2. Chronic Inflammation

- **If damaging stimulus is of short duration and does not persist then:**
  - tissue damage
  - acute inflammation
  - exudate
  - organization of exudate
  - granulation tissue
  - fibrous scar
3. Chronic Inflammation

Chronic Inflammation

- If damaging stimulus persists the process of continuing tissue necrosis, organization and repair all occur concurrently = chronic inflammation
  - Acute inflammation, immune system activated around the area of damage and tissues infiltrated by activated lymphoid cells; persists until damaging stimulus removed or neutralized
  - Histology – necrotic cell debris, acute inflammatory exudate, vascular and fibrous granulation tissue, lymphoid cells, macrophages and collagenous scar

(c) 2007, Michael A. Kahn, DDS

4. Chronic Inflammation

Chronic Inflammation

- The result of a balance between continuing tissue damage on the one hand and eradication of the damaging stimulus followed by healing and scar formation on the other
  - If the damaging stimulus eradicated or neutralized then further tissue necrosis does not occur and the repair response progresses to complete scarring
  - If the damaging stimulus cannot be eradicated or neutralized the balance between tissue damage and tissue repair is maintained in a stalemate and thus chronic inflammation will persist, often for years

(c) 2007, Michael A. Kahn, DDS
5. **Active Chronic Peptic Ulcer Biological Stalemate**

**Active Chronic Peptic Ulcer Biological Stalemate**

- **Example – Chronic Peptic Ulcer**
  - Protective mechanism of upper alimentary track breaks down
  - HCL and proteolytic enzymes destroy epithelium and supporting stroma - - -> ulceration of the wall stomach or duodenum) - - -> persistent damage

Image not available due to copyright restrictions.

(c) 2007, Michael A. Kahn, DDS

6. **Chronic Inflammation**

**Chronic Inflammation**

- **Example – Chronic Peptic Ulcer (cont’d)**
  - Acute inflammatory reaction occurs
  - formation of exudate close to the acid exposed surface while in the depths of the ulcer (farthest from the acid) attempts are made to organize the exudate and granulation tissue forms - - -> **collagenous scar**
  - Established ulcer has all these processes occurring simultaneously
  - Treatment aim = remove or greatly reduce acid and enzymes secreted
  - perforate
  - heal
  - persist

(c) 2007, Michael A. Kahn, DDS
7. Chronic Inflammation

Chronic Inflammation

- Key effector cells are lymphoid cells and macrophages (tissue-based immune response to the damaging agent)
  - Macrophages – phagocytic and activated to fulfill other immunological and secretory functions
  - Chronic inflammatory cells = lymphocytes, plasma cells, and macrophages

(c) 2007. Michael A. Kahn, DDS

8. Cellular Aspects of Chronic Inflammation

Cellular Aspects of Chronic Inflammation

<table>
<thead>
<tr>
<th>Cellular Aspects of Chronic Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophages</td>
</tr>
<tr>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Plasma Cells</td>
</tr>
<tr>
<td>Mast Cells</td>
</tr>
<tr>
<td>Basophils</td>
</tr>
</tbody>
</table>

(c) 2007. Michael A. Kahn, DDS
9. Chronic Inflammation: Slide 9

Source: TUSDM

(c) 2007, Michael A. Kahn, DDS

10. Chronic Inflammatory Cells

Source: TUSDM

(c) 2007, Michael A. Kahn, DDS
11. Chronic Inflammation

Chronic Inflammation

- **Macrophages**
  - Converted from inactive monocytes by trophic signals (e.g., gamma interferon)
  - Morphology changes with a subcellular apparatus to synthesize protein
    - Voluminous cytoplasm = epithelioid cell
    - Fusion of activated macrophages \( \rightarrow \) multinucleate histiocytic giant cells
    - Now have phagocytic and secretory functions against injurious agents and impt. in cell-mediated immunity (e.g., antigen presentation)

(c) 2007, Michael A. Kahn, DDS

12. Chronic Inflammation

Chronic Inflammation

- **Macrophages secrete**
  - Mediators of acute inflammation
    - Platelet activating factor and arachidonic acid metabolites
  - Highly reactive oxygen metabolites
    - Bacterial and cell killing
  - Proteases and hydrolytic enzymes
    - Dissolution of extracellular matrix
  - Cytokines IL-1 and TNFalpha
    - Fibroblast proliferation and collagen synthesis - repair
  - Growth factors (PDGF, EGF, FGF)
    - Stimulate growth of b.v. and division/migration of fibroblasts

(c) 2007, Michael A. Kahn, DDS
13. Chronic Inflammation: Slide 13

14. Chronic Inflammation

**Key Facts**
- Predisposed by factors that prevent elimination of a damaging stimulus
- Tissue damage, acute inflammation, granulation tissue, repair, and immune response all take place concurrently
- Infiltration by lymphocytes demonstrates immune response in tissues
- May develop after acute inflammation or may be a primary response to certain stimuli
- Predisposing factors include persistent damaging stimulus, inadequate host response to infection, and persistent autoimmune disease
15. Chronic Inflammation

Chronic Inflammation

- Granulomatous inflammatory reactions
  - In certain disease, acute inflammatory response dominated by neutrophils is transient and quickly replaced by immune-based cellular reaction w/ aggregation of lymphocytes and macrophages
  - Granulomas = discrete clusters of macrophages and a pattern of this is granulomatous inflammation

16. Nonspecific Granulomatous Inflammation

Nonspecific Granulomatous Inflammation

Images not available due to copyright restrictions.

(c) 2007, Michael A. Kahn, DDS
17. Nonspecific Granulomatous Inflammation – Coalescing Granulomas

Image not available due to copyright restrictions.

(c) 2007, Michael A. Kahn, DDS

18. Chronic Inflammation

Chronic Inflammation

– Examples of damaging stimuli that provoke granulomatous inflammatory reaction
  • Microorganisms of low inherent pathogenicity but excite an immune response
    – Ex. – mycobacteria – intracellular pathogens with resistant lipoprotein coating to the cell membrane (TB, leprosy)
  • Non-living foreign material deposited in tissues (e.g., keratin, urate crystals, inhaled inorganic dust)
    – Cannot be destroyed by neutrophil enzymes
  • Certain fungi
    – Cannot be dealt with by neutrophils
  • Unknown factors (e.g. sarcoidosis)

(c) 2007, Michael A. Kahn, DDS
19. Chronic Inflammation

Chronic Inflammation

- Tuberculosis - type IV hypersensitivity reaction
  - Granulomatous inflammation example
  - M. tuberculosis inhaled into alveolar spaces of lung; other tissues affected ---> transient marked immune-mediated response -- >
  - T-cells produce cytokines
  - Neutrophils cannot degrade cell wall so acute inflammation becomes chronic inflammation -- > cytokines aggregate macrophages (granulomas called tubercles) -- > central caseous necrosis (ricotta cheese appearance)

(c) 2007, Michael A. Kahn, DDS

20. Chronic Inflammation

Chronic Inflammation

- Tuberculous granuloma
  - Central caseous necrosis surrounded by a collection of large, activated macrophages that have a minimal resemblance to epithelial cells and thus termed "epithelioid" cells
  - Langhans' giant cells = activated macrophages that fuse to form large multinucleated cells; many nuclei around the periphery and a large central cytoplasmic mass
  - Outside and around the macrophages is a collar border of lymphocytes
  - Over time some fibroblasts appear in the lymphocytic collar and outside it ("macrophage cytokine recruitment")

(c) 2007, Michael A. Kahn, DDS
21. Chronic Inflammation: Slide 21

Source: TUSDM

(c) 2007. Michael A. Kahn, DDS

22. Lymph Node

Image not available due to copyright restrictions.

(c) 2007. Michael A. Kahn, DDS
23. Physiologic and Inflammatory (pathology) Giant Cells

Physiologic and Inflammatory (pathology) Giant Cells

Image not available due to copyright restrictions.

24. Langhans type giant cell and epithelioid macrophages in tuberculous granuloma

Langhans type giant cell and epithelioid macrophages in tuberculous granuloma

Image not available due to copyright restrictions.
25. Tumor Giant Cells in Pathology

Tumor Giant Cells in Pathology

Image not available due to copyright restrictions.

(c) 2007, Michael A. Kahn, DDS

26. Chronic Inflammation

Chronic Inflammation

• Tuberculous granuloma
  – Outcome of tubercles depends on balance between conflict of extension of infection vs. containment / healing / eradication
  – Factors predisposing to extension
    • Ingestion of large numbers of highly virulent organisms
    • Poor immune response (malnutrition, extreme youth or old age, intercurrent disease, immunosuppressive therapy)
  – Factors to containment / eradication
    • Ingestion of small numbers of poorly virulent organisms
    • Good immune response (health, immunization)
    • Antibiotic administration

(c) 2007, Michael A. Kahn, DDS
Chronic Inflammation

- Tuberculosis
  - Most severe in patients with poor natural immunity (e.g., malnourished, poor) or immunosuppressed via AIDS or iatrogenically (e.g., transplant patients)
    - New M. tuberculosis strains are resistant to formerly successful meds
  - Three pulmonary tissue patterns (host immunity dependent)
    - Primary – no previous exposure
    - Secondary – previously exposed, sensitized to organism
    - Exposure, but immunosuppression - - -> primary

(c) 2007. Michael A. Kahn, DDS

---

Chronic Inflammation

- Primary tuberculosis
  - Organism inhaled, proliferate in the lung alveoli at periphery of lung, just below pleura - - -> Ghon focus
  - Organism causes cell death in adjacent lung
  - Ineffective acute inflammatory response with bacterial organism not destroyed

(c) 2007. Michael A. Kahn, DDS
Chronic Inflammation

Primary tuberculosis (cont’d)
- Bacteria then conveyed to local nodes at lung hilum
  - - - - - > proliferate - - - - - > 3 weeks, immune response
develops - - - - - > macrophages recruited by T-cells to
lung and nodes - - - - - > granulomatous inflammation
and caseation
  • Often no clinical symptoms
  • Outcome depends on balance of host response and
  virulence of organisms

(c) 2007, Michael A. Kahn, DDS

Chronic Inflammation

Primary tuberculosis (cont’d)
- Vast majority of Ghon focus and caseating
  granulomas in lymph nodes (i.e., primary
complex) heal by deposition of collagen
around the tubercles - - - > central yellowish
caseation surrounded by wall of dense
collagen with calcium salts deposited, in
both, at times

(c) 2007, Michael A. Kahn, DDS
31. Chronic Inflammation

Chronic Inflammation

• Primary tuberculosis (cont’d)
  – Once immune system exposed to organism then patient has been sensitized and the disease does not progress as it is walled off by the dense collagen BUT viable organisms may remain walled off within the healed primary complex (latent tuberculosis)

32. Primary Tissue Pattern - TB

Primary Tissue Pattern - TB

Image not available due to copyright restrictions.

(c) 2007, Michael A. Kahn, DDS
33. Healed Ghon Complex at the Periphery of the Lung –

Healed Ghon Complex at the Periphery of the Lung –

thin fibrous capsule

Image not available due to copyright restrictions.

34. Chronic Inflammation

Chronic Inflammation

• **Primary tuberculosis (cont’d)**
  – If patient is not able to mount a vigorous immune and reparative response then further spread of organism occurs with continuing enlargement of caseating granulomas in the lymph nodes (progressive primary TB)
    • Enlarging nodes erode through bronchus wall or into thin-walled blood vessel
    • Ghon focus usually remains small although rarely it may rupture through the visceral pleura → discharge organisms into pleural cavity → tuberculosis pleurisy

(c) 2007. Michael A. Kahn, DDS
35. Caseating TB in a Peribronchial Lymph Node

Caseating TB in a Peribronchial Lymph Node

Source: TUSDM (c) 2007, Michael A. Kahn, DDS

36. Tuberculous Bronchopneumonia

Erosion of bronchial wall by enlarged caseous nodes with tubercle bacilli entry

Image not available due to copyright restrictions.

(c) 2007, Michael A. Kahn, DDS
37. Chronic Inflammation

Chronic Inflammation

• Primary tuberculosis (cont’d)
  ❖ Tuberculous caseous material with live tubercle bacilli pass down bronchi and bronchioles via gravity - - -> furthest reaches of the lung - - -> confluent caseating granulomatous lesions (galloping consumption) - - -> rapidly fatal

(c) 2007, Michael A. Kahn, DDS

38. Chronic Inflammation

Chronic Inflammation

• Primary tuberculosis (cont’d)
  ❖ Tuberculous caseous material with live tubercle bacilli erode blood vessel wall - - -> bloodstream - - -> many parts of the body (miliary TB – kidney, liver, spleen)
  • If into pulmonary artery - - -> remainder of lung

(c) 2007, Michael A. Kahn, DDS
39. Tuberculous Bronchopneumonia

Tuberculous Bronchopneumonia

New caseating granuloma formed in lower lobe near an infected bronchiole down which the tubercle bacilli have passed

Source: TUSDM

(c) 2007, Michael A. Kahn, DDS

40. Miliary TB

Miliary TB

Enlarged caseous node draining into pulmonary vein --> systemic dissemination (e.g., kidney, liver, spleen)

Image not available due to copyright restrictions.

(c) 2007, Michael A. Kahn, DDS
41. Miliary TB

Miliary TB

Drainage into the pulmonary artery → lungs

Images not available due to copyright restrictions.

42. Chronic Inflammation

Chronic Inflammation

- Secondary tuberculosis
  - Organisms acquired exogenously or from healed primary tuberculosis
  - Assmann focus – an apical lung lesion that begins as a small caseating tuberculous granuloma
Chronic Inflammation

Assmann focus (cont’d)

- Histopathology is similar to Ghon focus with central caseous necrosis surrounded by granulomatous inflammatory response
- Usually destruction of lung → cavitation
- Little involvement of lymph nodes due to vigorous tissue-based hypersensitivity response
- Therefore, outcome of infection depends entirely on what happens to the Assmann focus

Secondary tuberculosis (cont’) - outcome

- If vigorous immune response then healing of the apical lesion via exact process as for Ghon focus so containment of the infection with no further spread of the organism
- But, if fibrous wall breaks down then latent TB can lead to spreading infection at a much later stage (reactivated fibrocaseous TB)
45. Healed Fibrocaseous TB

Healed Fibrocaseous TB

At apex of lung – healing of a small Assmann focus

Source: TUSDM

(c) 2007, Michael A. Kahn, DDS

46. Chronic Inflammation

Chronic Inflammation

- Secondary tuberculosis (cont’d) - outcome
  - If poor immune response then progressive enlargement of apical lesion with caseous necrosis destroying lung tissue -> large caseous mass surrounded by thin cellular reaction with little collagen wall (progressive pulmonary TB) with increase risk of erosion into blood vessels or airways
  - Release of tubercle bacilli into main bronchi allow them to be coughed into the atmosphere as droplets -> transmission to other people (open TB) and producing TB bronchopneumonia (passage down to lower lobes)

(c) 2007, Michael A. Kahn, DDS
Chronic Inflammation

- **Metastatic (isolated organ) TB**
  - Only small number of tubercle bacilli escape into blood and if host defense effective then most die but some can settle in specific organ and remain dormant there for years
    - Especially in adrenal glands, kidney, fallopian tubes, epididymis, brain and meninges, and bones/joints
    - Can proliferate and produce overt disease at later date

---

Metastatic (isolated organ) TB

Epididymis \ Renal pelvis and calyces

Images not available due to copyright restrictions.

---

(c) 2007. Michael A. Kahn, DDS
Chronic Inflammation

Reactivated pulmonary TB
- After years of primary or secondary walled off focus with immune defense waning the organisms escape into adjacent lung - - -> proliferate rapidly - - -> tissue necrosis - - -> new caseation and granulomatous inflammation
  - - -> rapid spread - - -> miliary TB or bronchopneumonia TB and commonly fatal

(c) 2007. Michael A. Kahn, DDS

Chronic Inflammation

Tuberculosis key facts
- Caused by Mycobacterium tuberculosis
- Induces type IV hypersensitivity response
- Histopathology hallmark is caseating granulomatous inflammation
- Main site of infection is in lungs
- Lung infection in childhood comprises Ghon focus and nodal disease (primary complex)
- Infection in adult life causes Assmann focus
- Blood-borne spread lead to miliary tuberculosis
- Bronchial spread leads to tuberculous bronchopneumonia
- Reactivation of disease may take place in later life if host response is weakened

(c) 2007. Michael A. Kahn, DDS
51. Chronic Inflammation

Chronic Inflammation

- **Other mycobacterial diseases**
  - *M. avium-intracellulare*
    - Macrophage laden with organism in many organs or caseating granuloma of lung; AIDS patients
  - Chronic inflammatory granulomatous response with little induction of acute inflammatory response
  - *Leprosy* (M. leprae) – chronic, indolent mainly of skin; granulomas may form (tuberculous form) or if immunity low then intracellular proliferation in phagocytic cells (lepromatous form)
  - *Bovine TB* – cervical neck nodes infected due to drinking infected cows’ milk
  - *M. marinum* – chronic skin lesions usually hands
  - *M. scrofulaceum* – enlarged lymph nodes of the neck

52. Mycobacterium Avium-intracellulare

Mycobacterium Avium-intracellulare

Images not available due to copyright restrictions.
53. **Mycobacterium Leprae - Leprosy**

Images not available due to copyright restrictions.

54. **Other Causes of Granulomatous Inflammation**

- **Foreign material** (organic or inorganic) introduced into tissues commonly excites a predominantly macrophagic reaction
  - neutrophils are unable to phagocytize and destroy the material
- Granulomatous aggregates with giant cells form around foreign material or irregular, ill-defined
  - Endogenous
    - Keratin, urate crystals, degenerated altered collagen, degenerated altered elastin (artery walls)
  - Exogenous
    - Sutures, talcum powder, vegetable matter
55. Chronic Inflammation: Slide 55

56. Other Causes of Granulomatous Inflammation

Other Causes of Granulomatous Inflammation

- **Sarcoidosis**
  - Etiology unknown
  - Clinical
    - Lungs and lymph node enlargement – can result in pulmonary fibrosis
    - Slowly progressive but often burns out
  - Discrete granulomas with histiocytic giant cells mainly in lymph nodes, lungs, liver, spleen and skin (rarely brain, bone)
57. Other Causes of Granulomatous Inflammation

Other Causes of Granulomatous Inflammation

- **Sarcoidosis – cont’d**
  - Granulomas are multiple, slowly increase in size often becoming confluent
  - Histopathology resembles TB although no true caseation
  - Giant cells may have laminated calcific spherical concretions (*Schaumann bodies*), or stellate shapes (*asteroid bodies*)

58. Asteroid and Schaumann Bodies – Sarcoidisis

Asteroid and Schaumann Bodies – Sarcoidisis

Images not available due to copyright restrictions.