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Pathology

Doctor 2018 | Medicine | JU

Sheet Slides

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This sheet has been written based on section's 2 record.

please refer to the highlighted notes (comments) to make sure everything is clear.

Other Cells in Chronic Inflammation

a) Eosinophils: abundant cells in **four** different types of reactions of inflammatory response:

1- *Acute allergic* (acute anaphylactic or acute atopy).

2- *Parasitic or Helminthic infestation*.

3- *Chronic inflammation*.

4- *Eosinophilic inflammation*: The main cells involved in this type of inflammation are eosinophils. Examples on *eosinophilic inflammation* include eosinophilic esophagitis, eosinophilic gastritis & eosinophilic colitis.

b) Mast cells:

*Abundant in soft tissues

*Active in both acute and chronic inflammation

*Mast cells and basophils express FceRI which binds with FC portion of IgE leading to degranulation; releasing Histamine and PG (seen in food allergy, venom and drug allergy)

*In chronic inflammation: secreting cytokines that promote inflammatory reactions.

c) NEUTROPHILS: Although **neutrophils infiltration** is a characteristic of acute inflammation, many forms of chronic inflammation, lasting for months, continue to show large number of neutrophils, induced either by persistent microbes or by cytokines and other mediators produced by activated macrophages and T lymphocytes (Such as Th17 which secrets IL-17 aiding in recruitment of neutrophils).

EXAMPLES of **chronic diseases** involving **neutrophils**:

a- ***Chronic osteomyelitis***: an acute infection in the bone and bone marrow, which must be immediately recognized and diagnosed correctly. It is a dangerous disease as it begins as an acute inflammation with symptoms like redness near the leg, edema & fever and if it wasn't cured, it would become chronic and could progress to bone cancer.

b- **Smoking** induces lung damage by the infiltration of neutrophils.

c- **Acute on top of chronic inflammation**: For example, patients with inflammatory bowel diseases such as **crohn disease** and **ulcerative colitis**, which are chronic

conditions, may sometimes face acute attacks causing bleeding by rectum (so the acute reaction attracted neutrophils).

Granulomatous Inflammation

It is a ***specific*** type of ***chronic*** inflammation that can appear in any tissue. This type of inflammation is **characterized** by the **presence of granuloma**, so what is granuloma? And what are the types of granuloma?

Granuloma: *A collection of activated macrophages (called **epithelioid histiocytes**) surrounded by some lymphocytes and plasma cells.*
** **Epithelioid histiocytes** (epithelial-like cells): activated macrophages that may develop abundant cytoplasm (swollen), small nuclei and begin to resemble epithelial cells.*

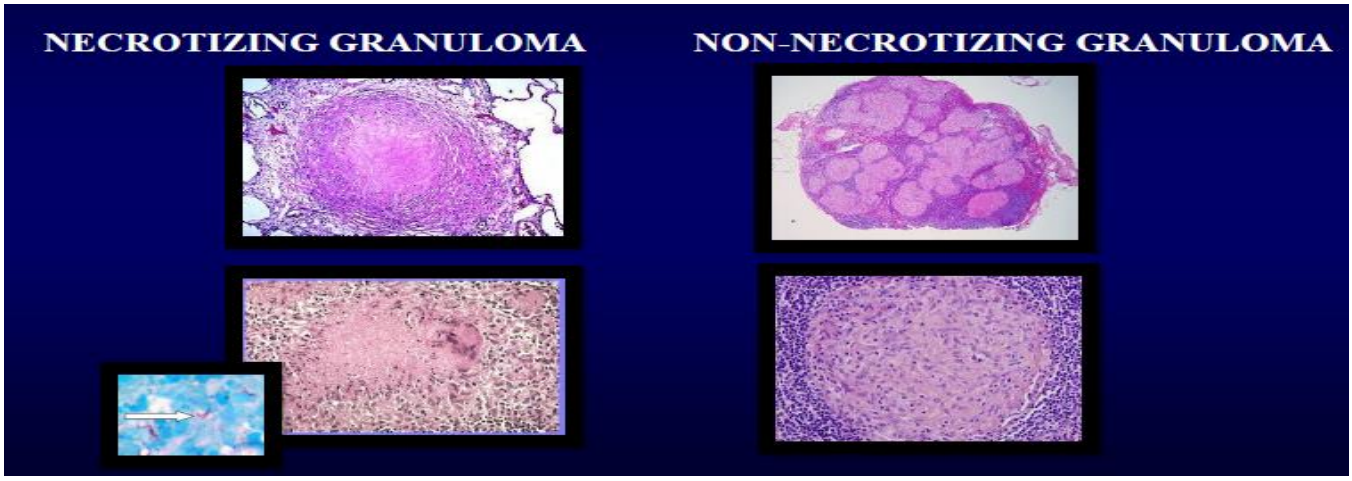
Granuloma formation is a cellular attempt to contain an offending agent that is difficult to eradicate. In respect to their **pathogenesis**, granulomas are of two types:

1- ***Immune granulomas***: It is caused when a persistent microbe or self-antigen cannot be readily eliminated thus inducing a persistent T Cell-mediated immune response (because 95% of the lymphocytes in granulomas are T-lymphocytes (90% are CD4+)). Examples include rheumatoid arthritis and type 4 delayed hypersensitivity reaction.

2- ***Foreign body granulomas***:For example, when needles are injected in the hand and are accidentally broken there, and since they are too big to be phagocytosed by macrophages and are **not immunogenic** (they do not activate cell-mediated response), fusion of several macrophages takes place to surround the foreign body.

Morphology of granulomatous inflammation

Granuloma can be seen ***microscopically*** in two different morphologic appearances, Necrotizing and Non-Necrotizing granuloma.



Let's discuss both types:

1- Necrotizing Granuloma: It is associated with central necrosis in which the granuloma surrounds a central necrotized region. This region appears grossly as granular, cheesy region of caseous necrosis giving the name (caseating granuloma).

Examining the pictures on the left, they represent lung alveolus and we can clearly see the granuloma (Epithelioid histiocytes with some plasma cells and lymphocytes) surrounding the central necrotic region.
Different causes can lead to necrotizing granulomatous inflammation, but ***mycobacterium tuberculosis*** is the prototype of it, and we can see it using *acid fast stain (also named ziehl-neelsen stain)* *the small blue picture on the left*.
Fungi can also cause necrotizing granuloma and we use fungal stains (silver stain).

2- Non-Necrotizing Granuloma: It is not associated with necrosis.

Look at the pictures on the right, we can see the lymph node with granuloma (the whitish area and surrounding lymphocytes) but without necrosis.
Sarcoidosis is the prototype of non-necrotizing granulomatous inflammation.

NOTE: Even though non-necrotizing granulomatous inflammation is not associated with necrosis, **it does disrupt the tissue** (in the pictures we can see how granuloma replaced lymph-node cells and this can happen everywhere either in heart or liver…etc.).

THE IMPORTANCE OF DIFFERENTIATING BETWEEN NECROTIZING AND NON-NECROTIZING GRANULOMA

It is very important to differentiate between these two patterns in order to treat diseases appropriately. We treat sarcoidosis with steroids (which inhibits phospholipases thus inhibiting immune response). Now imagine if we diagnose a patient with sarcoidosis although he has TB, and then we gave him steroids, what would happen? Unfortunately, he will die, because mycobacterium tuberculosis is a very dangerous infectious agent and we have no defense against it, because we used steroids.

Diagnosis of ***Sarcoidosis*** is by **exclusion,** that means we need to exclude other diseases such as TB, FUNGAL INFECTION…etc. Since the management of sarcoidosis is special (It is of unknown etiology), we can't use usual methods such as staining to diagnose it.

NOTE: Sometimes when we use acid-fast stain to detect TB, we get negative result, but that does not mean that the patient is uninfected (there might be a little number of bacteria), so we take another sample and we culture it and that takes weeks. But because we cannot wait that long, we give him treatment for TB and see if he gets better (this is called empirical treatment).

Table 3.9 Examples of Diseases With Granulomatous Inflammation

Disease	Cause	Tissue Reaction
Tuberculosis	*Mycobacterium tuberculosis*	Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli
Leprosy	*Mycobacterium leprae*	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	*Treponema pallidum*	Gumma: microscopic to grossly visible lesion, enclosing wall of macrophages; plasma cell infiltrate; central cells are necrotic without loss of cellular outline; organisms difficult to identify in tissue
Cat-scratch disease	Gram-negative bacillus	Rounded or stellate granuloma containing central granular debris and recognizable neutrophils; giant cells uncommon
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease (inflammatory bowel disease)	Immune reaction against undefined gut microbes and, possibly, self antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate

THE DOCTOR SAID WE NEED TO MEMORIZE THIS TABLE

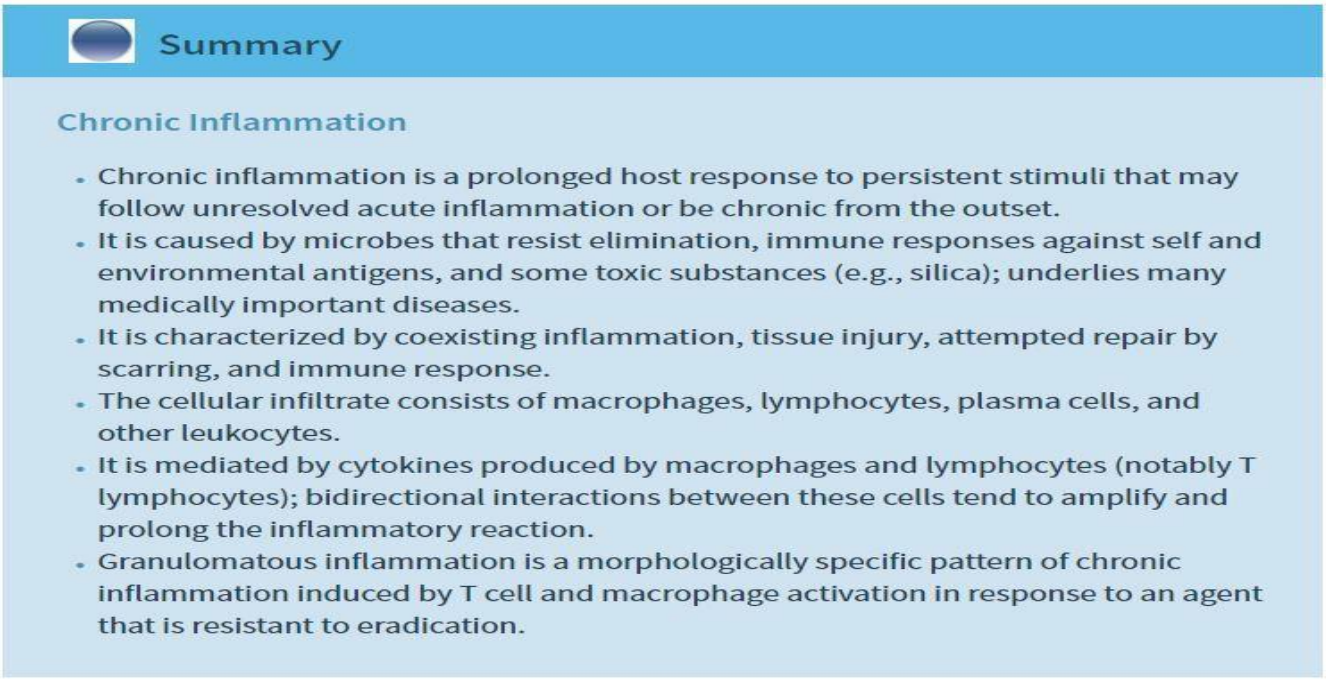
NOTES about the table:

1- In tuberculosis, the ***Caseating Granuloma*** is called ***tubercle*** and it looks white grossly.

2-Leprosy is seen in ***skin***.

3- In cat-scratch disease: it is a ***necrotizing granulomatous lymphadenitis*** and it's called geographic large granuloma.

4- Sarcoidosis could be seen to cause a necrotizing granulomatous inflammation, but it is more commonly causing a non-necrotizing one.



Systemic Effects of Inflammation

Any inflammatory response (acute or chronic) produces mediators that travel in the blood to all over the body producing systemic effects of inflammation called ***(acute-phase response).***

The acute-phase response consists of several clinical and pathological changes:

1- ***Fever***: Normal body temperature is (36.9-37.4°C). Any increase above this range (usually by 1 to 4 degrees) is considered a fever. Fever is induced by mediators called ***pyrogens*** *that are either exogenous or endogenous.* Bacterial products, such as LPS (called *exogenous pyrogens*), stimulate leukocytes to release cytokines such as IL-1 and TNF (called *endogenous pyrogens*) that increase the enzymes (cyclooxygenases) that convert arachidonic acid into prostaglandins (PGE2) leading to increase in temperature.

2- ***Acute phase proteins***: Plasma proteins, mostly synthesized in the liver, whose plasma concentrations may increase several hundred-fold as part of the response to an inflammatory stimuli. Ex: C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen (which is used to measure erythrocyte sedimentation rate (ESR)) & Hepcidin. These tests indicate non-specific response.

3- ***Leukocytosis (increased number of WBCs)*:** The normal number of WBCs in the blood is 8-11 thousand cells. In acute inflammations, this number increases to 15- 20 thousand

cells by mediators acting at the bone marrow for the synthesis of more WBC'S. Sometimes, we notice that the number can go up to 40, 50 or even 100 thousand. These extreme elevations are referred to as ***leukemoid reactions***, because they are similar to leukemia. To distinguish between leukemia and leukemoid reaction, we take the sample to the lab and see on a machine whether the cells are **monoclonal** (cancerous) or **polyclonal** (not cancerous and the body simply gave an exaggerated response).

4- ***Other manifestations***: Tachycardia, Increase BP, Chills, Rigors (shivering due to the fever, rigor is a more intense type of shivering compared to chill), decreased sweating, anorexia(lack or loss of appetite for food), somnolence (state of strong desire for sleep), and malaise(general feeling of discomfort, illness, or unease).

SEPSIS & SEPTIC SHOCK:

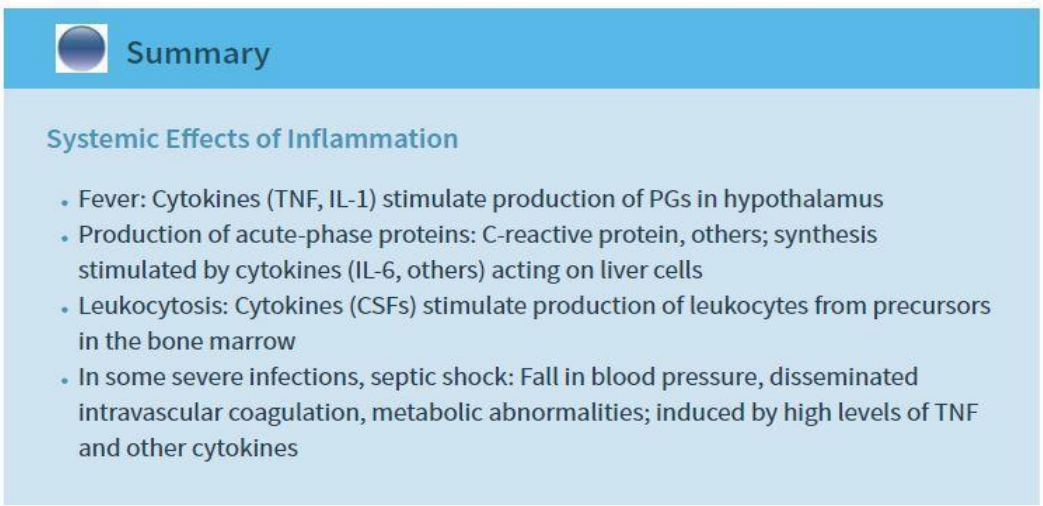
- Sepsis, septic shock and septicemia indicate severe bacterial infection which may be fatal.
- Large amounts of mediators (TNF & IL-1) lead to multiple complications such as:

1. -Disseminated intravascular coagulation (**DIC**): A condition in which blood clots form throughout the body, blocking small blood vessels causing multiple infarcts (brain, heart…).
2. -Hypotensive shock.
3. -insulin resistance and hypoglycemia.

NOTE: Gram-Negative sepsis is very dangerous.

Sepsis May be caused by ***non-infectious etiology***: *pancreatitis, severe burns and severe trauma.*

As sepsis develops due to mediators, the conditions described above fall under the category of "systemic inflammatory response syndrome" (SIRS).



Good luck mates!