SHEET NO. 11

PATHOLOGY

DOCTOR 2019 | MEDICINE | JU

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بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

As we mentioned previously that the inflammatory response also needs additional inflammatory cells and one of those is the lymphocytes. So here we go:

LYMPHOCYTES:

T & B lymphocytes gets activated by multiple agents, microbes, and environmental antigens.

They are also part of the components of cellular infiltrate & they are the main cells seen in tissue with chronic inflammation.

The T-cells are divided into multiple sub variants one of them is what we call:

- CD4 +ve (T-helper cells) and they can secrete cytokines which will induce inflammation.

CD refers to cluster of designation (also known as the cluster of differentiation) which are basically cytoplasmic membranous antigens defining each cell type from the other ones.
We have more than probably 200 CDs now for lymphocytes, but the major ones are the T and the B cells, there are certain markers for T-cells and certain markers for B-cells.

Mature cell markers for T-cell is CD3, CD2, CD5, CD7 and then either CD4 or CD8. CD4 +ve are the T-helper cells, and CD8 +ve are the T-suppressors.

Keep in mind that is not only the t cells play a role in the inflammatory response. The B-cells and plasma cells also play a role in production of antibodies and the plasma cells are a major cell which infiltrate in chronic inflammation.

There are different types of CD4 +ve T-cells or T-helper cells in the peripheral blood and tissue. So, we know that the T-helper cells are not one single clone.

CD4+ T CELLS:

TH1 (T-helper 1)	Secrete interferon gamma INF-ℵ, , they are the ones which are pro-inflammatory they augment the inflammatory response, activate Macs (Macrophages) in classic pathway to induce more mediators.
TH2 (T-helper 2)	They produce different types of cytokines; Interleukins IL-4, IL-5 & IL-13; activates eosinophils and Macs alternative pathway which means suppressing/ controlling/decreasing the intensity of the inflammatory response .
TH17 (T-helper 17)	Secretes IL-17, inducing more cytokines production (chemokines secretion), and recruits PMNs. They are playing a role both in acute and chronic inflammation. The acute inflammation: by recruiting more neutrophils.

TH1 (T-helper 1) they are the most abundant at early stages of inflammation.

The following figure is just to help you understand the close relationship between the neutrophils and the monocytes, and how they interact very closely in the production of cytokines, recruitment different phases of inflammation, presenting the antigens to the T-cells, activating the monocytes in the classic pathway or at the end in the alternative pathway.

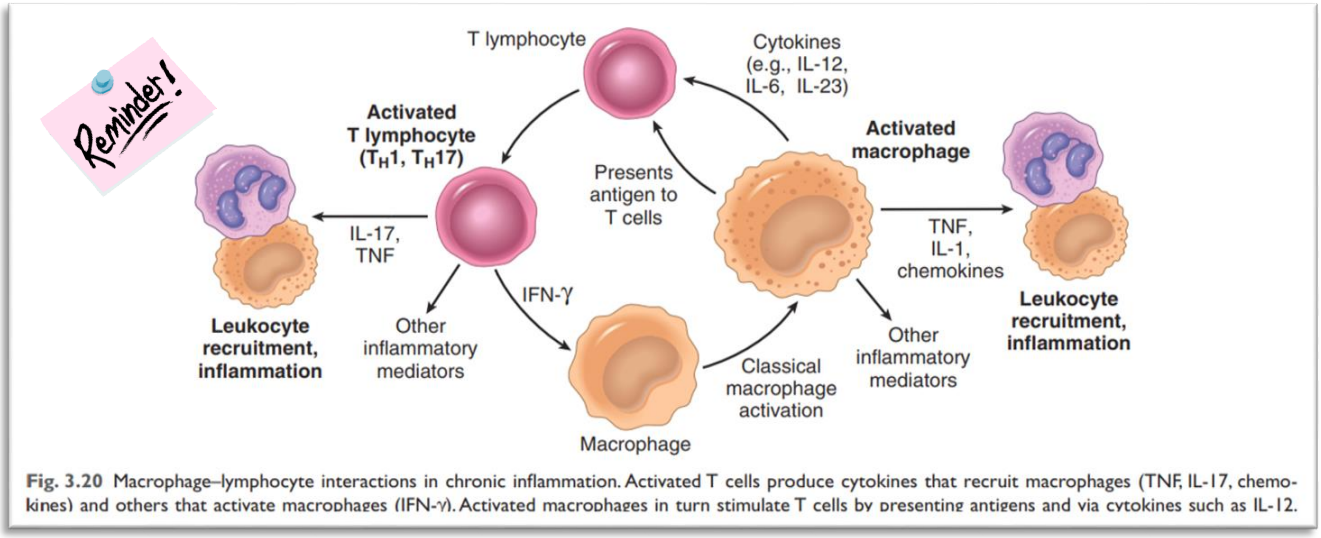


Fig. 3.20 Macrophage–lymphocyte interactions in chronic inflammation. Activated T cells produce cytokines that recruit macrophages (TNF, IL-17, chemokines) and others that activate macrophages (IFN-γ). Activated macrophages in turn stimulate T cells by presenting antigens and via cytokines such as IL-12.

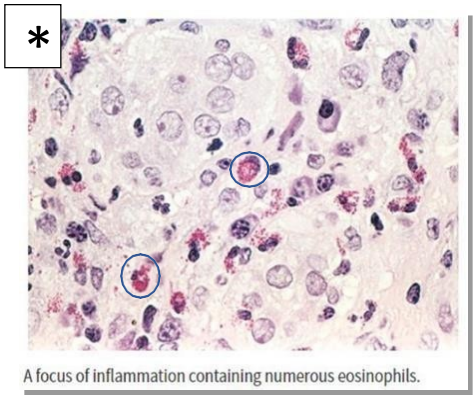
So, just try to look at this diagram a couple of times to really connect about the complexity and the relationship between them, and they both have similar functions for example phagocytosis is one of the things which both macrophages and neutrophils can do.

About the picture above *(This wasn't mentioned during the lecture) :*

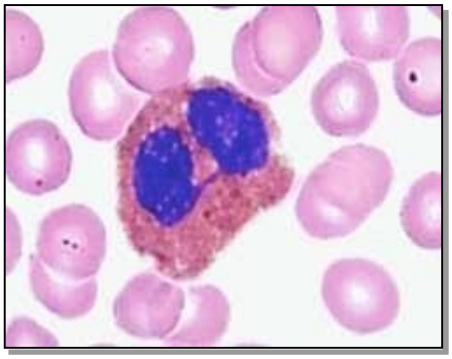
Macrophages display antigens to T-cells, and express membrane molecules that activate T-cells, and produce cytokines (IL-12, IL-6, IL-23) that also stimulate T cell responses.
Activated T-lymphocytes, in turn, produce cytokines (e.g. IFN-ℵ), which recruit and activate macrophages, promoting more antigen presentation and cytokine secretion. The result of this is a cycle of cellular reactions that fuel and sustain chronic inflammation.

EOSINOPHILS:

Eosinophils named like this because of the eosinophilic color of the cytoplasm. The cytoplasm is pink and granulated, (bilobed nucleate) a nucleus with 2 lobes, ***granular pink cytoplasm is the hallmark feature of eosinophils.*** So, this is how we recognize eosinophils in the peripheral blood or in tissue. Eosinophilic means pink.



This figure is in the tissue image with too many eosinophils where the cytoplasm is pink.



This is a peripheral blood image. Eosinophilic granules.

Eosinophils are closely related to IgE (Immunoglobulin E) production, which is important in Allergic anaphylactic reactions, and it is probably the main cell infiltrate whenever we get exposed to parasitic infection (The main cell defense mechanism against parasitic infections).

So, whenever we see a lot of Eosinophils in tissue, we suspect either allergic reaction or parasitic infection (Infestation).

Those cytoplasmic granules contain major basic proteins toxic to parasites, which can be used in the lysozyme and phagosome functions of eosinophils.

However too much infiltration of the eosinophils into tissue can cause some tissue damage.

Actually, in the last 10 to 15 years we are getting exposed to a new type of chronic inflammation, a specific type of inflammation is called ***eosinophilic inflammation.*** Examples on eosinophilic inflammation include eosinophilic esophagitis, eosinophilic gastritis & eosinophilic colitis.

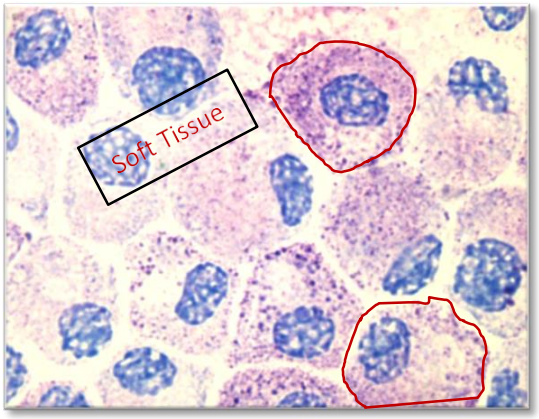
So, we have sometimes something called ***eosinophilic gastritis*** where the stomach is filled with eosinophils.

We have ***eosinophilic esophagitis***, many times every week or two weeks we receive a GI biopsy from a child or from a young female that they are an eosinophilic esophagitis patient so we have to look at the tissue sections and make sure that the tissue section doesn't have too many eosinophils or just few of them or none. And this is the main definition of ***Eosinophilic Inflammation***, they are specifically chronic, and that can occur in any organ, they are characterized by huge numbers of eosinophils and tissue like the picture which you saw previously (The picture with the * mark).

MAST CELLS:

- They are part of the inflammatory cell response.
- They are abundant in soft tissue (especially soft tissue tumors), whenever we receive leiomyoma, or lipoma, the soft tissue neoplasm or tumor will be full of those mast cells.
- They are involved both in acute and chronic inflammation. (They have more role in chronic inflammation than in acute inflammation by producing many cytokines).
- MC (Mast cell) and basophils express FceRI (aka FceR1) receptors that binds with FC portion of IgE leading to degranulation and releasing of Histamine and PG specifically whenever we get exposed to (food allergy, venom (bite snake), drug allergy). So, they are closely related to the eosinophils function.
- However, they can be abundant in different types of tissues.

- They are heavily granulated.
- The N:C ratio [**The nuclear-cytoplasmic ratio**] is low and the color of the granule is slightly basophilic.



Mast cell (Red)

NEUTROPHILS IN CHRONIC INFLAMMATION:

As we mentioned before neutrophils, or PMNs polymorphonuclear cells, or mickey mouse cells. Their main role is in acute inflammation. However, this does not mean that there is no role for neutrophils in chronic inflammations.

- Can stay longer after acute inflammation (persistent microbes or continuous activation by cytokines). So, sometimes you can see both lymphocytes, macrophages, and plasma cells at the site of chronic inflammation and there are also a neutrophils in the neighborhood.
- You can see them also frequently in cases of Chronic osteomyelitis.
- Although the **osteomyelitis** which is the inflammation of the bone and the bone marrow is mainly a chronic process but in chronic osteomyelitis you can see in addition to plasma cells, macrophages, and lymphocytes the neutrophils.
- Lung damage by **smoking** (is also mediated by neutrophils in lung tissue).
- Many types of inflammation they are acute but there are sometimes acute on chronic (or **acute on top of chronic inflammation**), so you see both the background of chronic inflammation on top of that there is acute inflammation.

  For example: Patients with inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, which are chronic, may sometimes face acute attacks causing bleeding by rectum (So the acute reaction attracted neutrophils).

We come now across an important subtype of chronic inflammation, which is:

GRANULOMATOUS INFLAMMATION:

A form of specific chronic inflammation and the specificity of this chronic inflammation is characterized by the presence of granulomas in the tissue (The infiltration or the destruction of tissues by granulomas).

Granuloma: The collection of activated macrophages (***epithelioid histiocytes***); lymphocytes and sometimes plasma cells.

So, the collection of epithelioid histocytes, which are activated macrophages, plus lymphocytes and plasma cells forming a module, or a collection of those cells is called a granuloma and this will be demonstrated in the figures and will be explained what that means.

Histocytes : Since it is in the tissue, so it is histiocyte.

Epithelioid : Because it becomes a swollen with abundant cytoplasm. It takes the shape of an epithelial cell. So, they call it epithelioid.

There are two types of granulomas:

1. Necrotizing (central necrosis), which has central necrosis.
2. Non-necrotizing (no necrosis), which has no central necrosis.

This is an important division because whenever I have a kidney biopsy, liver biopsy, skin biopsy, lung biopsy and if I see granulomas I must decide if these granulomas are necrotizing and there is differential for that or if they are non-necrotizing which have a different type of differential.

In the old days they used to call those as:
1. Necrotizing (“Caseating”) granulomas.
2. Non-necrotizing ("Non-caseating") granulomas.
Because grossly, looks like cheesy white. Caseous means white, or cheesy, or milky. But the proper pathologic name is necrotizing granulomas or non-necrotizing granulomatous inflammation.

There is also something called immune granulomas and there are foreign body type granulomas.

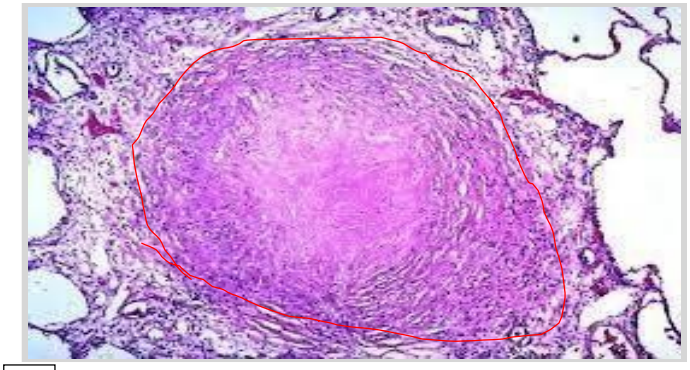
Foreign body type: Whenever you have a foreign body entering your tissue there's an inflammatory reaction against those from tissue and you can see them in the microscope.

Example (This wasn't mentioned during the lecture):
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.

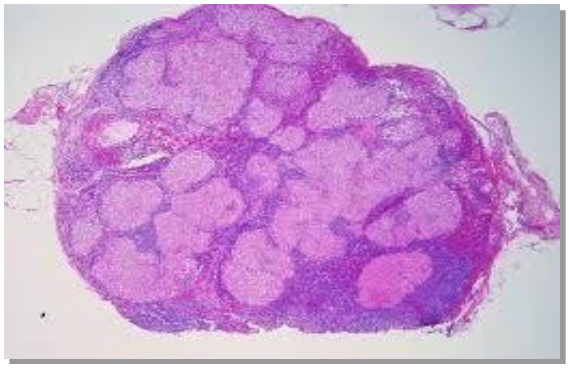
Immune granulomas: Are different, this is the ones which we see sometimes in rheumatoid arthritis which are induced by autoimmune diseases.

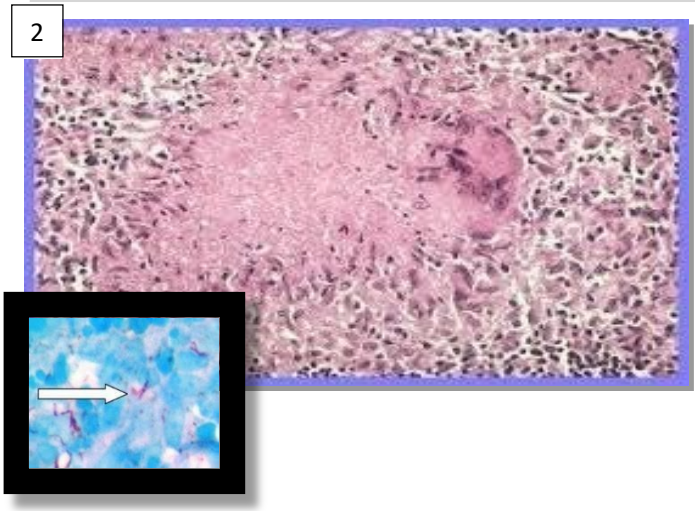
Morphology of granulomatous inflammation:

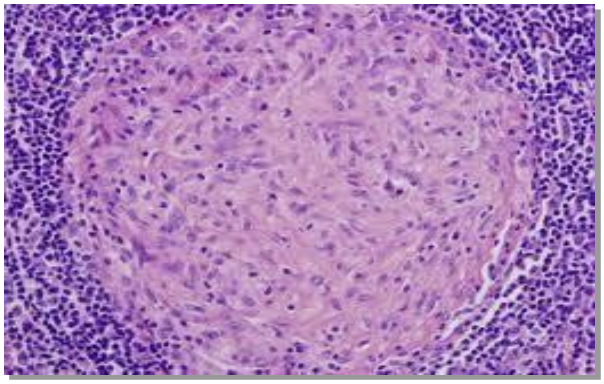
Necrotizing Granuloma:
lung biopsy



Non- Necrotizing Granuloma:
lymph node







How we can recognize central necrosis in histology?
By the presence of pinkish material without blue nuclear material.

1. **Necrotizing Granuloma**: Examining the pictures on the left, I look at this granulomatous inflammation and see if there is central necrosis.

   Examining the first picture from the both sides, they represent lung alveolus, you can see that the alveoli which were destroyed and replaced by this collection and we can clearly see the granuloma (Epithelioid histiocytes with some plasma cells and lymphocytes) surrounding the central necrotic region.

   The second picture: This is multinucleated giant cells it has probably 15 to 20 nuclei they called multinucleated germ cells.
   Lymphocytes, histocytes and plasma cells in the background so this is a granuloma or granulomatous inflammation and there is a central necrosis.

   Different causes can lead to necrotizing granulomatous inflammation, but ***mycobacterium tuberculosis*** is the prototype of it, regardless of the tissue involved, and we can see it using acid fast stain, also named as (Ziehl–Neelsen stain). *The small blue green picture on the left*, and you can see the mycobacterium organisms they are called red snappers (Red pink bacilli.).

   So, whenever you have necrotizing granules inflammation regardless of the tissue involved you must do acid fast stain to make sure this is not TB. So, automatically those stains are done, we do both fungus and TB stains.

   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. Second picture, I don't see the pinkish material here, so this is non-necrotizing granulomatous.

   Even though non-necrotizing granulomatous inflammation is not associated with necrosis, it does disrupt the tissue.

> Go the extra mile, it's never crowded.

> Your own sins should distract you enough from focusing on the faults of others.

THE DOCTOR SAID WE NEED TO MEMORIZE THIS TABLE

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

NOTES about the table:

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

2- Leprosy which is caused by another species of the mycobacterium organism is called mycobacterium leprae.

3- In cat-scratch disease: People who have cats at home they can get scratched and the organism is transferred and causing granulomatous inflammation of the lymph nodes, the axilla, and the cervical lymph nodes due to the cat scratch organisms. It is a necrotizing granulomatous lymphadenitis and it's called geographic large granuloma.

4- Sarcoidosis: The major hallmark of tissue damage by this disease is the presence of non-caseating, or non-necrotizing granulomas. This is a disease of unknown etiology.
It is a disease which is mainly diagnosed after exclusion. You may not be able to make the diagnosis of sarcoidosis until you rule out all other diseases, so this is what we call diagnosis by exclusion.

Further Understanding: 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.

5- Group of inflammatory bowel disease that affects mainly the colon and the terminal ilium they are called ***inflammatory bowel diseases.***
There's two types Crohn's disease and Ulcerative colitis. They affect mainly the terminal ilium and one of the major characteristic features of Crohn's disease is the presence of non-necrotizing granulomas.

So, this is why you have to investigate any time you see tissue with granulomatous inflammation you have to investigate is it necrotizing or non-necrotizing and then you have to do the organism stain to delineate the specific etiology of that disease.

SUMMARY

CHRONIC INFLAMMATION

- Chronic inflammation is a prolonged host response to persistent stimuli that may follow unresolved acute inflammation or be chronic from the outset.
- It is caused by microbes that resist elimination, immune responses against self and environmental antigens, and some toxic substances (e.g., silica); underlies many medically important diseases.
- It is characterized by coexisting inflammation, tissue injury, attempted repair by scarring, and immune response.
- The cellular infiltrate consists of macrophages, lymphocytes, plasma cells, and other leukocytes.
- It is mediated by cytokines produced by macrophages and lymphocytes (notably T lymphocytes); bidirectional interactions between these cells tend to amplify and prolong the inflammatory reaction.
- Granulomatous inflammation is a morphologically specific pattern of chronic inflammation induced by T cell and macrophage activation in response to an agent that is resistant to eradication.

SYSTEMIC EFFECTS OF INFLAMMATION:

Any inflammation can be associated with systemic effects due to cytokines release, predominantly what we call it:
" ACUTE PHASE RESPONSE " and this is in a way is a good thing because this will make the patient sick and will push him to go to the emergency room or to the clinic to seek medical help.
The acute phase response is predominantly mainly due to multiple cytokines secretion like (**TNF, IL-1, IL-6, & type 1 interferons)**.

Fever (1-4 C) elevation	Exogenous pyrogens (LPS) & endogenous pyrogens (IL-1 & TNF). All induce PGE2 secretion
Acute phase proteins	CRP, SAA, ESR, Hepcidin
Leukocytosis (increase WBC)	15-20 K if more than 40 (leukemoid reaction), left shift
Others	Tachycardia, Increase BP, Chills, Rigors, decreased sweating, anorexia, somnolence, and malaise

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), stimulating leukocytes to release cytokines such as IL-1 and TNF (called endogenous pyrogens) that all will 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 stimulus. 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. We can measure them in the lab, but they are non-specific they do not indicate specific disease. However, they can give you and idea that the patient has severe acute inflammation.

3- Leukocytosis (increased number of WBCs): Many of these mediators will go to the bone marrow and induce hematopoiesis.

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 like leukemia. To distinguish between leukemia and leukemoid reaction, you do the white blood count and the white blood count is 45000 and you look at the differential count it's many neutrophils, most of the time it's a leukemoid reaction, this is when we take the sample to a certain machine to see whether

the cells are monoclonal (cancerous) or polyclonal (not cancerous and the body simply gave an exaggerated response).

Leukemoid means leukemia-like. So, it's not really malignancy. However, you must do investigate these by specific delineation by immunophenotyping of the peripheral blood white blood cells to make sure that those are non-neoplastic white blood cells. We do usually flow cytometry in those to reassure the patient they were only leukemoid reactions. So, this is an exaggerated response as a systemic effect inflammation called leukocytosis.

4- Other manifestations: Tachycardia, Increase BP, Chills القشعريرة , Rigors, decreased sweating, anorexia فقدان الشهية,somnolence النعاس , and malaise ضيق. They all indicate that a patient is sick. All of those can be seen in different types of inflammation and some of them are present, some of them are absent. All of them are induced by the effects or the impacts of the circulating mediators.

SEPSIS & SEPTIC SHOCK:

Sepsis, septic shock, and septicemia indicate severe acute **bacterial infection** which may be fatal. (It's a common disease, you will see it mostly like in the different sectors of ICU)

Large amounts of mediators (TNF & IL-1) lead to multiple complications such as:

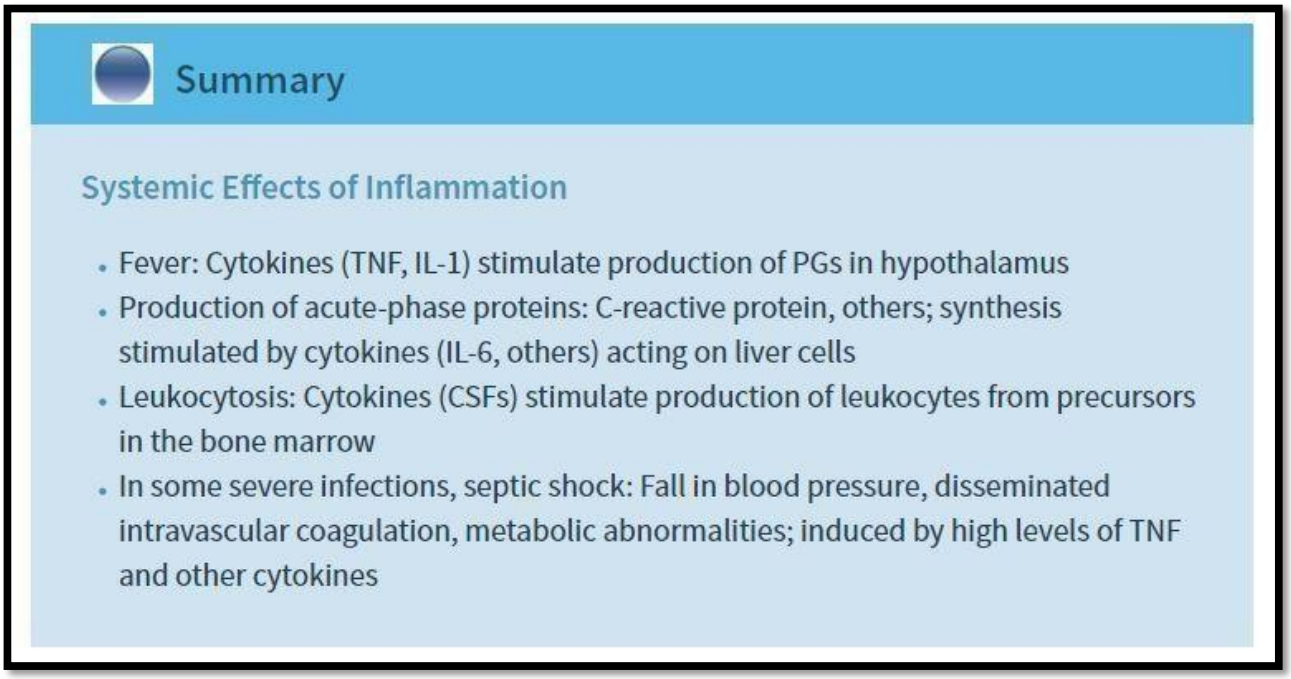
1. Disseminated intravascular coagulation (DIC): A condition in which blood clots form throughout the body, blocking small blood vessels causing multiple infarcts (Heart rate will go up…).
2. Hypotensive shock.
3. Insulin resistance and hypoglycemia.

All those features are features of septic shock and this is an acute emergency patient has to be treated quickly otherwise if he reaches to a point of irreversible septic shock most of the time the patient will end up with multi-organ failure and then death.

NOTE: Gram-Negative sepsis is very dangerous.

Sepsis May be caused by non-infectious etiology: Pancreatitis, severe burns, and severe trauma. All of these cases will have a lot of mediators impacting all

your vital function causing a shock state. As sepsis develops due to mediators, the conditions described above fall under the category of "**systemic inflammatory response syndrome**" (SIRS). Probably this will be like the end result of too much acute severe inflammation with tissue damage and a lot of mediators and probably this is what's happening in Corona or Covid-19 nowadays.



حاجة القلوب إلى ذكر الله كحاجة الأبدان إلى الطعام، وكل فاقد لحاجته منهما فهو ميت قال ﷺ «مثل الذي يذكر ربه والذي لا يذكر ربه مثل الحي والميت» ...

اللهم لا تكلنا إلى أنفسنا فنعجز، ولا إلى الناس فنضيع!

وصلى الله على نبينا محمد صلى الله عليه وسلم وعلى آله وصحبه وسلم تسليما كثيرا...