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Mechanism involved in the process of inflammation

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Abstract
Inflammation is the immune system's response to harmful stimuli, such as pathogens, damaged cells, toxic compounds, or irradiation, and acts by removing injurious stimuli and initiating the healing process. Inflammation is therefore a defense mechanism that is vital to health. Usually, during acute inflammatory responses, cellular and molecular events and interactions efficiently minimize impending injury or infection. This mitigation process contributes to restoration of tissue homeostasis and resolution of the acute inflammation. However, uncontrolled acute inflammation may become chronic, contributing to a variety of chronic inflammatory diseases. Here, we review clinical signs of inflammation, different types of inflammation and mechanism of Inflammation.

Keywords: inflammation, clinical signs, inflammatory process, marigination, chemotaxis

Introduction
A localized physical condition in which part of the body becomes reddened, swollen, hot, and often painful, especially as a reaction to injury or infection. The inflammatory process is the response to injurious stimulus. It can be evolved by variety of noxious agents. E.g: infections, antibodies or physical injury. A normal inflammatory response is essential to fight infections and is part of repair mechanism and removal of debris. Inflammation can also cause disease due to damage of healthy tissue.

Clinical Signs of Inflammation
Following are clinical signs of inflammation:
- Heat (calor)
- Redness (rubor)
- Swelling (tumor)
- Pain (dolor)
- Loss of function (function laesa)

Different Types of Inflammation
There are different types of inflammations based on different parameter. The parameter are as follows:

1. Organs and Anatomic Modifiers
Various organs influenced by inflammation and their anatomic modfiers are indicated below:
- **Nephritis**

It refers to inflammation of kidney, its anatomic modifiers can be interstitial-, glomerulo- etc.

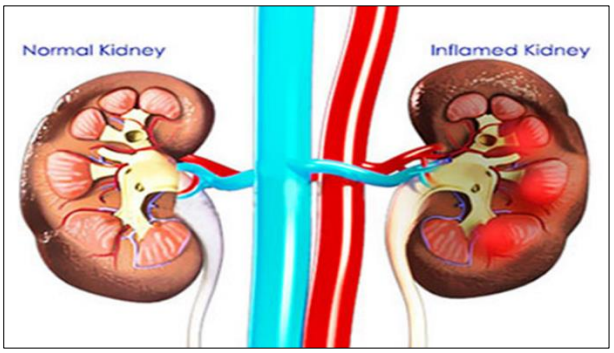

Fig 1

- Inflammation of GIT is termed as enteritis.

Fig 2

- Inflammation of muscle is termed as **myocytis.**

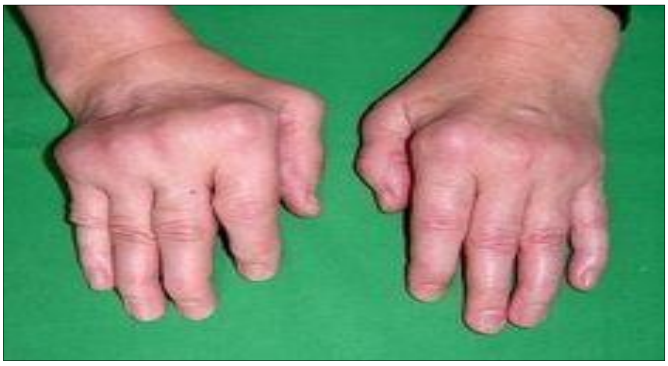

Fig 3

2. Exudates

The inflammatory process can be classified according to predominant type of inflammatory cells and/or the kind of fluid/exudates associated with it.

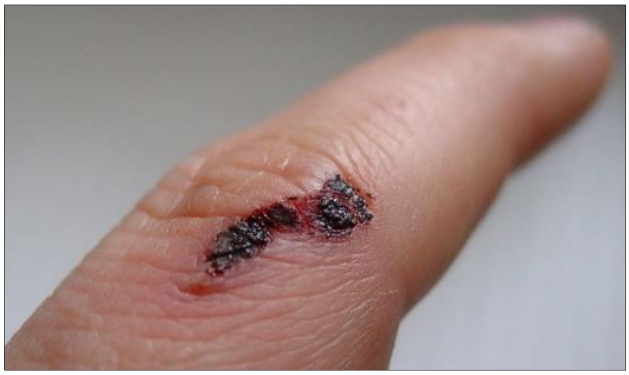

Fig 4

- **Fibrinous exudates**

It refers to **accumulation of fibrin**, resulting from increased vascular permeability due to injury to the epithelium and basement membranes membranes and subsequent leakage of plasma proteins, including fibirinogen.

- **Necrotizing inflammation**

It is characterized by **necrosis** with usually small amounts of vascularand leucocytes contributions.

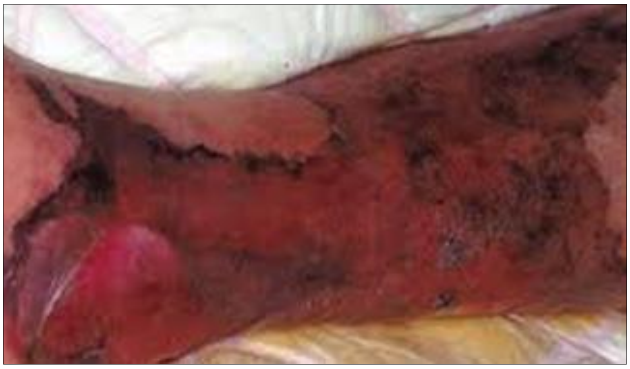

Fig 5

c. Suppurative (purulent) exudates: It is called as **pus** and is composed of large number of neutrophils and dead tissue cells i.e. cellular debris.

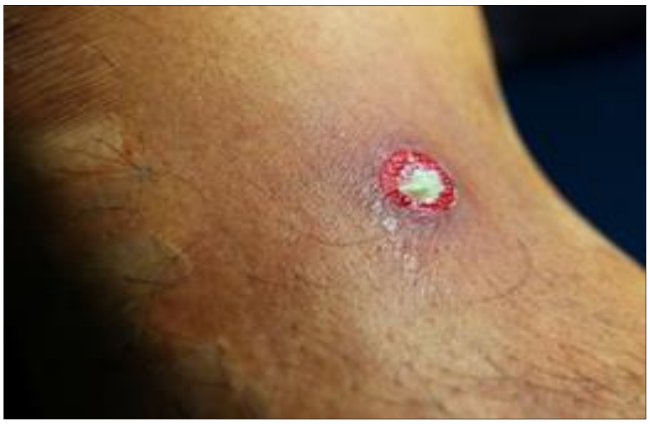

Fig 6

d. Granulomatous exudates/ inflammation

It is inflammatory response where macrophages predominates along with more or less abundant lymphocytes, plasma cells.

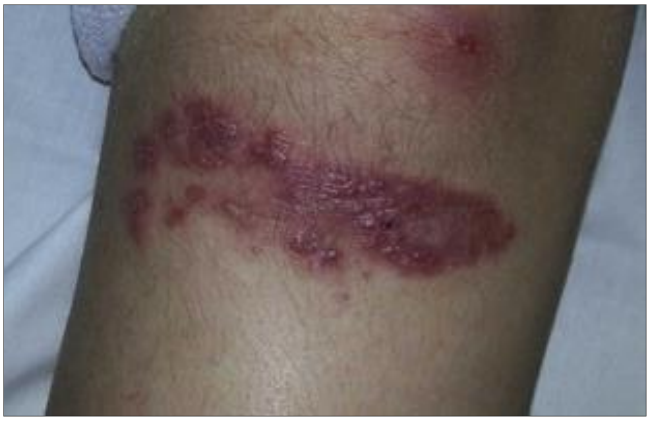

Fig 7

e. Hemorrhagic (sanguineous) inflammation

In this case haemorrhage is the predominant feature; it occurs due to severe injury to blood vessels or marked diapedesis.

f. Serous exudation

It is accumulation of fluid relatively rich in protein on body surface with little cellular infilterate.

g. Mucoid exudates

It consists of mucus as well as variable number of inflammatory cells.

h. Eosinophilic inflammation

Sometimes eosinophils may contain granules to give a green tinge to tissue.

i. Non-Suppurative inflammation: It is microscopic diagnosis with predominates mononuclear cells like lymphocytes and plasma cells.

3. Distribution

It indicates the location of the lesion within organ and indirectly how much affected.

It may be:

- focal
- Multifocal
- Extensive
- Diffuse

4. Duration

It indicates how long the process has been underway.

a. Pre-acute inflammation: It occurs between 0-4 hours.
b. Acute inflammation: It begins with hours and can last for 3-5 days.
c. Sub-acute inflammation: It lasts for few days to about one week.
d. Chronic inflammation: It persists over a time of few weeks to months.
e. Chronic active inflammation: It can be due to repeated overlapping episodes of inflammation usually because the host has been unable to limit the insighting agent.

5. Severity

It is divided into three types:

- Mild
- Moderate
- Severe

Mechanism of Inflammation

There are various cellular events related to leucocyte adhesion cascade. Accumulation of leucocyte is most important feature. Leucocytes get to site of inflammation by adhesion to vascular walls and transmigration through them. The process is regulated by "leucocyte adhesion cascade" which is characterised by binding of complementary adhesion molecules on membranes of leucocytes and endothelial cells.

Following sequence of events involved in actions of leucocytes.

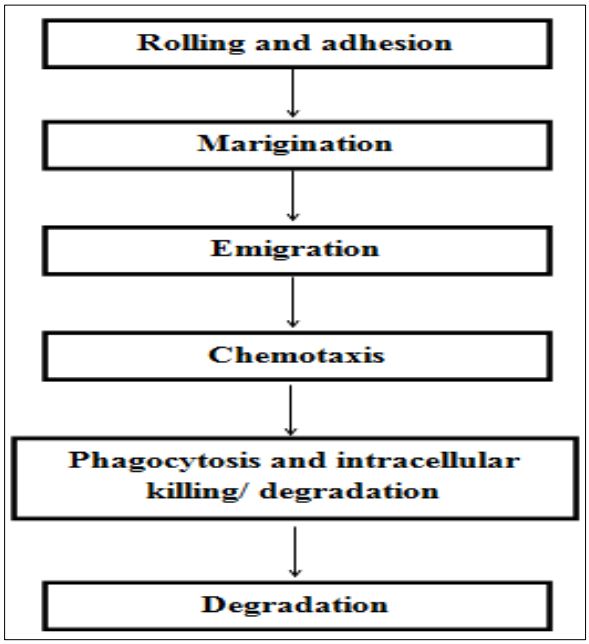

Fig 8

1. Marigination

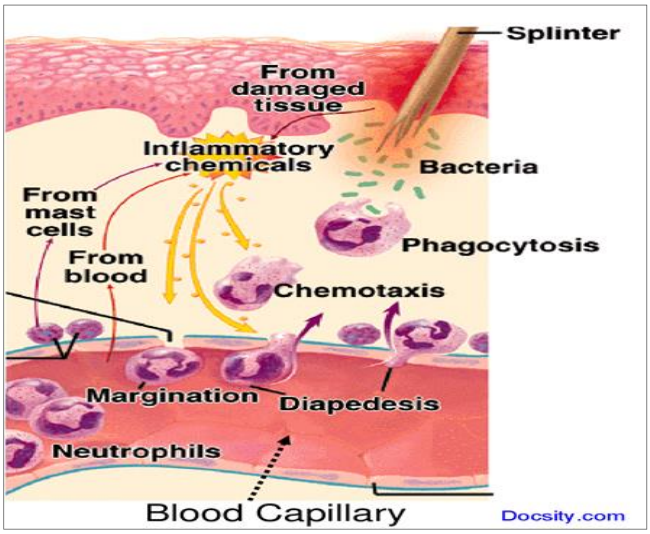

Fig 9

There is slowing and stagnation of blood flow due to vasodilation (widening of blood vessels & relaxation of smooth muscle) and increased vascular permeability. Leucocytes fall out of major blood vessels till they come in contact with the surface of endothelial cells (main type of cell found inside lining of blood vessels) of capillaries and post-capillary venules.

2. Rolling and adhesion

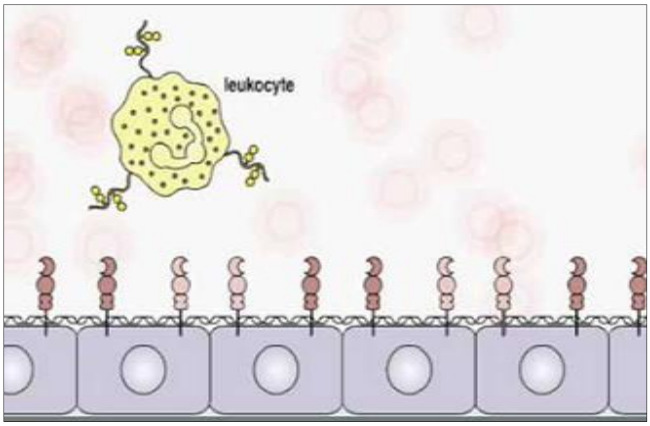

Fig 10

Marginated leucocytes line the endothelium. They start to adhere to the surface endothelial cells through various adhesion molecules. Once adhesion is firm, the leucocytes become stationary and can begin to migrate through the endothelium into the site inflammation.

3. Emigration

The process by which leucocytes escape from the blood to perivascular tissues, moving to the site of inflammation is called as emigration. It occurs in post-capillary venule because adequate number of endothelial gaps and histamine receptors are found to be located on it. Neutrophils are the first to emigrate, the Predominate for the first 6-24 hours, peaking at 4-6 hours. In viral

infections, lymphocytes are the first to arrive and in some hypersensitive reactions, eosinophils are the first to arrive.

4. Chemotaxis

The directional migration in response to a chemical gradient to chemo-attractant receptor-mediated and allows leucocytes to travel from the perivascular (adipose tissue surrounding blood vessels) space to the site. All leucocytes respond to chemotactic stimuli. Neutrophils are the fastest reach (within 90 min), followed by monocytes (several hours) and lymphocytes (last one to reach). Chemo-attractants/ chemotaxins can be exogenous or endogenous.

5. Phagocytosis and intracellular killing/degradation

a. Phagocytosis

The purpose of phagocytosis is to engulf, kill and degrade foreign material, most commonly bacteria. The involved steps are as follows:

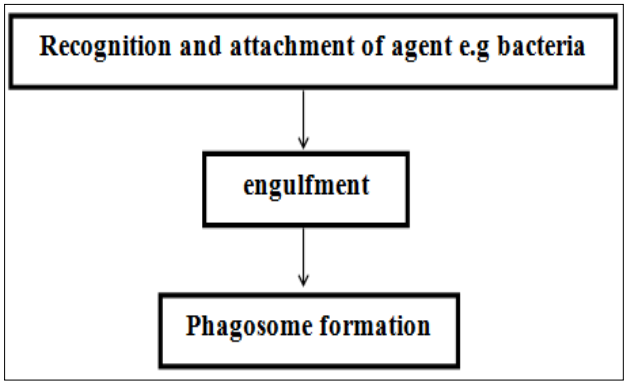

Fig 11

b. Intracellular killing

Oxygen dependent and independent mechanisms of bactericidal activity occur in phagolysosome (cytoplasmic body formed by fusion of a phagosome). The mechanism are as follows:

Oxygen dependent mechanisms

- Formation of super oxide anion, hydrogen peroxide
- Nitric oxide
- Haber-weiss reaction

Oxygen independent mechansims

- Lysozyme
- Major basic protein
- Trypsin and chymase

6. Degradation

After the microorganism has been phagocytised, pH in the phagolysosome drops to 4-5.The acidic pH is optimal for activity of degradative enzymes wthin lysosomes.

7. Extracellular release of leucocyte products

Leucocytes not only release toxic metabolites or enzymes into phagolysosome, but they also release them at the site of inflammation. This event helps in killing microorganisms, enhancing the inflammatory reaction; but it also causes tissue necrosis.

Following
4 mechanisms are involved in releasing potent mediators.

- Lysosomal suicide (Cytotoxic release)
- Regurgitation during feeding
- Reverse endocytosis (frustrated phagocytosis)

- **Alteration in Vascular permeability and blood flow**

The hallmark of acute inflammation is increased vascular permeability leading to escape of protein-rich exudates.
Five mechanisms of increased permeability are as follows:

1. Retraction of endothelial cells (in venules)
2. Direct endothelial injury
3. Leucocyte-dependent endothelial injury
4. Increased transcytosis(active transport mechanism)

1. Retraction of endothelial cells (in venules)

It is divdied into 2 stages: endothelial cell contraction and delayed prolonged leakage.

- **Endothelial cell contraction** is rapid, transitory (15-30 min) and reversible. Binding of mediator to receptor leads to contraction of endothelial cell which results in widening of intercellular junctions.

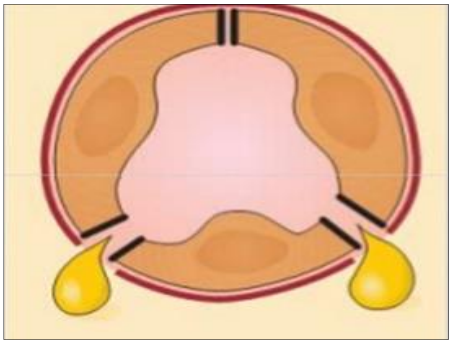

Fig 12

- **During delayed prolonged leakage**, there is vascular leakage beginning after 2-12 hours and lasting for several hours to days and develop temporary gaps.

2. Direct endothelial injury

It affects arterioles, venules and capillaries. Severe injurious stimuli e.g. severe burns cause endothelial necrosis and appearance of physical gaps.

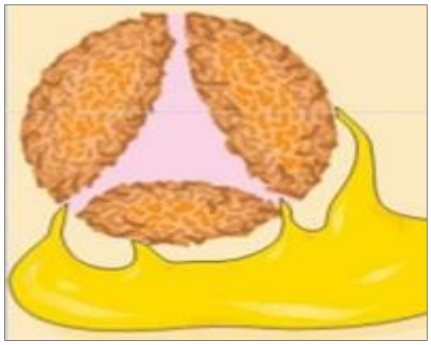

Fig 13

There is immediate sustained response i.e. leakage starts immediately and lasts several hours to days till damaged vascular structures are repaired/ thrombosed.

3. Leucocyte-dependentendothelial injury

Neutrophils which adhere to the endothelium during inflammation may also injure the endothelial cells and amplify inflammation.

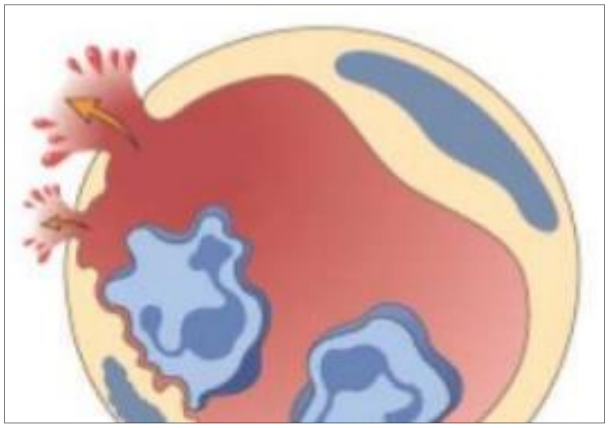

Fig 14

4. Increased transcytosis (active transport mechanism)

Normally there is some transport of fluid through of fluid through endothelial cells by channels of interconnected, uncoated vesicles and vacuoles.

5. Leakage drom new capillaries

During the repair process, proliferating endothelial cells are leaky.

- **Migration of WBCs in inflammation**

Cellular events are required to deliver to the site of inflammation so that they can internalise pathogens through phagocytosis and kill or digest them by releasing proteolytic enzymes, chemical mediators and reactive oxygen species. Information about leucocytes involved in inflammation is presented below:

1. Neutrophils

They have rapid amoeboid movement responding to a variety of chemotactic compounds and have good phagocytic and bactericidal activities to kill microbes, tumour cells and eliminate foreign material. They do not divide. Their average life time is very small (6 hours to few days). They have three types of granules. Each type contains specific/ molecules. They are as follows:

a. Azurophil granules (primary granules): Myeloperoxidase, lysozyme, elastase.
b. Specific granules (secondry granules): Leucocyte adhesion molecules, lysozyme histaminase.
c. Tertiary granules (gelatinase granules): Gelatinase, lysozyme, leucocyte adhesion molecules.

- Functions of neutrophils are as follows:
- Phagocytosis
- Mediate tissue injury
- Regulate inflammatory response

2. Eosinophils

They are numerous at inflammatory sites and result from parasites and allergic/ immune mediated disease. Some of they stay in tissues like intestine, skin, lung and mucus membranes. The main component of granules are as follows:

a. Major basic protein: It induces histamine release from mast cells.
b. Eosinophilic cationic protein: It shorens coagulation time.
c. Histaminases: It inactivates histamine.

- Functions of eosinophils are as follows:
- Kill or damage helminths and other pathogens by antibody dependent cell mediated cytotoxicity.
- Regulate inflammation, particularly to mast cell products.

3. Basophils and mast cells

Basophils are rare circulating granulocytes. Mast cells are numerous and are found in organs like lungs, GIT, mucus membrane and skin. Both of these cells share many characteristics:

- They contain abundant granules which are rich in histamine, proteases and potent inflammatory mediators. Unlike neutrophils, they continue to survive after releasing their granules.
- Mast cells are major source of histamine in acute inflammation.

4. Macrophages/ monocytes

Macrophages are derived from circulating blood monocytes originating from bone marrow. They remain in circulation for 24-72 hours. They are motile, they need 8-12 hours to get at the site of inflammation; but they are sluggish as compared to polymorphonuclear lymphocytes.

- Functions of monocytes are as follows:
- They are phagocytic and antimicrobial: oxygen radicals, lysozyme.
- They stimulate or modulate other cell activity: vascular effects.
- They clean up debris: host and foreign.

5. Lymphocytes/ plasma cells:

Lymphocytes and plasma cells are the main cells of immune reactions. They are needed for antibody response, delayed hypersensitivity responses and down regulation of the immune system. They are less motie than neutorphils and monocytes.

Conclusion

Inflammation participates importantly in host defenses against infectious agents and injury, but it also contributes to the pathophysiology of many chronic diseases. Interactions of cells in the innate immune system, adaptive immune system, and inflammatory mediators orchestrate aspects of the acute and chronic inflammation that underlie diseases of many organs. A coordinated series of common effector mechanisms of inflammation contribute to tissue injury, oxidative stress, remodeling of the extracellular matrix, angiogenesis, and fibrosis in diverse target tissues. Atherosclerosis provides an example of a chronic disease that involves inflammatory mechanisms. Recruitment of blood leukocytes characterizes the initiation of this disease. Its progression involves many inflammatory mediators, modulated by cells of both innate and adaptive

immunity. The complications of established atheroma, including plaque disruption and thrombosis, also intimately involve inflammation. Mastery of the inflammatory response should aid the development of novel strategies to predict disease susceptibility, target and monitor therapies, and ultimately develop new approaches to the prevention and treatment of chronic diseases associated with aging, such as atherosclerosis.

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