General Pathology

Infection & Tuberculosis

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Infection

Objectives:

i. Identify different aspects of infections as toxemia, bacteremia, septicemia and pyemia.

ii. Know pathological features of various bacterial (tuberculosis and syphilis)

Definition of infection:
Invasion of the living tissue by pathogenic micro-organism with development of pathological changes.

Pathogenicity:
The capacity of the organism to cause the disease, however the body has non-specific and specific defense mechanisms to protect against infection.

- Pathogenic micro-organisms may be
  - Bacteria
  - Viruses
  - Fungi
  - Protozoa

- Pathogenic bacteria can cause disease by many mechanisms e.g.
  1. Toxin production …endo or exotoxins.. which cause cell injury reversible or irreversible cell injury.
  2. Direct induction of inflammation (acute or chronic) or cell death.
  3. Stimulation of hypersensitivity reactions (especially types III and IV).

Barriers and predisposition to infection:

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<th>Barriers to invasion</th>
<th>Predisposition to infection</th>
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<tr>
<td>Keratin of skin</td>
<td>Wounds, insect bites</td>
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<tr>
<td>Glandular secretions and IgA e.g. in gut and lungs</td>
<td>Reduced in isolated IgA deficiency</td>
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<td>Secretion currents e.g. in respiratory tract</td>
<td>Reduced by cigarette smoking</td>
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<td>Bacterial commensals e.g. in vagina and gut</td>
<td>Changed by antibiotic therapy</td>
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Methods of Infection

I- Exogenous from patients or carriers by:
1- Skin or mucous membrane contact
2- Ingestion: Typhoid fever & T.B.
3- Inhalation: T.B and other Respiratory infection.
4- Blood transfusion : malaria, AIDS & viral hepatitis
5- Sexual transmission : $ & AIDS.
6- Transplacental from infected mother to her fetus: $ & Toxoplasmosis.

II- Endogenous

1) Commensals: Bacteria that are normally present in body and when body defense mechanisms are overcomed or bacteria change their position, they turn pathogenic e.g. strept viridans in mouth, E coli in intestine.

2) Septic focus: like tonsillitis.

Spread of infection

- **Local spread** …this route is facilitated by local tissue destruction especially if exotoxins are produced by the organism.

- **Natural passages** …trachea, ureters,…etc

- **Lymphatic spread** …organism is taken by macrophages to lymph nodes or may gain access in lymphatic fluid. Enlargement of the draining lymph node may be due to immune response or infection by the micro-organism.

- **Hematogenous spread** …organism may travel in plasma (bacteria and hepatitis B virus) or within cells as monocytes (herpes virus & HIV).

- **Tissue fluids spread** …in the pleural and peritoneal cavities.

- **Neural spread** …Rabies virus produce infection by traveling along the nerves.

There are several terms used to describe blood spread of an infecting agents or their toxin e.g bactremia (viremia), toxemia, bacteremia, septicemia & pyemia.
**Viremia- Bactremia**

Passive carriage of small numbers of bacteria/viruses without growth in the blood.

**Toxaemia**

**Definition:** circulation of toxins in blood causing clinical and pathological manifestations.

**Types of bacterial Toxins**
- Exotoxins from gram positive bacteria as diphtheria, staph and strept.
- Endotoxins from gram negative bacteria as typhoid bacilli.

**Types of toxaemia**
1. Acute toxaemia: when large doses of toxins reach blood within a short period of time as in Diphtheria.
2. Chronic toxaemia: when small doses of toxins reach blood within long period of time as in T.B & $.$

**Manifestations of toxaemia**
1. **Clinical:** fever, headache, rigors, loss of body weight & appetite.
2. **Pathological:**
   a. **Inflammation**
   b. **Degeneration:** cloudy swelling, steatosis & amyloidosis.
   c. **Necrosis** and Haemorrhage of adrenal cortex that may be fetal.
   d. **Anaemia:** due to bone marrow depression by toxins and hemolysis of RBC.s

**Bacteraemia**

**Definition:** Circulation of bacteria without multiplication.

**Sources of bacteria**

1. **Endogenous**
   - Commensals as strept viridens with tooth brushing and extraction.
   - Septic foci in body: boils, otitis media, salpingitis.

2. **Exogenous:** in early stages of certain disease as typhoid fever.

**Effects of bacteraemia**
- **Small dose with high resistance no effect.**
- **Large dose with low resistance the bacteria lodge in already diseased tissue e.g. strept viridans cause subacute bacterial endocarditis.**
**Septicaemia**

**Definition:** Circulation of large number of virulent micro-organisms with multiplication and toxin production e.g. strept haemolyticus in puerperal sepsis.

- **Effects of septicaemia:**
  1. R.B.C.s haemolysis by haemolysin causing anaemia.
  2. Capillary destruction by toxins causing petechiae & septic shock.
  3. Cloudy swelling, steatosis & focal necrosis in heart, liver, kidney.
  4. Septicaemic spleen (**acute splenic swelling**)

**N/E:**
- Size : enlarged
- Shape : preserved
- C/S: congested red pulp which is easily washed under tap water (Diagnostic sign)

**M/E:**
- Dilated congested sinusoid
- Atrophy of the lymphoid follicles.
- Infiltration by neutrophils, lymphocytes plasma cells and macrophages.

(5) Septicaemic heart : The heart becomes enlarged, flappy with vegetation.
(6) Bone marrow : at 1st there is leucocytosis followed by leucopenia.

**Pyaemia**

**Definition:** Circulation of septic emboli in the blood stream & with their impaction in different organs.

**Aetiology:** Septic emboli arise from detached septic thrombi usually by staph aureus.

**Types:** It may be pulmonary, systemic or portal pyaemia.

**Effects of pyemia:**
- * Capillary impaction : **Pyemic Abscesses**

**N/E:**
- Multiple small abscesses & equal in size.
- Rounded in shape & peripheral in position.
- Yellowish in color & they surrounded by red zone of hyperaemia.

**M/E:** Necrosis, excess neutrophils and congested capillaries.

* Arterial impaction produce septic infarction.

**Prognosis:** It is usually fatal.
**Definition:** Chronic infective granuloma affecting nearly all body systems mainly - lungs.

**Epidemiology:**
- 1.7 billion individuals are infected worldwide, 8-10 million new cases develop each year and 3 million deaths per year.
- TB is the 6th leading cause to death worldwide.
- The incidence increased abruptly after the increase of HIV infection.
- TB is the disease of poverty, crowding, old age, and debilitating diseases.
- The emergence of drug resistant new strains added to the difficulty in controlling the disease.

**Predisposing Factors:**
- Environmental
- Personal

**Causative Agent:**
- TB bacilli are aerobic, acid-fast, non-motile, non-toxigenic
- Structure of TB bacilli: 3 layers: CHO, lipid & protein
- Types of TB Bacilli: Human, Bovine, others.
**Pathogenesis of tuberculosis**

- Organism is phagocytosed by macrophage which is not able to destroy virulent micro-organism.

- In the early phase of primary tuberculosis, (in the non immunized person), there's uncontrolled proliferation of bacilli within pulmonary alveolar macrophages with resulting bactremia and seeding of multiple sites.

- After 3 weeks of infection, cell mediated immunity develops. Macrophages process mycobacterial antigen and present it to unstimulated CD4+T\(_h\)0 cells.

- Under effect of IL-12 secreted by macrophages, CD4+T\(_h\)0 cells mature into CD4+T\(_h\)1 cells which secrete IFN-\(\gamma\).

- IFN-\(\gamma\) activates macrophages to secrete a group of mediators including:-
  1. TNF… causing recruitment of monocytes, their activation, differentiation to epithelioid cells. It also causes:
    a. Increased NO production which generate free radicals able to destroy the micro-organism.
    b. Secretion of IL-8 which is chemotactic for lymphocytes and monocytes.
  2. IFN-\(\gamma\) …. which helps in
    a. Macrophage activation for more phagocytosis, antigen presentation and microbial killing.
    b. Secretion of TGF-\(\beta\) which stimulate fibroblastic proliferation
**Types of TB infection:** TB may be primary or secondary

*Comparison between 1ry T.B and 2ry T.B.*

<table>
<thead>
<tr>
<th>1ry T.B</th>
<th>2ry T.B</th>
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<tr>
<td><strong>Occurs in</strong></td>
<td>Occurs in</td>
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<tr>
<td>• Young ages (childhood type)</td>
<td>• middle age (adulthood type)</td>
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<tr>
<td>• 1st infection</td>
<td>• 2ry infection</td>
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<tr>
<td>• non immunized persons</td>
<td>• in patient taking 1ry infection or B.C.G vaccine</td>
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**Methods of infection:** exogenous by

1) Inhalation
2) Ingestion
3) Direct contact

**Site of 1ry complex:**

1) Lung 2) Intestine
3) Tonsils 4) Skin
5) Nose

**Reaction of the body against bacilli:**

* Proliferative reaction:
  Primary complex formed of:
  1) Parenchymatous lesion; tubercles with minimal caseation
  2) T.B. lymphadenitis
  3) T.B. lymphangitis

**Complications:**

- spread: mainly lymphatic and blood

**N/E of Tubercle:**

Tubercle is 1-3 mm with central yellow caseation & grey white periphery.

**M/E of Tubercle:**

Central caseous material (structurless eosinophilic material without cellular details by H&E) epithelioid cells, macrophages, langhan's giant cells, lymphocytes & peripheral fibroblastic reaction.

M/E: Epitheliod cells are larger than macrophagas with large vesicular nuclei, esinophilic cytoplasm & indistinct cell borders.
**Pulmonary T.B.**

Favorable site for T.B due to easy inhalation & good aeration.

Predisposing factors of T.B in any organ:
A) Environmental factors: low socioeconomic state, overcrowding, pollution, …

B) Personal factors: Negroes, DM, malnutrition, immune deficiency state, ….

**Primary Pulmonary T.B.**

**Iry pulmonary complex**: It is formed of:
1) **Ghon's focus**: Parenchymatous tuberculous lesion in right lung
   - in upper part of lower lobe or in lower part of upper lobe
   - 1-2 cm in diameter under pleura grayish yellow & caseous

2) **T.B. lymphangitis**: lymph vessels show multiple tubercles

3) **T.B. lymphadenitis**

**Fate**:
1) **Good**: healing
   * Small foci: are replaced by fibrous tissue.
* Large foci: undergoes fibrous capsulation, dystrophic calcification & the organisms may remain dormant in some cases.

II) Bad: spread

1) Local spread from Gohn's focus to:
   - Pleura: T.B pleurisy & empyema if 2ry infected
   - Bronchioles: Bronchiolitis

2) Lymphatic spread: to hilar, para tracheal & mediastinal L.N.

3) Bronchial spread:
   Ghon's focus may open in a bronchus & causes T.B bronchopneumonia & T.B lobar pneumonia.

4) Blood spread:
   - Small dose removed by immune system.
   - Moderate dose causes isolated T.B.
   - Large dose
     * If TB bacilli reach pulmonary vein: They causes generalized miliary T.B.
     
     * If TB bacilli reach pulmonary artery:
       They return back to the lung & causes miliary T.B. of lungs.

   Secondary Pulmonary T.B

   - Adult hood type (middle age & elderly).
   - Human type of bacilli.

   Source of infection:
   Endogenous: re-activation of dormant focus.
   Exogenous: Re-infection by inhalation.

N/E:
Assman-Simon's focus: it is formed by fusion of many tubercles.

It is apical or sub-apical & more in right lung due to:
* Good ventilation (aerobic organism).
* Increased lymphoid tissue in apical part.
* Decrease blood flow as right pulmonary artery is narrower than left.

They enlarged, caseate & become confluent to produce large lesion.
They are surrounded by fibrous capsul. It is 1-2 cm from pleural surface.
No associated lymphangitis or lymphadenitis (no complex).
Assman- Simons Focus

Fate :
- Good fate : regression & healing by fibrosis or calcification.
- Bad fate : progressive T.B types

I) Cavitary fibrocaseous T.B.

II) Tuberculous caseous pneumonia

Exudative reaction with numerous T.B bacilli with exaggerated hypersensitivity.

** Cavitary fibrocaseous T.B

It occur with moderate dose & moderate resistance.

N/E & pathogenesis :

Apical focus extends to adjacent bronchial wall then caseous material become discharged through bronchioles leaving a mother cavity.

The mother cavity is
- Surrounded by fibrous capsule.
- Lining is irregular ragged , shreddy , yellowish due to caseous material.
- The walls show ridges of remnants blood vessels & bronchi.

The caseous material extend in bronchioles & alveoli resulting in formation of small acinar cavities at the base of lung (daughter cavities).

Fibrosis as a trial for healing extends in between the cavities causing shrunken lung and bronchiectasis.
M/E:
Multiple caseating tubercles that heal by fibrosis, epithelialization of cavities or calcification.

Complications of progressive pulmonary T.B.

I) local tissue destruction:
• Hemoptysis
• Pneumothorax
• Pyo – pneumothorax
• Secondary amyloidosis

II- Spread:

1. Local to pleura causing T.B pleurisy exudation may: serous, serefibrinous, hemorrhagic or pus (empyema).

2. Blood spread (less than 1ry T.B) leads to miliary T.B.

3. Lymphatic spread.

4. Through natural passage: bronchial spread more than 1ry T.B.
   • lung: T.B. bronchopneumonia & T.B. lobar pneumonia.
   • Trachea & Larynx: T.B laryngitis, usually posterior.
   • Tongue: T.B ulcer occurs on the tip due to accumulation of sputum.
   • 2ry intestinal T.B. due to swollen sputum.

III) Peptic ulcer (20%) due to stress.

IV) Fibrosis of lung causes bronchiectasis, pulmonary hypertension & cor-pulmonale.

Miliary T.B.

• Definition: Sever form of T.B due to haematogenous spread of large dose of T.B bacilli in a patient with very low immunity.

• N/E: cut sections & outer surfaces of all organs show:
  (Multiple – rounded- yellowish- equal sized- small foci related to blood vessels & not surrounded by red zone of hyperaemia).

• M/E: tubercles with central caseation and few Langhans giant cells.
- Differential diagnosis: pyaemic abscesses

- Prognosis: fatal

**Tuberculoma**

- T.B. tumor like mass.

- Progressive primary lesion or rarely regressive secondary lesion.

-site: any organ- usually brain-kidney-spinal cord.

-N/E:
- Number : multiple or solitary
- Size : 0.5 -10 cm.
- Consistency : firm.
- Surface : nodular.
- Color : gray yellowish caseous material surrounded by capsule.

- M/E: Tubercles with caseation.
Summary, Pulmonary tuberculosis

T.B of skin

- **Primary T.B:** 1ry skin complex.
- **Secondary T.B:**
  - Part of generalized miliary T.B.
  - Lupus vulgaris: Hematogenous infection mainly in the face.
  - Scrufulosorum: Cutaneous tuberculosis with ulcer formation

* Characters of T.B Ulcer

**N/E:**
Shape: Irregular
edge: undermined (destruction is more in the deeper layers)
Margin: irregular & cyanotic.
Floor: Caseation
Base: indurated (fibrosis).
**M/E:** The ulcer shows tubercles & caseation.

**D.D.:** Syphilitic and malignant ulcers.

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**Gross morphology of T.B. ulcer**

**T.B. ENTERITIS**

* Swallowing of bacilli rarely affect mouth, pharynx or esophagus due to their stratified squamous epithelium

* Stomach is not affected due to its acidity so large dose are needed to reach intestine

**Type:**

**1ry Intestinal T.B.**

- Childhood type.
- It is caused by ingestion of bovine bacilli in milk.

- It is formed of 1ry intestinal complex:
  1) Intestinal parenchymatous lesion: bacilli are engulfed by macrophage of peyer's patches followed by tubercle formation that undergoes ulceration.
  2) T.B. lymphangitis.
  3) T.B lymphadenitis (Tabes mesentrica): The mesenteric LNs are enlarged & fused together (matted) due to peri-lymphadenitis.

**Fate:**

* **Good:** healing
* **Bad:** spread
  - Local spread to peritoneum, fallopian tube.
  - Lymphatic spread to other L.Ns.
  - Blood spread: miliary T.B.
  - Natural passages spread.
2ry Intestinal T.B.

It is due swallowing of sputum in patient with pulmonary T.B.

I- Ulcerative type:
* It starts in peyer's patches as T.B. reaction that destroys the submucosa & mucosa forming T.B. ulcer.

* Ulcer is at 1st parallel to the long axis of the intestine, take the shape of peyer's patches later due to extension in lymphatic vessels the ulcer take a girdle shape ulcer (encircle the bowel) with its axis perpendicular to that of the intestine (transverse ulcer)

* Characters of T.B. ulcer
N/E:
- Shape : girdle ulcer
- Margin : irregular & cyanotic
- Edge : undermind
- Floor : yellow & caseous
- Base : indurated
- Axis : perpendicular to long axis of intestine. (Transverse ulcer)
- The peritoneal covering shows multiple tubercles.
- No affection of L.N.

Gross morphology of T.B ulcer

M/E : as tubercles

II- Hyperplastic type: Ileo caecal T.B.

* The wall of terminal ileum, caecum & ascending colon are diffusely affected & thickened with narrowing of the lumen & chronic obstruction

* Complication of intestinal T.B.
  1- Hemorrhage.
  2- Intestinal obstruction.
  3- Fecal fistula & perforation.
  4- Spread to peritoneum, fallopian tubes, …..
  5- Amyloidosis.
**T.B. Lymphadenitis**

Common Cause of lymphadenopathy in children.

**Method of infection:**
- Part of 1ry complex
- lymphatic spread
- Hematogenous spread (rare).

**N/E :**
- L.N. enlarged, soft, C/S shows creamy caseous material.
- Affection of the capsule results in matting (fusion) of the L.Ns
- If caseation is liquefied by enzymes of polymorphs it is called (COLD ABSCESS) that may open on the skin by a sinus discharging caseous material.

**M/E :**
*Non Caseating T.B lymphadenitis:*
Multiple non caseating tubercles at periphery then go centrally.
They are separated by thin rim of nodal tissue

*Caseating TB lymphadenitis:*
Caseation starts in the tubercles fuse together replace the whole LN

**Complications :**
Spread, rupture and sinus formation & secondary amyloidosis.

![Gross of T.B lymphadenitis](image)

**Tuberculosis of bone (TB osteomyelitis)**

- **Sites of affection…**
  - Spine (especially thoracic and lumber vertebrae).
  - Knee and hip joints.
- **TB osteomyelitis is a destructive disease which is difficult to control.**
T.B of vertebrae (Pott’s disease)

- Commonest site of T.B of bone
- More in the thoraco-lumber region.
- Produces destruction of vertebral bodies and intervertebral discs.

- **Complications**
  1. **Deformity**…Kyphosis or scoliosis
  2. **Cold abscess**

Extensive caseous destruction of bone resulting in the formation of tuberculous pus that may track to the surface.

**Sites of cold abscess**
- Posterior mediastinal cold abscess.
- Psoas abscess in the inguinal region

3. Secondary amyloidosis…due to chronic tissue destruction.

4. Paraplegia in 10-25% of cases due to
   a. Compression by collapsed vertebrae
   b. Extra dural cold abscess

**T.B of male genital tract**

- Mostly hematogenous spread from a pulmonary lesion.
- Affects mainly globus minor of the *epididims*
- If it ulcerate, it opens as a *POSTERIOR* sinus
- Testis may be affected
- Less commonly TB infection of the male genital tract occurs as a consequence of spread from renal and urinary tract tuberculosis.
- In this case it usually affects the **prostate and seminal vesicles**

**Tuberculosis of the female genital tract**

**Tuberculous salpingitis**
- Most common site of affection in the female genital tract.
- Infection occurs by hematogenous spread from pulmonary lesions.
- It is an important cause of infertility in areas where TB is prevalent.

**Renal Tuberculosis**

**Sources of infection**
- Hematogenous spread (secondary tuberculosis)
- Ascending from the U.B

**Results in:-**
1. TB pyelonephritis (surgical kidney).
2. Miliary T.B
3. Tuberculoma

**T.B pyelonephritis (surgical kidney)**
- Affection may be unilateral or bilateral.
- Infection starts renal and by time it enlarges and rupture into the pelvicalyceal system leading to TB ureteritis, cystitis and in the male prostatitis and epididymo-orchitis.

**Grossly**… The affected kidney is enlarged, bosselated, C/S shows a white caseous material filling the pelvicalyceal system.

- With time, there’s destruction of cortex and medulla and at the end stage of the disease, the affected kidney is reduced to a cystic mass containing partially calcified caseous material.

- If both kidneys are affected, renal failure results.
Miliary tuberculosis of the kidney

- The kidney receives a large number of TB bacilli spreading from a fulminating lung lesion.
- There are very large numbers of small tuberculous granulomas scattered throughout both kidneys.
M/E: Uniform small epithelioid granulomas with little caseation.

Tuberculosis of the CNS

- TB infection of the CNS is due to hematogenous spread from a pulmonary lesion.
- There are two patterns of CNS affection
  a. TB meningitis.
  b. Tuberculoma.

Tuberculous meningitis

- An exudative lesion.
- Characterized by numerous granulomas in the leptomeninges.
  - Infection is most marked around the base of the brain.
  - Meningeal fibrosis occurs leading to serious complications (hydrocephalus and compression of cranial nerves).

- Characters of CSF in tuberculous meningitis
  - Cellular 70% lymphocytes
  - No mesothelial cells
  - Decreased sugar and chloride
  - Increased protein…….web formation
  - ZN stain ..Positive for TB bacilli

C.N.S Tuberculoma

- It is firm, lobulated mass with central caseation and a surrounding fibrous capsule.
  - It may reach up to 10 cm. in diameter.
- Treatment with antibiotics is usually ineffective and surgical excision is required.

Gross morphology of tuberculoma