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اسم المحاضرة الأولى باللغة الإنكليزية: Inflammation

- INFLAMMATION
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INTRODUCTION

- **Definition:** Inflammation is the response of a living vascularized tissue to harmful agents.
- Inflammation is intended to localize and eliminate the causative agent , to limit tissue injury and to restore tissue to normality or close to normality .

Causes:

Causes of inflammation are apparently causes of diseases such as:

- **physical agents -** mechanical injuries, alteration in temperatures and pressure, radiation injuries.
- **chemical agents-** drugs and toxins.
- **biological agents (infectious)-** bacteria, viruses, fungi, parasites
- **immunologic disorders-** hypersensitivity reactions, autoimmunity, immunodeficiency states
- **genetic/metabolic disorders-** examples gout, diabetes mellitus
- **tissue necrosis-** infarction.

- **Components of inflammation:**
- Plasma fluid proteins, circulating leukocytes, blood vessels, and cellular and extracellular constituents of connective tissues.
- The circulating leukocytes include: neutrophils, monocytes, eosinophils, lymphocytes, basophils, in addition to platelets.
- The connective tissue cells are: mast cells, fibroblasts, macrophages, and lymphocytes.

- The extracellular matrix consists of : - Structural proteins (collagen, elastin), -Adhesive glycoproteins (fibronectin, laminin), -Proteoglycans.

- The typical inflammatory reaction develops through a series of sequential steps:

1• The offending agent, which is located in extravascular tissues, is recognized by host cells and molecules.
2• Leukocytes and plasma proteins are recruited from the circulation to the site where the offending agent is located.
3• The leukocytes and proteins are activated and work together to destroy and eliminate the offending substance.
4• The reaction is controlled and terminated.
5• The damaged tissue is repaired

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 examples pneumonia, typhoid fever, etc….

Classification:

- Inflammation is classified crudely based on duration of the lesion and histologic appearances into acute and chronic inflammation.
- TYPES OF INFLAMMATION
- I. ACUTE INFLAMMATION
- - Sudden onset (minutes or hours).
- - Short duration (several hours to few days)
- - Characterized by the exudation of fluid and plasma proteins (edema).
- - The emigration of leukocytes, predominantly neutrophils.

- II. CHRONIC INFLAMMATION:
- Longer duration.
- More tissue destruction.
- Associated histologically with the presence of lymphocytes and macrophages, proliferation of blood vessels and fibrosis.

- May follow acute inflammation or arise de novo.
- Usually causes permanent tissue damage.

- III. SUBACUTE INFLAMMATION:
- - intermediate between acute & chronic inflammation

- IV. GRANULOMATOUS INFLAMMATION
- - specific form of chronic inflammation

- Definitions
- Transudate : A non inflammatory oedema fluid :
- - Oedema in heart failure
- - Low protein content/low specific gravity (< 1020)
- - Low cellular content
- Exudate:
- - Seen in inflammation
- - High protein content and specific gravity (> 1020)
- - High cellular content
- Pus : collection of liquified material .
- - Consists of neutrophils, necrotic debris ,with high protein content
- - High specific gravity (> 1020)

- Abscess: Localized collection of pus caused by suppurative inflammation.

- M/E.: central mass of acidophilic (pinkish) amorphous semi-fluid debris composed of dead tissue cells & dead WBCs (liquifactive necrosis), surrounded by highly vascularized C.T. (granulation tissue), acts as a barrier for further spread.

- Ulcer :

- Loss in the continuity of the lining epithelial surface , i.e local defect or excavation of the surface of the skin , or mucosal surface of GIT, Resp.T, or GUT, produced by sloughing of inflamed necrotic tissue.

ACUTE INFLAMMATION

Events of acute inflammation:

- Acute inflammation is categorized into an early vascular (hyperemia & edema) and a late cellular responses (neutrophilic infiltration).

1) The vascular response: chemical mediators mediate the vascular events of acute inflammation which has the following steps:

- a) **Immediate (transient) vasoconstriction** in seconds due to neurogenic or chemical stimuli.

- b) **Persistent Vasodilatation of arterioles and venules** resulting in increased blood flow.

- **c) Increased vascular permeability** which leads to slowing of blood flow & stasis that is most remarkably seen in the post-capillary venules.

- Protein-rich fluid oozes into extravascular tissues (exudate) . The presence of the exudates clinically appears as swelling.

- The appearance of inflammatory oedema due to increased vascular permeability of microvascular bed is explained on the basis of **Starling's hypothesis**. In normal circumstances, the fluid balance is maintained by two opposing sets of forces:

- i) Force that causes **outward movement** of fluid from microcirculation is *intravascular hydrostatic pressure*

- ii) Force that causes **inward movement** of interstitial fluid into circulation **caused by proteins** is *intravascular colloid osmotic pressure.*

- In inflamed tissues, the endothelial lining of microvasculature becomes more leaky. Consequently, intravascular colloid osmotic pressure decreases resulting in excessive outward flow of fluid and protein into the interstitial compartment which is exudative inflammatory edema.

MECHANISMS OF INCREASED VASCULAR PERMEABILITY.

- In acute inflammation, endothelial layer of microvasculature becomes leaky. This is explained by one or more of the following mechanisms :
- **i) Contraction of endothelial cells**. The endothelial cells develop temporary gaps between them due to their contraction.
- **ii) Retraction of endothelial cells.** In this mechanism, there is structural re-organisation of the cytoskeleton of endothelial cells.
- **iii) Direct injury to endothelial cells.** Direct injury to the endothelium causes cell necrosis and appearance of physical gaps at the sites of detached endothelial cells. It may occur following thermal injury and radiation injury.
- **iv) Endothelial injury mediated by leucocytes.** Adherence of leucocytes to the endothelium at the site of inflammation may result in activation of leucocytes. The activated leucocytes release proteolytic enzymes and toxic oxygen species which may cause endothelial injury and increased vascular leakiness.

2) Cellular response

The cellular response has the following stages:

- A. Margination, rolling, pavementing, & adhesion of leukocytes
- B. Transmigration of leukocytes
- C. Chemotaxis
- D. Phagocytosis
- Normally blood cells including leukocytes in venules are confined to the central (axial) zone and plasma assumes the peripheral zone. As a result of increased vascular permeability , more and more neutrophils accumulate along the endothelial surfaces (peripheral zone).

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

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

- Rolling: rows of leukocytes slowly roll over the endothelial cells lining the vessel wall.
- Pavementing: the appearance of the endothelium being lined by white cells.
- Adhesion of leukocytes with the endothelium is facilitated by cell adhesion molecules such as selectins, immunoglobulins, integrins, etc.

B)Transmigration of leukocytes

- Leukocytes escape from venules and small veins but only occasionally from capillaries. The movement of leukocytes by extending pseudopods through the vascular wall occurs by a process called diapedesis.
- The most important mechanism is via widening of interendothelial junctions after endothelial cells contractions. Leukocytes traverse the basement membrane and escape into the extravascular space.

- In most forms of acute inflammation, neutrophils predominate in the inflammatory infiltrate during the first 6 to 24 hours.
- Then are replaced by monocytes in 24 to 48 hours.
- In viral infections, lymphocytes may be the first cells to arrive.
- In some hypersensitivity reactions and parasitic infestations, eosinophils may be the main cell type.

C) Chemotaxis:

- A unidirectional attraction of leukocytes from vascular channels **towards the site of inflammation** within the tissue space guided by chemical gradients (higher concentration of chemotactic factors , bacteria and cellular debris) is called chemotaxis.
- The most important chemotactic factors for neutrophils are components of the complement system (C5a), bacterial and mitochondrial products of arachidonic acid metabolism such as leukotriene B4 and cytokines (IL-8).

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 (neutrophils), monocytes and tissue macrophages.

Phagocytosis involves three distinct but interrelated steps.

- **1) Recognition and attachment of the particle to be ingested by the leukocytes:**
- Opsonins are certain plasma proteins that enhance recognition and phagocytosis of bacteria.

The three major opsonins are:

- the Fc fragment of the immunoglobulin IgG,
- components of the complement system C3b, and
- the carbohydrate-binding proteins – lectins.

2) Engulfment

Neutrophils send cytoplasmic processes surrounding bacteria , then bacteria internalized within a phagosome, which will be fused with lysosomes forming a phagolysosome and the engulfed particle is exposed to the degradative lysosomal enzymes causing degranulation.

3) Killing or degradation

- The ultimate step in phagocytosis of bacteria is killing and degradation. There are two forms of bacterial killing:

a) Oxygen-independent mechanism:

- This is mediated by the release of granules containing proteolytic enzymes such as defensins, elastases, lysozymes, and cationic proteins.

b) Oxygen-dependent mechanism:

There are two types of oxygen- dependent killing mechanisms:

- **Non-myeloperoxidase dependent:** formation of reactive oxygen species such as hydrogen peroxide (H_2O_2), super oxide (O^-_2) and hydroxyl ion (OH^-). The destructive effects of H_2O_2 in the body are gauged by the action of the glutathione peroxidase and catalase.

- **Myloperoxidase–dependent:** The bactericidal activity of H_2O_2 involves the lysosomal enzyme myeloperoxidase which **is the most efficient bactericidal system in neutrophils**.

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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:

- **Plasma-derived mediators:**

Three enzyme cascades, each composed of series of proteases, the activation of which releases chemical mediators. They are :
1- Coagulation cascade & fibrinolytic system.
Coagulation factors (such as thrombin) or anticoagulant proteins (such as activated protein C) may activate specific cell receptors on mononuclear cells or endothelial cells which may affect cytokine production or inflammatory cell apoptosis.

2- Kinin system. Activated Haegman factor (XII) results in recruitment of four systems: the kinin, the clotting, the fibrinolytic and the complement systems leading to increased vascular permeability, vasodilatation, pain & bronchoconstriction.
3- Complement system.

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

- **b) Cell-derived chemical mediators:**

- a. ready-made within intracellular granules (e.g., histamine in mast cell granules) or

- b. synthesized when needed (e.g., prostaglandins, cytokines) in response to a stimulus.

- The major cellular sources are platelets, neutrophils, monocytes/macrophages, and mast cells.

Cell-derived chemical mediators include:

- 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.
- Effects of mediators
- Vasodilatation
- -Histamine
- - Prostaglandin's (PGE2)
- - Nitric oxide
- Increased Vascular Permeability:
- - Histamine
- - Complement component (C3a , C5a)
- - Bradykinin
- - Leukotrienes C4, D4 ,E4
- - Platelet activating factor

- Chemotaxis, leukocytes activation
- - C5a
- - leukotrienes B4
- -bacterial products
- - chemokines (IL-8)
- Fever
- - IL-21, IL-6, TNFα
- - prostaglandins

- Pain
- - prostaglandins
- - bradykinin
- Tissue damage
- - neutrophils & macrophage lysosomal enzymes
- - oxygen metabolites
- -nitric oxide

- **Cells of inflammation**

There are different morphologic types of acute inflammation:

1) Serous inflammation

- This is characterized by an outpouring of a thin fluid that is derived from either the blood serum or secretion of mesothelial cells lining the peritoneal, pleural, and pericardial cavities. It resolves without reactions.

2) Fibrinous inflammation

- More severe injuries result in greater vascular permeability that ultimately leads to exudation of larger molecules such as fibrinogens through the vascular barrier.
- Fibrinous exudate is characteristic of inflammation in serous body cavities such as the pericardium (butter and bread appearance) and pleura.

Course of fibrinous inflammation include:

- Resolution by fibrinolysis
- Scar formation between parietal and visceral surfaces i.e. the exudates get organized.
- Fibrous strand formation that bridges the pericardial space.

3) Suppurative (Purulent) inflammation

- This type of inflammation is characterized by the production of a large amount of pus.
- Pus is a thick creamy liquid, yellowish or blood stained in colour and composed of:
- A large number of living or dead leukocytes (pus cells)
- Necrotic tissue debris

- Living and dead bacteria
- Edema fluid

There are two types of suppurative inflammation:

A) Abscess formation:

- An abscess is a circumscribed accumulation of pus in a living tissue. It is encapsulated by a so-called pyogenic membrane, which consists of layers of fibrin, inflammatory cells and granulation tissue.

B) Acute diffuse (phlegmonous) inflammation

- This is characterized by diffuse spread of the exudate through tissue spaces. It is caused by virulent bacteria (eg. streptococci) without either localization or marked pus formation. Example: Cellulitis

4) Catarrhal inflammation

- This is a mild and superficial inflammation of the mucous membrane. It is commonly seen in the upper respiratory tract following viral infections where mucous secreting glands are present in large numbers, eg. Rhinitis.

5) Pseudomembranous inflammation

- The basic elements of pseudomembranous inflammation are extensive confluent necrosis of the surface epithelium of an inflamed mucosa and severe acute inflammation of the underlying tissues.
- The fibrinogens in the inflamed tissue coagulate within the necrotic epithelium, and the **fibrinogen, the necrotic epithelium, the neutrophilic polymorphs, red blood cells, bacteria and tissue debris form a false (pseudo) membrane** which forms a white or colored layer over the surface of inflamed mucosa.
- Pseudomembranous inflammation is exemplified by Dipthetric infection of the pharynx or larynx and Clostridium difficile infection in the large bowel following certain antibiotic use.

Effects of acute inflammation:

A. Beneficial effects

- **1. Dilution of toxins:** 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: which** 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. 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.
- **5. Promotion of immunity:** Micro-organisms and their toxins are carried by the exudates along the lymphatics to local lymph nodes where they stimulate an immune response with the generation of antibodies and cellular immune mechanisms of defense.

B. Harmful effects

- **Tissue destruction:** Inflammation may result in tissue necrosis and the tissue necrosis may, in turn, incite inflammation.
- **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.
- **Inappropriate response:** The inflammatory response seen in hypersensitivity reactions is inappropriate (i.e. exaggerated).

Outcome of acute inflammation

Acute inflammation may end up in:

- **1. Resolution:** i.e. complete restitution of normal structure and function of the tissue, example: lobar pneumonia.
- **2. Healing by fibrosis** (scar formation).
- **3. Abscess formation** {Surgical law states you should drain all abscesses.} 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.