Pathophysiology of inflammation

Inflammation

Inflammation is response of higher organisms to pathological factors of physical, chimical or biological nature that induce tissue damage. It developed during evolution. The main mechanisms and principles of inflammation are general. Intensity of involvement of individual factors and particular manifestations differ in details in dependence on provoking cause, intensity, organism reactivity, localization, time course of pathological process etc.

4 local classical manifestations of inflammation were described by a Romanian physician Cornelius Celsus in the 1st century and are known udder their Latin terms:

- **rubor** = redness - due to hyperemia as a consequence of local vasodilation
- **calor** = inflamed area is warmer - caused by hyperemia
- **dolor** = pain - due to acid pH and algogenic substances (inflammatory mediators, substances released form damaged cells)
- **tumor** = swelling - caused by vasodilation and increased permeability of the vessel wall
- **functio laesa** = functional deterioration - tissue damage and/or change of its function

The 5th sign (functio laesa) was added later. According to some resources, the author is Galenos (129 – 201), others mention Virchow in the 19th century.

These signs (mainly 1 – 4) are detectable by on the skin if the inflammation is superficial. In deeper tissues, the changed due to inflammation are analogous but they are not so easy detectable during physical examination of the patient.

Stages of inflammation

1. Stage of alteration

– hyperemia due to dilation of arterioles and overfilling of capillaries by blood, the wall of the capillaries becomes more permeable for non-cellular as well as cellular components of the blood (see the next stage)

2. Stage of exudation and infiltration

– increased blood perfusion with penetration of intranasal fluid and cellular elements into the interstitial

3. Stage of proliferation (reparation)

- it deals namely with the epithelia, endothelial, fibroblasts and their metabolic activity

The aim of proliferation is to reconstruct damaged components of the tissue. Nevertheless, the recovery and reparation is not always complete and functional. The consequence can be, for instance, formation of granulomas. See also wound healing pathophysiology.

Mediators of the inflammation

Injuries of various kinds (mechanical, chemical, thermic) activate the same endogenous substances, that are considered to be mediators of the inflammatory response. That is why there is some general principle of the inflammatory response.

- Among the first ones, vasoactive amines belong **- histamine, serotonin**, source of which are activated mast cells (basophilic granulocytes that travelled rom the blood to the tissues) - **responsible for vascular changes during the first stage.**

- Plasmatic enzymatic systems of immunocompetent cells are a rich source of substances such as: **immunoglobulins, bradykinin** (a peptide, that induces further dilation of vessels and increases permeability of their walls).

- Through the vessel wall, **phagocyting polymorphonuclear leucocytes**, penetrate first and followed by **lymphocytes** producing antibodies and **macrophages**, that initiate specific phase of the inflammation.

- **Arachidonic acid derivate** such as **prostaglandins, thromboxane and leukotrienes** are also important. They have a wide range of vasoactive and chemotactic effects.

  Acetylsalicylic acid and other NSAID (non-steroid anti-inflammatory drugs) suppress their production by inhibition of cyclooxygenase activity. Cyclooxygenase (COX) in an enzyme catalyzing synthesis of these mediators from the arachidonic acid. Because these mediators play also a role in regulation of body temperature (endogenic pyrogenes), mechanisms of nociception, and regulation of platelet aggregation (thromboxane), COX-inhibitors have not only anti-inflammatory effects but also antipyretic, analgesic and anti-aggregative, and in dependence on their COX1/COX2 specificity also negative side effects (e.g. gastric erosions).

Reaction of the organism to inflammation

Inflammation can be local or generalized, systemic (see SIRS). Even in the case of local inflammation, the organism reacts with a general response.

Lymphokines released by lymphocytes and macrophages (e.g. IL 1, 6, prostacyclins and prostaglandins) act on the stress HPA-axis (CNS – CRH – ACTH – corticoids) and transforms this way local inflammation to generalized stress response. Thus, inflammation is a stressor.

Fever is a next general sign of inflammation, that occurs simultaneously with local signs of inflammation. Although fever is caused by many factors, its final pathway is always mediated by release of endogenic pyrogenes (namely from the macrophages and neutrophilic granulocytes). They act in the thermoregulation center in the hypothalamus, where they set a higher temperature level (fever).

Fever is not just a symptom, but also a very effective protective mechanism, that increases the number of peripheral leucocytes, efficiency of phagocytosis, production of antibodies, cytotoxic activity of T-lymphocytes etc.

Reaction of the organism to inflammation

- Inflammatory process also stimulates the bone marrow with a subsequent increase of leukocytes in the blood - leukocytosis (15 000 - 25 000 leukocytes / 1 µl).

- Plasmatic protein spectrum is also changed, including appearance of new proteins such as CRP (C-reactive protein). Immunoglobulin level increases. Erythrocyte sedimentation is accelerated (changes suspension stability of the blood).

- Also levels of some metals are changed in the blood. E.g. higher Cu level, lower Zn and Fe.

- Local inflammation is also often accompanied with unspecific sings such as restlessness, anorexia, reduction of physical and mental fitness.

- Some of these manifestations and related to blood and endocrine changes, but some remain unclear.

Systemic inflammatory response syndrome = SIRS

- In the case of SIRS, there is no infection focus in the body. Provoking factor is more generalized. If infectious focus is found it is not SIRS but sepsis.

SIRS

- high levels of mediators in the blood
- activation of the endothelia together with macrophages and neutrophils in the whole system
- generalized endothelial dysfunction

The cause can be a severe trauma, acute pancreatitis or a state after a circulatory shock.
Deregulated systemic inflammation induces negative hemodynamic changes:

- systemic vasodilation
- myocardial depression
- affection of microcirculation with transfer of fluid into the interstitium and subsequent interstitial edema
- formation of microthrombi

Clinical signs of SIRS

- body temperature higher than 38 °C or less than 36 °C
- heart frequency less than 90 beats/min
- respiratory frequency more than 20/min
- number of leukocytes more than 12 000/µl or less than 4 000/µl of the blood

Sepsis

= SIRS due to infectious causes

Hemodynamic changes during sepsis are the same like in SIRS.

Bacteremia = presence of living bacteria in the blood

Sepsis can also develop form a focal infection, that can be often in the oral cavity!

Septic shock
= a circulatory shock caused by sepsis
- It is a distribution type of shock - see pathophysiology of the cardiovascular system.

The end