4. Acute inflammation I.

PATHOLOGY OF ACUTE INFLAMMATION

ACUTE INFLAMMATION IN GENERAL
Process by which vascularized tissue reacts to injury

Site of inflammation: extravascular space around vessels of the microcirculation (arterioles, capillaries, venules)

Role of inflammation
• to isolate injury
• to destroy invading microorganisms and inactivate toxins

Nomenclature
The inflammation of a given organ is named using the suffix: -"itis", e.g. meningitis, myocarditis, arthritis. Exceptions: pneumonia, pleurisy

Causes
• Infections: bacteria, viruses, fungi
• Physical injury: trauma, UV-light or other ionising radiation, burns, frostbite
• Irritant and corrosive chemicals
• Necrotic tissue
• Immunologic (hypersensitivity) reactions

Clinicopathologic features
• Sudden onset
• Short duration (lasting for a few days)
• Formation of inflammatory exudate in the extravascular space: a fluid rich in plasma proteins, cellular debris, + neutrophilic granulocytes (if infection is the cause, microorganisms are also present); specific gravity >1020

Outcome
• Repairs completely, e.g., rhinitis
• Heals by connective tissue replacement (fibrosis), e.g., abscess
• Becomes more severe, e.g., serous inflammation turns into purulent
• Progresses to chronic inflammation, e.g., osteomyelitis
• Results in death, e.g., pneumonia in prolonged bed rest

ACUTE INFLAMMATION INDUCED BY BACTERIA
• Many bacteria are harmless except in patients with impaired defences (opportunistic infections)
• Pathogenic (harmful) bacteria cause disease by toxins and enzymes that damage host tissues
• Most pathogenic bacteria are eliminated by neutrophil granulocytes (NGs); immunoglobulins and complement molecules cooperate in the elimination

Cardinal signs formulated by Celsus, the Roman encyclopedist (B.C. 30? – A.C. 38?)
• calor (warmth)
• rubor (redness)
• tumor (swelling)
• dolor (pain)
• loss of function

Gross signs explained by changes occurring at microscopic level
• Warmth and redness. Bacteria multiply in the extravascular space and induce vasodilation in the surrounding arterioles and venules (active hyperemia); NGs arrive at the site of infection
• Local swelling. Vasospasms of venules occurs, increased permeability of capillaries develops and protein-rich extravascular fluid is formed
• Pain and loss of function. NGs emigrate from the capillaries and venules, phagocytose and kill bacteria, and mediate tissue damage

Basis of increased capillary permeability
• Endothelial contraction or swelling ⇒ opening of interendothelial gaps (vessel injury: not present). Mediators: histamine; C3a, C5a; leukotriene-C4, -D4, -E4; PAF
• Necrosis/fragmentation of microvascular endothelial cell (vessel injury: present). Mediated by endothelium-adhered NGs in Gram-negative bacterial infection

Events of emigration of neutrophils
• Slowing of the circulation: stasis. Leakage of protein-rich fluid into the extravascular tissue induce concentration of RBCs and increased viscosity of blood
• Peripheral orientation of NGs along the venules, a process called margination and rolling, culminating in the adhesion of NGs to the endothelium
• NGs insert pseudopods into the interendothelial junctions and traverse through the vessel wall (emigration)

NG-endothelial cell interactions
• IL-1, TNF released from NGs activate endothelial cells to express adhesion molecules (VCAM, ICAM-1, P-selectin).
• These adhesion molecules bind to the integrin molecules present on the surface of NGs ⇒ the NGs bind to the endothelial cells. PECAM-1 expression by NGs and endothelial layers is the starting event of transmigration.

Neutrophils in the extracapillary space

1
4. Acute inflammation I.

- NGs emigrate toward the site of bacteria (chemotaxis)
- Phagocytosis: incorporation and killing of bacteria; degradation of the ingested material
- During phagocytosis, extracellular release of toxic substances ⇒ tissue damage

**Recognition of microbes**
With receptors for opsonins, toll-like receptors, etc.
Opsonisation enhances phagocytosis
1) Previous infection ⇒ formation of bacterium-specific IgG (opsonin)
2) Reexposure. Bacteria become coated with specific IgG and complement
3) The Fc-R and C3b-R receptors on NGs bind to the bacteria coated with IgG and complement

markedly enhanced incorporation of bacteria and clearance from the bloodstream/tissue sites

**Killing of microbes**
- The bacterium is engulfed into a phagosome. In turn, the phagosome fuses with the primary lysosome and phagolysosome is formed
- Lysosomal myeloperoxidase produces hypochlorous acid radical, which kills bacteria in phagolysosomes
- The killed bacteria undergo digestion

**Tissue damage by extracellular release of toxic substances during phagocytosis**
- Lysosomal proteases: elastase, collagenase
- Toxic free O-radicals (HO, H₂O₂, HOCl)

Anti-proteases check neutral proteases in the serum and tissue fluid
- α-1-antitripsin inhibits neutrophil elastase
- α-1-antitripsin-deficiency (autosomal recessive): pulmonary emphysema and liver cirrhosis

**Cessation of inflammation**
- Phagocytosis and killing of bacteria by neutrophils
- Phagocytosis of debris by macrophages, delivery to regional lymph nodes
- Fibrinolysis
- Disappearance of vascular dilation
- Regeneration of necrotized tissue or replacement with newly formed connective tissue (fibrosis)

**BACTERIA IN THE BLOOD**
Bacteria may enter into the bloodstream from sites of infection

**Bacteremia**
- Following dental surgery, endoscopy of the urinary tract, GI tract, etc.)
- The number of organisms per ml is low
- Usually no symptoms because neutrophils rapidly eliminate bacteria

**Septicemia**
- The bacteria multiply in the blood and cause severe toxemia
- Frequently lethal

**Systemic inflammatory response sy (SIRS)**
An acute phase response to cytokines (TNF, IL-1, IL-6) triggered either by bacterial endotoxin or other inflammatory stimuli: trauma, burns or acute pancreatitis

**Clinical symptoms and laboratory signs**
- Fever (rectal temp. >38.3°C) or hypothermia (< 36°C)
- Tachycardia (heart rate > 90/min)
- Tachypnea (respiratory rate >30/min or hypocapnia [PaCO₂ < 32 mmHg])
- Granulocytosis (WBC >12000/µl) or granulopenia (WBC < 4,000/µl)

**Sepsis**
A clinical sy defined by the presence of both infection and symptoms of SIRS.
In severe sepsis, the cytokine level is high and results in:
- Systemic vasodilation (decreasing blood pressure)
- Diminished myocardial contractility
- Widespread endothelial injury and activation, with granulocyte adhesion and pulmonary alveolar capillary damage
- Thrombocytopenia

**Septic shock:** the patients have arterial hypotension (systolic BP < 90 mmHg) despite adequate fluid resuscitation

**Consequences of generalized hypoperfusion: multigorgan failure**
- Lactate acidosis
- Pulmonary damage (ARDS) ⇒ arterial hypoxemia
- Acute tubular necrosis of kidneys ⇒ oliguria
- CNS: loss of conciousness
- Paralytic ileus (absent bowel sounds)
- Liver injury (plasma total bilirubin > 70 mmol/l)

Septic shock has a high mortality (25-50%)
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**Defects in neutrophil granulocyte function** (endothelial adherence, phagolysosome formation, and killing)
- Genetic or acquired defects lead to an increased susceptibility to bacterial infections
- Acquired defects in diabetes, immunodeficiencies, hemodialysis (pathomechanism is not entirely clear); leukemia
- Chemotherapy, certain drugs, radioactive ionization suppress the granulopoiesis in the bone marrow: first neutropenia: \(<1000/\text{mm}^3\), then agranulocytosis: \(<200/\text{mm}^3\) \(\Rightarrow\) lethal bacterial infection within days