# بسم الله الرحمن الرحيم

# Type III Hypersensitivity

Immune complex reaction

# Type III: Immune Complex Mediated Reaction

*When antibodies (Ig G or Ig M) and antigen coexist immune complexes are formed

*Immune complexes are removed by reticuloendoth. syst.

*Some immune complexes escape phagocytosis

*Immune complexes deposited in tissues on the basement membrane of blood vessels and cause tissue injury

# Mechanism Of Tissue Injury

Immune complexes trigger inflammatory processes:

1) Immune complexes —activate→ the complement —release→ anaphylatoxins C3a, C5a

—stimulate→ degranulation of basophiles and mast cells —release→ histamine

Histamine ↑ vascular permeability and help deposition of immune complexes

2) Neutrophils are attracted to the site by immune complexes and release lysosomal enzymes which damage tissues and intensify the inflammat. Pro.

3) Platelets are aggregated with two consequences

a- release of histamine

b- form of microthrombi which lead to ischemia

# Clinical conditions of Type III Hypersensitivity

Diseases produced by immune complexes are those in which antigens persists without being eliminated as:

a- Repeated exposure to extrinsic antigen

b- injection of large amounts of antigens

c- Persistent infections

d- Autoimmunity to self components

# 1- Arthus Reaction

* This is a local immune complex deposition phenomenon e.g. diabetic patients receiving insulin subcutaneously

* Local reactions in the form of → edema, erythema, necrosis

* Immune complexes → deposited → in small blood vessels

leading to → vasculitis, microthrombi formation, vascular occlusion, necrosis

# 2- Serum Sickness

* A systemic immune complex phenomenon
* Injection of large doses of foreign serum
* Antigen is slowly cleared from circulation
* Immune complexes are deposited in various sites

* 10 days after injection
  - fever
  - urticaria
  - arthralgia
  - lymphadenopathy
  - splenomegaly
  - glomerulonephritis

e.g. treatment with
- antidiphtheritic serum
- penicillin
- sulphonamides

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3- **Post-streptococcal glomerulonephritis**

glomerulitis associated with infective endocarditis

4- **Hypersensitive pneumonitis (farmer lung)**

immune complexes deposition in lung after repeated inhalation of dust , mold spores

5- **Endogenous antigen antibody complexes** involved in autoimmune diseases

e.g. **SLE, rheumatoid arthritis**

# Clinical types of hypersensitivity III in animals

- **Local type III**

- There are some diseases in the domestic animals in which type III reactions play a major role.
- 1-Blue-eye
- Blue-eye is a condition in a small proportion of dogs that have been either infected or vaccinated with live canine adenovirus type-1

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- **2-hypersensitivity pneumonitis**
- Animal lung---- inhalation of Ag
- Examples:
- Cattle housed during winter and exposed to dust from hay (thermophilic actinomyces will grow)
- (Micropolyspora faeni spores)
- Chronic obstructive pulmonary disease (COPD) in horses (hay dust).

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- **In man we also have**
- A-farmer’s lung (M.faeni)
- B-pigeon breeder’s lung (pigeon feces).
- C-mushroom grower’s disease (spores from soil).
- D-librarian’s lung (dust from old books

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- 3-staphylococcal hypersensitivity
- Staphylococcal hypersensitivity is a pruritic pastular dermatitis of dogs. Skin testing suggested the involvement of type I, III, and IV. But type III may predominant in some cases.

# Generalized type III hypersensitivity

- Serum sickness (result from passive immunization).
- The disease can be induced experimentally in rabbits and the anima develop a glomerulonephritis and arteritis.

# OTHER IMMUNE COMPLEXES

- 1-Purpora Hemorrhagic
- Occur in horses recovered from an acute streptococcal infection (Streptococcus equi).
- 2-Dietary hypersensitivity
- In case of feeding the very young calves with soy protein causing hypersensitivity and loss of weight.

- 3-Polyarthritis
- Immune complexes can be readily found in the blood and synovial fluid of animals with rheumatoid arthritis.
- 4-Drug hypersensitivity:
- Similar to that of type II
- -anemia
- Thrombocytopenia
- -granulocytopnia.

# Type IV
# Cell Mediated
# Delayed Type Hypersensitivity

# Type IV: Cell Mediated Delayed Type Hypersensitivity

mechanism

* 1- T-cells cause tissue injury by
  - triggering DTH reactions by TH1
  - or
  - directly killing target cells by CD8

* 2-TH1 and CD8 T cells secrete cytokines (IFN-γ and TNF)

*3- Cytokines
- attract lymphocytes
- activate macrophages
- induce inflammation

* 4-Tissue damage results from products of activated macrophages

# Tuberculin –Type Hypersensitivity

Mechanisms:

*1- When tuberculin antigen(PPD) intradermally in sensitized person

PPD=Purified Protein Derivative

*2- Local indurated area appears injection site (48-72 hs)

*3- Indurations due to accumulation Of:

macrophages and lymphocytes

* Similar reactions observed in diseases

e.g. brucellosis, lepromin test in leprosy, Frei's test in lymphogranuloma venereum

# Type IV Hypersensitivity Clinical Conditions

A-Granulomatous lesions

Examples:

* In chronic diseases : T.B., Leprosy, schistosomiases

Mechanisms:

*1- Intracellular organisms resist destruction by macrophage.

*2- Persistent antigen in tissues stimulate local DTH reaction

* 3-Continuous release of cytokines leads to accumulation of macrophages which give rise to epithelial and giant cell granuloma

B-Contact Dermatitis

Examples:

* Contact of skin with chemical substances or drugs
  e.g. poison, hair dyes, cosmetics, soaps, neomycin

Mechanisms:

*1- These substances enter skin in small molecules

* 2-They are haptens that attached to body proteins, form immunogenic substances

*3- DTH reaction to these immunogenic subst. lead to:

inflammatory reaction of skin in → eczema, rash, vesicular eruption

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C- Auto immune diseases and graft rejection are due to in part to delayed hypersensitivity reactions

D- Insulin dependent diabetes mellitus

T-cells invade the pancreatic islets and specifically destroy insulin secreting beta cells

# Tuberculin Reaction In Animals

- Tuberculin: is the name given to extracts of Mycobacterium tuberculosis, M. bovis, or M. avium used to skin test animals in order to identify those with tuberculosis.
- PPD: Purified Protein Derivative tuberculin.
- This PPD is prepared by growing organisms in synthetic medium, killing them with steam, and filtering.

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- The PPD tuberculin is precipitated from this filtrate with trichloracetic acid, washed, and finally resuspended in buffer ready for use. Its major antigenic component is probably a heat shock protein (HSP65).

# Mechanism

- PPD injected into the skin of:
- Normal animal → no significant response.
- Sensitized animal (TB infected) → DTH is developed (a red indurated swelling slowly develops at the injection site.
- The inflammation begins between 12 and 24 hrs, reaches its greatest intensity by 24-72 hrs and may persist for several weeks before gradually fading.

# Tuberculin reactions in cattle

- This do detected TB infected animals
- Skin testing of cattle may be performed in several ways:
- 1-single intradermal (SID) test.
- 0.05 ml of PPD is injected into one anal fold ⟶ 72-96 hrs and compare it with un injected folds.

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- Advantage: simple
- Disadvantages:

a-cannot distinguish between tuberculosis and infection with other mycobacteria (M.avium, M.paratuberculosis and Nocardia.

b-False positive results due to vaccination or M. faeni.

c-False negative in animals:

- with advanced tuberculosis
- With very early infection
- That calved within the preceding 4-6 wks.
- Very old cows
- Tested within the preceding 1 to 10 wks.

# 2-Comparative

- The comparative test, for example, involves intradermal inoculation of both avian and bovine tuberculins
- And examined 72 hrs later and compared:
- If the swelling observed on avium PPD= +ve for M.avium or M.paratuberculosis.
- If the swelling observed on tuberculosis PPD=+ve for M.bovis or M.tuberculosos.

# 3-Short thermal

- In which a large volium of tuberculin solution is given subcutaneously and animal is examined for a rise in temperature between 4-8 hrs later.
- PPD → T cells → cytokines → macrophage → IL-1 causes increase in body temp.

# 4-Stormont

- The Stormont test relies on the increased sensitivity of a test site, which occurs after a single injection.
- It is performed by giving two doses of tuberculin at the same injection site 7 days apart.

# Tuberculin Reaction In Other Animals

- In pig and dog the best test is a SID test given in the skin behind the ear.
- In cat the short thermal test is the best.
- In sheep and goats the antigen is usually given in anal fold.
- Horses appear to be unusually sensitive to tuberculin, and the dose used must be reduced accordingly.
- In birds, good reactions may be obtained by inoculating tuberculin into the wattle or wing web.

# JOHNIN REACTIONS

- DTH in animals infected with M.paratuberculosis.
- Johnin Ag .Intradermal injection
- +ve like SID
- Or
- False -ve

# Best alternative of Johnin

- Johnin A.g IV measure animal temerature a rise in temp. of 1C or a neutrophilia after 6hrs is considered a positive result.
- These tests are probably of limited usefulness in individual animals but may be used for the identification of infected herds.

# Other skin tests

- Brucellin : a filtrate of a 20-day broth culture, and brucellegen, a nucleoprotein extract.
- Mullein : in horses with glanders *(Pseudomonas mallei).* It is a skin test used in either a short thermal or an ophthalmic test by dropping the Ag solution into an eye leads to conjunctivitis.

- Histoplasmin : is used in histoplasmosis.
- Coccidioidin : is used coccidioidomycosis
- Toxoplasmin : is used in toxoplasmosis.
- **Note** :the last two tests are not specific and may induce Ab formation in uninfected animals to become serologically positive.

# Thanks