Acute Inflammation

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What is Inflammation?

- A reaction of a living tissue & its micro-circulation to a pathogenic insult.
- A defense mechanism for survival.
- Designated with ‘itis’
  - Ex: appendicitis
Inflammation

- Tissue reaction to injury
- Definition - *a protective response involving host cells, blood vessels, and proteins and other mediators that is intended to eliminate the initial cause of cell injury, as well as the necrotic cells and tissues resulting from the original insult, and to initiate the process of repair.*

https://www.inkling.com/read/robbins-basic-pathology-kumar-abbas-aster-9th/chapter-2/overview-of-inflammation-and
Inflammatory Response

- Complex response that involves:
  - circulatory (hemo-dyanamic) changes
  - changes in vessel wall permeability
  - response of white blood cells
  - release of soluble mediators
Protective Role of inflammation

- Although inflammation is a necessary process, it must be controlled.
- It serves to inform the individual that an area has been injured.
- It restricts function to prevent further injury to the area.
- Preparation for the healing process
- Means of removal or destruction of the offending agent
Types of inflammation

- **Acute inflammation** –
  - rapid in onset and of short duration, lasting from a few minutes to as long as a few days, and is characterized by fluid and plasma protein exudation and a predominantly neutrophilic leukocyte accumulation.

- **Chronic inflammation** — more insidious, is of longer duration (days to years), and is typified by influx of lymphocytes and macrophages with associated vascular proliferation and fibrosis (scarring).
Acute inflammation

Definitions

- rapid tissue response to trauma or any other injurious agent
- the local tissue response of living tissue to injury
- the reaction of vascular tissue and other supportive elements of a tissue to an injury which results in formation of an exudates
Causes

Causes of acute inflammation

- Mechanical trauma – abrasions, lacerations, cut injuries
- Chemical injury
- Radiation injury – (UV, α, β, γ, X rays)
- Extreme temperatures (heat, cold)
- Injury associated with necrosis
- Infections
- Immunological injury – hypersensitivity
Final Outcome of acute inflammation

- Final outcome will depend on
  - type of injurious agent
  - extent of damage imparted by the agent
  - type of tissue involved
  - genetic make up of the individual and etc.

- Final outcome may be *Resolution, Chronic inflammation* or *Scarring*
Injury

Acute inflammation

Chronic inflammation

Resolution

Repair

Abscess
Presentation

1. **Clinical presentation - cardinal signs**

   Redness and heat - due to increased blood flow to the inflamed site
   
   - Swelling - caused by accumulation of fluid
   
   - Pain - due to release of chemicals that stimulate nerve endings. Pain only happens where the appropriate sensory nerve endings exist in the inflamed area —
     
     e.g. acute pneumonia - no pain unless the inflammation involves the parietal pleura, which has pain-sensitive nerve endings
   
   - Loss of function has multiple causes
Presentation contd..

HYPEREMIA

NORMAL

Arteriole  Venule

HYPEREMIA

erythema

Increased inflow

(e.g., exercise, inflammation)
Cardinal Signs of Inflammation

Latin terms
1. Calor (heat)
2. Rubor (redness)
3. Tumor (swelling)
4. Dolor (pain)
5. Loss of function
Presentation contd..

Cardinal Signs of Inflammation contd...
2. **Pathological presentation**: vasoconstriction followed by vasodilatation, stasis, hyperemia, accumulation of leukocytes, exudation of fluid, and deposition of fibrin.
Time course

- Acute inflammation: Less than 48 hours
- Chronic inflammation: Greater than 48 hours (weeks, months, years)

Cell type

- Acute inflammation: Neutrophils
- Chronic inflammation: Mononuclear cells (Macrophages, Lymphocytes, Plasma cells).
How Does It Occur?

- The vascular & cellular responses of inflammation are mediated by chemical factors (derived from blood plasma or some cells) & triggered by inflammatory stimulus.

- Tissue injury or death ---> Release mediators
Pathogenesis

1. **Hemodynamic changes**
   - Changes in caliber of blood vessels
   - Changes in the blood flow (redness and warmth)

2. **Increased vascular permeability**
   - Margination and emigration (swelling, pain & loss of function)

3. **Leukocytic Infiltration**
• Integrated chain of events activated by chemical mediators, but perhaps transiently initiated by neurogenic mechanisms.

• There is chronologic overlap among the 3 reactions and they may share common mediator mechanisms.

• However, since the structural and biochemical basis of each of these responses is sufficiently different, they are best discussed separately.
Changes in caliber of blood vessels

1. Initial vasoconstriction
   - First response of arterioles to injury (3-5 secs or mins)
     - mild injury: it disappears within 3-5 seconds.
     - Severe injury: may remain for several minutes.
   - The mechanism of this vasoconstriction is unknown, but is probably neurogenic or adrenergic in origin
   - Due to direct mechanical stimulation of small blood vessels
2. Persistent vasodilatation

- Follows initial vasoconstriction
- Persists for the whole duration of inflammation
- Initially, involves arterioles- result in opening of new capillaries and venular beds in the area.
- Active process
- Mainly chemical mediator mediated and is also contributed by neuronal mechanisms
Increased blood flow contd...

Persistent vasodilation
1. **Turbulent flow - disturbed axial flow**

   - The blood cells especially white cells come in to contact with vessel wall and making adhesions between vessel wall and WBCs.

http://flipper.diff.org/app../items/5845
Changes in blood flow contd..

2. Increased velocity of blood flow –
   • transient (temporary)
   • due to the arteriolar dilatation

3. Increased amount blood flow
   – Initially involves arterioles (see Persistent vasodilatation)
   – Subsequent to vasodilatation, there is increased blood flow to the affected areas (this is the hallmark of the early hemodynamic changes in acute inflammation).
- Persistent
- Dilated capillaries (endothelial cells & basement membrane).
- Blood flow is not effectively regulated
- Results in
  - Adhesion of platelets and WBCs in to the damaged endothelial cells
Changes in vascular permeability

- Hallmark of acute inflammation-increased vascular permeability
- Concomitant with increased blood flow
- Pathogenesis – will happen according to Starling’s law
  - *outward movement*: O.P of interstitial fluid & I.V hydrostatic pressure
  - *inward movement*: O.P of plasma protein & tissue hydrostatic

http://jeffersonnotes.blogspot.com/2012/07/phys-fluids.html
Outcome: retardation of blood flow - Slowing and/or stasis of the blood flow

Disrupts the laminar flow pattern and thereby displace the cellular elements to the periphery of the microvessels.

WBC fall out of the central column of flow and assume positions in contact with the endothelium.
Changes in vascular permeability contd..

Outcomes of changes in vascular permeability

1. **Initial transudation** - in the earliest stages of inflammation, vasodilatation, stasis increased hydrostatic pressure causes transudation of fluid

   - An ultrafiltrate of blood plasma
     - permeability of endothelium is usually normal
     - low protein content (mostly albumin)
However, with the appearance of increased vascular permeability, there is exudation of large amounts of plasma proteins.

2. **Exudate formation** - formation of protein and cell rich extra vascular component produced mainly by inflammation (two components - protein rich fluid and cells)
   - Fluid exudates
   - Cellular exudate
Phases of exudates formation

1. Immediate transient phase
   - Begins: immediately after mild injury,
   - reaches peak: 5 - 10 minutes
   - phase out: within 15 to 30 minutes
   - Affects venules: the site of increased permeability and leakage (the capillaries are not affected).
   - Mediated by Histamine and other mediators
   - Due to contraction of endothelial cells which leads to the formation of intercellular gaps.
A NORMAL VENULE

B VASOACTIVE MEDIATOR-INDUCED INJURY

Immediate Transient Response

Immediate Sustained Response

C DIRECT INJURY TO ENDOTHELium

Delayed Prolonged Response
2. **Immediate prolonged phase**
   - Appears immediately, high peak for several hours and persists for days until the damaged vessels are thrombosed or repaired
   - Associated with severe injury causing direct endothelial cell damage
   - Site of increased permeability and vascular leakage—all levels of the microcirculation (venules, capillaries and arterioles).
   - Mechanism for increased permeability—"direct damage" to the vascular endothelium.
3. Delayed prolonged phase

- Develops 4-24 hrs (latent period) after the trauma lasts for several hours or days depending on form of injury.
- Due to direct injury to the endothelium and chemical mediators.
- Occurs after mild to moderate thermal injury, or x-ray or ultraviolet irradiation, with certain bacterial toxins and in delayed hypersensitivity reaction.
- Mechanism- unknown
Fluid exudates-
Mechanisms of production of fluid exudates
  • Increased vascular permeability to proteins
  • Increased capillary hydrostatic pressure
  • Breakdown of large molecular proteins
  • Increased fluidity of tissue ground substances
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<td>+++</td>
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<tr>
<td>Albumin</td>
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<td>Cells</td>
<td>Lymphocytes</td>
<td>Neutrophils</td>
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Cellular events

1. Cellular recruitment-
   - Emigration of the leukocytes from the circulation and accumulation in the focus of injury
   - Extravasation- The sequence of events of moving leukocytes from the vessel lumen to the interstitial tissue

   I. Margination and rolling along the vessel wall
   II. Firm adhesion to the endothelium
   III. Transmigration between endothelial cells
   IV. Migration in interstitial tissues toward a chemotactic stimulus
2. Activation of the leukocytes- enabling to eliminate the offending agent.

- The principal leukocytes in acute inflammation: neutrophils (polymorphonuclear leukocytes).
Leukocytic Infiltration

Cellular exudate formation

- Basic steps
  1. Adhesion - margination and pavementing and rolling
  2. Emigration
  3. Chemotaxis
  4. Phagocytosis
1. **Adhesion of WBCs to the endothelium**
   - Circulating leukocytes from the central blood flow move toward the endothelial surface.
   - Then, initial temporary adhesions form and later more firm adhesions occur.
   - Margination- Leukocytes localize at outer margin of the blood flow adjacent to the vascular endothelium.
   - Pavementing- Leukocytes line the surface
   - Rolling- Mediated by the action of endothelial P-and E-selectins loosely binding to leukocytes and producing a characteristic rolling movement of the WBCs along with the endothelial surface
**Rolling** - Process of WBC tumbling on the endothelial surface.

- Process involved:
  - Locally produced cytokines and other mediators activate the endothelial cells.
  - They express adhesion molecules to which the leukocytes attach loosely.
  - Then, WBCs bind and detach and start tumbling which leads rolling of WBC.

- The weak and transient interactions involved in rolling are mediated by the *selectin* family of adhesion molecules.
The rolling leukocytes sense changes in the endothelium and initiate firm adhesion to endothelial surfaces.

This adhesion is mediated by integrins expressed on leukocyte cell surfaces.
2. Emigration of white cells
Definition: the active process by which motile leukocytes escape from the blood vessel lumen into the perivascular tissues (neutrophils, basophils, monocytes and lymphocytes all use the same pathway).

Process:
- Adhered white cells produce pseudopodia through the endothelial cells
- Then the rest of the cytoplasm and the nucleus are pushed to the other side
Initially neutrophils are migrated
Later monocytes are migrated
In the tissue monocytes become macrophages
Lymphocytes emigrate later and in specific types of infections (eg, viral)
Emigration of leucocytes is driven by chemokines produced in extravascular tissues, which stimulate movement of the leukocytes toward their chemical gradient.

- Diapedesis- trans-migration of WBCs across the endothelium
MARGINATION
3. Chemotaxis

- Definition: directional movement of leukocytes toward sites of infection or injury along a chemical gradient
- In inflammation the neutrophils and other leucocytes move due to the chemotaxis.
- Chemotaxins or chemotactic agents: The chemical agents involved in chemotaxis
Chemotaxins

- activate the white cells- leukocyte activation
- increase the concentration of Ca inside the cells
- assembly of cytoskeletal contractile elements including actin filaments thus aiding movements
Leukocyte activation

• Stimuli for activation - microbes, products of necrotic cells, and several chemical mediators
• Leukocyte activation results in the enhancement of
  1. *Phagocytosis* of particles
  2. *Intracellular destruction of phagocytosed microbes and dead cells* by substances produced in phagosomes, including reactive oxygen and nitrogen species and lysosomal enzymes
  3. *Liberation of substances that destroy extracellular microbes and dead tissues*, which are similar to the substances produced within phagocytic vesicles.
  4. *Production of mediators*, including arachidonic acid metabolites and cytokines, that amplify the inflammatory reaction, by recruiting and activating more leukocytes
<table>
<thead>
<tr>
<th>Chemotactic agents for</th>
<th>Neutrophils</th>
<th>Eosinophils</th>
<th>Monocytes</th>
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<td>antigen antibody complexes dead tissue fragments complements (C5a) LTB4 (leukotrine B 4) PAF (Platelet activation factor)</td>
<td>Ig E Histamine</td>
<td>C5a PDGF (platelet derived growth factor) TGF β (transformation growth factor) TNF (tumour necrosis factor) peptide regulatory factors</td>
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Leukocyte Activation

4. Phagocytosis

- Engulfment of a cell or cell debris by another cell
- **Opsonisation** - is a process where the organisms are rendered more palatable to the phagocytic cells. The chemicals involved are known as opsonins.
- Eg- the bacteria are opsonized by antibodies before they get phagocytosis by neutrophils and macrophages.
- **Common opsonins** - Immunoglobulins, Complement products, Fibronectin and etc
- Phagocytosis is an energy dependant process - they use anaerobic glycolysis.
- Once phagocytosed the intracellular organisms are killed by forming free radicals.
ROS

- Reactive oxygen species are
  - molecules like hydrogen peroxide
  - ions like the hypochlorite ion
  - radicals like the hydroxyl radical - most reactive among all
  - the superoxide anion which is both ion and radical.
- A radical (also called a "free radical") is a clusters of atoms one of which contains an unpaired electron (shown in red) in its outermost shell of electrons. This is an extremely unstable configuration, and radicals quickly react with other molecules or radicals to achieve the stable configuration of 4 pairs of electrons in their outermost shell (one pair for hydrogen).
• synthesized by dedicated enzymes in phagocytic cells like neutrophils and macrophages
  • NADPH oxidase (in both type of phagocytes)
  • myeloperoxidase (in neutrophils only)
Phagocytosis

(1) recognition and attachment of the particle to the ingesting leukocyte
(2) engulfment, with subsequent formation of a phagocytic vacuole
(3) killing and degradation of the ingested material.
We will see the video
Types of acute inflammation

- Classification (Other Types of Inflammation)
  - Based on Exudate
  - Based on Histological Features
  - Based on Causative Agent
Types of Inflammation Based on Exudate:
1. Suppurative (purulent) inflammation: pus
2. Serous inflammation: effusion
3. Catarrhal inflammation (inflammation of mucous membranes)
4. Fibrinous inflammation: fibrinogen - fibrin
5. Pseudomembranous inflammation: surface necrosis
6. Ulcerative inflammation
Suppurative (purulent) inflammation: pus

- large amount of pus, which consists of neutrophils, dead cells, and fluid.
- Infection/ localized proliferation of pus-forming organisms by pyogenic bacteria such as staphylococci, streptococci, gram–negative bacilli, anaerobes
- Large, localised collections of pus enclosed by surrounding tissues are called abscesses.
Serous inflammation: effusion

- Thin, watery exudate
- Example - blister in second-degree burns, viral pleuritis
- Characterized by the abundant effusion of non-viscous serous fluid, commonly produced by mesothelial cells of serous membranes, but may be derived from blood plasma. Skin blisters exemplify this pattern of inflammation.
Catarrhal inflammation (inflammation of mucous membranes)

- Marked secretion of mucus.
- Infections, eg, rhinitis in common cold (rhinovirus);
Types of acute inflammation

1. Fibrinous inflammation:
   - Resulting large increase in vascular permeability
   - Allows fibrin to pass through the blood vessels.
   - If an appropriate procoagulative stimulus is present, such as cancer cells, a fibrinous exudate is deposited.
   - Commonly seen in serous cavities, where the conversion of fibrinous exudate into a scar can occur between serous membranes, limiting their function.
• Exudate rich in fibrin
• Relatively severe inflammation
• Common with bacterial infections
Pseudomembranous inflammation: surface necrosis

- Bacterial toxins damage mucosal lining, producing a membrane composed of necrotic tissue
- Example — pseudomembranes associated with Corynebacterium diphtheriae produces a toxin causing pseudomembrane formation in the pharynx and trachea.
A greenish-yellow exudate covers most of the mucosal surface.
Ulcerative inflammation:

- Inflammation occurring near an epithelium can result in the necrotic loss of tissue from the surface, exposing lower layers. The subsequent excavation in the epithelium is known as an ulcer.
- Example — Ulcerative colitis
ULCERATIVE
The summary of inflammatory response

Injury

- Transient vasoconstriction
- Arteriolar dilatation

- Pre-capillary sphincters open
- Post-capillary venules dilate and fill with rapidly flowing blood

- Increased blood flow - previously functioning capillaries and inactive capillary beds

Active hyperemia of microvasculature at the site of injury

- Increased permeability of venules and capillaries

- Slowing of blood
- Frictional resistance to flow
- Escape of fluid
- Increase blood viscosity

Stasis
Stasis

Disrupt normal flow

Margination, pavementing, rolling and adhesion

Emigration

Phagocytosis
Sequale of acute inflammation

1. Resolution

- The complete restoration of normal condition of the tissue i.e. structural and functional normalcy after acute inflammation.

- Occurs
  - injury is limited or short-lived
  - no or minimal tissue damage
  - injured tissue is capable of regenerating
Factors aiding the resolution

- minimal cell death and tissue damage
- complete elimination of causative agent
- local conditions favoring the removal of debris and fluid
Before resolution the acute inflammatory response has to be terminated. This involves

- neutralization, decay, or enzymatic degradation of the various chemical mediators
- normalization of vascular permeability
- cessation of leukocyte emigration, with subsequent death (by apoptosis) of extravasated neutrophils.
Basic steps involves in complete resolution

- Solution of fibrin by enzymes (polymorphs and fibrinolysins)
- Removal of excess fluid by blood vessels and lymphatics
- Removal of debris by phagocytotic cells
- Reduction of blood flow and restoration of normal flow

The best example for complete resolution is resolution of pneumococcal lobar pneumonia.
Infection or Injury

Acute inflammation

Resolution
Return to homeostasis

Scar

Chronic inflammation

- Atherosclerosis
- Asthma
- Multiple sclerosis
- Rheumatoid arthritis
- Inflammatory bowel disease
- Obesity
- Cancer
2. **Suppuration**

- Suppuration is the formation of pus, a mixture of living, dying and dead neutrophils and bacteria, cellular debris and sometimes globules of lipid.
- The causative stimulus must be fairly persistent and is virtually always an infective agent, usually pyogenic bacteria (i.e., Staphylococcus aureus, Streptococcus pyogenes, Neisseria species or coliform organisms).
- Once pus begins to accumulate in a tissue, it become surrounded by a 'pyogenic membrane' consisting of emerging capillaries, neutrophils and occasional fibroblasts.
Such a collection of pus is called an abscess, and bacteria within the abscess cavity are relatively inaccessible to antibodies and to antibiotic drugs (thus, for example, acute osteomyelitis, an abscess in the bone marrow cavity, is notoriously difficult to treat).
Abscess formation:

- "A localized collection of pus (suppurative inflammation) appearing in an acute or chronic infection, and associated with tissue destruction, and swelling."
• Site: skin, subcutaneous tissue, internal organs like brain, lung, liver, kidney, ......

• Pathogenesis: the necrotic tissue is surrounded by pyogenic membrane, which is formed by fibrin and help in localize the infection.
Evolution of an abscess

- Bacteria causes tissue damage and necrosis
- Bacteria multiply.
- The polymorphs packed in the central zone and the periphery shows hyperemia and oedema.
- Pus forms in the centre and demarcation of abscess by pyogenic membrane. Pyogenic membrane consists of newly formed capillaries, polymorphs and fibroblasts.
Pus is usually liberated through an epithelial surface and rest of the tissue is healed with a scar.
Pus is discharged in to a blood vessels multiple abscess and septicemia occurs.
Pus may solidify, calcify and later form a calcific nodule
With a partial discharge of pus chronic sinus occurs.
With the discharge in to two epithelial surfaces fistula occurs.
Organization and fibrosis

- Organisation of tissues is their replacement by granulation tissue.
- Organization occurs during acute inflammatory process with
  - when there is an excessive exudation
  - large amounts of fibrin are formed, which cannot be removed completely by fibrinolytic enzymes from the plasma or from neutrophil polymorphs
  - when there is an excessive necrosis (tissue damage)
  - when the local conditions are unfavorable in removing debris
in certain types of tissue (e.g., pleura)

Progression to chronic inflammation

Process

- new capillaries grow into the inert material (inflammatory exudate)
- macrophages migrate into the zone
- fibroblasts proliferate
- fibrosis
3. Chronic inflammation

- If inflammatory the agent is not removed, progress to the chronic stage.
- In addition to organisation of the tissue just described, the character of the cellular exudate changes, with lymphocytes, plasma cells, and macrophages (sometimes including multinucleate giant cells) replacing the neutrophil polymorphs.
Thank you!!