Chronic Inflammation

Gábor Lotz MD Ph.D.
Phasis of inflammation

- Acute
- Subacute
- Chronic
Description of chronic inflammation

- Under conditions in which the inflammatory response is unable to eliminate the injurious agent or restore injured tissue to its normal state, the process may become chronic.

- Chronic inflammation may occur
  - as a sequel to acute inflammation or
  - as a primary immune response to certain foreign or autoantigens (e.g. viruses, parasites, autoantigens, malignant tumor cells – neoantigens).

- Chronic inflammation primarily serves to contain and remove a pathologic agent or process within a tissue.
Causes of chronic inflammation

- recurring acute inflammatory episodes (pyelonephritis); acute inflammation in persons with impaired healing capacity (weaken, cachectic patients)

- Persistent infections
  viruses (hepatitis C)
    - inflammatory infiltrate which is rich in lymphocytes, plasma cells and macrophages
  TB, syphilis, fungi
    - Deleyed type hypersensitivity (T-cells), and macrophages (granuomatous reactions)

- Prolonged expositions of toxic agents
  (exogenous: silica – silicosis; endogenous: lipids - atherosclerosis)

- Immun-mediated inflammatory diseases
  - Autoimmun diseases (rheumatoid arthritis, PBC, PSC, SLE, etc.)
  - Diseases caused by exogenous allergens (asthma bronchiale)
Chronic inflammation:

- Inflammation of prolonged duration (weeks, months, years)

- Simultaneously occurs:
  - inflammation,
  - tissue destruction,
  - repair

- Cells: Mononuclear cell ("small round cell") infiltrate (macrophages, lymphocytes, plasma cells), secondary lymphoid follicles

Other cells can occur under special conditions:
- mast cells (Fc-IgE), eosinophils (IgE- parasitic, allergic), neutrophils (PMNs), multinucleated giant cells
Accumulation of macrophages (Ma)

- Ma are **key cells in chr infl**, components of mononuclear phagocytic system
  - Bone marrow: stem cells,
  - Blood: monocytes,
  - Tissue: macrophages (microglia, Kupffer cells, alveolar Ma, sinus histiocytes, osteoclasts),
  - activated Ma (secretion of biologically activated products)

- Cont. recruitment of monocytes from the circulation (chemotactic factors, GFs etc)
- Local proliferation of Ma (atheromatous plaque)
- Immobilization of Ma (cytokines, oxidized lipids)
Accumulation of macrophages (Ma)

Role of the activated macrophages in chronic inflammation

- Chemotactic mediators (cytokines, others)
  - Recruitment
  - Division
  - Immobilization

Accumulation of macrophages (Ma)

- Tissue macrophage
- Activated macrophage
- Activated T cell

Tissue injury:
- Toxic oxygen metabolites
- Proteases
- Neutrophil chemotactic factors
- Coagulation factors
- AA metabolites

Fibrosis:
- Growth factors (PDGF, FGF, TGFβ)
- Fibrogenic cytokines
- Angiogenesis factors (FGF)
- *Remodeling*
Tissue alterations in chronic inflammation

- Tissue destruction
- Regeneration
  - Integrity of the ECM is preserved: complete healing - restitutio ad integrum
  - The ECM is damaged - reparation:
    - Healing by fibrosis directly or via granulation tissue (in the case of significant damage of the basic tissue structure)

**Granulation tissue:** richly vascular, newly formed connective tissue
(proliferating capillaries /angiogenesis/, macrophages /sometimes granulocytes, lymphocytes/, abundant fibroblasts, collagen synthesis & maturation, subsequently scar formation)
Fibrinous pleuritis - acute inflammation (fibrin on the surface)

→

Healing via granulation tissue (organisation – scar formation)

→

**Fibrous** pleuritis - chronic inflammation:

Pleuritis chronica adaesiva. (Adhaesiones)
Granulomatous inflammations

- **Gr.Infl.**: specific type of chr.infl. Characterized by accumulation of modified Ma (epitheloid cells), initiated by a variety of infectious and noninfectious agents
- **Granuloma**: circumscribed mass (focal area) of granulomatous inflammation, aggregation of infl cells
- **Cell types**:
  - **Epitheloid cells**: epithelial-like Ma (pink cytoplasm with distinct cell boundaries)
  - **Giant cells**: fused epitheloid cells (40-50 um, 20 or more Nu) – foreign body type, Langhans-type, Touton-type
  - **Lymphocytes, plasma cells**
  - **Fibroblasts** (in older granulomas)
GRANULOMATOUS INFLAMMATION

- **Foreign body granuloma** ("walls off" the agent)
- **Immune granuloma: Infectious granulomas**
  - Tuberculosis
  - Syphilis
  - Lepra
  - Cat-scratch disease
  - Whipple-disease
  - Brucellosis
  - Leishmaniasis
  - Schistosomiasis
  - Fungal infections
- **Immune granuloma: Non infectious granulomas**
  - Unknown (?) etiology (*sarcoidosis*, Crohn-disease, PBC etc)
  - Rheumatic fever
  - Granulomas associated with vasculitis (Wegener- gr, polyarteritis nodosa, etc)
  - Hypersensitiv pneumonitis
  - Others (panniculitis, malakoplakia, paraneoplastic syndrome, berilliosis etc)
TUBERCULOSIS (TB or TBC)

- **Agent:** *Mycobacterium tuberculosis* (Koch bacillus, 0.2-0.6 um x 1-10 um rods, waxy cell wall, high lipid content – acid fast (retain stains, Ziehl-Neelsen stain - carbol fuchsin)

- **Epidemiology:** 8-10 million new cases/yr, 1.7 billion infected individuals, person-person inf, delayed hypersensitivity

- **Pathogenesis:** depends on the exposition (previous inf.: anti-mycobacterial cell-mediated immunity)
  
  - (1) M.tbc. enters Mas,
  - (2) replication – blocks phagolysosome formation
  - (3) 3 weeks: Th1 cells produce IFN-gamma
  - (4) Ma iNOS↑ – NO↑ – Mas become bactericidal
  - (5) granuloma formation, caseation (TNF-epitheloid cells)
Forms of tuberculosis

- **Primary TB**: develops in previously unexposed, unsensitized (immunocompetent) person
  - Primary complex (Gohn-Ranke complex):
    - (1) tuberculum (Ghon focus, middle, close to pleura, central caseation),
    - (2) lymphangitis tuberculosa,
    - (3) lymphadenitis tuberculosa

- **Secondary**: develops in previously sensitized host, after primary TB or reactivation/superinfection
  - Apical, both lungs, tuberculum (first 1-2 cm), central caseation – cavitation (bacteria in sputum!), fibrosis, fibrocalcification
  - Low grade fever (systemic symptom), night sweats, hemoptoe, pleuritic pain
  - Progressive pulmonary tuberculosis
A. PRIMARY PULMONARY TUBERCULOSIS (0-3 weeks)

Mannose-capped glycolipid
Macrophage mannose receptor

"Endosomal manipulation"
- Maturation arrest
- Lack of acid pH
- Ineffective phagolysosome formation

Unchecked bacillary proliferation

Bacteremia with seeding of multiple sites

B. PRIMARY PULMONARY TUBERCULOSIS (>3 weeks)

Alveolar macrophage

IL-12

Class II MHC
T-cell receptor

MTB antigen

γ-IFN

T-cell

Th1

"Activated" macrophage

TNF, chemokines

Monocyte recruitment

Sensitized T-cell

Epithelioid granuloma ("hypersensitivity")

Tuberculin positivity ("hypersensitivity")

Bactericidal activity ("immunity")
Localization of primary TB

- **Lung**: most common: right lobe, middle, subpleural
- Pharynx: through the tonsilles
- Intestines: through the terminal ileum, *M. bovis*, mesenterial lymph node involvement („tabes mesaraica“)
- Skin: occupational disease (in stockmen)
Outcome of primary TB

- Elimination of bacteria and healing of the primary lesions (scar)
- Dormant Mycobacteria in the residual fibrotic lesions (this is the most common outcome; reactivation of bacteria: secondary TB)
- Progressive primary TB (in case of impaired immunoreactivity; the symptoms are resembling to the progressive secondary TB: cavitation in the lung, massive hematogenous dissemination - miliary TB)
Forms of tuberculosis

- **Primary TB**: develops in previously unexposed, unsensitized (immunocompetent) person
  - **Primary complex (Ranke-Ghon)**:
    - (1) tuberculum (middle, close to pleura, central caseation),
    - (2) lymphangitis tuberculosa,
    - (3) lymphadenitis tuberculosa

- **Secondary (postprimer)**: develops in previously sensitized host, after primary TB or reactivation/superinfection
  - Apical, one or both lungs, tuberculum (first 1-2 cm), central caseation – cavitation (bacteria in sputum!), fibrosis, fibrocalcification
  - Low grade fever (systemic symptom), night sweats, hemoptoe, pleuritic pain
  - Progressive pulmonary tuberculosis (next slide)
Progression of TB

- Directly to the adjacent structures
- Lymphogen
- Haematogen
- Canalicular (bronchogen, urinary, genital organs)
- On serous membranes (pleural, peritoneal)
Progressive pulmonary tuberculosis

- Apical lesion enlarges,
  - Erosion into bronchi, cavity formation (caseous material lined)
  - erosion of blood vessels (bleeding), (cor pulmonale)

- Miliary tuberculosis (hematogenous spread)
  - Milium (millet seeds): lesions of 1-2 mm, yellow-white through the parenchyma,
  - Extension of the infection: miliary TB in other organs (liver, kidney serous membranes, fallopian tubes, epididymis etc)

- Isolated organ tuberculosis
  - In any organ (seeded hematogenously)
  - Most common: tuberculous meningitis, renal TB, adrenal, bones, fallopian tubes TB
  - Pott’s disease: vertebrae affected
  - „cold” abscess: paraspinal caseous mass along the spine
  - Lymphadenitis: common form of extrapulmonary TB, in cervical region: „scrofula”
  - Intestinal TB: from contaminated food/milk
General immunity status (in secondary TB)

Immunity against TB

Hypersensitivity (cellular /tissue/ immunoreactivity against TB)

Productive (fibrotic tissue producing, cell-rich) lesions

Exudative (caseous exudate producing) lesions
Miliary TB
(10.26.)
Caverna (cavitation)

Cavity containing air, communicating with the bronchial tree. Caseous inner surface in the early stage.

Formation:
Tuberculotic inflammation destroys the wall of a bronchus and the caseous necrotic mass of fused granulomas empties via the bronchial tree.

Progressive pr.TB. Apical cavernas
Complication of secondary TB

- Infection of caverna (cavities) with other bacteria (abscessus, gangraena) or fungi (Aspergilloma)
- Empyema pleurae, pyopneumothorax
- Haemoptoe, pulmorrhagia due to extensive bleeding from Rasmussen’s aneurysm (Dilation of a branch of a pulmonary artery in a tuberculous cavity due to tuberculotic inflammation of the arterial wall. It may lead to rupture and haemorrhage.)
- Cavernacarcinoma (via squamous metaplasia of the lining bronchial epithelium of the healed inner surface of caverna)
- Canalicular progression of lung TB to contralateral lung and other organs (larynx, pharynx, intestine etc)
Large cavity in the upper lobe is filled with hematoma:
Bleeding from a Rasmussen aneurysm
Secondary TB in extrapulmonary localizations

- Kidney
- Reproductive system:
  - Female (fallopian tube),
  - Male (epididymis)
- Bone
- Central nervous system
SYPHILIS (Lues)

- **Agent:** Treponema pallidum (slender corkscrew-shaped, 0.1-0.2x6-20 um)
- **Stages:** sexually transmitted disease (STD), chr venereal disease
  - **Primary:** 3 weeks after contact (9-90 days)
    - **Endarteritis** and inflammation,
      - Ulcus durum (chancre: firm, red lesion at the site of the invasion),
      - bubo indolens (enlarged, painless lymphnode)
    - Heals in 3-6 weeks (without therapy)
    - Spreading through the body by hematologic and lymphatic dissemination
  - **Secondary:** 10-12 weeks after the primary
    - Skin, mucous membrane lesions: Maculopapulous exanthemes, condyloma latum (broad based elevated pagues), lymphadenopathy
    - Infectious
  - **Tertiary:** Years after infection (5 or more)
    - Cardiovascular: syphilitic aortitis, aneurysm
    - Neurosyphilis: meningovascular, tabes dorsalis (myelopathy - damage of the posterior column of spinal cord + peripheral nerves, loss of proprioceptive feedback of the cerebellum; stamping gait), general paresis
    - Gummas: hepar lobatum, in bone, skin etc
Syphilis (tertiary): Aortitis luetica
- tree-bark pattern
  on the inner surface

Syphilis (tertiary):
Aorta aneurysm
Congenital syphilis

- Transplacental infection mainly in 3. trimester

- Manifestations:
  - (1) Early (infantile, Treponema sepsis),
    - Intrauterine death, perinatal death
    - Pemphigus syphiliticus (bullous rash of the skin of the hands, feet etc)
    - Hepatosplenomegaly
    - Pneumonia alba
    - Dubois abscesses in the thymus
  
  - (2) Late (tardive)
    - Hutchinson triad (notched central incisors, interstitial keratitis with blindness, deafness)
    - Osteochondritis luetica, skeletal abnormalitis
Congenital syphilis

Osteochondritis luetica: Broadened bone-cartilage border in the femur and in a rib

From the Hutchinson triad:
notched central incisors

Normal nasal bridge

Low nasal bridge
LEPROSY (Lepra)

- **Infectious agent:** Mycobacterium leprae (Hansen 1873), temperature optumum 32-34 °C
- **Entrance:** bronchi, skin,
- **long incubation period (for yrs), slow progression**
- **Forms**
  - **Tuberous** (tuberculoid) leprosy (in persons with good immunoreactivity against M. leprae): granulomas, affecting superficial nerves and skin, marginally active (indurated, elevated, hyperpigmented), centrally depressed, depigmented lesions in the skin
  - **Lepromatous leprosy** (in persons with impaired immunoreactivity against M. leprae): bacteria laden clear, foamy macrophages in the dermis (skin deformities - leonine facies, peripheral nerve lesions); eyes, upper airways and testes can also be affected
Tuberculoid leprosy

Lepromatous leprosy (leonine facies)
Non-infectious immune granulomas

- Unknown (?) etiology (sarcoidosis, Crohn-disease, PBC etc)
- **Rheumatic fever**
- Granulomas associated with vasculitis (Wegener-gr, polyarteritis nodosa, etc)
- Hypersensitiv pneumonitis
- Others (panniculitis, malakoplakia, paraneoplastic syndrome, berilliosis etc)
Sarcoidosis: Non-necrotizing (non-caseous) granuloma

- Lung sarcoidosis
- Skin sarcoidosis
- Mediastinal lymph node sarcoidosis
Rheumatic fever

- Immunologically mediated, multisystem inflammatory disease
- Occurs a few weeks after an episode of group A streptococcal pharyngitis
- Antibodies directed against the M protein of streptococci are cross-react with autoantigens in the heart
- Main pathologic features of the rheumatic heart disease:
  - endocardial lesions: sterile endocarditis on the left sided valves (long-term consequences: valvular deformation, stenosis and insufficiency)
  - myocardial lesions: granulomas (Aschoff bodies) with Anitschkow cells (characteristic macrophages with abundant cytoplasm and caterpillar-like nucleus or nuclei)
  - pericardial lesions: fibrinous pericarditis and Aschoff bodies in the subepicardial fat tissue
Rheumatic fever

Rheumatic endocarditis

Rheumatic granuloma
(Aschoff body)
in the myocardium