DOCTOR 2020 | JU

PATHOLOGY

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- in this lecture we will discuss the immunologic cells which have a roles in Both chronic and acute inflammation

outcomes of acute inflammation :

1. ***Chronic inflammation*** : When we cannot get rid of acute inflammation because a virulent injurious agent or bad immunity, it will become chronic inflammation which may be sever and cause a damage for that organ.

2. ***Complete resolution*** :
   The 99% of the tissue is repaired and returns to the pre-inflammatory stage. It is the most preferred outcome. However, this does not happen in real time

3. **Healing by fibrosis** :

Consist of scar formation which may have a negative impact on the cosmetic appearance or function of that organ .

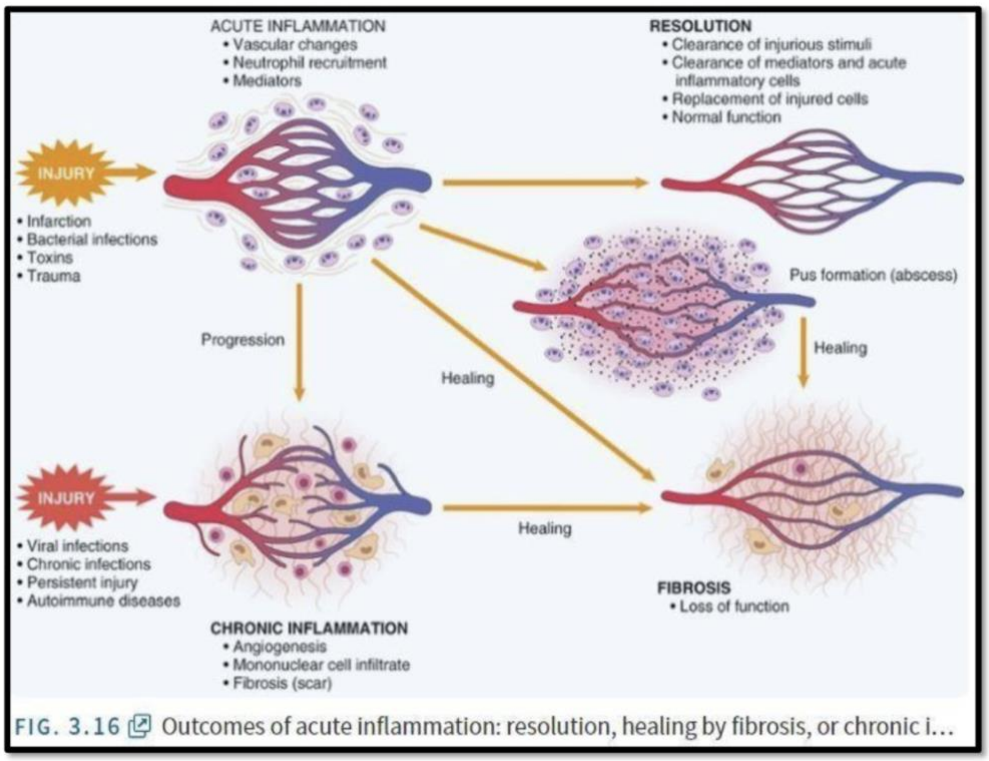

FIG. 3.16 Outcomes of acute inflammation: resolution, healing by fibrosis, or chronic i…

(Chronic inflammation)

It is prolonged inflammation (weeks- months -years). Associated with tissue injury and body attempts to repair it at the same time with varying degree.

• But it also may continues and form a sever scar and fibrosis that negatively impact the function of that organ. like the active hepatitis for 10 – 15 years leads to liver failure.

• usually it follows acute inflammation but may be insidious(مخادع)or smouldering when the acute inflammatory phase is subclinical and does not bother، in the other words chronic inflammation doesn't always follow recognisable episode or acute attack so sometimes the acute inflammation keeps destroying your tissue without feeling of it (subclinical) e.x:some cases of hepatitis c .

- **Causes of chronic inflammation :**

1. **Persistent infections (not easy organism to get rid of):** Mycobacteria (TB), تسبب مرض السلّ, viruses, fungi, parasites. Delayed hypersensitivity reaction (type 4 immunologic reaction **),**and -
   Granulomatous inflammation.: specific and stronic chronic inflammation because we have specific granulomas(collection of phagocytes cells) in the tissue to destroy it , it may happen in different tissues like liver and cardiac tissues.

2. **Hypersensitivity diseases:** RA (rheumatoid arthritis), asthma, MS (multiple sclerosis) . May end in fibrosis of end organs .

3. **Prolonged exposure to toxic agent:**
   ***exogenous :** like silica (silicosis) exposing to silica for long times will cause severe interstitial lung disease end up with respiratory failure.

***endogenous :** like Atherosclerosis (cholesterol) this disease cause chronic ischema leading to top one cause of mortality worldwide in adults .

4. **Other associated diseases:** Alzheimer's, Metabolic syndrome of DM (new term of obesity it can be calculated by certain equation) .

- **Morphological features of chronic inflammation:**

1 – The first critical feature is the infiltration of the chronic inflammatory cells (macrophages, lymphocytes and plasma cells).

2 - Tissue destruction (damage) at varying levels .

• The sever tissue destruction leads to sever changes like the replacement of the normal liver parenchyma by thick bands of fibrosis.

3 - Attempts at healing and repair by angiogenesis (producing new blood vessels) and fibrosis.

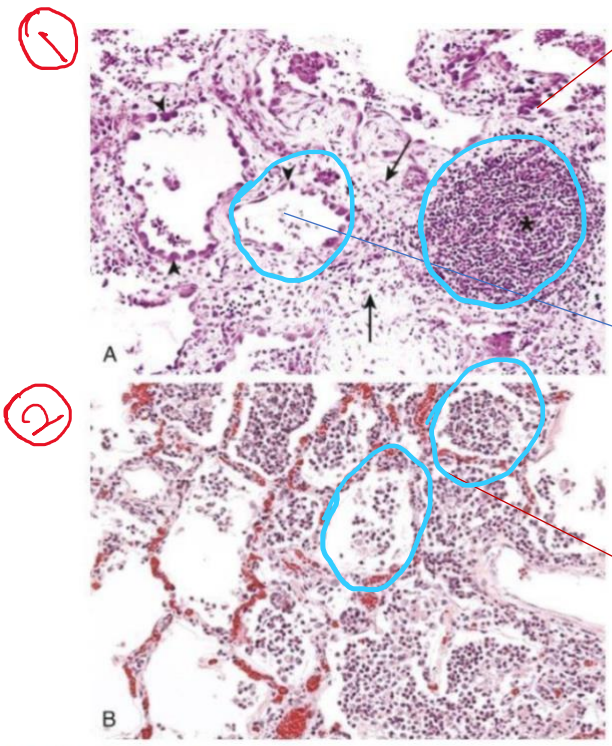

FIG. 3.17 (A) Chronic inflammation in the lung, showing all three characteristic hist

This is a chronic inflammatory follicle contains inflammatory cells (macrophages, lymphocytes ,plasma cells)

this is a damaged alveoli replaced by fibrosis tissue notice that the tissue architecture didn't preserve

These are alveolus filled with acute inflammatory cells (neutrophils)so it is acute nemonia if this acute Nemonia was close to the bronchies we called it acute bronchoamonia which one of the major causes of death in elderly hospitalised patients notice that the tissue architecture is constant and well preserved

- **Cells and mediators of chronic inflammation:**

1 – Macrophages → They are mainly cells mediating the pathogenesis of chronic inflammation

2 – Lymphocytes

3 – Eosinophils

4 - Mast cells

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(Macrophages)

The monocyte circulates in the blood but when it resides in the tissue it is called a Macrophage.

1- They secret some mediators such as TNF, IL1 and Chemokine's.

2- They have a strong connection with T lymphocyte. It gives the macrophage a feedback about the increasing or decreasing inflammatory response.*Feedback loop*

3- Phagocytosis is the peculiar function of the macrophage. Also neutrophils can participate in phagocytosis.

• It produced in the bone marrow and mature in the right side . in the fetal life it produced in the yolk sac and mature in the tissue.

• The half-life of the circulating monocyte is approximately 1 day if it didn't meet its antigen then it will be die but when it gets into the tissue the half-life is extended for weeks or months and it will get specific names .

• Tissue Macrophages: (mononuclear phagocytic system) Kupfer cells (liver), sinus histiocytes (lymph nodes) , alveolar macrophages (lung) , microglia (brain).

• The monocyte is less granule and has a kidney shaped nucleus.

- **Explanation of the image below :**

As you know the phagocytes include mainly neutrophils and macrophages and both of them get maturation in the bone marrow (in adults) and in yolk sac in case of fetus these cells will get many changes when they travel by the right shifting in order to get mature and circulate in order to function or recruiting within the tissues . This changes include (we have macrophage here as an example)

1- Size of nucleus : large in LS and small in RS. (RS = right side ,Ls =left side)

2- Cytoplasmic nuclear ratio (cytoplasmic/ nuclear) : high in RS low in LS

3-general size of the cell : large in R/S , small in LS

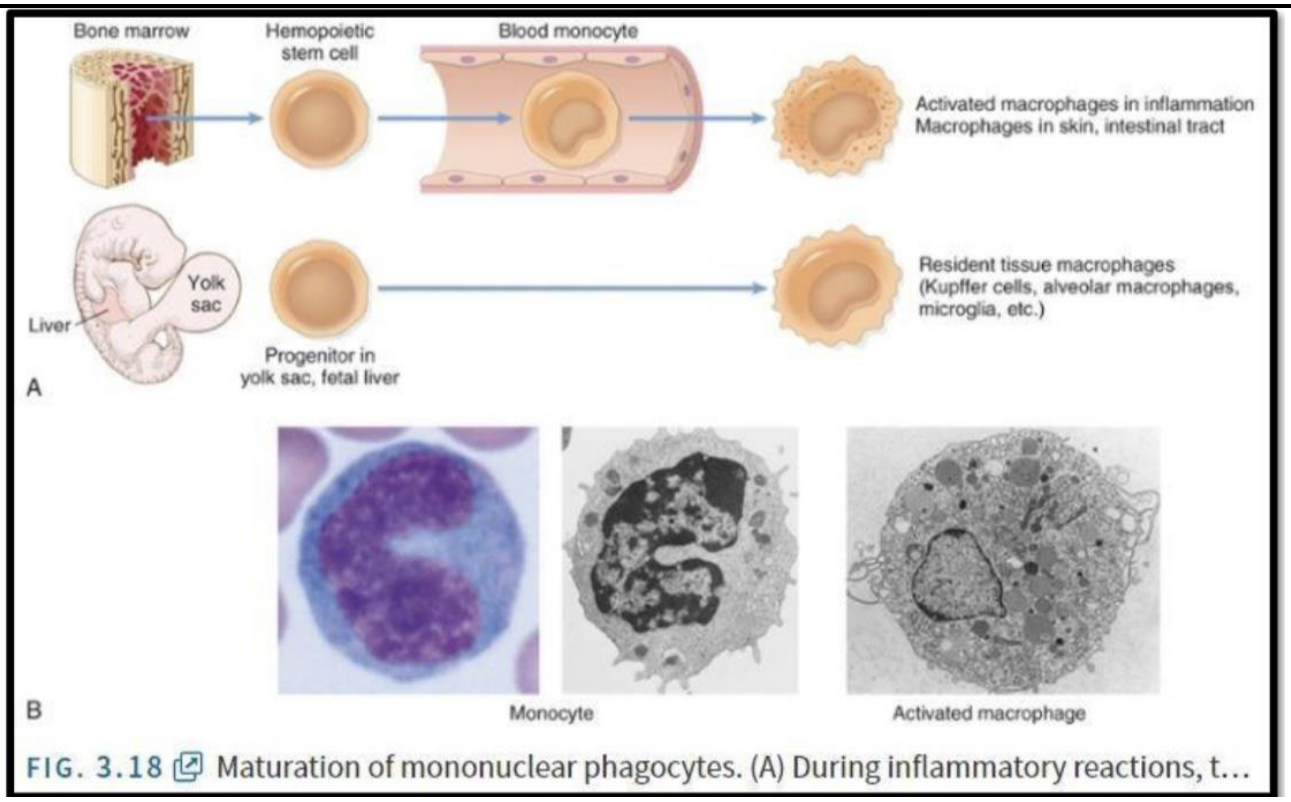

FIG. 3.18 Maturation of mononuclear phagocytes. (A) During inflammatory reactions, t…

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•The activation of Macrophages by : M1 classic pathway or M2 alternative pathway.

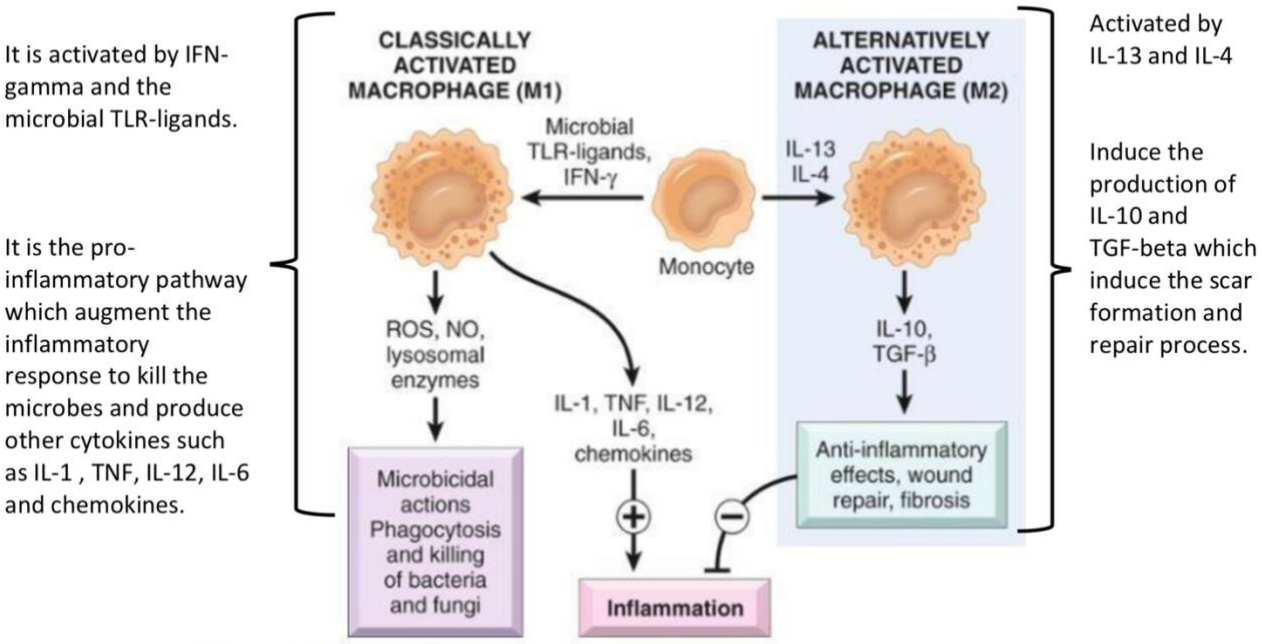

FIG. 3.19 Classical and alternative macrophage activation. Different stimuli activate m…

Lymphocytes

- T& B lymphocytes gets activated by multiple agents, microbes, and environmental antigens.
- ***Note :*** concentration of T cells more than concentration of B cell in the body

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.
- When the B cells activate it will be converted to plasma cells which can produce antibodies (when you look to plasma cell under microscope you will notice that it have abundant cytoplasm and big organelles like Golgi apparatus in order to synthesis of Ig (immunoglobulin) .
- This table shows types of T helper cells and their functions :

CD4+ T CELLS:

TH1 (T-helper 1)	Secrete interferon gamma INF-ɣ, , 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.

*this diagram shows you the continuous collaboration and the feed back loop between the lymphocytes , macrophages and the monocytes here we need different mediators and recruit more macrophages in order to enter the M1 classical pathway because I need more inflammatory reactions and when things Cooling down we will go back to normal state and decreasing of inflammatory responses .

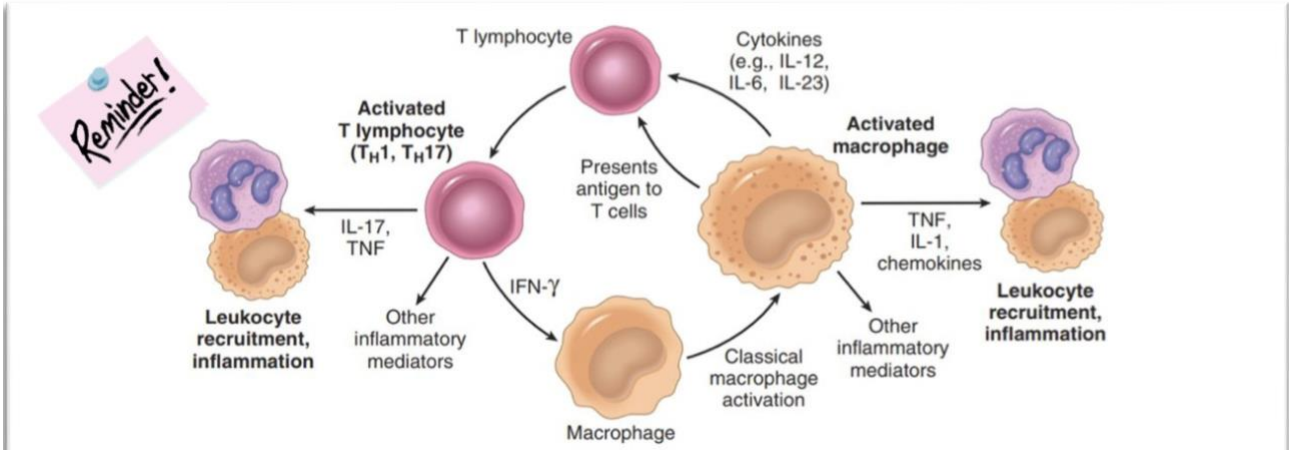

Fig. 3.20 Macrophage–lymphocyte interactions in chronic inflammation. Activated T cells produce cytokines that recruit macrophages (TNF, IL-17, chemokines) and others that activate macrophages (IFN-γ). Activated macrophages in turn stimulate T cells by presenting antigens and via cytokines such as IL-12.

- 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.

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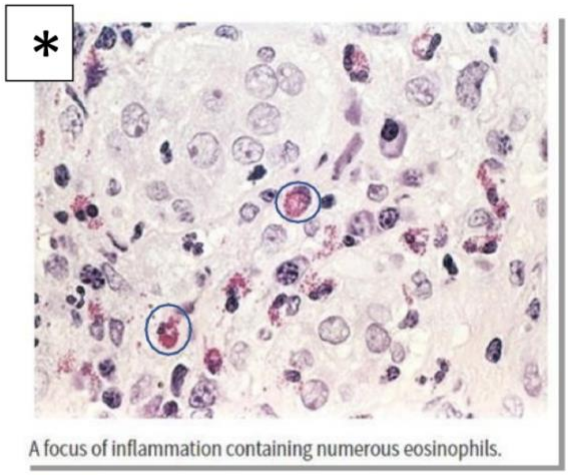
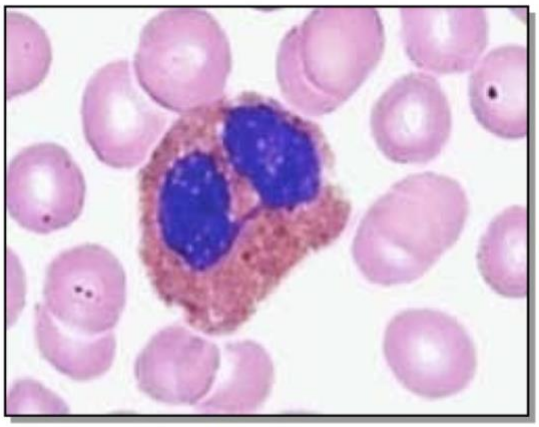
Eosinophils

- 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).

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Mast cells

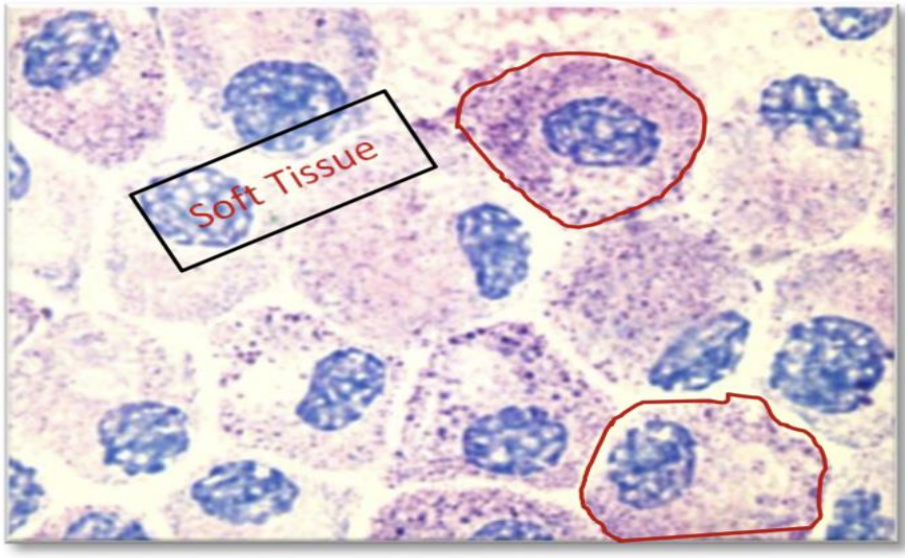
- They are part of the inflammatory cell response

- It is abundant in soft tissue (especially soft tissue tumors), whenever we receive a leiomyoma, or lipoma, the soft tissue tumor or tumor will be filled with these mast cells.

- They are involved in both acute and chronic infections. (It has a greater role in chronic inflammation than acute inflammation by producing many cytokines.)

- MC (mast cells) and basophils express the FceRI receptor (also known as FceR1) that binds to the FC portion of IgE resulting in granulolysis and release of histamine and PG specifically when we are exposed to (food allergy, venom (snake bite), allergy Medicine) . Therefore, they are closely related to the function of eosinophils

- However, it can be abundant in different types of tissues.
- They are highly granulated.
- N:C ratio (nuclear-cytoplasmic ratio] is low and the color of the granule is slightly basal.



Mast cell (Red)

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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 inflammations

- **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).

The End