the liver in this context are TRIGLYCERIDES. As we mentioned before, lipids accumulate because of a deficiency in the proteins needed to transport them outside the cell, so logically, patients having protein malnutrition will suffer from lipid accumulation in the liver.

3. **DM**.

4. **Obesity**.

5. **Anoxia** (differentiate between anoxia and hypoxia, hypoxia is a decrease in oxygen supply, while anoxia means loss of oxygen supply).

CHOLESTEROL AND CHOLESTERYL ESTERS

- **Phagocytic cells become overloaded with lipid (triglycerides, cholesterol, and cholesteryl esters)**
- **Increased intake or decreased catabolism**
- **Atherosclerosis**

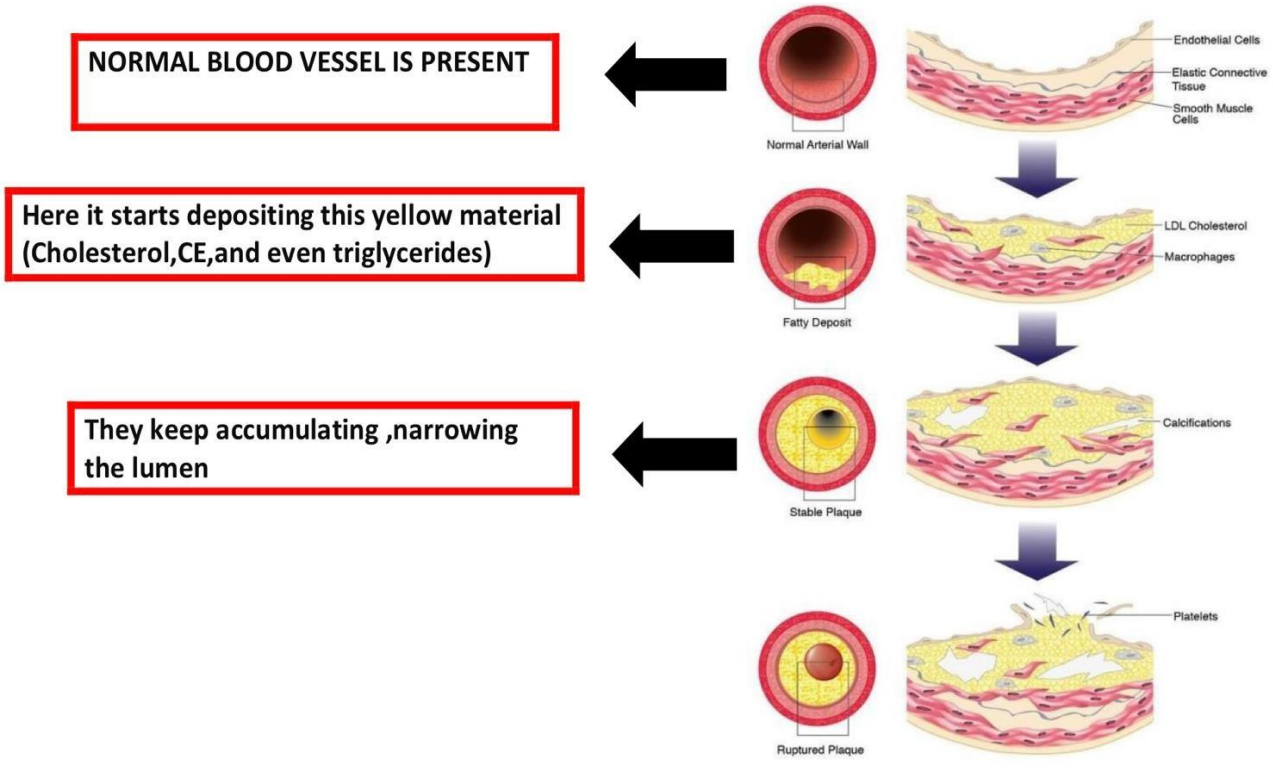
➢ The most common site for deposition is in the walls of the blood vessels.

➢ Phagocytes and macrophages in the walls of the blood vessels uptake the fat, then they become overloaded with these lipids (triglycerides, cholesterols, and cholesterol esters).

➢ The cause is either increased intake or decreased catabolism of these cholesterol and cholesterol esters.

➢ The best example is Atherosclerosis which can predispose to coronary heart disease or cerebrovascular accidents.

Look at the histological section of the blood vessel, we can see these lipids, accumulating sometimes in **MACROPHAGES**, they intake these lipids in the wall of the blood vessel.



PROTEINS

- **Much less common than lipid accumulations**
- **Either excess external or internal synthesis: proteins can be either produced inside the cell or derived from outside the cell.**
  - **Examples:**

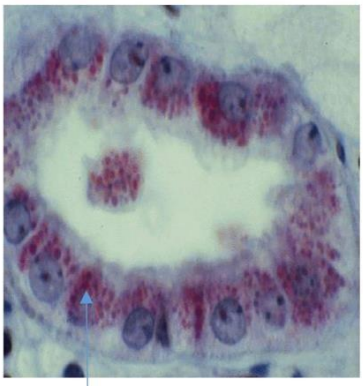
1. **Proximal renal tubules in nephrotic syndrome**
2. **Russell bodies in plasma cells**
3. **Alcoholic hyaline in liver of alcoholic patient**

4. Neurofibrillary tangles in neurons protein accumulations in the neurons of the brain (Alzheimer disease)

1. nephrotic syndrome (increasing in albumin conc.)

An example is what happens in the cells of kidney, particularly proximal renal tubules, in nephrotic syndrome.

What happens is that patients suffer from a high rate of eliminating protein (albumin) in the urine. Normally, glomeruli prevent the escape of proteins from the blood to urine.But here in this disease, the permeability of glomeruli for proteins is abnormally high, so we start to lose these proteins in the urine.As a response, the renal tubules will try to conserve as much amount of proteins as they can, so they reabsorb them from the urine in order to bring them back to blood.

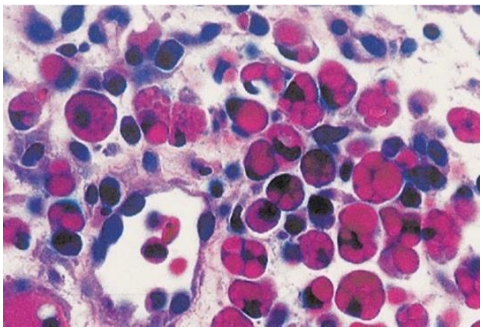


Epithelial cells of renal tubules

**NOTICE HERE the pinkish appearance of accumulating proteins inside proximal renal tubular cells.

2. Russell bodies in plasma cells

We already know that plasma cells are a main source of antibodies, which are proteins. So when an inflammation or tumor occurs, plasma cells produce so much antibodies that will accumulate in their cytoplasm, these are called Russell bodies.

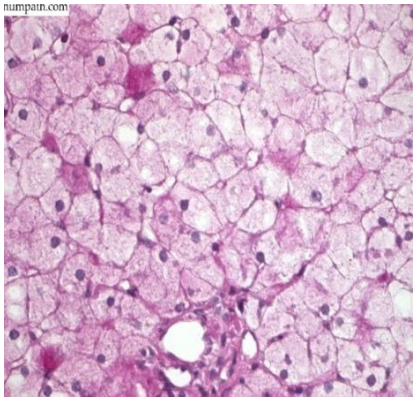


Notice here the heavy pinkish appearance of the cytoplasm-this is how Russell bodies The dark blue-black bodies are nuclei

*Russell bodies:excessive protein(antibody) deposition in the cytoplasm of plasma cells

GLYCOGEN

- **Abnormality in glucose or glycogen metabolism (glycogen storage disease, deficiency of glycogen-metabolizing enzymes, leads to glycogen deposition)**
  - **DM (glycogen deposition in renal tubules, heart, B (beta) cells of pancreas, liver).**
- **Glycogen storage diseases (inherited abnormality) may manifest in the bone marrow, where bone marrow biopsies show macrophages full of deposited glycogen.**



Liver section, look at the hepatocytes. Normally, the cytoplasm appear pinkish in color, but in this case of excessive glycogen deposition we notice that it becomes faint or slightly white.

PIGMENTS

(ANY COLORED MATERIAL DEPOSITED INSIDE CELLS)

1. **Exogenous**
   - **Most common exogenous, carbon (coal dust, air pollution, smoking)**

All people exposured will have carbon deposited in their lungs.

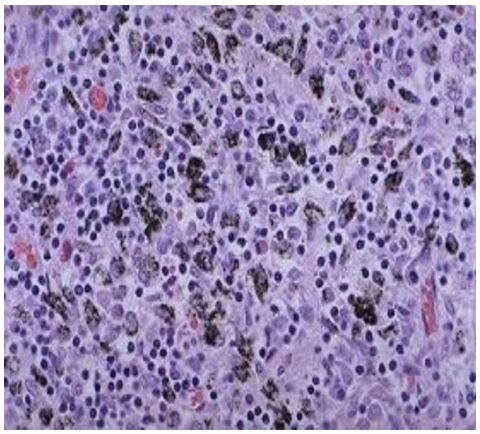
- **Alveolar macrophages → lymphatic channels → tracheobronchial LN**

Deposition can occur in the lung tissue itself, or in the alveoli.

If deposited in alveoli, it will be up taken and engulfed by → lymphatic channels → tracheobronchial lymph nodes, and it may reach mediastinal lymph nodes.

- **Anthracosis**

- Anthracosis = carbon deposition.
- Steatosis = fat deposition.



Notice that the black discolorations here represent carbon deposition, which is called ANTHRACOSIS

Carbon is an undegradable substance, thus appears as black deposits.

Endogenous

1.Lipofuscin

'wear-and-tear pigment'

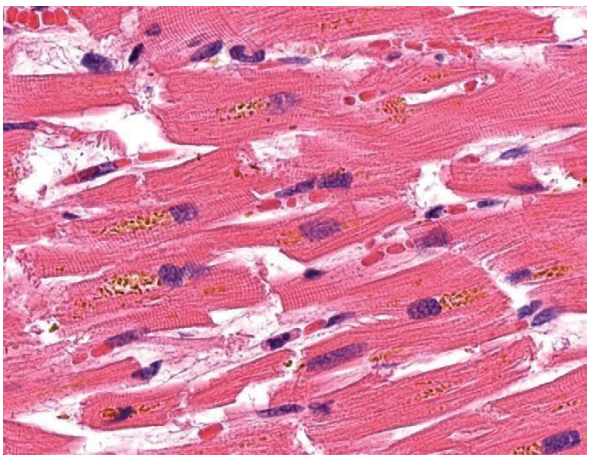
Age/atrophy

Heart, liver, and brain

Lipid and protein

Marker of past free radical injury

brown atrophy



Brown pigment as appears in the pic taken from a cardiac or skeletal muscle (mostly it is cardiac)

Tissues affected: **heart, liver , brain** and skeletal muscles

Its deposition indicates **aging**, **atrophy**, or previous **cell injury** mostly mediated by free radicals.

Both aging and atrophy are considered as physiological causes , atrophy is an adaptation mechanism in which the cell undergo autophagy .

It is a lipid and protein-derived (composition): mostly due to the membrane damage or organelles damage in the cell.

When the tissue is severely atrophied, and it turns brown, due to lipofuscin atrophy, it appears as 'BROWN ATROPHY'

Also named 'wear-and-tear pigment'. حت و تهرئة

Pic 1

Endogenous

2 Melanin

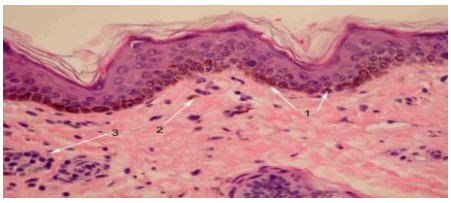
Source: melanocytes

UV protection

Accumulates in dermal macrophages

and adjacent keratinocytes

Freckles



Pic 2

It offers up protection against UV light

In cases of increased exposure to UV light, especially fair-skinned people, they develop excessive production of melanin, which can also be transported to adjacent keratinocytes and dermal macrophages.

Examples on skin mainfestions: FRECKELS, which are brown dots (discolorations) due to UV light exposure in fair-skinned people.

Note in pic 2 all of the changes are found within the basal layer and , the brown-colored cells are NOT only melanocytes, it is also keratinocytes which take the pigment, but they don't produce melanin-MELANOCYTES DO -,theyonly take it, also macrophages in the dermis take the pigment

3 Hemosiderin

Hb-derived granular pigment

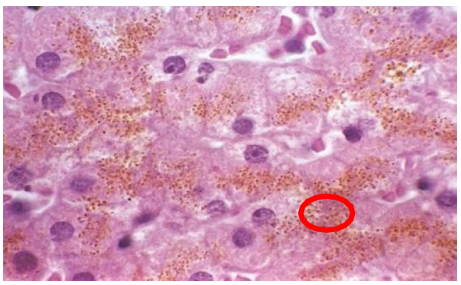
iron + Apoferritin= ferritin

micelles

Physiologic in the mononuclear phagocytes of the BM. spleen. and liver, from RBC turnover

Bruise: local pathologic deposition from hemorrhage

Hemosiderosis: systemic pathologic deposition of hemosiderin (hemochromatosis, hemolytic anemias, repeated blood transfusions)



→ Hb-derived iron pigment (produced from hemoglobin degradation)

****Iron** in cells usually binds to **apoferritin** (protein), to give ferritin micelles

Deposition of Iron can be physiologic or pathologic

1. Physiologic in organs or tissues that have frequent RBCs turnover activity such as:bone marrow,the factory of RBCs synthesis,also RBCs die in BM before even being transported to blood,thus we'll find iron deposition in BM when examining biopsies,which is a normal finding.Also,we see Iron deposition is tissues or organs that destroy

RBCs like spleen and liver,as a result its normal to find a lot of deposited Iron in spleen and –to a less extent- in the liver.

2. Pathological

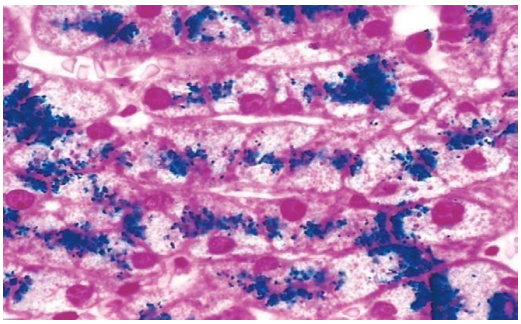
in localized depositions such as bruises (from hemorrhage),here the affected region will express different discolorations(e.g:bluish then yellowishor brownish discolorations) the yellow or brown one indicates Iron deposition. After a while,macrophages will arrive ,engulf Iron,in order to return to the blood ,where it can be used again in RBC production.

In hemosiderosis: generalized systemic pathologic deposition of hemosiderin can result from hemochromatosis, hemolytic anemias and repeated blood

transfusion.

Pathologic deposition can be generalized, systemic, everywhere(skin, heart ,liver, muscles).

Q:: How can we make sure that the brown pigment in the liver is an iron pigment, not lipofuscin pigment or melanin pigment for example?



We use Prussian blue stain (special stain), Prussian blue stain gives these granules the blue color if it contains iron, but if it is lipofuscin or melanin it will not take the stain.

There are different causes of hemosederosis:

1.HEMOLYTIC ANEMIA

-Sickle Cell Anemia,Thalassemia

*Any condition that increases RBCs destruction is hemolytic anemia ,and it can cause general deposition of Iron.

*Hemolytic anemia patients were found to have a deeply brownish skin.

2.HEMOCHROMATOSIS

Autosomal dominant condition that causes high Iron deposition in different organs in the body, for example deposition is the heart may lead to heart failure, deposition in the pancreas may lead to Diabetes and so on

3.REPEATED BLOOD TRANSFUSIONS

e.g:thalassemia,leukemia

-Patients with thalassemia receive blood transfusions approximately every 3 months, so you can imagine how much Iron will get deposited in their bodies

Pathologic calcification

Abnormal deposition of calcium salts, together with smaller amounts of iron, magnesium, and other mineral

Dystrophic Calcification

Deposition in dead/injured tissues

Normal Ca2+ metabolism

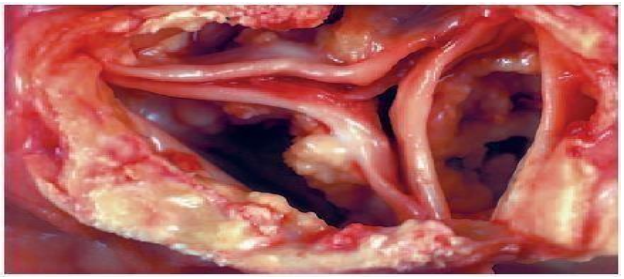
Exacerbated by Hypercalcemia

Metastatic Calcification

Deposition in normal tissues

Almost always abnormal Ca2+ metabolism (hypercalcemia).

Dystrophic calcification Necrosis of any type (e.g. atherosclerosis, aging or damaged heart valves, aortic stenosis, tuberculosis) } Incidental finding indicating insignificant past cell injury } May be a cause of organ dysfunction.



As shown here,this heart valve is severely filled with deposited calcium that has a white-chalky appearance, and this may lead to HF,sothe valve should be changed, because of organ dysfunction.

Necrosis of any type in any tissue:coagulative,caseous(TB),fat necrosis(acute pancreatitis).Atherosclerosis,aging,damaged heart valves,aortic stenosis

-Atherosclerosis has recently been considered an inflammatory reaction,because of macrophages being at the site engulfing lipids in the walls of blood vessels,so atherosclerotic vessels can deposit calcium,thus vessels become more rigid. -Aging of cells can also lead to calcium accumulation,like aged heart valves that underwent degeneration as a consequence for aging,they show calcium deposition. -Aortic stenosis,either due to aging or other earlier conditions,can lead to calcium accumulation in aortic heart valves,making them more stiff.

-Complications depend on the degree of calcium accumulation,that is,small trace amounts of deposited calcium in necrotic doesn't indicate clinical significance,because the problem here is the necrosis itself,and calcium deposition won't be worse.But sometimes aged heart valves may have excessive amounts of calcium deposited.

calcium depositions may be an incidental finding indicating past insignificant cell injury

Long-term calcium accumulation may eventually cause organ dysfunction.

Metastatic calcification

- Hyperparathyroidism (primary and parathyroid hormone related protein)
- Bone destruction (metastasis, MM, leukemia, Pagets, immobilization)
- Vit-D intoxication,
- Sarcoidosis.
- Renal failure with 2ry hyperparathyroidism.
- VESSELS, LUNG, KIDNEY

METASTATIC CALCIFICATON (The same tissue doesn't have any problems, except for elevated calcium levels in the blood):

CAUSES OF HYPERCALCEMIA:

1-Hyperparathyroidism(elevated Parathyroid hormone in the blood,and we know it is the main responsible hormone for calcium balance,so disordered levels of it would induce hypercalcemia)

**Hyperparathyroidism can be primary(problem in the parathyroid itself) or secondary(problem in the hypothalamus) and 2ry is usually associated with renal failure or it could be a tumor (lung cancer as an example) that produces PTH-like proteins in the blood,exerting the same effect of PTH,hypercalcemia.

2-Bone destruction: any destruction to the bone causes calcium release to the blood,causing hypercalcemia.It can be caused by different conditions like metastasis(breast cancer,prostatic cancer,… can metastatize to bones thus elaborating calcium from them to the blood leading to hypercalcemia.Another cause is Multiple

Myeloma(MM),which is a tumor in plasma cells –which are present in the bone,in BM_,thus hypercalcemia happens. Also Leukemia,which occurs in the bone marrow,can eventually lead to bone

destruction.Pagets disease,which is a benign disease,is a cause of bone destruction,presents with excessive bone turnover and

remodeling(breakup and synthesis at the same time).Immobilization can also lead to hypercalcemia.

3-Vit D intoxication:Vit D increases calcium absorption from kidneys,GIT,… to the blood.So people taking vit D without prescription will continuously build up high levels of it in their blood,causing intoxication,thus hypercalcemia.

4-sarcoidosis:autoimmune systemic disease accompanied with hypercalcemia

5-Renal failure:presents with low phosphate levels in the blood

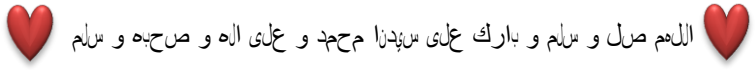
(hypophosphatemia),this will trigger sec. hyperparathyroidism in order to absorb more phosphorus (and PTH elevation at the same time leads to more calcium absorbance(hypercalcemia)). Renal failure is usually associated with 2ry parathyroidism

* Calcium deposition can occur in various organs in the body such as kidney,lung and blood vessels

* Metastatic calcification is a MISNOMER(MISNAMED),because metastasis in conventional medicine means spread of cancer(malignancy) to distant sites in the body ,but here metastasis is NOT malignant,although it can accompany malignancies,but calcification isn't generally malignant,so it was named as metastatic because it can spread everywhere.

A student asked how to treat calcium deposition ?

Answer : we can’t remove the deposition but we should treat the hyper-calcemia by treating the reason causing it for example deal with kidney failure .



V2

صفحة 12 تم اضافة:

“Almost always abnormal Ca2+ metabolism (hypercalcemia)”

V3

صفحة 9:

تم تعديل **Hapoferritin =ferritin micelles**

الى **iron +Apoferritin =ferritin micelles**