الكلية: الطب

القسم او الفرع: الامراض والطب العدلي

المرحلة: الثالثة

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اسم المادة باللغة العربية: الامراض

اسم المادة باللغة الإنكليزية: Pathology

اسم المحاضرة الأولى باللغة العربية: الالتهاب المُزمن

اسم المحاضرة الأولى باللغة الإنكليزية: Chronic inflammation

CHRONIC INFLAMMATION

Definition: Chronic inflammation can be defined as a prolonged inflammatory process (weeks or months) where an active inflammation, tissue destruction and attempts at repair are proceeding simultaneously.

It is characterized by infiltration with mononuclear cells including lymphocytes, plasma cells and macrophages and marked by formation of new connective tissue.

Causes of chronic inflammation:

1. Persistent infections

- such as tuberculosis, leprosy, certain fungi etc characteristically cause chronic inflammation. These organisms are of low toxicity and evoke delayed hypersensitivity reactions.

2. Prolonged exposure to potentially toxic agents, either exogenous or endogenous. Endogenous (cholesterol and other lipids which result in atherosclerosis) or exogenous substances such as silica, asbestos.

3. Progression from acute inflammation: Acute to chronic transition occurs when the acute inflammatory response cannot be resolved, as a result of either:

**persistence of the injurious agent

- Or :

**interference with the normal process of healing (foreign body, sinus/fistula) .

4. Hypersensitivity and Autoimmuniy: such as bronchial asthma, rheumatoid arthritis and systemic lupus erythematosis. Such diseases may show morphologic patterns of mixed acute and chronic inflammation because they are characterized by repeated bouts of inflammation. Fibrosis may dominate the late stages.

- Chronic cholecystitis with cholelithiasis
- Morphologic Features of chronic inflammation

1. Infiltration with mononuclear cells, which include macrophages, lymphocytes, and plasma cells.
2. Tissue destruction, induced by the persistent offending agent or by the inflammatory cells .
3. Attempts at healing by connective tissue replacement of damaged tissue, accomplished by angiogenesis (proliferation of small blood vessels) and fibrosis.

Cells of chronic inflammation:

- **Monocytes and Macrophages are the primary cells in chronic inflammation.** Macrophages are professional phagocytes that act as filters for particulate matter, microbes, and senescent cells. Macrophages arise from the common precursor cells in the bone marrow, which give rise to blood monocytes. From the blood, monocytes migrate into various tissues and differentiate into macrophages (in the liver (Kupffer cells), spleen, lymph nodes (sinus histiocytes), lungs (alveolar macrophages), bone marrow, brain (microglia), skin(Langerhan's cells), etc.…
- These cells constitute the mononuclear- phagocytic system.
- The half-life of blood monocytes is about 1 day, whereas the life span of tissue macrophages is several months or years.

- There are two major pathways of macrophage activation, called classical and alternative . Which of these two pathways is taken by a given macrophage depends on the nature of the activating signals.
- Classical macrophage activation may be induced by microbial products such as endotoxin, and by T cell–derived signals, importantly the cytokine IFN-γ.
- Alternative macrophage activation is induced by cytokines other than IFN-γ, such as IL-4 and IL-13, produced by T lymphocytes and other cells.
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The products of activated macrophages causes:

1.Elimination of injurious agents such as microbes.

2.Active inflammation and tissue destruction:

- ❖ Reactive oxygen and nitrogen species are toxic to microbes
- ❖ Proteases cause destruction of extracellular matrix .
- ❖ Cytokines and chemotactic factors cause influx of other cell types.

3.Repair:

Growth factors (FGF, VEGF) cause fibroblast proliferation and angiogenesis .

- Functions of macrophages in chronic inflammation:
- 1. Macrophages secrete mediators of inflammation, such as cytokines (TNF, IL-1, chemokines, and others) and eicosanoids (prostaglandins and leukotreins). Thus, macrophages are central to the initiation and propagation of inflammatory reactions.
- 2. Macrophages display antigens to T lymphocytes and respond to signals from T cells, thus setting up a feed back loop that is essential for defense against many microbes by cell-mediated immune responses.
- **chemokines=chemotactic factors.

Other cells in chronic inflammation:

1. **T-Lymphocytes** are primarily involved in cellular immunity with lymphokine production, and they are the key regulator and effector cells of the immune system.
   - They interact with macrophages in a bidirectional way:
   - Macrophages secrete cytokines (IL-12) that activate T-lymphocytes.
   - Activated T lymphocytes produce cytokines (lymphokines), which recruit monocytes from the circulation and activate macrophages.
2. **Plasma cells develop from activated B-lymphocytes** produce antibodies.
3. **Mast cells and eosinophils** appear predominantly in response to parasitic infestations & allergic reactions (type 1 hypersensitivity reaction).

** lymphokines=cytokines produced by lymphocytes.

Classification of chronic inflammation:

- Chronic inflammation can be classified into the following two types based on histologic features:
- **1) Nonspecific chronic inflammation:** This involves a diffuse accumulation of macrophages and lymphocytes at site of injury that is usually productive with new fibrous tissue formation. E.g. chronic cholecystitis.

2) Specific inflammation (granulomatous inflammation):

- **Definition:** Granulomatous inflammation is a distinctive pattern of chronic inflammation characterized by the presence of granuloma. A granuloma is a microscopic aggregate of epithelioid cells. Epithelioid cell is an activated macrophage, with a modified epithelial cell-like appearance. The epithelioid cells have a pale pink granular cytoplasm with indistinct cell borders and a vesicular nucleus that is oval or elongated. The epithelioid cells can fuse with each other & form multinucleated giant cells. The granuloma is usually surrounded by a cuff of lymphocytes and occasional plasma cells.

There are two types of giant cells:

- **a. Foreign body-type giant cells** which have irregularly scattered nuclei in presence of indigestible materials.
- **b. Langhans giant cells** in which the nuclei are arranged peripherally in a horse –shoe pattern which is seen typically in tuberculosis, sarcoidosis etc…

Causes:

Major causes of granulomatous inflammation include:

- **Bacteria:** Tuberculosis, Leprosy, Syphilis
- **Fungi:** Aspergillus, Cryptococcus, Candida
- **Parasites :** Schistosomiasis (bilhariziasis), Leishmaniasis, Toxoplasmosis
- **Inorganic material:** silicosis
- **Idiopathic:** Crohn's disease, sarcoidosis
- **Foreign body:** talc , suture , wood

Pathogenesis:

- There are two types of granulomas, which differ in their pathogenesis.

A. Foreign body granuloma

- These granulomas are initiated by inert foreign bodies such as talc(associated with intravenous drug abuse), sutures (non-absorbable), fibers, etc… that are large enough to prevent phagocytosis by a single macrophage and do not incite an immune response. The foreign material

can usually be identified in the center of the granuloma, particularly if viewed with polarized light, in which it appears refractile

B. Immune granulomas

- These are caused by insoluble, poorly degradable or particulate particles, typically microbes that are capable of inducing a persistent T cell mediated immune response.
- This type of immune response produces granulomas usually when the inciting agent cannot be readily eliminated, such as a persistent microbe or a self antigen.
- In such responses, macrophages activate T cells to produce cytokines, such as IL-2, which activates other T cells, perpetuating the response, and IFN-γ, which activates the macrophages and transforms them into epithelioid cells and multinucleate giant cells.

Tuberculosis

- The typical example of an immune granuloma is that caused M. tuberculosis.
- In tuberculosis, the granulomatous reaction is referred to as a tubercle and is classically characterized by the presence of central caseous necrosis (Grossly,has a granular, cheesy appearance. Microscopically, this necrotic material appears as amorphous, structureless, eosinophilic, granular debris, with loss of cellular details) whereas caseation is rare in other granulomatous diseases

Multinucleated GC
Epithelioid cells
Caseation
Lymphocytes
fibroblasts

- TB bacilli are engulfed by macrophages ,inducing immune response resulting in transformation of macrophages into epithelioid cells and T-lymphocyte infiltration.

- The diagnosis of tuberculosis should be confirmed by using special stains (acid-fast stains or called Zeil –Nelson stain) , by culture and by molecular techniques (PCR).
- Pulmonary tuberculosis spread by inhalation of droplets containing Mycobacterium tuberculosis (tubercle bacilli).
- The non-pulmonary form is caused by ingestion of infected cow milk.
- The granulomas in Crohn disease, sarcoidosis, and foreign body reactions tend to not have necrotic centers and are said to be noncaseating.
- Sarcoidosis is a granulomatous inflammatory disease which affects many tissues, including lymphoid tissue. The etiologic agent is unknown and the diagnosis is that of exclusion.
- Healing of granulomas is accompanied by fibrosis that may be extensive.

SYSTEMIC EFFECTS OF INFLAMMATION

Inflammation, even if it is localized, is associated with cytokine-induced systemic reactions that are collectively called the acute-phase response. The systemic effects of inflammation include:

1.Fever

- Fever (elevation of body temperature, usually by 1° to 4°C) is the most important systemic manifestation of inflammation. It is caused by prostaglandins (especially PGE_2) that are produced in the vascular and perivascular cells of the hypothalamus. Cytokines (IL -1, IL-6, TNF-α) released from macrophages and other cells increase the enzymes (cyclooxygenases) that convert arachadonic acid into prostaglandins.

2. Acute-phase proteins

- Are plasma proteins, synthesized in the liver, their concentrations increase several hundred-fold as part of the response to inflammatory stimuli. Best-known of these proteins are C-reactive protein (CRP),fibrinogen and Serum Amyloid A (SAA).

- Synthesis of these molecules in hepatocytes is stimulated by cytokines.
- CRP and SAA, bind to microbial cell walls, and they may act as opsonins.
- Fibrinogen binds to erythrocytes and causes them to form stacks (rouleaux) that sediment more rapidly at unit gravity than do individual erythrocytes. This is the basis for measuring the *erythrocyte sedimentation rate (ESR)* as a simple test for an inflammatory response.
- Another peptide whose production is increased in the acute-phase response is the iron-regulating peptide hepcidin. Chronically elevated plasma concentrations of hepcidin reduce the availability of iron and are responsible for the anemia associated with chronic inflammation.

- **3. Leucocytosis** is also a common feature of inflammation, especially in bacterial infections. The leukocyte count usually climbs to 15,000 or 20,000 cells/μL.
- The leukocytosis occurs initially because of accelerated release of cells from the bone marrow postmitotic reserve pool (caused by cytokines, including TNF and IL-1) and is therefore associated with a rise in the number of more immature neutrophils in the blood.
- Most bacterial infections induce neutrophilia. Some viral infections such as infectious mononucleosis, & mumps cause lymphocytosis. Parasitic infestations & allergic reactions such as bronchial asthma & hay fever induce eosinophilia.
- Certain infections (typhoid fever and infections caused by some viruses, rickettsiae, and certain protozoa) are associated with a decreased number of circulating white cells (leukopenia), likely because of cytokine-induced sequestration of lymphocytes in lymph nodes.

4. Other manifestations

- Increased heart rate and blood pressure; decreased sweating, mainly because of redirection of blood flow from cutaneous to deep vascular beds, to minimize heat loss through the skin; rigors (shivering), chills (search for warmth), anorexia and malaise, probably because of the actions of cytokines on brain cells.

5. Weight loss

- Due to the action of IL-1 and TNF-α which increase catabolism in skeletal muscle, adipose tissue and the liver with resultant negative nitrogen balance.

6. Septic shock

- In some sever infections: Fall in blood pressure, disseminated intravascular coagulation, metabolic abnormalities including insulin resistance and hyperglycemia; induced by high levels of TNF and other cytokines (IL1).

- C-Reactive Protein (CRP)
- CRP is a member of the class of acute phase reactants as its levels rise dramatically during inflammatory processes occurring in the body.
- It is thought to assist in complement binding to foreign and damaged cells and affect the humoral response to disease.
- It is also believed to play an important role in innate immunity, as an early defense system against infections.
- Elevated serum levels of CRP serve as a marker for increased risk of myocardial infarction in patients with coronary artery disease. Inflammation involving atherosclerotic plaques in the coronary arteries predisposes to thrombosis and subsequent infarction.

- CONSEQUENCES OF DEFECTIVE OR EXCESSIVE INFLAMMATION
- Defective inflammation typically results in

1. Increased susceptibility to infections
2. Delayed healing or repair of wounds
3. Tissue damage

- Excessive inflammation is the basis of many categories of human disease that include allergies and autoimmune diseases.