Doctor022

PATHOLOGY

Sheet no. 5

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Complement system functions

We've mentioned so far the most important chemical mediators of inflammation ,but there are others and the number is increasing ,so whenever five, ten years from now , one of you will become a pathologist you will see that the list is much more and probably there will be more important factors.

OTHER MEDIATORS:

- Platelet activating factor(PAF):platelet aggregation and other functions.
- Protease activating receptors (PARs): platelet aggregation

those are incriminated in the pathogenesis of atherosclerosis and thromboembolic diseases

- Kinins:Vasoactive peptide, Bradykinin the active; VD(vascular dilatation), increase permeability, smooth muscle contraction and pain (which makes them play a role in active labor after the end of pregnancy and they have also therapeutic implicationwhich we will talk in pharmacology).

the most important prototype is bradykinin

- Neuropeptides: Subtance P and neurokinin A

*An important table

TABLE 3.8 Role of Mediators in Different Reactions of Inflammation

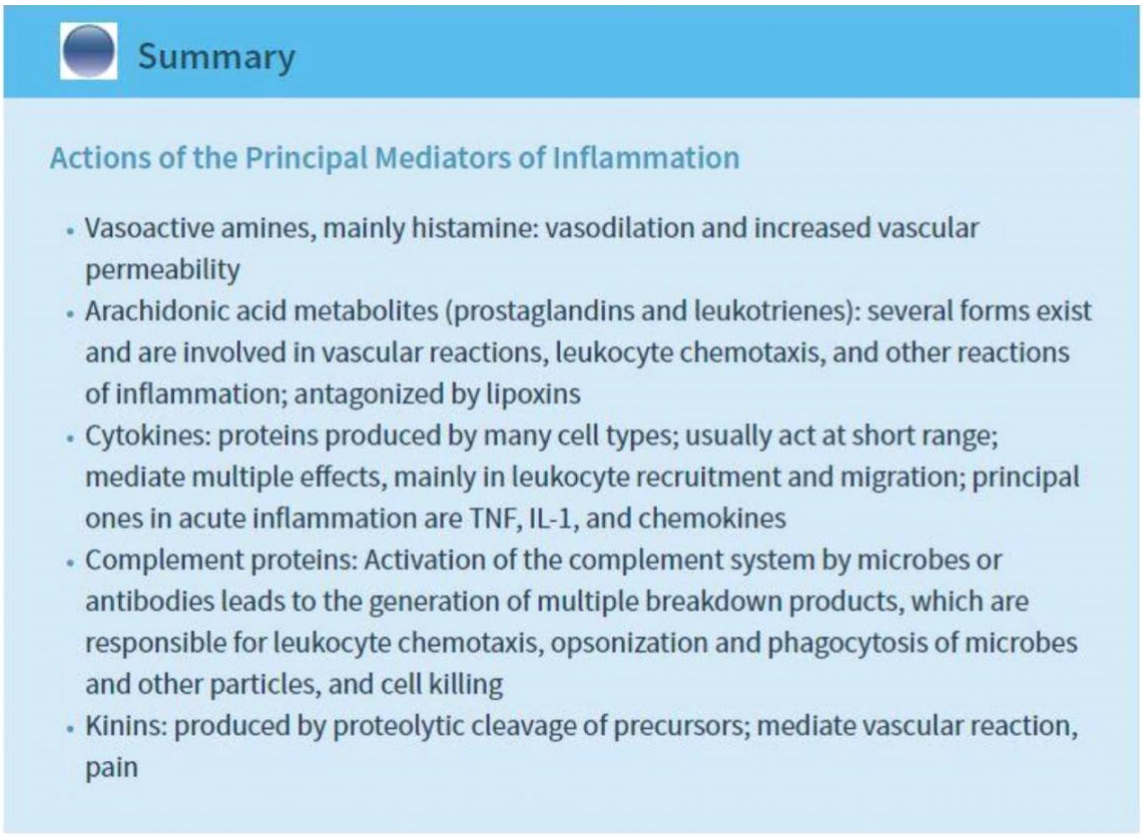
Reaction of Inflammation	Principal Mediators
Vasodilation	Histamine
	Prostaglandins
Increased vascular permeability	Histamine
	C3a and C5a (by liberating vasoactive amines from mast cells, other cells)
	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte recruitment and activation	TNF, IL-1
	Chemokines
	C3a, C5a
	Leukotriene B_4
Fever	IL-1, TNF
	Prostaglandins
Pain	Prostaglandins
	Bradykinin
Tissue damage	Lysosomal enzymes of leukocytes
	Reactive oxygen species

Fever is a manifestation of acute inflammation

leukotriene B4 is probably a very potent and chemotactic agent

IL-1, TNF and Prostaglandins: some of those are targeted by a certain medications to decrease the impact of fever on human tissue

Prostaglandins and Bradykinin also targeted in treatment



Summary

Actions of the Principal Mediators of Inflammation

- Vasoactive amines, mainly histamine: vasodilation and increased vascular permeability
- Arachidonic acid metabolites (prostaglandins and leukotrienes): several forms exist and are involved in vascular reactions, leukocyte chemotaxis, and other reactions of inflammation; antagonized by lipoxins
- Cytokines: proteins produced by many cell types; usually act at short range; mediate multiple effects, mainly in leukocyte recruitment and migration; principal ones in acute inflammation are TNF, IL-1, and chemokines
- Complement proteins: Activation of the complement system by microbes or antibodies leads to the generation of multiple breakdown products, which are responsible for leukocyte chemotaxis, opsonization and phagocytosis of microbes and other particles, and cell killing
- Kinins: produced by proteolytic cleavage of precursors; mediate vascular reaction, pain

MORPHOLOGY OF ACUTE INFLAMMATION

How is the tissue will look like in the presence of acute inflammation?

- The critical issue is(initial vascular phase) blood vessel dilatation and accumulationof WBCs and fluids in the extravascular tissue.

there are a lot of phases in the inflammatory response, but morphologically thing you can see in your eye or you need to look at regular microscope sometimes there are things you need an electron microscope to look at like neutrophil traps.

The organ which is involved in acute inflammation will be edematous, enlarged.

Edema	Fluid and proteins in interstitium
Redness	*rubor*
Warmth	*calor*
Swelling	*tumor*
Loss of function	*Functio laesa*
Pain	*dolor*

- **Edema**:too much fluids and proteins in the interstitium after the initial vascular phase ans vascular dilatation and increased vascular permieability, fluids and proteins leaks out to the interstitium.
- **Redness**:explained by the presence of too many blood vessels in that area.
- **Warmth**:because of the presence of this active angiogenesis and vascular changes, the organ which is involved will be heart.
- **Swelling**:explain against because of the edema, the organ will be swollen and enlarged
- **Loss of function**:because of the presence of the pain, there will be loss of function because of the presence of pain and edema also both of them play a role in making you less functional in that specific organ
- **Pain**: the pain is also as we mentioned that there are certain mediators which mediate the production of pain and this is a good thing and bad thing, the bad thing it's not good to have pain and the good thing that the pain will take you to yhe doctor and treatment will start earlys

Serous inflammation:

what are the gross and microscopic features of some of these common morphological changes in inflammation(acute inflammaion mainly)?

- Cell poor fluid (Transudate)

It is basically an acute inflammatory response which is transitive nature ,so it's transudate, so there is too much fluid, but very little cells and debris and those are called serious inflammatory responses.

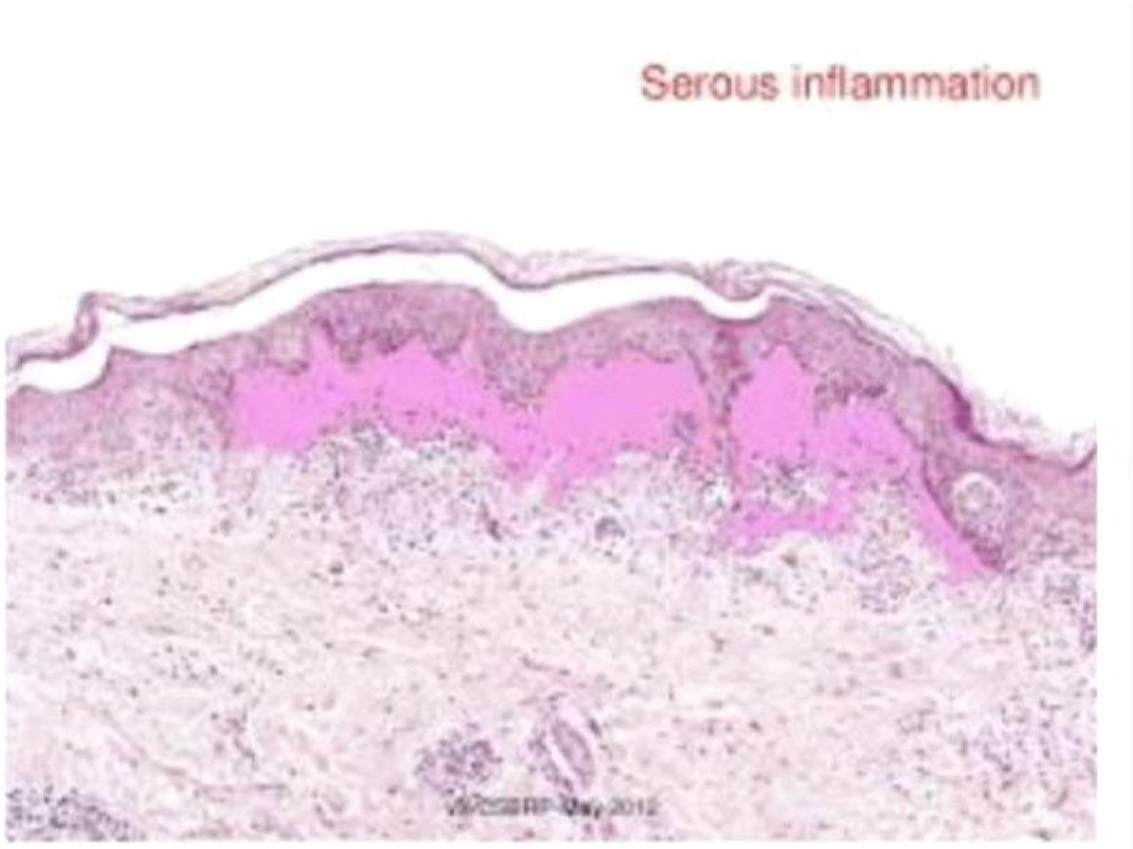
- Serous effusions

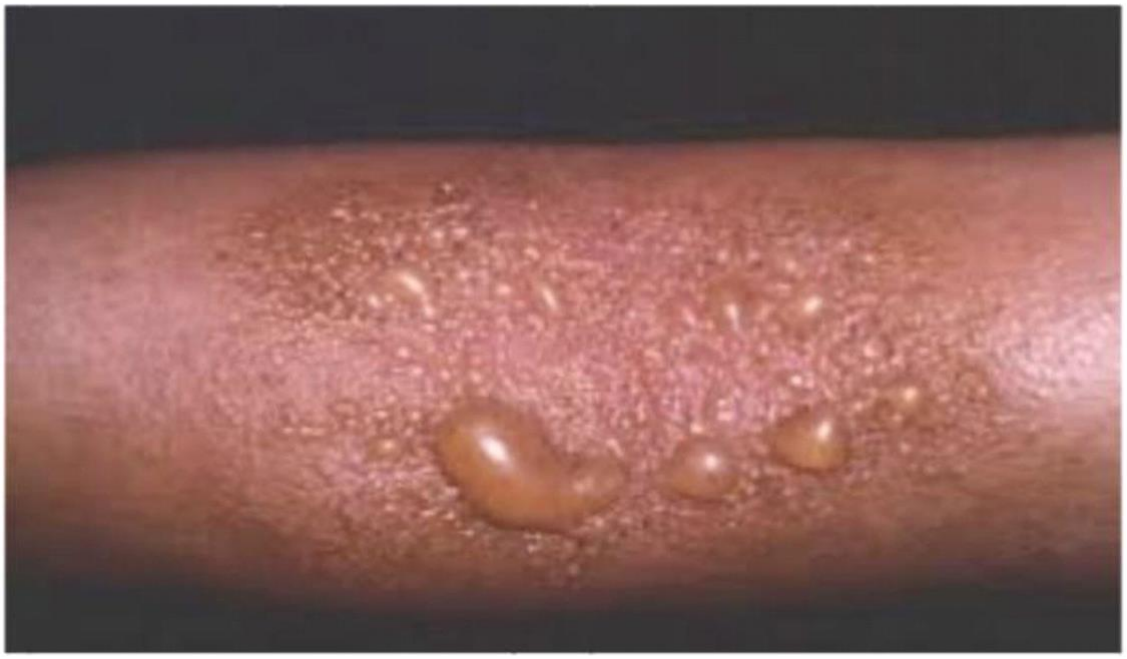
The patient has bilateral pleural effusion due to heart faliure or Hyponatremia from liver failure or liver disease, the oncotic prussure is decreased more fluids leak out to the interstitium and there will be body fluids in your cavity or on your inter-abdominal acidic fluid area, so whenever we tap those to examine for malignancy or culture them or measure the proteins ,they will look like yellow color.

We examine them on microscope ,the solidarity is very low.

- Skin blisters

Many of you have gone to the Dead sea or Aqaba and they have those first degree burn.





What is present in those areas is acually serous transudate

- Seromas

It is a sac or collection of serum which is transudate inflammatory fluid.

Those are common after surgery, certain surgeries will induce the production of seromas like hernia repair ,breast surgery , sometimes one week, two weeks or three weeks after the surgery they come back with a swollen and when you aspirate them, they look like clear yellow, you keep sometimes tapping them two or three times until the disappear.

FIBRINOUS INFLAMMATION:

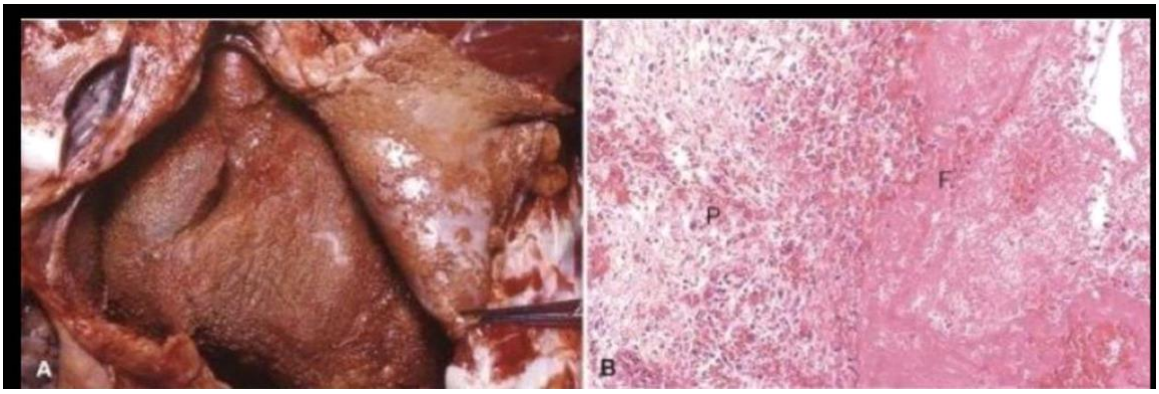
It is a little bit similar to the serous inflammation ,however this time the vascular leakage is big and in addition to that there are a lot of coagulation which occurs in the fluid pouring out into the area.

- Large vascular leakage +coagulation.
- Body cavities:pericardium.

The fibrinous inflammation is characteristically seen in certain body cavity.

Sometimesif a patient come with fibrinous pericarditis, he has to be treated quickly because otherwise the thickened peicardium because the fibrinous inflammation with large vascular leakage and a lot of coagulum and proteins and platelets.

This will sometimes cause fatal consequences in the heart unless it is treated quickly.



PURULENT (SUPEPURATIVE) INFLAMMATION, ABSCESS:

- Pus:exudate(not Transudate), rich in PMNs(neutrophil)+debris+edema

PMNs indicate that there is severe acute inflammation to the point of the body can't copr with this inflammatory response and they will form a small pockets of suppurative inflammation, purulent inflammation or pus.

- Bacteria(staph.)(staphylococcus aureus).
- Abcess:localized collection of pus.

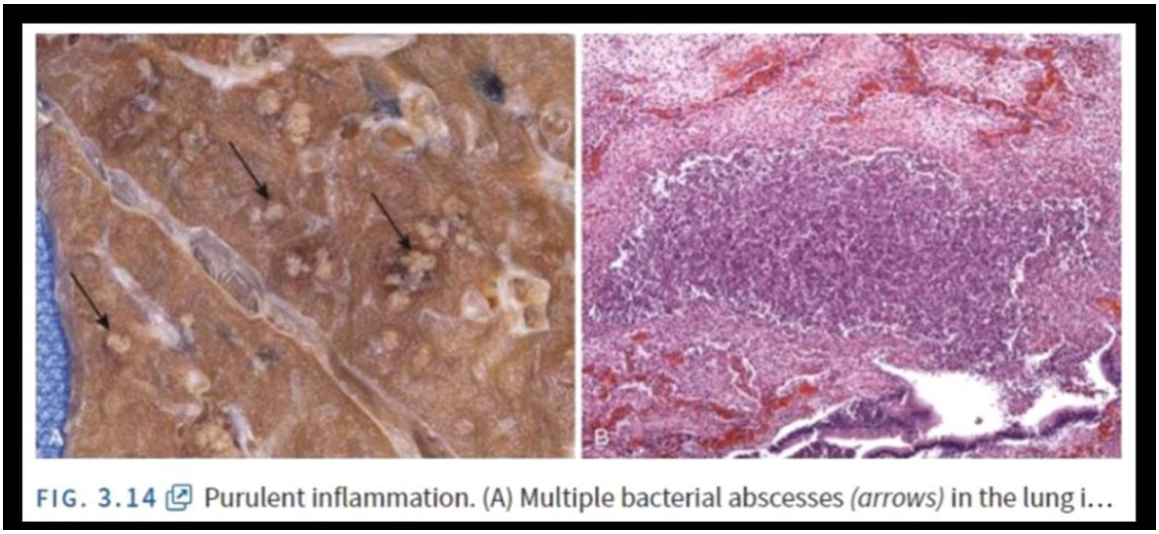


FIG. 3.14 Purulent inflammation. (A) Multiple bacterial abscesses *(arrows)* in the lung i…

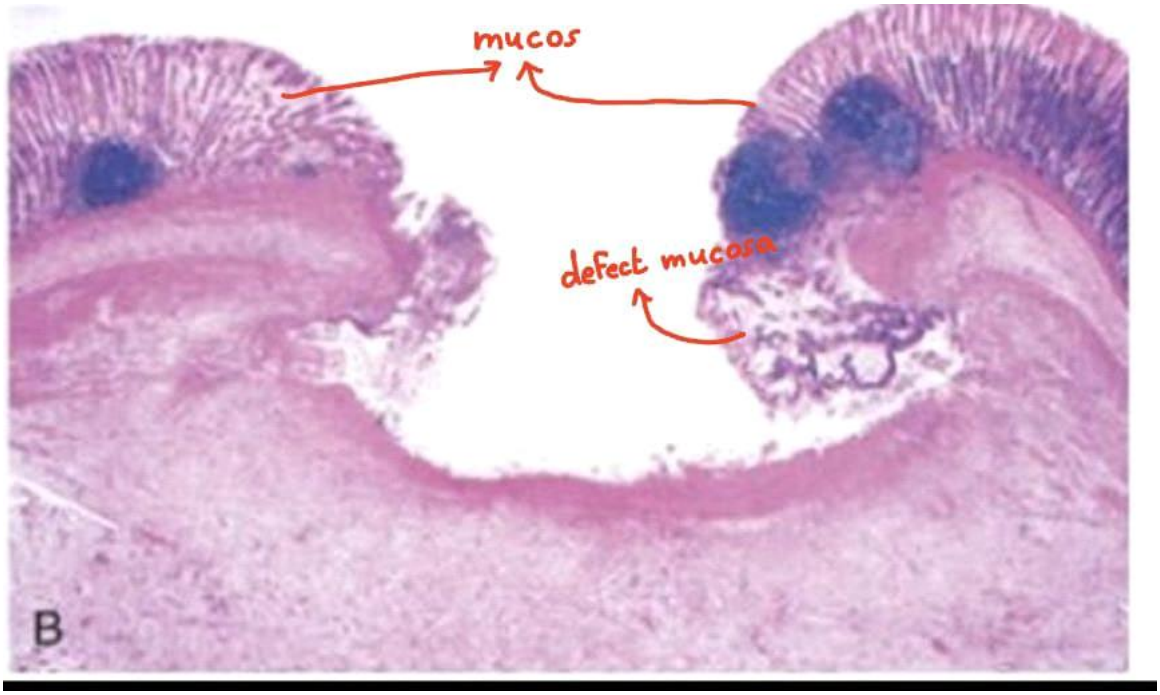
This is longitudinal section of patient who died from severe pneumonia .

This is a collection of neutrophil (this is an abcess) (reactive lung tissue)

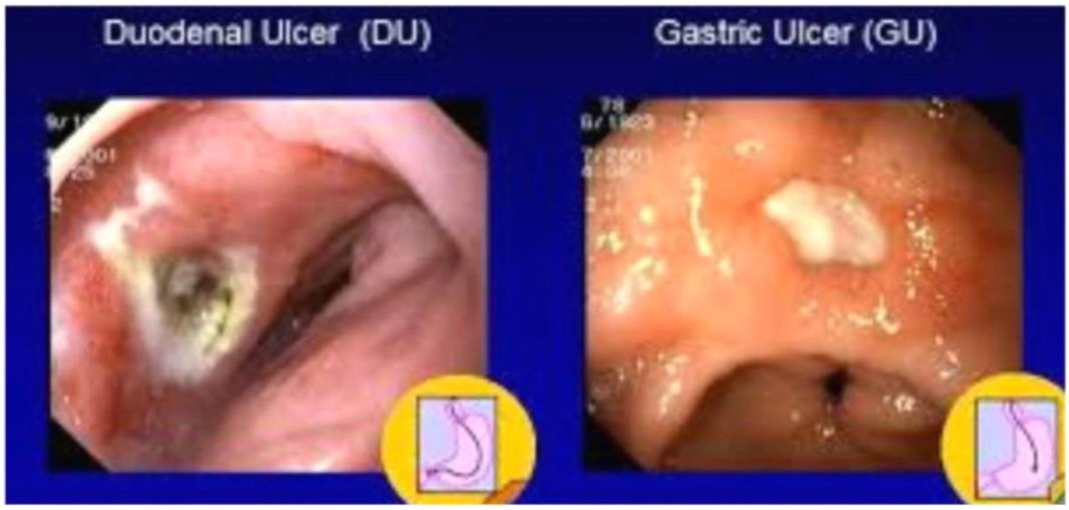
ULCERS: (Ulcerative inflammation)

- Defect on a surface(mucosal cell surface)(discontinuity of mucosal surface).
- Common in mucosal surfaces and skin.
- mostly acute and chronic inflammation and sometimes they can be acute on top of chronic.

Stomach picture



those blue collections are actually just lymphoid follicles which chronic inflammation at the adjacent of acute and chronic inflammation.



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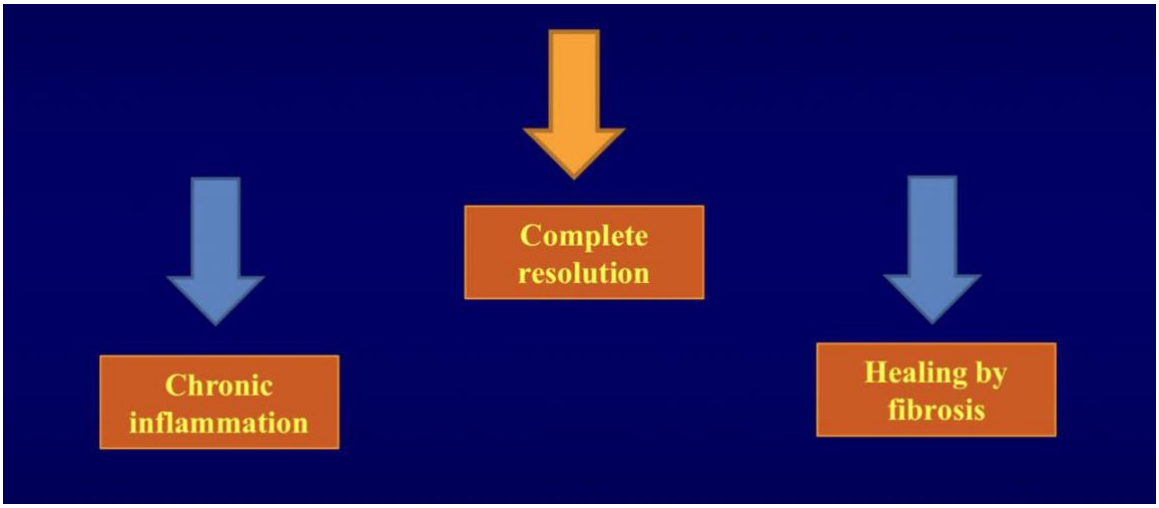
OUTCOMES OF ACUTE INFLAMMATION:



Each one of us will have an acute inflammatory response at a certain time in oue life.

Most of us 95% will go back to normal, almost go back to the normal or almost go back to the normal.

However, there are different types of outcomes of acute, the preffered outcome and the most common outcome is complete resolusion.

The acute inflammation comes, it goes through 5 stages which we have mentioned and then tissue repair will start and most of the time 98-99% the tissue goes back completely to the preacute episode phase.

However, this isn't what happen in real life, so either there's a complete resolution, some of those will go and heal, but the hea;ing process consists of

fibrosis and scar formation which will have sometimes a negative impacts on the cosmetic appearence of that organ or the function of that organ.

If you have an attack of acute inflammation with a small scar fibrotic healing peocess, it doesn't look good ,but sometimes, it doesn't impact your function.

However, if this process was severe enough to the point that the fibrous scar is so big and huge.

The outcomes:-

1-complete resolution

2-healing by fibrosis

3- we can't get rid of the acute inflammation due to certain reasons and this acute inflammation will transform to chronic inflammation comes and goes and whenever there is an attack , there is tissue damage at the end somtimesthe chronic inflammation will be so severe and prolonged and progressive with damaging that order

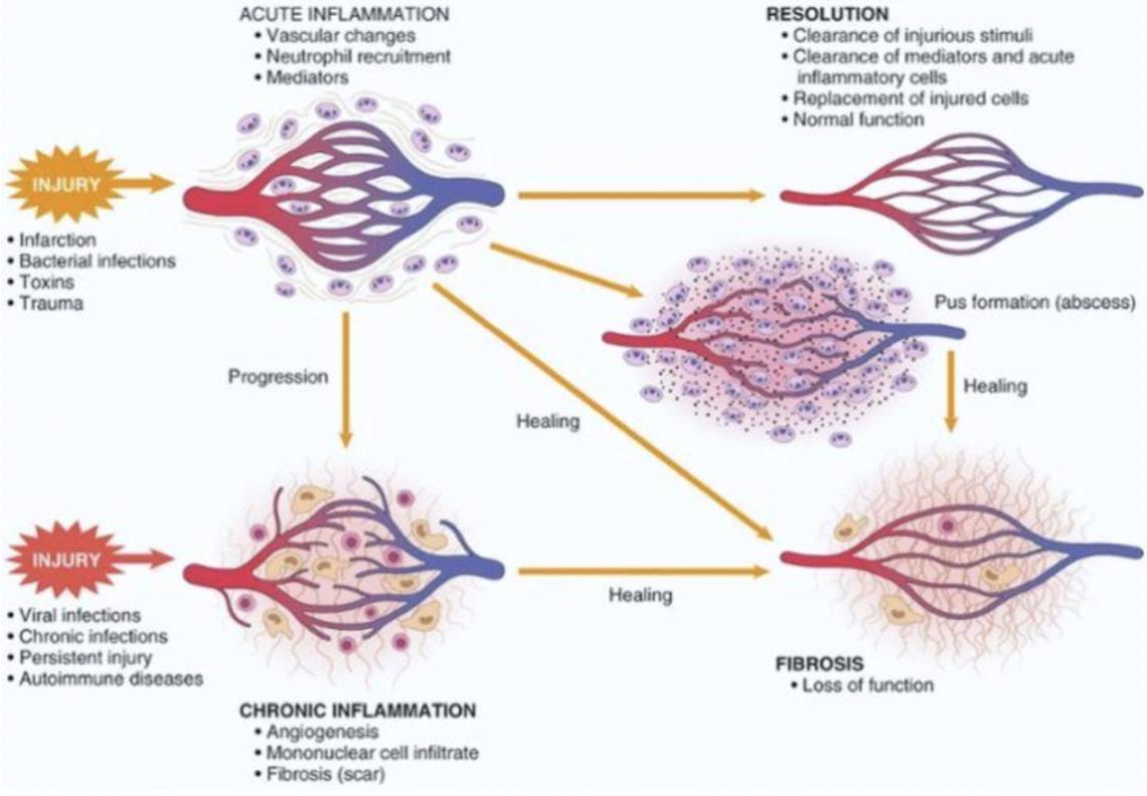


FIG. 3.16 Outcomes of acute inflammation: resolution, healing by fibrosis, or chronic i…

To summarize the outcomes of acute inflammation:-

- this is the diagram which is drawn to explain the initial injury, the vascular phases and the presence of acute inflammation .

- at the end of this acute inflammation, there will be a complete resolution and the tissue will go back to preinflammatory stage, so this is the first outcome which we would like to have most of the time.
- the second outcome in the presence of too much tissue destruction or severe acute inflammation and there is a healing process needing tissue repair forming fibrosis scar in that area, the tissue characters here isn't exactly the same as the pre-inflammatory stage
- however, there is a scar tissue here and depending on this scar tissue or fibrosis tissue, the impact on the function will ensure if the acute inflammation was progressive due to a virulent injorious agent or bad immunity there will be chronic inflammation with new vascularization too much changes in the tissue and sometimes severe fibrosis and scar formation leading to loss of function.

CHRONIC INFLAMMATION :

- Let's talk about chronic inflammation it's defined by prolonged inflammation the exact date and time is not really clear, but it's at least weeks and months and sometimes years with this prolonged chronic inflammatory response, they are associated tissue injury with each tissue injury your body is attempting or attempted to repair it at the same time with various degrees of " repair-injury – repair – injury) and then at the end if the chronic inflammation did not stop and continues there will be severe scar and fibrosis imparking on the function of that organ, an ex: If you have a chronic active hepatitis for 10 years at the end cirrhosis and fibrosis of the liver will lead to liver failure (weeks- months-years): inflammation , tissue injury and attempts at repair coexist at the same time with varying degrees .
- May follow acute inflammation but may be insidious and smoldering. Most often time chronic inflammation follow acute inflammation in certain circumstances that's not the case , sometimes the acute inflammation phase is so subclinical it does not bother you anymore so the chronic inflammation continues ,insidious or smoldering it will not present itself clinically and those slightly dangerous because sometimes when the clinical is presented sometimes it's too late .

CAUSES OF CHRONIC INFLAMMATION :

Persistent infections	**Mycobacteria (TB), viruses, fungi, parasites. Delayed hypersensitivity reaction. Granulomatous inflammation.**
Hypersensitivity diseases	**RA, asthma, MS. May end in fibrosis of end organs**
Prolonged exposure to toxic agents (exogenous or endogenous)	**Silica (silicosis) Atherosclerosis (cholesterol)**
Other associated diseases	**Alzheimer's, Metabolic syndrome of DM**

- persistent: especially with certain tough virulent bad organisms causes specific type of inflammation which we called it granular inflammation which is specific type of chronic inflammation .viruses: Hepatitis C Virus.
- Hypersensitivity: They are big group of auto immune disease .
  - RA: rheumatoid arthritis
  -MS: multiple sclerosis
- Prolonged exposure :
  - Silica : A disease called silicosis due to the silica , the patient occupation will expose them daily on parts of silica inhaled into lung tissue ,then this will induce fibrosis and silicosis.
  - Atherosclerosis: Due to the cholesterol clusters which are actually produced Endogenously.

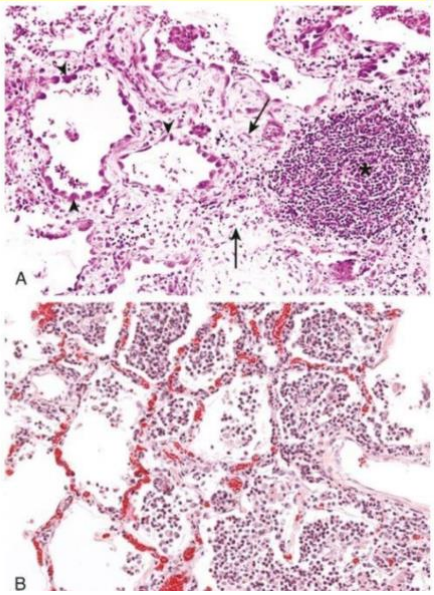
MORPHOLOGIC FEATURES OF CHRONIC INFLAMMATION :

- Infiltration by chronic inflammatory calls (macrophages , Lymphocytes , Plasma cells) If you have a tissue with chronic inflammation ,What are the microscopic features of the chronic inflammation response ? In the acute inflammatory response the cell

infiltrate is predominantly by neutrophils , in chronic inflammation the inflammatory cells which are present and can seen under the microscope (macrophage , lymphocytes ,plasma cells) when ever we see those this is chronic inflammation so the first critical feature of chronic inflammation is the infiltrate the tissue by chronic inflammatory cells , not only that in addition to filtration you can see that there is tissue damage or tissue destruction so many times the chronic inflammatory response will be associated with tissue destruction in varying degrees , if there is severe tissue destruction you will see severe changes like replacement of the normal liver parenchyma by thick bands of fibrosis.

In addition to that your body is not standing always attempting to induce repair and healing y production of new blood vessels a process which we called it Angiogenesis and then replacement of lost tissue by scar tissue rich in collagen and those can be seen under the microscope these are the major morphological features of chronic inflammation .

Chronic pneumonia



- In the upper image we can see a chronic inflammation of the lung with fibrosis …" The alveoli has been damaged and replaced with fibrosis tissue".
- The lower image.. The alveoli is full of those. Neutrophils and this is severe acute labor pneumonia where the alveoli is filled with acute inflammatory cells which is neutrophils each one of those is a micky

mouse cells or PMN or neutrophil ,so this is chronic inflammation the architecture is preserved .

- This acute inflammation of the lung with too many neutrophils.

CELLS AND MEDIATORS OF CHRONIC INFLAMMATION :

- MACROPHAGES
- LYMPHOCYTES
- EOSINOPHILLS
- MAST CELLS

The mediators which we have talked about they are not only involved in acute inflammation , chronic inflammation also requires a meditators of chronic inflammation ,all these cells play a role in producing many of these chemical mediators similar to acute inflammatory response so as well as acute inflammation response requires a mediators .

MACROPHAGES:

- Secretion of mediators (TNF,IL-1,CHEMKINES)
- Feedback loop with T-cells.
- Phagocytosis

  When they are circulating they are actually monocytes , they secrete cytokines, in addition they have strong connection T-cell there is always a communication between T-cell and macrophages also gives the macrophages feedback about increasing and decreasing of inflammatory response .
- Circulating monocytes(one day half day)

  The macrophages when they circulating in the blood before they get recruited and activated into the tissue to transform to tissue macrophages or tissue monocytes to or tissue histiocytes. The half life of monocytes is one day ,but when they get to the tissue the half life extended weeks and months
- Tissue macs: kupfer cells cells of the liver " they are originally monocytes when they sit insidethe liver they transform to macrophages ,sinus histiocytes,alveolar macrophages in the lung , microglia in the brain(non nuclear phagocytic system), half life month.

- Activation of macs:M1 classic pathway , M2 alternative pathway

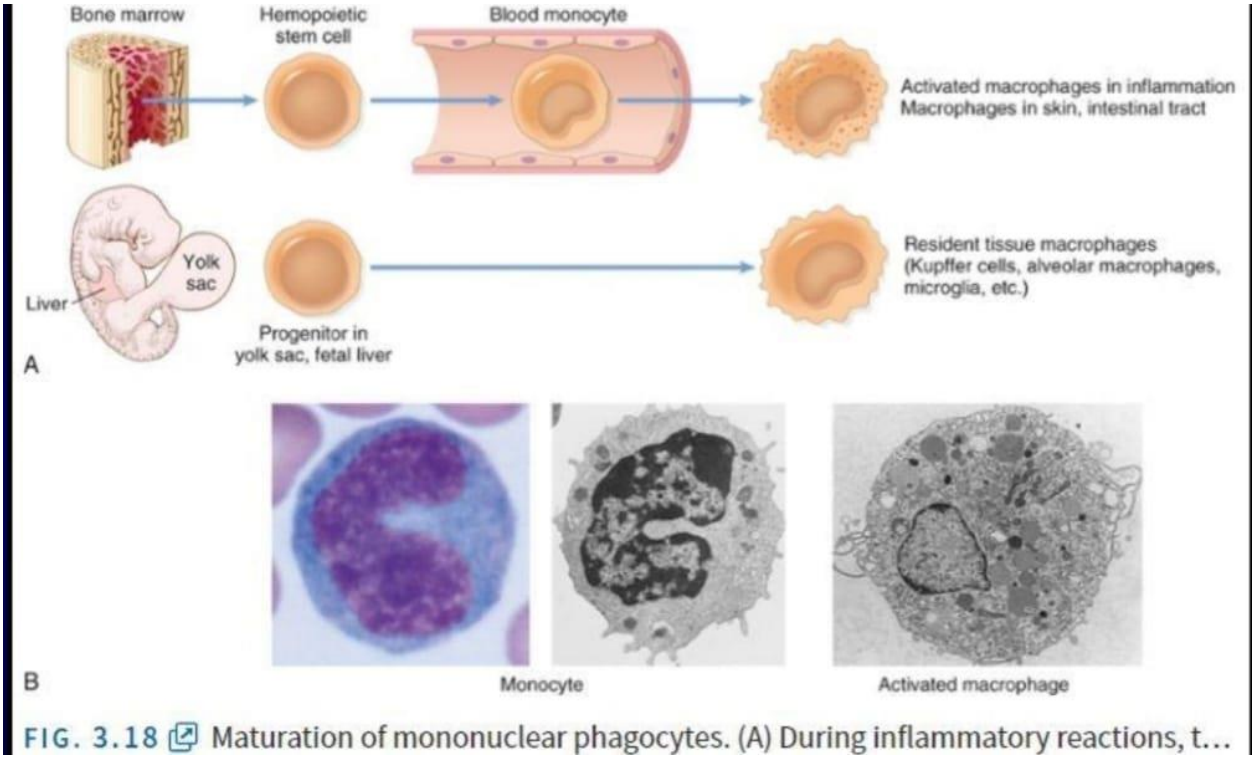


FIG. 3.18 Maturation of mononuclear phagocytes. (A) During inflammatory reactions, t…

-The macrophages are produced by bone morrow ,in adults 'HEMATOPOIETIC STEM CELLS'

- The first drawing is the classic appearance of those circulating monocytes' (Abundant in cytoplasm and less granules) it has coffee bean shaped or kidney shaped nucleus , when they get activated it get released to activated macrophages In the tissue they become bigger, more granulated , the neuclear Cytoplasmic ratio is less and they are called tissue macrophages Depending on the origin , and sometimes in fetal life they are Produced from yolk sacs as a progenitor cells and mature in the tissue)

-The second drawing → morphologically this is the way the monocyte looks like in circulating " the colored one"

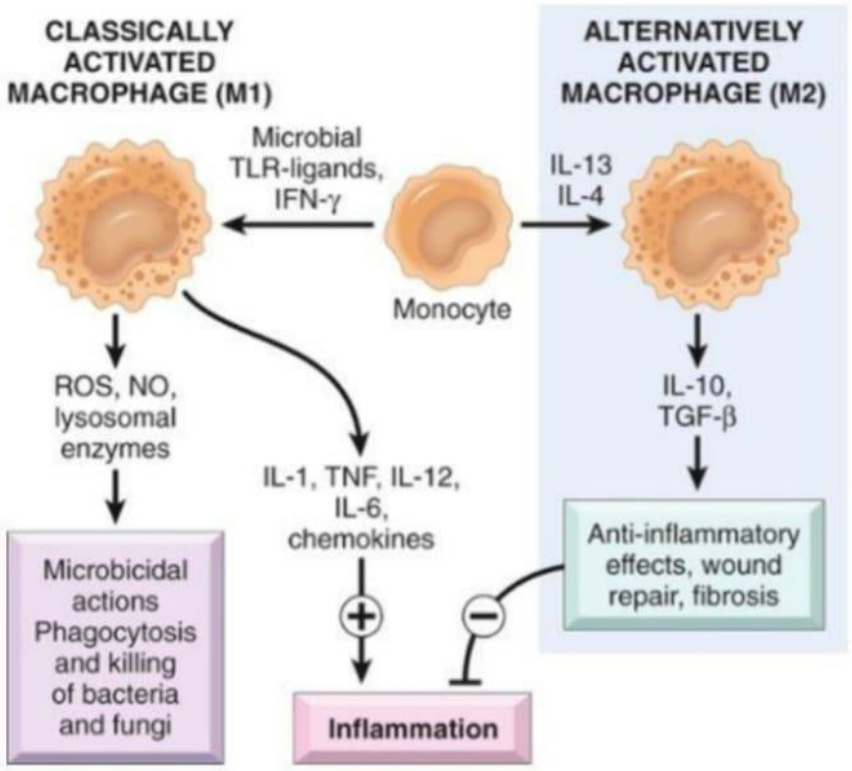


FIG. 3.19 Classical and alternative macrophage activation. Different stimuli activate m...

The classic M1 pathway of the macrophages is pro- inflammatory that induce excess inflammatory mediators and they are active in trying to fight invading organisms .

The major driver of recruitment of those monocytes in the M1 pathway are different stimuli (microbial drugs, TLR-LIGANDS,IFN-Y) which leading to secretion (IL-1,TNF,IL-6,CHEMOKINES) ending up augmenting the inflammatory response .

The alternatively pathway M2 there are certain cytokines specifically (IL-13,IL-4) they will push the monocyte in this pathway leading to activation of those M2 macrophages secreting (IL-10,TGF-B) they we have anti-inflammatory effects (inhibit the inflammatory response)

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)when they get activated it get released to activated macrophages In the tissue they become bigger, more granulated , the neuclear Cytoplasmic ratio is less and they are called tissue macrophages Depending on the origin , and sometimes in fetal life they are Produced from yolk sacs as a progenitor cells and mature in the tissue)

instead of (when they get activated it leads to activated macrophages in the tissue they become more granulated , the cytoplasmic ratio is less and they are called tissue macrophages depending on the origin , and some times in fetal life they are produced by yolk sacs as a progenitor cells and mature in the tissue.)

*The modification in Red

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Hyponatremia instead of Hypernatremia