INFLAMMATION

Definition: Inflammation is a local response (reaction) of living vasculaized tissues to endogenous and exogenous stimuli. The term is derived from the Latin "inflammare" meaning to burn. Inflammation is fundamentally destined to localize and eliminate the causative agent and to limit tissue injury. Thus, inflammation is a physiologic (protective) response to injury.

Causes:

Causes of inflammation are apparently causes of diseases such as:

1- Physical agents: mechanical injuries, alteration in temperatures and pressure.

2- Chemical agents: including the drugs and toxins.

3- Biologic agents (infectious): bacteria, viruses, fungi, parasites.

4-Immunologic disorders: hypersensitivity reactions, autoimmunity, immunodeficiency states.

5- Genetic/metabolic disorders- examples gout, diabetes mellitus… etc.

Nomenclature:

The nomenclatures of inflammatory lesion are usually indicated by the suffix 'itis'. Thus, inflammation of the appendix is called appendicitis and that of meninges as meningitis, etc.… However, like any rule, it has its own exceptions example pneumonia mean inflammation of the lung.

Classification:

Inflammation is classified depend on

1- Duration (time) of the lesion and histologic appearances into: Acute and chronic inflammation.

2- Type of exudate classified in to: (serous, fibrinous, catarrhal, suppurative, hemorrhagic , lymphocytic inflammation).

1- Acute Inflammation

Acute inflammation is an immediate and early response to an injurious agent and it is relatively of short duration, lasting for minutes, several hours or few days. It is characterized by exudation of fluids and plasma proteins and the emigration of predominantly neutrophilic leucocytes to the site of injury.

The five cardinal signs of acute inflammation are:

a. Redness (rubor) which is due to dilation of small blood vessels within damaged tissue as it occurs in cellulitis.

b. Heat (calor) which results from increased blood flow (hyperemia) due to regional vascular dilation

c. Swelling (tumor) which is due to accumulation of fluid in the extravascular space which, in turn, is due to increased vascular permeability.

d. Pain (dolor), which partly results from the stretching & destruction of tissues due to inflammatory edema and in part from pus under pressure in as abscess cavity. Some chemicals of acute inflammation, including bradykinins, prostaglandins and serotonin are also known to induce pain.

e. Loss of function: The inflamed area is inhibited by pain while severe swelling may also physically immobilize the tissue.

Events of acute inflammation:

Acute inflammation is categorized into an early vascular and a late cellular responses.

1. The Vascular response has the following steps: a. Immediate (momentary) vasoconstriction in seconds due to neurogenic or chemical stimuli. b. Vasodilatation of arterioles and venules resulting in increased blood flow. c. After the phase of increased blood flow there is a slowing of blood flow & stasis due to increased vascular permeability that is most remarkably seen in the postcapillary venules. The increased vascular permeability oozes protein-rich fluid into extravascular tissues. Due to this, the already dilated blood vessels are now packed with red blood cells resulting in stasis. The protein-rich fluid which is now found in the extravascular space is called exudate. The presence of the exudates clinically appears as swelling. Chemical mediators mediate the vascular events of acute inflammation.

2- Cellular response:

The cellular response has the following stages:

A. Migration, rolling, pavementing, & adhesion of leukocytes

B. Transmigration of leukocytes

C. Chemotaxis

D. Phagocytosis

Normally blood cells particularly erythrocytes in venules are confined to the central (axial) zone and plasma assumes the peripheral zone. As a result of increase vascular permeability (See vascular events above), more and more neutrophils accumulate along the endothelial surfaces (peripheral zone).

A) Migration, rolling, pavementing, and adhesion of leukocytes

- Margination is a peripheral positioning of white cells along the endothelial cells.

- subsequently, rows of leukocytes tumble slowly along the endothelium in a process known as rolling

- In time, the endothelium can be virtually lined by white cells. This appearance is called pavementing

- Thereafter, the binding of leukocytes with endothelial cells is facilitated by cell adhesion molecules such as selectins, immunoglobulin's, integrins, etc which result in adhesion of leukocytes with the endothelium.

B). Transmigration of leukocytes

Leukocytes escape from venules and small veins but only occasionally from capillaries. The movement of leukocytes by extending pseudopodia through the vascular wall occurs by a process called diapedesis.

- The most important mechanism of leukocyte emigration is via widening of interendothelial junctions after endothelial cells contractions. The basement membrane is disrupted and resealed immediately.

C) Chemotaxis:

A unidirectional attraction of leukocytes from vascular channels towards the site of inflammation within the tissue space guided by chemical gradients (including bacteria and cellular debris) is called chemotaxis.

- The most important chemotactic factors for neutrophils are components of the complement system (C5a), leukotriene B4 and cytokines (IL-8). All granulocytes monocytes and to lesser extent lymphocytes respond to chemotactic stimuli.

- How do leukocytes "see" or "smell" the chemotactic agent?

This is because receptors on cell membrane of the leukocytes react with the chemoattractants resulting in the activation of phospholipase C that ultimately

leads to release of cytosolic calcium ions and these ions trigger cell movement towards the stimulus.

D) Phagocytosis

 Phagocytosis is the process of engulfment and internalization by specialized cells of particulate material, which includes invading microorganisms, damaged cells, and tissue debris.

 These phagocytic cells include polymorphonuclear leukocytes (particularly neutrophiles), monocytes and tissue macrophages.

Phagocytosis involves three steps

1)Recognition and attachment of the particle to be ingested by the leukocytes: Phagocytosis is enhanced if the material to be phagocytized is coated with certain plasma proteins called opsonins. These opsonins promote the adhesion between the particulate material and the phagocyte's cell membrane

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2)Engulfment: During engulfment, extension of the cytoplasm (pseudopods) flow around the object to be engulfed, eventually resulting in complete enclosure of the particlewithin the phagosome created by the cytoplasmic membrane of the phagocytic cell.As a result of fusion between the phagosome and lysosome, a phagolysosome is formed and the engulfed particle is exposed to the degradative lysosomal enzymes

3)Killing or degradation The ultimate step in phagocytosis of bacteria is killing and degradation.

Chemical mediators of inflammation

Chemical mediators account for the events of inflammation. Inflammation has the following Sequence

: Cell injury Chemical mediators' acute inflammation (i.e. the vascular & cellular events).

Sources of mediators:

The chemical meditors of inflammation can be derived from plasma or cells.

a) Plasma-derived mediators:

i) Complement activation

- increases vascular permeability (C3a, C5a)
- activates chemotaxis (C5a)
- opsoninization (C3b,C3bi)

ii) Factor XII (Hegman factor) activation Its activation results in recruitment of four systems: the kinin, the clotting, the fibrinolytic and the compliment systems.

b) Cell-derived chemical mediators

Most mediators perform their biologic activities by initially binding to specific receptors on target cells. Once activated and released from the cells, most of these mediators are short lived. Most mediators have the potential to cause harmful effects

Cellular mediators	Cells of origin	Functions
Histamine	Mast cells, basophiles,	Vascular leakage & platelets
Serotonin	Platelets	Vascular leakage
Lysosomal enzymes	Neutrophils	destruction Bacterial & tissue macrophages
Prostaglandines	All leukocytes	Vasodilatation, pain, fever
Leukotriens	All leukocytes	Broncho and vasoconstriction
Chemoattractant	LCD4, & LE4 LC4,	Broncho and vasoconstriction
Platelet activating factor	All leukocytes	Bronchoconstriction and WBC priming
Activated oxygen species	All leukocytes	Endothelial and tissue damage
Nitric oxide	Macrophages	Leukocyte activation
Cytokines	Lymphocytes, macrophages	Leukocyte activation

Effects of acute inflammation:

A. Beneficial effects

1- Dilution of toxins: The concentration of chemical and bacterial toxins at the site of inflammation is reduced by dilution in the exudate and its removal from the site by the flow of exudates from the venules through the tissue to the lymphatics.

2- Protective antibodies: Exudation results in the presence of plasma proteins including antibodies at the site of inflammation. Thus, antibodies directed against the causative organisms will react and promote microbial destruction by phagocytosis or complement-mediated cell lysis

3- Fibrin formation: This prevents bacterial spread and enhances phagocytosis by leukocytes.

4- Plasma mediator systems provisions: The complement, coagulation, fibrinolytic, & kinin systems are provided to the area of injury by the process of inflammation.

5- Cell nutrition: The flow of inflammatory exudates brings with it glucose, oxygen and other nutrients to meet the metabolic requirements of the greatly increased number of cells. It also removes their solute waste products via lymphatic channels.

6- Promotion of immunity: Micro-organisms and their toxins are carried by the exudates, either free or in phagocytes, along the lymphatic to local lymph nodes where they stimulate an immune response with the generation of antibodies and cellular immune mechanisms of defense.

B. Harmful effects

1- Tissue destruction Inflammation may result in tissue necrosis and the tissue necrosis may, in turn, incite inflammation.

2- Swelling: The swelling caused by inflammation may have serious mechanical effects at certain locations. Examples include acute epiglottitis with interference in breathing; acute meningitis and encephalitis with effects of increased intracranial pressure.

3- Inappropriate response: The inflammatory seen in hypersensitivity reactions is inappropriate (i.e. exaggerated).

Fate of acute inflammation.

Acute inflammation may end up in:

1- Resolution: i.e. complete restitution of normal structure and function of the tissue, eg. lobar pneumonia.

2- Healing by fibrosis (scar formation).

3- Abscess formation However, if it is left untouched, it may result in

- Sinus formation - when an abscess cavity makes contact with only one epithelial lining.

- Fistula formation: when an abscess tract connects two epithelial surface. Or very rarely to septicemia or Pyemia with subsequent metastatic abscess in heart, kidney, brain etc.