Hyper sensitivity reactions 2

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Type 3 hypersensitivity reaction

It involves soluble antigens that are not bound to cell surfaces When these antigens bind antibodies, immune complexes of different sizes are formed

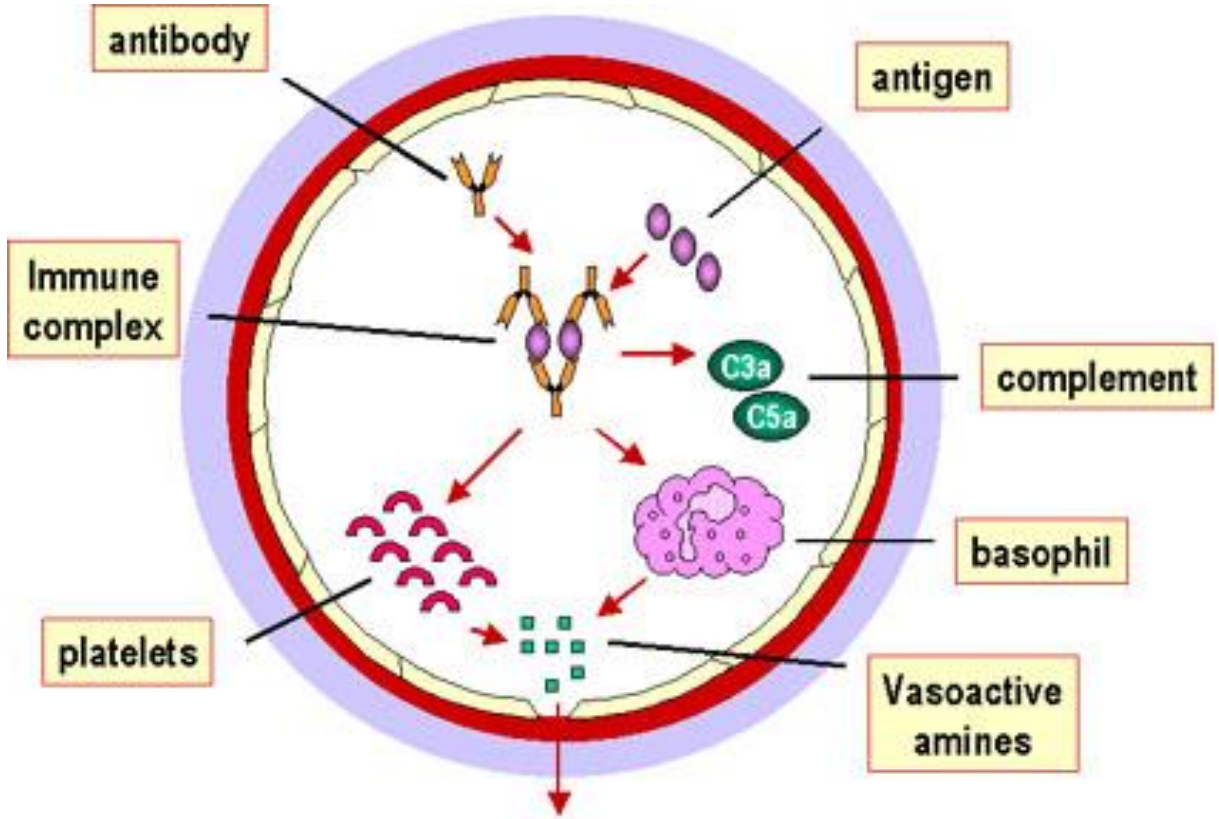
Circulating Immune complex deposition, it is generally due to high quantity of **soluble antigens and/or antibody**:

- **Persistent infection**: strep. Viral hepatitis
- **Autoimmune disease**: SLE, Rheumatoid arthritis
- **Frequent inhalation of antigen** : extrinsic allergic alveolitis (IgG)
- **Injection of large quantity of Ag** (injection of high quantity of penicillin or antitoxins for long period called serum sickness)
- **Impaired clearance of the immune complex as in SLE**

Pathophysiology.

- complexes can be cleared normally by macrophages or transferred by erythrocytes (have CR1) to spleen
- but for some reasons as decrease complement level or increase complex formation rate
- they have difficulty in the disposal of immune complexes. These immune complexes insert themselves into tissues as small blood vessels, joints, and glomeruli, causing symptoms and diseases.
- The tissue damage results from
  - Complement and Ab mediated recruitment of leukocytes causing platelet and basophils aggregation or release their mediators that increase vascular permeability
  - Increase anaphylatoxins (C3a, C5a)
  - Neutrophils and macrophages are attracted by C5a and react with complex because high immune complex size, they release mediators out side lead to inflammation and tissue damage. Activate macrophage release IL-1 and TNF alpha

Mechanism of damage in immune complex



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models of Type 3 hypersensitivity

- diphtheria infections were treated with serum from horses that had been immunized with the diphtheria toxin, which is an example of passive immunization against the toxin by the transfer of serum containing antitoxin antibodies. Von Pirquet noted that joint inflammation (arthritis), fever developed in patients (serum sickness), skin eruptions (mainly consisting of urticaria), and lymphadenopathy
- Identifying serum sickness was a landmark observation in understanding immune complex diseases.)
  type 3 hypersensitivity reaction →immuncomplex deposition in the kidney & joints (glomerulunephritis , arthritis)

arthus reaction

- **The Arthus reaction involves the local formation of antigen/antibody complexes after the intradermal injection of an antigen**
- **If the patient was stimulated in a second time(has circulating antibody) with the same antigen, an Arthus reaction occurs and manifests as local vasculitis due to deposition of immune complexes in dermal blood vessels.**
- **(** large and less identified erythema after 5-12 hrs)

Other examples

- Systemic lupus erythromatosus (SLE), high anti-DNA and anti-nuclear proteins antibody (ANA), immune complex in kidney, skin joints
- Post strept-glumerolonephritis, high ab against strep Ag- immune complex on joints
- Poly arteritis nodosa; chronic infection of viral hepatitis, high ab, immune complex on vessels

Testing

- Symptoms depending on site of precipitation
- Tissue biopsy and staining by Immunofluorescence (granular appearance)
- Assay for circulating immune complexes using patient serum (C1q binding assay)
- Low levels of C3 and C4 as in SLE; high immune complex formation (active disease) lead to high consumption of C3 and C4 and results in decrease solubility of immune complexes
- Treatment; Anti-inflammatory drugs as cortisone

Type 4 hypersensitivity reaction or Delayed hypersensitivity

- In second immune response to the same antigen, mediated by CD4 cytokines; memory TH1 and TH17 cells secrete cytokines (IFN gamma and IL-17) that recruit and activate monocytes and neutrophils (cytokine mediated)
  - Autoimmune; As in rheumatoid arthritis (RA), multiple sclerosis, type 1 diabetes, psoriasis, psoriasis and inflammatory bowel disease
  - non autoimmune is contact dermatitis (poison ivy , chemicals, heavy metals, etc.) and in TB test, the lesions are more papular.
- Mediated by cells;
  - CTLs may contribute to type 4 reaction as in type 1 diabetes (cell mediated) after viral hepatitis
  - lymphocytes and macrophages over activation is involved in the granulomas formation after intracellular infection result from.(leprosy, histoplasmosis, toxoplasmosis, leishmaniasis, etc.)

Table 3 - Delayed hypersensitivity reactions				
Type	Reaction time	Clinical appearance	Histology	Antigen and site
contact	hr 72-48	eczema	lymphocytes, followed by macrophages; edema of epidermis	epidermal (organic chemicals, poison ivy, ,heavy metals (.*etc*
tuberculin	hr 72-48	local induration	lymphocytes, monocytes, macrophages	intradermal (tuberculin, (.*etc* ,lepromin
granuloma	days 28-21	hardening	macrophages, epitheloid and giant cells, fibrosis	persistent antigen or foreign body presence (tuberculosis, (.*etc* ,leprosy

Contact dermatitis after 72hr

- Local eczema ; mostly from nickle or rubber ; the Ag is very small & lipophilic (hapten).
  These chemicals are haptens then react with self proteins, creating hapten-peptide complexes,
- **Two phases :**

  1- Sensitization after first exposure ; takes10-14days .
  cutaneous Langerhans' cells take up and process **antigen** , and then migrate to regional lymph nodes, where they **activateTc and TH cells toward TH1**, and TH17 with the consequent production of **memory T cells**, which end up in the dermis.

  2- In the elicitation (activation) phase in second exposure (gives the symptoms), further exposure to the sensitizing chemical leads to **antigen** presentation to memory **T cells** in the dermis, with release of T-cell cytokines such as **IFN**-γ and **IL**-17.
  This stimulates the keratinocytes of the epidermis to release cytokines such as **IL**-1, **IL**-6, **TNF**-α .
  These cytokines and chemokines enhance the inflammatory response by inducing the migration of macrophages (Giant cells), T cell accumulation with macrophages (granuloma)
- Cessation of reaction is as a result of : Removing the Ag , more IL-10 (from TH2 cells), TGF beta (from keratinocytes) & PGE (from macrophages)

Tuberculin test (PPD test or mantoux test) (after 72hr)

Tuberculin test :

patients who have been exposed to the bacteria, after exposure to tuberculin Ag, they develop a delayed hypersensitivity reaction manifested by inflammation and hardening in the dermis (from TB) → skin hardening and fever.

Mediated by memory Th1 and macrophages (IL-1, TNF and IFN gamma).

Most people with a positive TB skin test means they probably have TB germs in their body, latent TB infection or TB disease? should be confirmed by more tests. chest x-ray.

Used as for :

-general measure of the efficacy of cell mediated immunity by using injection with common antigens as candid albicans.
-Test for TB.

- A false positive result may be caused by nontuberculous mycobacteria or previous administration of BCG vaccine
- A false negative in Those who are immunologically compromised, especially those with HIV and low CD4 T cell counts

Granulomatous

-Results from aggregation of macrophages and lymphocytes (after 21-28 days)

-Granuloma formation is a strategy that has evolved to deal with those intracellular pathogens that have learned to evade the host immune system by various means like resisting phagocytosis and killing within the macrophages. Granulomas try to wall off these organisms and prevent their further growth and spread.

Causes :

1- immune granuloma as in

.TB, Leprosy, leishmania

. Immune mediated crohns and sarcoidosis (Ag is unknown)

2- Inorganic Antigen as talc and silica (non immune-granuloma, no T lymphocytes involvement)

Histology :

1- Epithelioid cells are activated macrophages resembling epithelial cells

2- giant cells from fusion and aggregation of epithelioid cells

3-granuloma

diagnosis

- Generally is biopsy; it will show infiltration by lymphocytes and monocytes, increased fluid between the fibrous structures, granuloma and some cell death

Cytokine treatment in type 4

- The first success with this class of biologic agents came with a soluble form of the TNF receptor and anti-TNF antibodies, which bind to and neutralize TNF. In rheumatoid arthritis (RA), Crohn's disease, and the skin disease psoriasis.
- Antibodies to the IL-6 receptor have been successfully used in trials for adult rheumatoid arthritis (RA).