PATHOLOGY

Medical Committee
The University of Jordan

■ SHEET

□ SIIDE

Lecture Number: 11

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Chronic Inflammation

☺ I believe that this sheet will not take more than 2 hours from you, just trust on yourself and go on ☺

** This sheet is talking about:

1- Difference between chronic and acute inflammation.
2- Main causes of chronic inflammation:
   a. Persistent infection
   b. Hypersensitivity and autoimmune reaction
   c. Prolonged exposure to toxic agent
3- Mechanism of chronic inflammation.
4- Cell of chronic inflammation:
   a. Macrophage
   b. Lymphocyte
   c. Other cells
5- Granulomatous Inflammation.

Written by Abdullah Shurman

Chronic Inflammation

The difference between Acute and chronic inflammation:-

* Acute inflammation is short lived and you can get rid of the causative agent, while the chronic inflammation is a prolonged response (lasts from weeks to months) and you can't get rid of the causative agent and it could be persistent infection.

* Also, in chronic inflammation, three characteristics must be seen **together** (happening together, coexistent):

1- The presence of mononuclear cells (the chronic inflammatory cells).

2- The presence of tissue damage.

3- Attempted repair, mainly by Fibrosis (The formation of fibrous tissue as a reparative process).

- In chronic inflammation, we can see all the cells that can be found in any tissue damage such as: Macrophage, mast cell, eosinophils, basophils, lymphocytes, plasma cells and neutrophils. Which are all called mononuclear cells.

- Neutrophils are the main cells in case of acute inflammation but with some macrophages, while the macrophages are the main cells in case of chronic inflammation and we can see also all the other types including neutrophils.

* Another type of inflammation called **Acute On Top Of Chronic Inflammation**, it happens when there is already a chronic inflammation for prolonged period, then an acute inflammation takes place over the existing chronic, an example is: acute on top of chronic "Cholecystitis" which is a painful chronic inflammation in gallbladder because of gallstones (solid accumulations of bile components) and may still be there for months or years, then the patient may get an acute inflammation on top of the chronic one.

Causes of chronic inflammation:

1- Persistent infection.

2- Allergic reactions (or Hypersensitivity) or autoimmune responses.

3- Prolonged exposure to certain toxic materials.

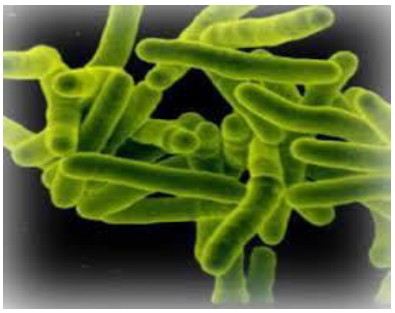
☒ Persistent infection:

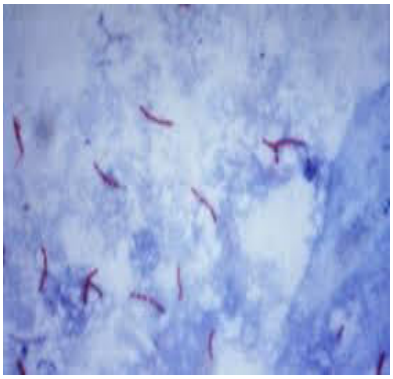
It can be either by the infectious agent itself which is difficult to be eradicated, like in case of TB (Tuberculosis), or the patient is not able to get rid of that infectious agent, like in case of some patients with pneumonia.

Slide (5) – Mycobacteria

-These are bacilli under LM (lower figure) and EM (higher part) called mycobacteria tuberculosis, also described as acid fast bacilli. They appear red bacilli when stained by ZN (Ziehl–Neelsen) stain (also called acid fast stain) which is used to recognize (acid fast bacilli) mycobacteria especially TB.

-A mycobacterial cell stays in the body, and the body cannot get rid of it (persistent), it might be dormant (inactive), but if the immunity decreases, it will be stimulated and becomes active and causes persistent infection (chronic inflammation).

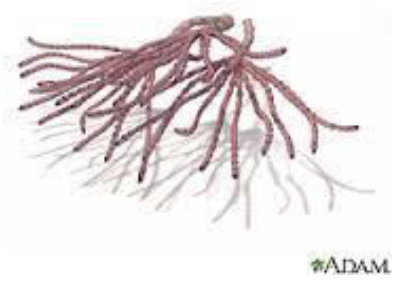




Slide (6) – Fungi

- Some forms of fungus can cause chronic inflammation.

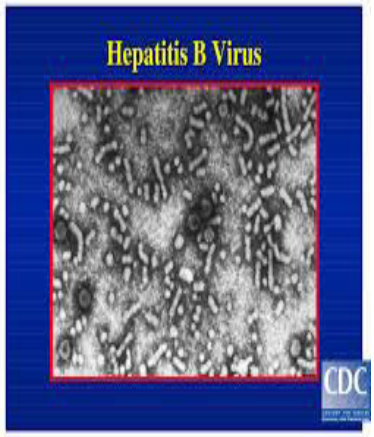
- This is how fungi look like, they're different from bacteria: branched, wider and longer.



Slide (7) – Viruses

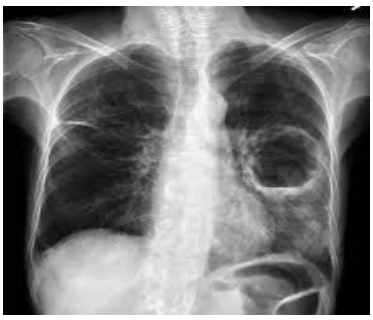
-Some viruses like hepatitis B, C or D can cause chronic Inflammation but not hepatitis A.

(Viruses are only recognized under EM (electron microscopy) only and cannot be seen under LM (light microscopy)).



Slide (8) – Chronic lung abscess

Some infections in the majority of people are treatable, like in pneumonia (infection of the lung, caused by bacteria), pneumonia can be treated in most patients by antibiotics and can be resolved as an acute inflammation, however, in elderly or immunosuppressed people the causative agent persists because those people can't get rid of this agent, so this will lead to progression of acute inflammation into chronic inflammation which results in a chronic lung abscess.



Note: So some inflammation start as acute then changes to chronic, others start as a chronic inflammation from the beginning; hypersensitivity and autoimmunes also starts as chronic inflammation.

☒ Hypersensitivity (or allergic reactions) and autoimmune response

Here the causative agent is persistent since it can be in the surrounding environment (e.g: inhaled with air) or in patient's body like in body's proteins. Thus, the inflammation is chronic.

-You have an inappropriate stimulation of immune system, either due to internal (autoimmune response) or external (hypersensitive, allergic response) agents.

-As an example is Asthma, which is an allergic reaction towards dust (mainly caused by hypersensitive immunologic response to inhaled dust particles). (Exogenous stimulus)

-Other examples are coeliac disease, Crhon's disease, and Rheumatoid arthritis. Which are autoimmune diseases. (Endogenous stimulus)

- Coeliac disease occurs when we have an anti-gliadin problem; a susceptible patient eats gliadin containing food, his body may produce antibodies against an enzyme in his body (that works gliadin) (intrinsically triggered autoimmune response).

☒ Prolonged Exposure to certain toxic materials

The body cannot get rid of those toxins, such as:

A) Coal → Causes Coalworker's pneumoconiosis

B) Asbestos → Causes Asbestosis

C) Silica → Causes Silicosis

They reach lungs by inhalation, and produce the black pigmentation (look at the picture), and the body is unable to get rid of these pigments, producing chronic inflammation.

Mechanisms of chronic inflammation:

-All mediator that act on acute inflammation, also act the same way with chronic inflammation (cytokines, arachidonic acid metabolites, chemokines, chemotactic agents ...).

- Also, the cellular changes (starting from margination, rolling, adhesion, transmigration and chemotaxis) apply to chronic inflammation.

- As a result; mechanisms are the same, mediators are the same, and actual response is the same. But the difference is in the cells; in acute inflammation the main cells are neutrophils while in chronic inflammation, the main cell type is macrophages and you can see all other cell types (including neutrophils).

Cells of chronic inflammation

✓ Macrophages:

- Dominant cells in ***most*** (becaause sometimes only lymphocytes) chronic inflammatory reactions.

- Functions:

1- Act in inflammation in:

A- Phagocytosis.
B- Stimulation and activation of lymphocytes.
C- Production of cytokines.

2- Act in tissue repair (can be considered a part of inflammation).

3- Act as cancer progenitors or inhibitors.

NOTE: **All inflammatory cells produce cytokines, but they may differ in the type of cytokines.**

- All macrophages come from bone marrow (first produced as monocytes circulating in the blood then they migrate to the specific tissue), but they differ in their names according to the place at which they exist:

1- Blood → monocyte (lives one day).

2- Tissue → Macrophage (lives for months).

3- Liver → Kupffer cell.

4- Spleen and lymph nodes → Histiocyte.

5- CNS → Microglial Cell.

They are all macrophages that originate from the same progenitor cells and have basically the same functions. But they may have little differences like their life time.

6- Lung → Alveolar Macrophage.

- Macrophage Activation:

During inflammation, macrophages are activated by two pathways:

1) Classical pathway -M1- (destruction phase):

-Stimulates the monocyte (Macrophage) to become Macrophage 1 (M1) cell.

-M1 is an inflammatory cell which evokes (causes) inflammation (the destructive part of inflammation).

-This activation is done under the influence of cytokines (Interferon Gamma "IFN - ɣ") and microbes.

-In other words, a macrophage stimulated by "IFN - ɣ" or by microbial agents will change to M1 (macrophage 1) cell which will cause inflammatory response, phagocytosis, and inflammation.

-Phagocytosis is held by the same mechanisms seen in acute inflammation → by free radicals, nitrogen oxygen radicals, and by lysosomal enzymes.

-M1 starts inflammation by production of cytokines which trigger all inflammatory steps and mechanisms.

2) Alternative pathway -M2- (repair phase):

-Stimulates the monocyte to become Macrophage 2 (M2) cell.

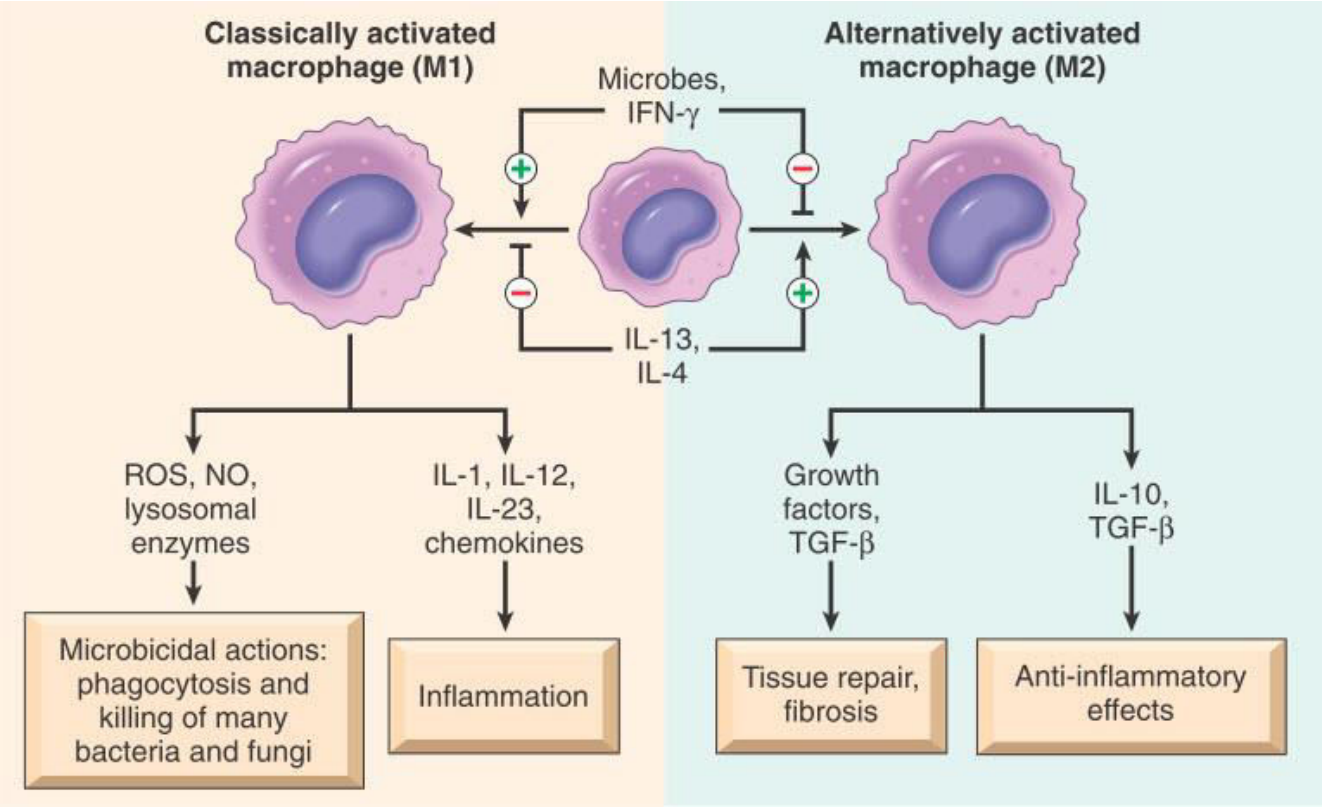
-M2 is an anti-inflammatory cell which starts tissue repairing after tissue damage in inflammation.

-This activation is done under the influence of two interleukins (IL4 or IL13).

-In other words, a macrophage stimulated by IL 4 or IL 13 will change to M2 (microphage 2) cell which will cause (1) tissue repair and (2) anti-inflammatory effects.

-Tissue repair is done by producing growth factors (they cause growth, repair and fibrosis). Anti-inflammatory effect is done especially by producing interleukin 10 (IL10).

CLASSICAL OPATHWAY	ALTERNATIVE PATHWAY
M1	M2
IFN, MICROBES	IL13, IL4
INFLAMMATION (CYTOKINES AND CHEMOKINES) (MICROBIL KILLING (ENZYMES, FREE RADICALS)	TISSUE REPAIR AND FIBROSIS (TGF BETA, GROWTH FACTOR. ANTI-INFLAMMATORY EFFECT (IL10 &TGF BETA



(** Extra information in the figure are not included.)

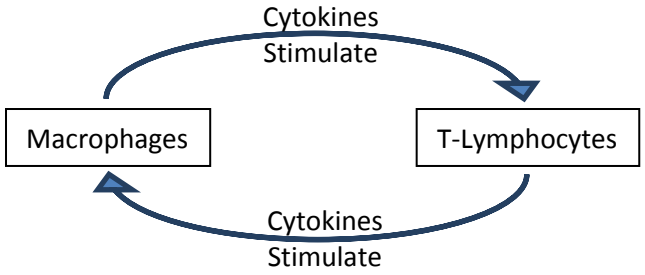
✓ Lymphocytes

Mainly B and T cells:

→ B-cells: secret antibodies.

→ T-cells:

Produce cytokines (like macrophages)
Macrophages produce cytokines that will stimulate lymphocytes, stimulated T-lymphocytes also produce cytokines that stimulate macrophages. A cycle of bi-directional stimulation.



So, in chronic inflammation, if there are macrophages and lymphocytes there will be prolonged severe inflammation (strong response) because of loads of cytokines resulted from the bidirectional stimulation.

✓ Other cells found in chronic inflammation:

- Eosinophils: which are important for parasitic infections and allergy.
- Mast cells: For Hypersensitivity reactions (also secrete cytokines).
- Neutrophils.

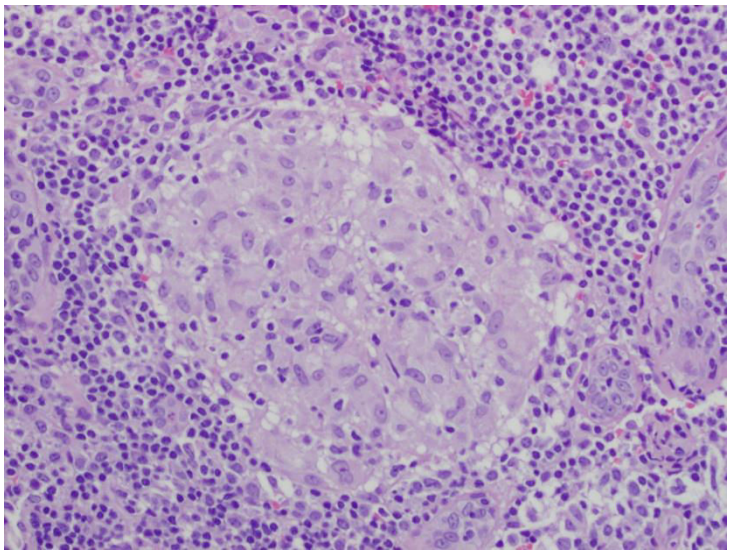
Some people mistakenly think that acute inflammation is more painful than chronic inflammation.

The word "acute" here does not necessarily mean stronger.

Strength of pain is not related to whether the inflammation is acute or chronic; it depends on the site, causes...

A special type of chronic inflammation

Granulomatous Inflammation:



Granuloma is an aggregation of macrophages forming a nodule (a small swelling or aggregation of cells in the body), also it is a special type of chronic inflammation happening in several diseases, mainly:

1- Tuberculosis "TB"
2- Sarcoidosis
3- Crhon's disease
4- Foreign body granuloma

*Other diseases cause granuloma: Fish–tang, Cat-scratch, Uric acid crystals, Gout, rheumatoid arthritis diseases and loads of other diseases. (We are required to know the upper four only)

- In the granuloma, the macrophage acquires loads of cytoplasm when it is activated. In this case, a macrophage which has loads of cytoplasm is called an **Epitheloid macrophage** (stimulated macrophage looks like epithelial cells because it acquires more cytoplasm). Activated (stimulated) macrophage needs more cytoplasm to synthesize cytokines.

- Cytokines (proteins) are synthesized by ribosomes, Golgi apparatus (for modification), and endoplasmic reticulum which are all found in the cytoplasm and thus we need more cytoplasm to hold a lot of those components to produce cytokines.

- Epitheloid macrophage means activated macrophage, and this is a morphologic description of how it looks like (like epithelial cells, and contains much cytoplasm).

Note: the doctor said that the following detailed information is not required.

---Sarcoidosis: is a systemic disease starts in the lungs and lymph nodes and it causes granuloma, the causes of this disease are unknown but they could be autoimmune.

---TB: also has granuloma but it differs from sarcoidosis because of presence of caseation.

--- Crhon's disease: it's inflammatory bowel disease in the intestine, it has two types:

1- Ulcerative colitis: starts from the rectum upwards and it is continuous to a certain point (differs among patient to patient) but doesn't have granuloma, it's obvious in large intestine.
2- Crohn's disease: patchy infection (area infected then area normal then area infected and so on), chronic inflammation of the large intestine, can affect the small intestine, the same with ulceration but it has granuloma.

* **B**oth types of Crhon's can lead to cancer.

❖ There are two types of granulomas:

1- Foreign body granuloma

A granuloma around a foreign body, so, under the microscope a fractile material which is the foreign body that will appear in the inside the granuloma.

Example: around sutures and tattoos, where macrophages aggregate around the foreign particles (of tattoos pigments and sutures) and try to degrade them but they can't get rid of them (macrophagial enzymes cannot degrade sutures), so macrophages aggregate forming granuloma.

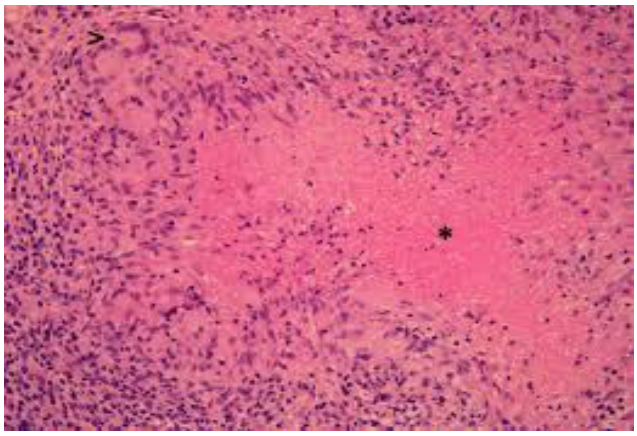
This granuloma is formed around an inert material (suture and pigment particles are inert materials), it doesn't evoke an immune response (doesn't produce cytokines and chemical mediators), and hence there will be aggregated macrophages but a very little amount of lymphocytes. It's only an activation of macrophages (inflammatory response) without an immune response. So, it's milder than the immune granuloma.

Asbestosis and Silicosis involve this type of inflammation.

2- Immune granuloma

A granuloma around an agent which can provoke (induce) an immune response, like in TB. In TB granulomas, which are caesiating granulomas, there are bacteria in the middle (not inert), and the bacterial cell itself has antigens which can stimulate both immune reactions and inflammatory reactions, so there will be lymphocyte and macrophages, also this type is more severe than foreign granuloma (because it activates two processes in the body, the inflammatory due to macrophages, and the immune due to lymphocytes).

❖ Caesious necrosis

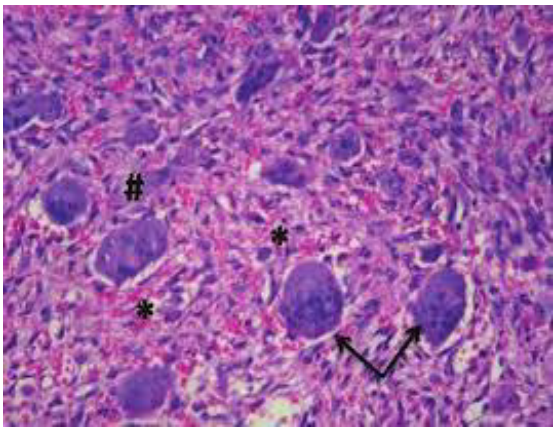


- Cheesy like material, necrotic tissue in the middle of granuloma,

- Causes of this necrosis are hypoxia (blood doesn't reach adequately to the middle of granuloma) and free radicals which are produced from macrophages, they kill the cells inside granuloma resulting in necrosis (caesious necrosis).

- It's seen in TB, the main cause of caesious necrosis is TB, caesiating granuloma is TB.

❖ Sometimes in granuloma, macrophages aggregate to form a single big cell with multiple nuclei swimming in the same cytoplasm (fused together), this big cell is called Giant cell. Giant cells are seen in several situations, such as in granulomas.



- There are several types of giant cells:

1- Foreign body type giant cell (a giant cell formed to contain the foreign body).
2- Langhan's giant cell (giant cell seen in granulomas).

* **Important**:

Langhan's cells are **not** Langerhan's cells.
They are different.

Everyday is a new chance to change your life

Shout-out to Mohammad Falahat
who gave me a hand in writing this sheet.

Don't forget us from your prayers.
Best wishes :)