Doctor 021

PATHOLOGY

Sheet no. 12

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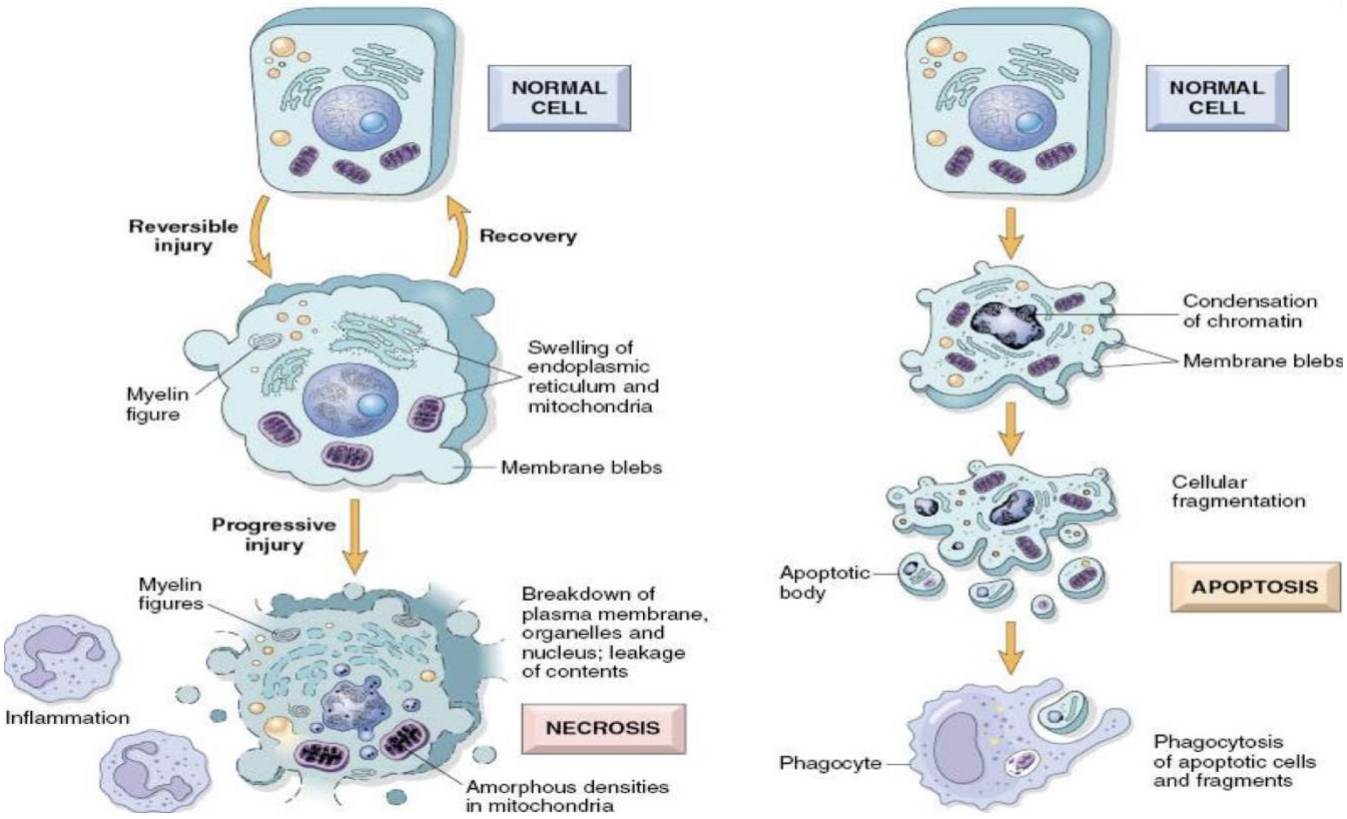
CELL INJURY, CELL DEATH, AND ADAPTATIONS

This lecture will be about the reversible & irreversible cell injury and patterns of necrosis (cell death).

Cell injury



As we can see in the figure, the normal cell has normal size and intact cell membrane and organelles. When the cell is exposed to any injurious stimulus (more than what the cell can adapt to), it will undergo reversible injury.

Notice that at reversible cell injury,

1- The cell and its organelles are swollen (increase in size, and that doesn't mean hypertrophy**), like a balloon, due to accumulation of fluids and water.
2- cell membrane has blebs, but it remains **intact** (which means it is **continuous**, so the contents still inside the cell) and once the injury has gone, the cell will return back to normal state and function normally (in reversible injury, the cell is alive but nonfunctional).
3- The nucleus hasn't really changed that much (still intact and more clumped chromatins)

When the cell is exposed to progressive injury, it will undergo irreversible cell injury, there will be a burst in the cell.

1- cell membrane will be disrupted, and the integrity of the membrane will be lost.
2- cell contents (enzymes, proteins, etc.) will leave to the outside, and they can get entry to the blood stream.
3- There will be more marked dilatation of the organelles (like mitochondria and ER) and there are black densities inside mitochondria, the cell here will be not alive and nonfunctional (dead cell), so it will not return back to the normal state.
4- after cell death (necrosis), inflammation should be done.
5- nucleus is fragmented and then disappears

**hypertrophy: increase in size, but it's an adaptive mechanism.

REVERSIBLE INJURY

If the damaging stimulus is removed >>>injured cells can return to normal.

Morphology changes during reversible injury:

1- Cellular swelling (because of accumulation of water and fluids inside the cell).

2- Fatty change

There are two types of morphology:

Macroscopically: you can see it on the tissue by naked eye.

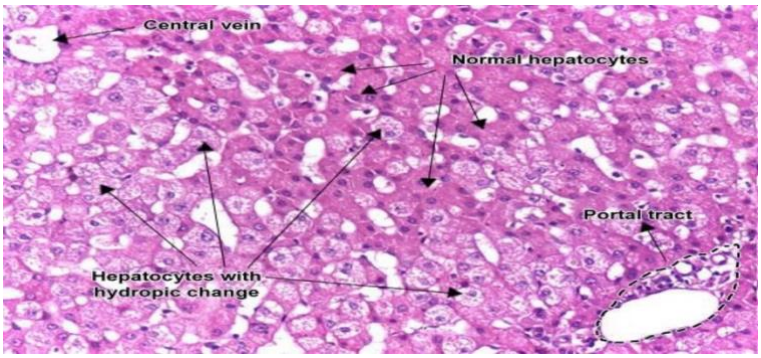
Microscopy: look under microscope (microscopic appearance), either light or electron microscope (ultra-structural findings needs EM).

REVERSIBLE DAMAGE – CELLULAR SWELLING

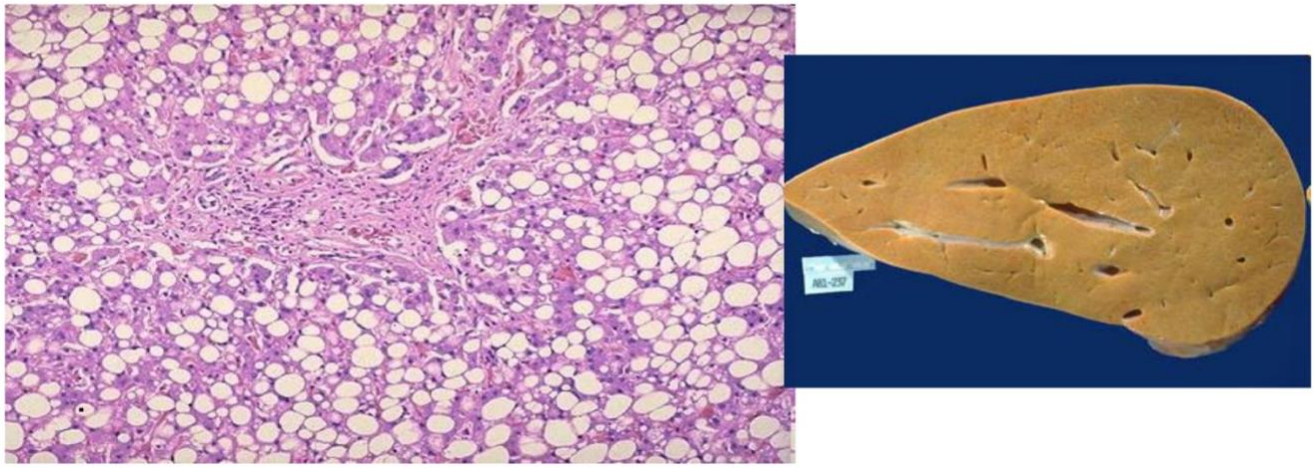
Macroscopic look: enlarged organ, ex: hepatitis (increased size of the liver).

Microscopic look: swollen hepatocyte, whitish discoloration cytoplasm due to accumulation of fluids.

H&E stain ➡



REVERSIBLE DAMAGE – FATTY CHANGE



Microscopy: hepatocytes are replaced with fat droplets, and it will look like adipocytes.

Fat in H&E looks white (colorless droplet) because during processing the fat will dissolve.

Macroscopically (grossly): you will see yellow color surface like adipose tissue.

Alcohol, diabetes, and obesity cause fatty liver disease (accumulation of fat in liver).

Note: fatty change is observed only in organs that are involved in lipid metabolism such as liver, whereas cellular swelling is observed in all types of cells.

OTHER CHANGES

Changes at ultra-structural level in reversible injury:

1) plasma membrane alterations (blebbing, blunting) but the membrane is still intact.

2) mitochondrial change (swelling and densities).

3) dilation of ER

4) nuclear clumping of chromatin (under microscope, the nucleus is dense and blue and nuclear envelope is still intact).

5) Cytoplasmic myelin figures (are derived from phospholipids in damaged membranes).

IRREVERSIBLE INJURY (NECROSIS)

- main features of irreversible injury :

1. Irreversible Mitochondrial dysfunction (after reversible injury it will return to its normal function - synthesis of ATP, but after irreversible one it will not)

2. Loss of plasma membrane and intracellular membranes (loss of continuity) **>>> cellular enzymes leak out** (they will access the blood)

3. Loss of DNA and chromatin structural integrity. (Because the nucleus is in its way to disappear)

After that**, local inflammation** should happen, in order to clean the dead cells.

MORPHOLOGY IRREVERSIBLE INJURY (NECROSIS)

Morphology changes during irreversible injury:

1- Increased cytoplasmic eosinophilia. Due to denaturation of proteins found in cytoplasm, so when Eosin stain bind to them, that will give us more bright color under the microscope.

2- Marked dilatation of ER , mitochondria.

3- Mitochondrial densities.

4- More myelin figures.

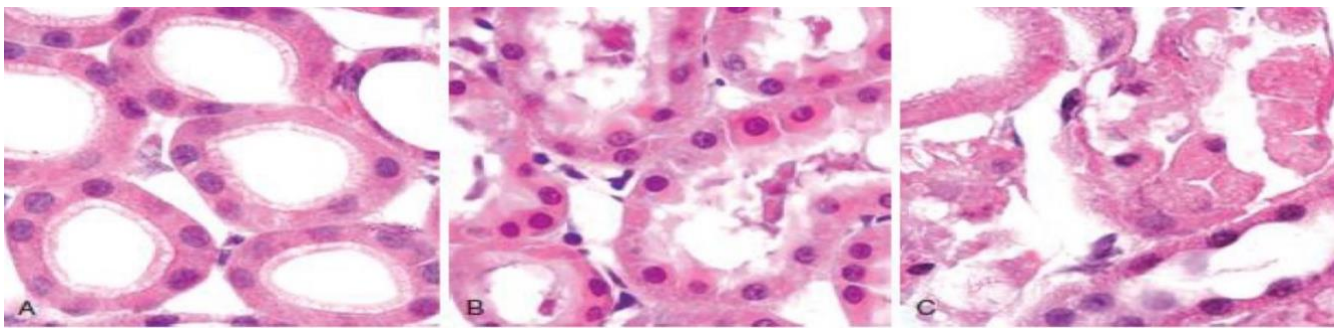
5- Nuclear changes (major alterations):

- Pyknosis: shrinkage and increased basophilia.

- Karyorrhexis :fragmentation; breaking down of nuclear material (DNA)

- Karyolysis (done by DNase enzyme**): basophilia fades** (the nucleus will disappear, so the cells will become anucleated)

Normal, REVERSIBLE, and irreversible Cell injury



*Sections from renal tubules

(A) Normal cells.

(B) Reversible injury, increase in the size, swelling cells and nucleus is darker with clamped chromatin.

(C) Irreversible injury, almost cells are without nuclei (dead cells).

CELL DEATH

Different mechanisms, depending on nature andseverity of injury.

Necrosis:

Rapid and uncontrollable.

Severe disturbances

Ischemia, toxins, infections, and trauma

Severe disturbances, such as loss of oxygen and nutrient supply and the actions of toxins, cause a rapid and uncontrollable form of death that has been called “accidental” cell death. Necrosis results from ischemia, exposure to toxins, various infections, and trauma. It’s almost always pathological there is no physiological necrosis .

Apoptosis:

Less severe injury.

Regulated by genes and signaling pathways

Controlled.

It is also called Peaceful death , cell committed suicide , programmed cell death . when the injury is less severe, or cells need to be eliminated during normal processes, they activate a precise set of molecular pathways that culminate in death(apoptosis) . This type of cell death is controlled by therapeutic agents or genetic mutation, so it is said to be “regulated” cell death. . But unlike necrosis, which is always an indication of a pathologic process, apoptosis also occurs in healthy tissues

Necroptosis.

In some instances, regulated cell death shows features of both necrosis and apoptosis, and has been called necroptosis.

The table is very important

تم وضع صورة الجدول من الكتاب لتكون بشكل واضح

Table 2.1 Features of Necrosis and Apoptosis

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-sized fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA and protein damage

CLINICAL IMPLICATIONS

- **Leakage of intracellular proteins through the damaged cell membrane and ultimately into the circulation provides a meansof detecting tissue-specific necrosis using blood or serum samples.**
- **Cardiac enzymes, liver enzymes**

Studying cell injuries helps us in diagnosing certain diseases. for example, when a cell is injured, its enzymes will be leaked into the blood, so when testing a blood sample, we can tell where the injury has taken place

Examples :

MI (Myocardial infarction) : ECG , cardiac enzymes blood test .

Pancreatitis : peripheral blood of pancreatic enzymes

Hepatitis (fever , abdominal pain , etc. …) : hepatic enzymes

If the enzymes of the liver are elevated, then there is something wrong .

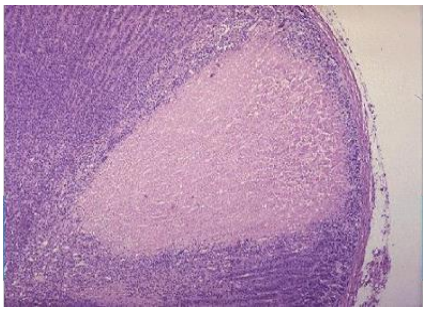
MORPHOLOGIC PATTERNS OF TISSUE NECROSIS

(ETIOLOGIC CLUES)

There are several morphologically distinct patterns of tissue necrosis that may provide etiologic clues.

COAGULATIVE NECROSIS

This type is usually caused by ischemia to the solid organs except in the CNS (spinal cord and brain).



} Conserved tissue architecture initially

} Anuclear eosinophilic on LM

} Wedge shaped following blood supply usually

} Leukocyte lysosomes and phagocytosis required for clearance

} Ischemia to all solid organ (infarcts) except the brain

Macroscopically : A wedge-shaped infarct (yellow) or pale due to decreased blood

supply with preservation of the outlines. The affected tissues take on a firm texture according to the shape of the area which is supplied by the blood vessel .

microscopically : pale and wedge-shaped what characterizes coagulative necrosis that it is a form of necrosis in which the underlying tissue architecture is preserved for at least several days after death of cells in the tissue . Presumably the injury denatures not only structural proteins but also enzymes, thereby blocking the proteolysis of the dead cells; as a result, eosinophilic, anucleate cells may persist for days or weeks. Leukocytes are recruited to the site of necrosis, and the dead cells are ultimately digested by the action of lysosomal enzymes of the leukocytes.

LIQUEFACTIVE NECROSIS

Focal infections Bacterial and fungal (pus)

CNS infarcts

Center liquefies and digested tissue is removed by phagocytosis

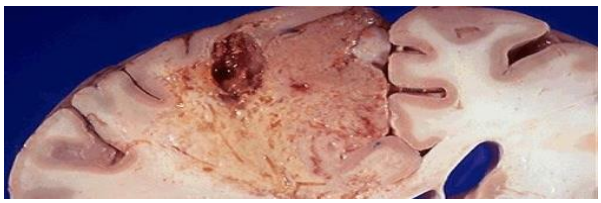
Liquefactive :area be semi liquid

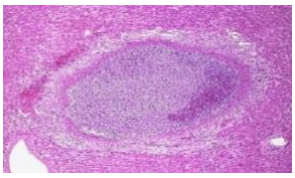
- ischemia to the CNS : lead to formation of cavity of semi liquid material because of digestion.

- localized infections: apses caused by localized bacterial infections (composed of semi liquid material)

It is seen in focal because microbes stimulate rapid accumulation of inflammatory cells, and the enzymes of leukocytes digest ("liquefy") the tissue. For obscure reasons, hypoxic death of cells within the central nervous system often evokes liquefactive necrosis .Whatever the pathogenesis, the dead cells are completely digested, transforming the tissue into a viscous liquid that is eventually removed by phagocytes.

Microscopically (3rd pic) : neutrophils and the microbes





GANGRENOUS NECROSIS

Clinical term

It is coagulative necrosis

Dry vs wet

Tissue looks black affects multiple tissue levels the same time . t usually refers to the condition of a limb (generally the lower leg) that has lost its blood supply and has undergone coagulative necrosis involving multiple tissue layers(again multiple tissue levels) . common in diabetic patients with atherosclerosis . it has two types of dry gangrene (without superimposed bacterial infection) and wet gangrene (with superimposed bacterial infection) . the second type (wet) is associated with purulent discharge and pus discharge .

CASEOUS NECROSI

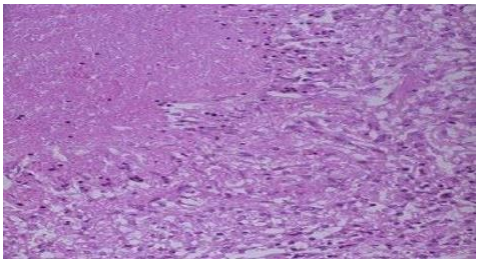
“Cheese like”

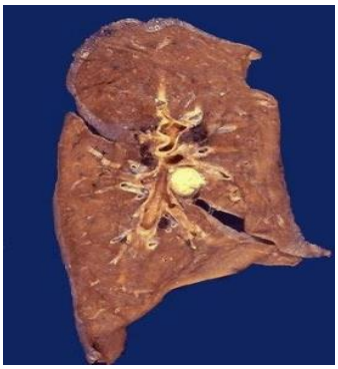
} Tissue architecture is not preserved

} Acellular center

} Usually enclosed in an granulomatous inflammatory border

} Most often seen in TB





In the second pic (Light microscope) the upper left

Part shows caseation and the lower right one

Represents the accumulated macrophages

Macroscopically it has cheesy like appearance the first pic represents a section from the lung .

The prototype example is tuberculosis (this king of bacteria lives in the caseous center)

It isn’t preserved at all, so it’s characterized by an acellular (no living cells)

FAT NECROSIS

Occurs in acute pancreatitis prototype example

Due to release of pancreatic lipases

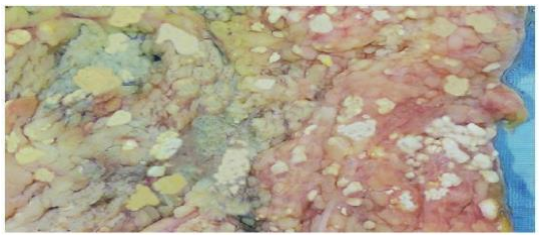
Focal fat destruction

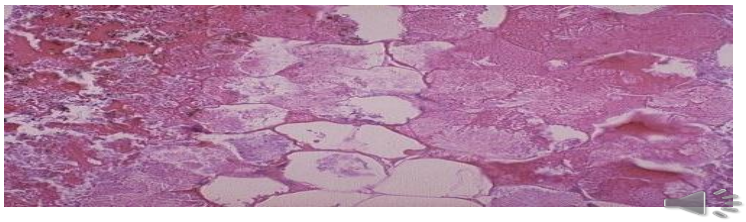
Released FA’s combine with Ca2+ (saponification) to produce the whitish chalky appearance

Shadows of necrotic fat cells

typically resulting from the release of activated pancreatic lipases into the substance of the pancreas and the peritoneal cavity. In this disorder, pancreatic enzymes that have leaked out of acinar cells and ducts liquefy the membranes of fat cells in the peritoneum, and lipases split the triglyceride esters contained within fat cells. The released fatty acids combine with calcium to produce grossly visible chalky white areas (fat saponification), which enable the surgeon and the pathologist to identify the lesions .

On histologic examination, the foci of necrosis contain shadowy outlines of necrotic fat cells and the nuclei are lost with pinkish discoloration of the cytoplasm sometimes .





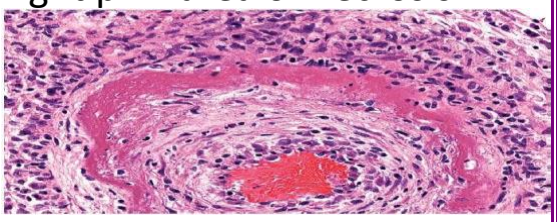
FIBRINOID NECROSIS

visible by LM

Deposits of antigen – antibody and fibrin complexes in arterial walls

Seen in vasculitis

The wall of the artery shows a circumferential bright pink area of necrosis with protein deposition and inflammation.



Vasculitis is the general term for inflammation of blood vessels , it is characterized by deposition of fibrinoid material and inflammation of the blood vessel . It usually occurs in immune reactions in which complexes of antigens and antibodies are deposited in the walls of blood vessels, but it also may occur in severe hypertension .

- Auto immune disease that characterized by the inflammation of the walls of blood vessels, leading to the accumulation of this pink material.

وَمَنْ جَهِلَتْ نَفْسُهُ قَدْرَهُ

رَأى غَيرُهُ مِنْهُ مَا لا يَرَى

دعواتكم و لكم بالمثل

V2

التعديل كالاتي :

ص ٧ تم وضع صورة الجدول من الكتاب لتكون بشكل واضح