

***Title of Lecture:*** clinical manifestations of inflammation

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***Sheet no: 6***

***Refer to slide no. : 2***

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Clinical manifestations of inflammation are very helpful in diagnosis of inflammation, and inflammation is something treatable and that’s why it's important to know how to diagnose it .so it's better to be inflammation than something else

First one of them is redness that inflammatory site show

Second one is heat at site of inflammation. And it's different from systemic heat which is called fever

Third one is swelling at the inflamed tissue and this one is caused by vascular changes like increased permeability of fluids at site of inflammation so fluids escape from blood to the tissue

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| Normal cases | Abnormal cases |
| Amount of extracellular fluid is very small and when fluids accumulate lymphatic system brings them back to circulation | At site of inflammation fluids will be present extracellular and this will add to the volume of tissue causing swelling at site of inflammation |

Number four is pain which is considered as constant presentation of inflammation, and it happens due to:

1-fluids that compress small nerves at site of inflammation

2-chemical (inflammatory) mediators that are released at site of inflammation like prostaglandins (serotonin for example)

Inflammatory changes like pain and edema can cause loss of function, for example: in case of arthritis (inflammation at any joint), movement of joint is going to be affected by edema and filling of joint space by fluid

All those clinical manifestations are explained by two main changes that happen at microscopic level:

1-vascular

2-cellular

Vascular changes

1-Dilatation of vessels (increase in the diameter) at the site of inflammation causing heat and redness

2-increase in permeability

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| Normal cases | Abnormal cases |
| Endothelial cells (lining of blood vessels) at the level of small blood vessels (capillaries , venules and veins) they overlap so gaps disappear , the lining is continuous and nothing can escape from blood to surrounding tissues, leading to minimal amount of fluids escaping to the outside which lymphatic system brings them back to circulation. | At site of inflammation there is changes by chemical mediators , endothelial cells retract and become smaller in size and gaps appear allowing fluids to escape  The escaping fluid is hypotonic. However, proteins will follow the fluid and eventually leukocytes which naturally exist in blood escape outside creating inflammatory response |

All those vascular changes are important and contribute in inflammation

When we are exposed to infectious agent vasoconstriction occur (transient and rapid) and this process prevents loss of blood

### The most important reactions is vasodilatation, amount of blood present at dilated vessels is larger than normal ones and this term is called stasis. And it causes redness and heat, the last one is due to the warmth of the coming blood. After this permeability will increase and that's why stasis is associated with decreased blood flow. Leakage of fluid will occur if this process is present with increased permeability.

### First of all the fluid formed is protein poor fluid which will cause increase in hydrostatic pressure that depends on volume of the liquid. When hydrostatic pressure increases the fluids will be pushed from inside to the outside and this fluid is called **transudates**

### However, proteins will follow the fluid and leak to the outside and when protein content increases, the fluid and cells like leukocytes leak it is called **Exudates.** And it's important in the buildup of inflammatory process as we will see.

**Edema** can be either transudates or Exudates and it can occur in different sites like lower limb edema. As a conclusion edema is more general than swelling and that's why we use the term swelling to describe inflammation

If we examine any site of inflammation especially in cavities we will find accumulated fluids, leukocytes and proteins like fibrins. For example in pneumonia disease we will notice accumulation of fluids in plural cavity.

When we talked about inflammation (abnormal cases, refer to the table) we mentioned chemical mediators and they have two types:

1-mediators with immediate effect that lasts for short periods of time like histamine, which is the first mediator to be release at site of inflammation and it's not enough because we need the permeability to increase for longer periods of time

2-mediators with delayed and prolonged action like: bradykinins and leukotrienes and they are important to accomplish the effect of inflammation

In order to reach the desired permeability we also need junctional retraction. And it means retraction of cells and the site of the cytoplasm which is very close to next cells will contract and this will keep permeability for prolonged time. This effect is produced by chemical mediators (another ones)

Another mechanism that is responsible about increased permeability is direct injury to endothelial cells which can cause detachment and thrombosis. This effect can be seen in veins and capillaries at the same site of infection not like other mechanisms.

We noticed that swelling exists for prolonged periods of time even if the site of inflammation has healed and that's due to the new blood vessels or new ***angiogenesis*** that help new cells to survive and grow. Those blood vessels are immature and leaky. And this explains the fact that edema is the last thing to disappear from site of infection

Cellular changes

These changes are very important due to leukocytic infiltration of the site of inflammation

We divide inflammation based on type of cells predominant at site of inflammation. For example when neutrophils are predominant we have acute inflammation at that site (this is going to be discussed later)

Cells normally exist in blood and because there are no gaps, those cells exist in blood only

Those cells are allowed to move due to changes in blood vessels and this process needs many proteins and chemical mediators in order to create gaps that allow the movement of cells to the outside.

But this is not the only problem , we don’t have potential spaces between cells of tissue to allow other cells movement so we need an active process and only in inflammatory site cells go through sequence of steps (please refer to slides)

***Migration*** is very important and cellular content of blood move in the center because leukocytes may cause damage to endothelium because they are full of mediators and chemicals and injury is something huge and bad and we don't want it to happen

However, when there is inflammation neutrophils come in contact with endothelium and this is very important and we call it ***margination***

***Adhesion***: First of all we have loose adhesion carried out by family of proteins called selectin (adhesion molecules in leukocytes and endothelial cells) and they interact forming firm adhesion between leukocytes and endothelium

This process is very active and needs participation of molecules and mediators that allow them to interact. Normally adhesion between neutrophils and endothelial cells is very minimal in order not to cause injury to endothelium

Selectin has many types and it's helpful in recognizing and identifying cell types

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| Normal cases | inflammation |
| Selectin is inactive and not expressed on the surface meaning that it's located intracellular or in the cytoplasm | They are expressed more and start to appear on the surface |

Adhesion molecules (located on nuclear surface) must interact with their receptors on endothelial surface and once they get firm attachment they start expressing other molecules to help cell in the passage between endothelial cells

One of the most important adhesion molecules is p-selectin that must be expressed in the surface to help neutrophils squeeze themselves in the gap. After that we need active process to help neutrophils move outside tissue (because we lack potential spaces) so it will actively interact with other cells in the tissue. It will accumulate at the site of inflammation in order to carry out function which is killing of bacteria (manifested at microscopic level)   
***Integrins*** are present on cell surface mainly at junctional area near gaps

***Chemokines*** are specific for neutrophils or eosinophils or whatever

-at the end of inflammatory process and after infectious agent is removed phagocytosis for dead and inflammatory cells takes place

-any defect in any process of inflammation causes disease

Please refer to slides.