Chronic Inflammation

Gábor Lotz MD Ph.D.
Phasis of inflammation

- Acute
- Subacute
- Chronic
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
    - Delayed type hypersensitivity (T-cells), and macrophages (granulomatous 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)
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
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
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

Immuno-compromised status
Caverna

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.
Secondary TB in extrapulmonary localizations

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

- **Agent:** Treponema pallidum (slender corkscrew-shaped, 0.1-0.2 x 6-20 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 lymph node)
    - 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 papules), 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
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
LEPROSY (Lepra)

- Infectious agent: Mycobacterium leprae (Hansen 1873), temperature optimum 32-34 °C
- Entrance: bronchi, skin,
- long incubation period (for yrs), slow progression
- Forms
  - **Tuberculous** (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
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)
Rheumatic fever

- Immunologically mediated, multisystem inflammatory disease
- Occurs a few week 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