Inflammation

Part II
Inflammatory phases:

- **Alteration** – damage (dystrophy and necrosis)
- **Exudation** – the reaction of microcirculation, formation of liquid exudate, migration of leukocytes and phagocytosis
- **Proliferation** - proliferation of cell of hematogenous (macrophages, lymphocytes) and histiogenous (fibroblasts) nature
The classification of inflammation

• According to the predominant phase:
  – alterative,
  – exudative,
  – proliferative (productive)

• According to the causative factors:
  – trivial,
  – specific
In contrast to exudative inflammation, which is distinguished by vascular changes, edema, and a largely neutrophilic infiltrate, productive inflammation is characterized by the following:

- Infiltration with mononuclear ("chronic inflammatory") cells, including macrophages, lymphocytes, and plasma cells
- Tissue destruction, largely directed by the inflammatory cells
- Repair, involving new vessel proliferation (angiogenesis) and fibrosis
INJURY
- Infarction
- Bacterial infections
- Toxins
- Trauma

ACUTE INFLAMMATION
- Vascular changes
- Neutrophil recruitment
- Mediators

Progression

RESOLUTION
- Clearance of injurious stimuli
- Clearance of mediators and acute inflammatory cells
- Replacement of injured cells
- Normal function

ABSCESSESS
- Healing

INJURY
- Viral infections
- Chronic infections
- Persistent injury
- Autoimmune diseases

CHRONIC INFLAMMATION
- Angiogenesis
- Mononuclear cell infiltrate
- Fibrosis (scar)

Healing

SCAR
- Dense fibrosis
- Loss of function

Healing

REGENERATION
- Clearance of injurious stimuli
- Clearance of mediators and chronic inflammatory cells
- Regeneration and remodeling of damaged tissue
- Normal function

Healing

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Three characteristic histologic features of chronic inflammation:
(1) collection of chronic inflammatory cells (*);
(2) destruction of parenchyma (normal alveoli are replaced by spaces lined by cuboidal epithelium [arrowheads]);
(3) replacement by connective tissue (fibrosis) (arrows).
Causes of productive inflammation

- **Viral infections.**
  - Intracellular infections of any kind typically require lymphocytes (and macrophages) to identify and eradicate infected cells.

- **Persistent microbial infections**
  - *Mycobacteria tuberculosis,*
  - *Treponema pallidum* (causative organism of syphilis),
  - certain fungi.

  These organisms are of low direct pathogenicity, but typically they evoke an immune response called delayed hypersensitivity, which may culminate in a granulomatous reaction.

- **Prolonged exposure to potentially toxic agents.**
  - nondegradable exogenous material such as inhaled particulate silica – chronic inflammatory response in the lungs (silicosis)

- **Autoimmune diseases,**
  - an immune response to self-antigens and tissues. Because the responsible antigens are in most instances constantly renewed, a self-perpetuating immune reaction results (e.g., rheumatoid arthritis or multiple sclerosis).
Outcomes

- Fibrosis
- Sclerosis
- Cirrhosis
- Chronic organ insufficiency
Types of productive inflammation

- Interstitial
- Inflammation with the formation of polyps and pointed condylomas
- Inflammation around parasites and foreign bodies
- Granulomatous inflammation
Granulomatous Inflammations

*General definition:* productive inflammation whose primary characteristic is large nodule of inflammatory cells of the macrophage system, often measuring several millimeters.

The focal concentration of cells of the macrophage system involved in forming the granuloma (macrophages, epithelioid cells, and multinucleated giant cells) varies among individual inflammations. As a result, a granuloma may be sharply demarcated or diffuse and ill-defined.
Classification of granulomas

I. Etiology:
   a) infectious (associated with bacteria, viruses, etc.),
   b) non-infectious (around foreign objects - particles of organic and inorganic dusts),
   c) of unknown etiology (sarcoidosis, Crohn's disease, etc.)

II. Pathogenesis:
   a) immune (usually reflect the reaction of delayed-type hypersensitivity - interaction of macrophages with T-lymphocytes),
   b) non-immune (mostly built of giant cells of foreign bodies, few of lymphocytes and plasma cell ), c) hypersensitive.

III. Morphology:
   immature (macrophage)
   mature (epithelial, giant-cell) with necrosis or without.
Granuloma Cells

• *Macrophages*  
  – can transform themselves into epithelioid cells

• *Epithelioid cells*  
  – have lost important membrane receptors for phagocytosis. However, their cytoplasm has entirely adapted to the secretion of proteases and cytokines.

• *Multinucleated giant* cells  
  – are created by macrophages and epithelioid cells that fuse to form a syncytium.
Multinucleated giant cells

Two types of giants cells occurring in granulomas may be distinguished according to their morphogenesis.

— **Foreign-body giant cells:**
unorganized giant cells have nuclei that are irregularly distributed throughout the cytoplasm.

— **Langhans giant cells:**
organized giant cells exhibit a ring-like or wreath-like configuration of nuclei in the periphery of the cell.
Types of granulomas

- Epithelioid granulomas
  - Sarcoidal granulomas
  - Tubercular granulomas
  - Pseudotubercular granulomas

- Histiocytic granulomas
  - Rheumatic granuloma
  - Rheumatoid granuloma
  - Foreign-body granuloma
Epithelioid granulomas

**Definition:** Sharply demarcated nodules consisting largely of densely grouped, specialized macrophages (epithelioid cells).

Types:

- *Sarcoidal granulomas*
- *Tubercular granulomas*
- *Pseudotubercular granulomas*
**Sarcoidal granulomas**

**Definition:** Small granulomas of epithelioid cells (noncaseating epithelioid granulomas) without central necrosis (caseation) and with an outer layer of collagen fibers and a tendency toward centripetal fibrosis.

**Examples:**
- Sarcoidosis.
- Crohn’s disease.
Abb. 13.11. Nichtnekrotische Epitheloidzellgranulome (Pfeil) bei Sarkoidose (Vergr. 50, HE)
Crohn’s disease (granuloma)
(HE) x 100
Tubercular granulomas

**Definition:** Large circumscribed granulomas consisting of epithelioid cells with central caseous necrosis and an outer layer of lymphocytic cells.

Examples:
- Tuberculosis
- Leprosy
- Syphilis
Take-home-message

• The granuloma in tuberculosis is referred to as a **tubercle**. It lacks a central blood vessel and has peripheral lymphocytes.

• The granuloma in syphilis is referred to as a **gumma**. It contains central blood vessels and peripheral plasma cells.
Abb. 13.12. Nekrotisches Epitheloidzellgranulum vom Tuberkulose-
typ mit zentral verkäsender Nekrose (VN) und mehrkernigen Riesenzellen (RZ) in der Lunge (Vergr. 50, HE)
Pseudotuberculous Granuloma

Definition: Often ill-defined granulomas consisting of macrophages and epithelioid cells with central necrosis with granulocytes.

Examples:
- glanders (syn: equinia, farcy, or malleus)
Histiocytic Granulomas

**Definition:** ill-defined nodular accumulations of primarily phagocytic histiocytes (foreign-body granuloma).

Histiocytic granulomas include:
- Rheumatic granuloma;
- Rheumatoid granuloma;
- Foreign-body granuloma.
Rheumatic Granuloma

**Synonym:** Aschoff’s lesion.

**Definition:** Histiocytic granuloma around a core of fibrinoid collagen necrosis, occurring primarily in the myocardium and only with rheumatic fever.
Rheumatoid Granuloma

**Definition:** Histiocytic granuloma around a core of fibrinoid collagen necrosis, often occurring at multiple locations in the subcutaneous tissue and in articular nodules in rheumatoid arthritis.
Rheumatoid arthritis
Foreign-Body Granuloma

**Definition:** Histiocytic granuloma surrounding material that the body can break down only with difficulty or not at all and that has lodged in or been released into tissue.
Specific inflammation

- Specific inflammation is a kind of inflammation, in which by morphology of granulomas or granulomatous tissue can be established etiology of disease without observing the pathogen.

- Tuberculosis, syphilis, scleroma, leprosy
Common signs of specific inflammation

1. Granulomas have a specific structure to each agent
2. Long and fluctuating course
3. Tendency to progression
4. Characterized by the appearance of necrosis, more often a caseous one
5. Presence of a specific pathogen in granulomas
Inflammation in tuberculosis.

Types of tubercles

By the nature of inflammation:

- **Alterative** (necrotic): caseous necrosis in the center, on periphery small amount of leukocytes and lymphocytes
- **Exudative**: caseous necrosis in the center, on periphery – lymphocytes
- **Productive**: epithelioid cell, giant-cell, mixed, granuloma.
Tuberculosis granuloma (tubercle)

In the center - caseous necrosis surrounded by epithelioid cells among which multinucleated Langhans giant cells are seen. Lymphocytes are on the periphery granuloma.

No blood vessels.

Fibers - argyrophilic in the stroma.

Outcomes: scarring, petrification could be ossification.
SCLEROMA

• **Etiological agent**
  – Gram-negative diplobacillus (Volkovych – Frisch bacillus) – Klebsiella scleromatis

• **Localization**
  – mucosa of the upper respiratory tract (nose, larynx, trachea)

• **Stages:**
  1. Serous inflammation
  2. Granulation tissue
SCLEROMA

Structure of granulation tissue: macrophages, lymphocytes, large cells with pale cytoplasm (Mikulicz cells), hyaline balls or Russell bodies, plasmocytes, vessels of all sizes.

Caseous necrosis is absent.
Fibres: argyrophilic and collagen, scar tissue with metaplasia in cartilaginous and bone tissue.
Outcomes – sclerosis, hyalinosis
Syphilis

- Etiology: Treponema pallidum
- **Syphilitic granuloma (gumma) and infiltration**—typical for **tertiary** syphilis
- In the center - caseous necrosis; on periphery – granulomatous tissue with numerous lymphocytes, plasma cells with admixture of epithelioid cells, fibroblasts, a single Langhans cells.
- Abundance of small vessels with endovasculitis.
- Fibers: collagenous on the periphery (connective tissue capsule).
- Outcomes – scarring, petrification
Syphilis

• Gummatous infiltration occurs in the walls of large vessels. It differs from gumma by the absence of caseous necrosis.

• In aorta – syphilitic mezaortitis, the outcome – aneurysm.
Congenital syphilis

1. Fetal syphilis (infection from 10 week up to 5 month)
2. Early congenital syphilis
3. Late congenital syphilis

Fetal syphilis: stillbirth, fetal – maceration, necrotic miliary gumma (usually liver) with lot of treponemes.
Congenital syphilis

- **Early congenital syphilis**: lacquered cracking (around the lips, nose wings), syphilitic pemphigus, hepatosplenomegaly, “silicon” liver, “white” pneumonia, osteochondritis and periostitis (long bones, ribs, vertebrae, finger bones).

- Cause of death - a secondary infection
Congenital syphilis

- **Late congenital syphilis.** Tissue changes are consistent with tertiary syphilis
- Hutchinson's triad: keratitis, saber legs, Hutchinson teeth
- CNS – mental retardation and deafness.
Leprosy / Hansen’s disease

• Etiology: Mycobacterium leprae (Hansen bacillus)
• Forms:
  – lepromatous (low immune resistance)
    • Leprosy granuloma in skin (Virchow's cells giant vacuolated cells with Hansen bacillus, packed in the form of cigarettes in a pack)
  – tuberculoid (high immune resistance),
    • skin and peripheral nerve lesion, epithelioid-cell granulomas resembling tubercular, mycobacterias are found rarely.
  – intermediate

Complications – ulcerative skin lesions, autoamputation
Sarcoidosis
(Besnier – Boeck – Shaumann disease)

• **Etiology**  – unknown
• **Localization**  – lymph nodes, lungs
• **Structure of granuloma** :
  – lymphocytes, epithelioid cells, single Langhans cells, fibroblasts and collagen fibers on the periphery
  – caseous necrosis and vessels are absent in surrounding tissue could be vasculitis.
• **Outcomes**  – sclerosis, hyalinosis
• **The differential diagnosis**: with tuberculosis and syphilis
Helminthic Infection
• Taenia solium
• Echinococcus
• Trichinella spiralis
Taenia solium

Pathogen that causes **cysticercosis**.

**Pathogenesis** (host cycle): Infection occurs by ingesting undercooked pork containing the parasite in its cysticercus stage. In the human small bowel, the tapeworm eggs hatch but do not normally cause pathologic changes. In rare cases involving fecal contamination of food, the larvae penetrate the wall of the bowel and migrate to the skeletal and cardiac muscle (and occasionally the lung, liver, and brain as well) by hematogenous dissemination. The parasite manifests itself in these tissues as larvae the size of millet grains (cysticercosis).

**Complications** (**neural cysticercosis**): Brain infestation manifests itself in clustered, cystic parasite structures that spread into the subarachnoid space.
**Taenia solium:** (skeletal muscle)  
cysticercus stage

**Cysticercus stage**  
(HE) x 7
Echinococcus granulosus

**Synonym**: Canine tapeworm (adult form: 3–6mm in length).
Pathogen that causes echinococcosis (hydatid disease).
Humans are intermediate hosts, not the definitive hosts.

**Pathogenesis** (host cycle): Parasites attach themselves to the mucosa of the small bowel by the thousands. The eggs hatch in the duodenum, releasing invasive larvae (oncospheres) that invade the branches of the portal vein. Lodging primarily in the liver, they mature to a second cystic larval form (hydatid or Echinococcus hydatidiosus).
Echinococcosis of the liver
Echinococcus multilocularis

Synonym: fox tapeworm.

Pathogen that causes alveolar echinococcosis.

Occurrence: The pathogen is endemic only in certain regions of Europe, including southern Germany, Austria, Switzerland, and the Balkans. Humans are intermediate hosts.

Pathogenesis (host cycle): The fox, the definitive host, excretes eggs in its feces. These are then ingested by small rodents such as field mice that serve as intermediate hosts. Multiple small, densely packed cysts containing infectious scolices (E. alveolaris) develop and proliferate in the entrails of these animals, which are prey for the fox. Human infestation occurs incidentally, such as in hunters skinning infected foxes. These cases lead to infestation of the liver and alveolar echinococcosis.

Clinical presentation: Patients present with a mass in or around the liver.
Trichinella spiralis

Pathogen that causes *trichinosis*.

Occurrence: ubiquitous.

**Sources** of infection include all carnivorous and omnivorous animals such as domestic pigs, wild boars, dogs, foxes, badgers, rats, and bears.

**Pathogenesis** (host cycle): The pathogen is ingested with meat contaminated with larval cysts. The parasites hatch in the small bowel, where they initially penetrate the intestinal wall and then temporarily return to the intestinal lumen. These organisms become sexually mature and mate within about one week. The fertilized females remain viable and able to reproduce for about four weeks. During this period, they give birth to about 1000 larvae. The larvae are then transported to the skeletal and cardiac muscle via the thoracic duct and circulatory system. There the spiral larvae encyst and may survive for up to 30 years. The next carnivore serves as a host for reproduction.