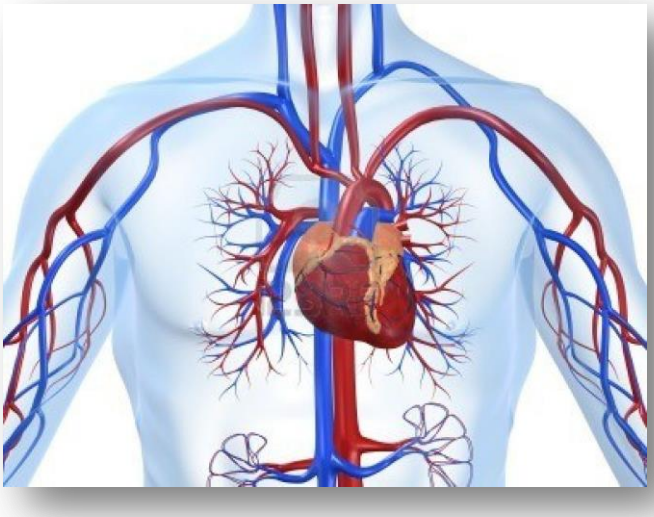
Rheumtic Fever and Rheumatic Heart Disease

Cardiovascular block

First lecture

Brought to you by:

Badr Almutairi
Abdullah Alfaifi
Muath Al$abih
Bayan Al-Amr
Maha Al-Luhaidan
$ara Habi$



Objectives:

- To understand basis of rheumatic fever as an immunologically mediated late complication of Streptococcal infection.
- To know that autoimmunity results from production of cross reacting antibodies against Streptococcal antigens.
- To describe rheumatic heart disease as one of the several manifestations of rheumatic fever.
- To know the signs, symptoms, pathogenesis, treatment and prophylaxis of rheumatic heart disease.

Cross reacting antibody: An antibody that reacts with an antigen normally found in our bodies but has similar sequence to the abnormal antigen (Streptococci group A in this case) that induced its production. So when it's done with the actual antigen (Streptococci group A) it will act against our normal body tissues causing local tissue damage due to similarity in sequence.

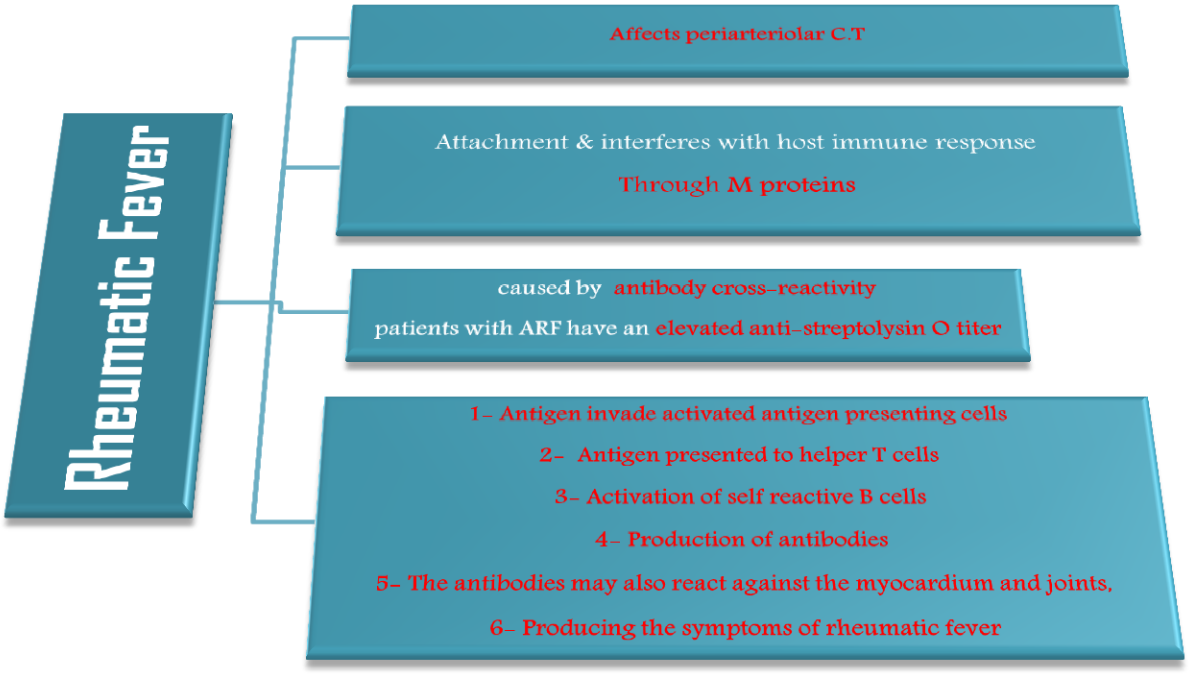
Black : Slides

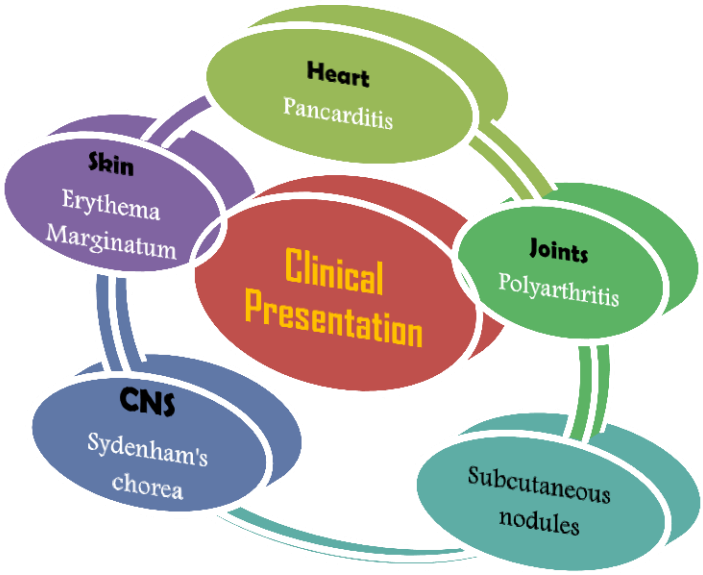
Purple: Extra notes for further understanding

Orange: Notes said by the doctor

Red : important

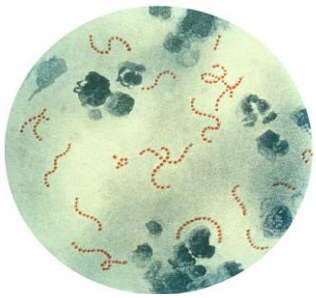
MIND MAPS

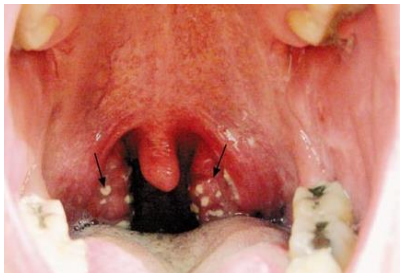

Rheumatic Fever
Affects periarteriolar C.T
Attachment & interferes with host immune response
Through M proteins
caused by antibody cross-reactivity
patients with ARF have an elevated anti-streptolysin O titer
1- Antigen invade activated antigen presenting cells
2- Antigen presented to helper T cells
3- Activation of self reactive B cells
4- Production of antibodies
5- The antibodies may also react against the myocardium and joints,
6- Producing the symptoms of rheumatic fever


Heart
Pancarditis
Skin
Erythema
Marginatum
Clinical
Presentation
Joints
Polyarthritis
CNS
Sydenham's
chorea
Subcutaneous
nodules

○ Introduction :

- **Rheumatic fever is an inflammatory disease which may develop after a Group A-Streptococcal (β-haemolytic) infection such as:**
  - **Strep. throat infection or scarlet fever (Scarlet fever is a disease caused by infection with the group A Streptococcus bacteria (the same bacteria that causes strep throat).**
  - **~3% of persons with untreated group A streptococcal pharyngitis develop rheumatic fever.**
  - **Can involve the heart, joints, skin, and brain**
  - **It commonly appears in children ages 5 through 15**
  - **15-20 million new cases a year in developing countries**
  - **Repeated streptococcal pharyngitis have more chance of developing rheumatic fever**
  - **Rheumatic fever is different from Rheumatoid arthritis . RA is chronic autoimmune disorder affects many organs but mainly small joint , serology marker is (Rheumatoid Factor).While Rheumatic fever affects bigger joints like knee joints for example.**
  - **Risk factors : Low standard of living , Crowding**





- **Individual (HLA) susceptibility is also important.**

- **Antigen-presenting cells bearing the HLA-DR7 molecule from RHD patients preferentially recognize heart-tissue protein. (People who carry HLA-DR7 gene are more prone to develop RF than who carry other genes.)**

- **Remember Antigen- presenting cells (Macrophages- B cells – Dendritic Cells).**

- **During Acute Rheumatic fever in young age patient will have fever but after that there is no fever.**

- **Antibody (Humoral immunity) and cellular immune response cross-reacts with human connective tissue**

- PATHOGENESIS:

  - **Rheumatic fever affect the peri-arteriolar connective tissue (Peri- arteriolar: tissues surrounds arterioles)**

  - **It is believed to be caused by antibody cross-reactivity**

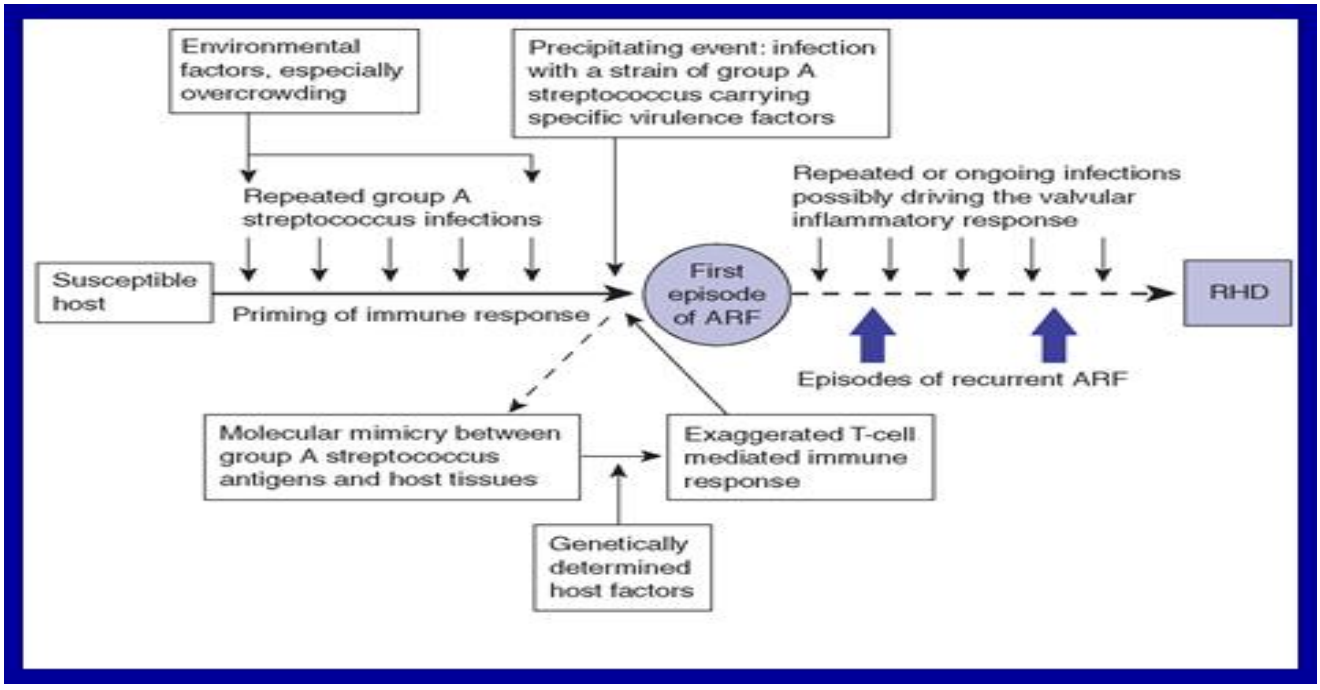
  - **This cross-reactivity is a Type II hypersensitivity reaction and is termed *molecular mimicry***

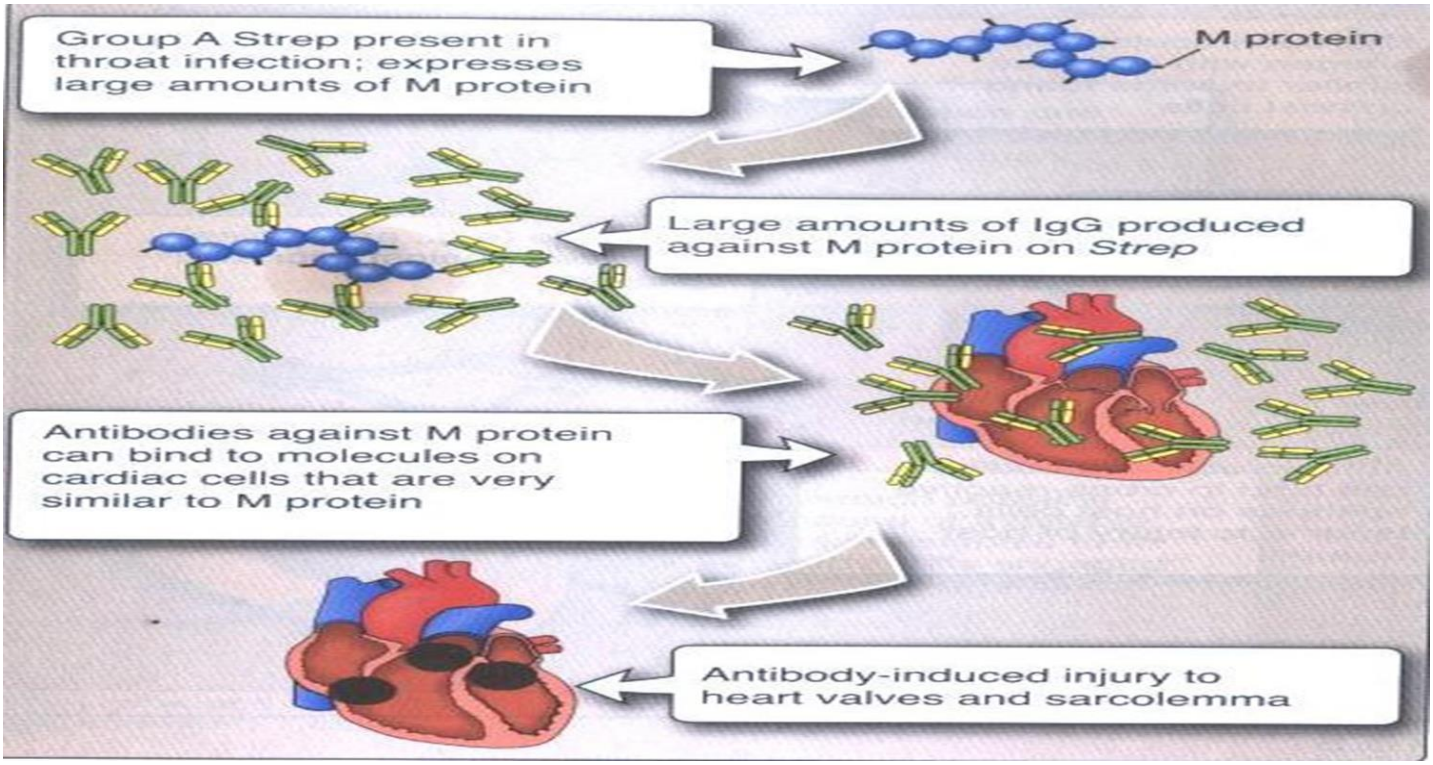
Antigen	Function
M proteins (most important)	Attachment & interferes with host immune response
Hyaluronic acid capsule	Camouflages the bacterium
Streptokinases	Dissolves blood clots
Peptidases	Degrades proteins involved in immune response
Pyrogenic toxins	Stimulate fever, rash & shock
Streptolysins	Lyse erythrocytes, leukocytes & platelets
Post streptococcal glomerulonephritis is caused by streptococcal antigen-antibody immune complexes (Type III hypersensitivity reaction)	

- Important notes:

- **In type II Hypersensitivity the Ab-Ag reaction occurs and damages locally on the tissues. (Associated with RF)**
- **In Post Streptococcal Glomerulonephritis the same Ab-Ag complexes are wandering in the circulation and then get deposited in the glomeruli.**
- **In Type III, preformed immune complexes cause remote (not local) damage. (NOT associated with RF)**
- **Hyaluronic acid capsule will make bacteria appear as something not foreign.**
- **Streptolysins : 2 types (L and O)**
- **M protein: is found on the surface of bacteria and it helps in attachment to mucosal surfaces.**
- **In myocardial infarction they use Streptokinases as a treatment to dissolve thrombus (Thrombolysis medication).**
- **Normally blood clots around the area of infection to prevent bacteria from spreading , here Streptococci releases Streptokinases that dissolves blood clots causing spread of infection.**

1. During a Strep. infection activated antigen presenting cells such as macrophages present the bacterial antigen to helper T cells
2. Helper T cells subsequently activate self reactive B cells and induce the production of antibodies against the cell wall of Streptococcus
3. Group A streptococcus pyogenes has a cell wall composed of branched polymers which sometimes contain "***M proteins***" that are highly antigenic
4. The antibodies which the immune system generates against the "*M proteins*" may cross react with cardiac myofiber protein myosin and smooth muscle cells of arteries and joint, inducing cytokine release and tissue destruction
5. This inflammation occurs through direct attachment of complement and Fc receptor-mediated recruitment of neutrophils and macrophages
6. producing the symptoms of rheumatic fever



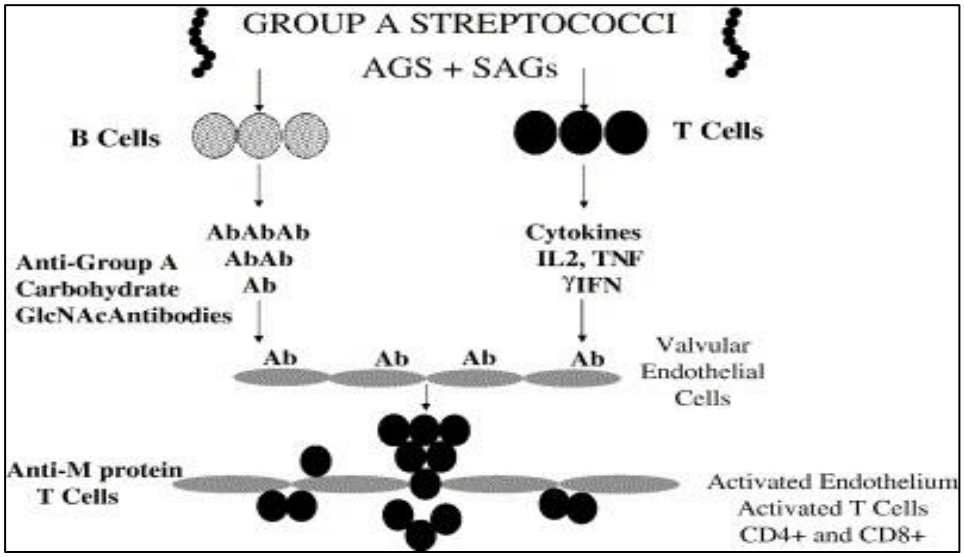


- **Antibodies are going to be found in high amount after 1-5 weeks after initial exposure.**
- **When antibodies that act against Streptococci decrease recurrent infection occurs.**
- **Whenever there is Ag-Ab reaction complements will be activated and then recruitment of neutrophils and macrophages will cause destruction.**

Both Humoral immunity and cell mediated immunity are involved but first humoral immunity (Abs) then cell mediated immunity (T-cells).

So again:

1. Antibodies released
2. Up regulates (VCAM-1)
3. T cells act



Both T and B cells will be activated. When the antibodies are formed they will attach to the heart valve and activate the complement system which leads to activate of the endothelium of the heart valve. Activation of the endothelium means it express vascular cell adhesion molecule-1 (VCAM-1) which will attract T cells to penetrate the valve and cause inflammation

-When endothelium is damaged by antibodies sequestered antigens will appear (hidden antigens) and the immune system will see sequestered antigens as foreign proteins.

-The end result = Granuloma formation (hypersensitivity type 4 delayed type of hypersensitivity)

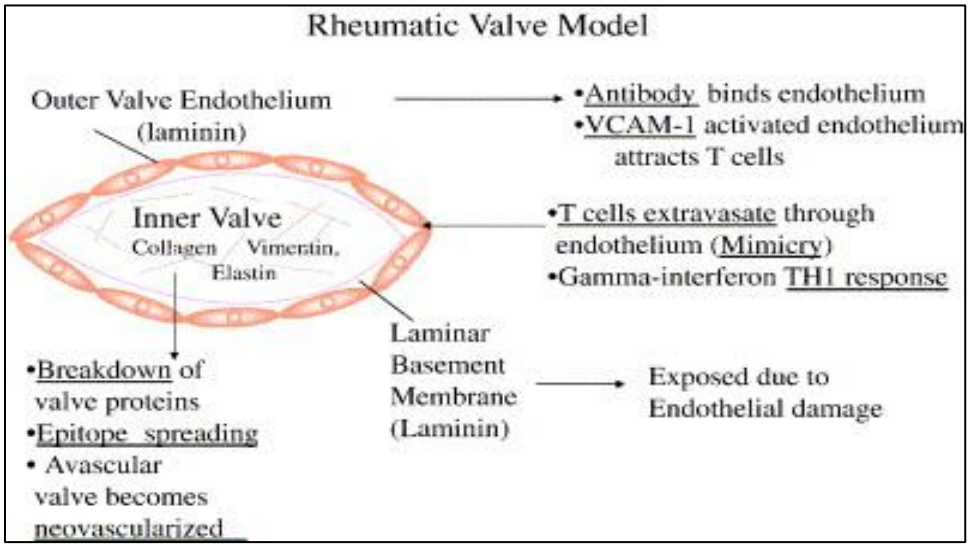
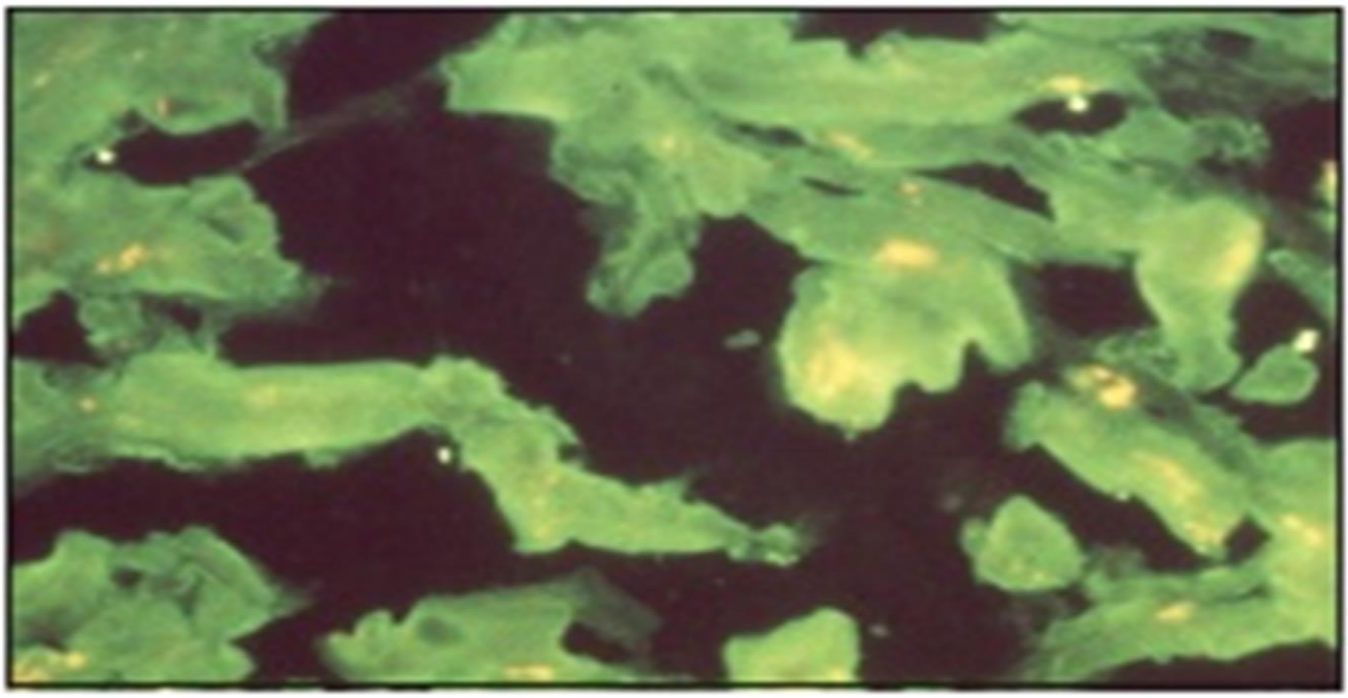
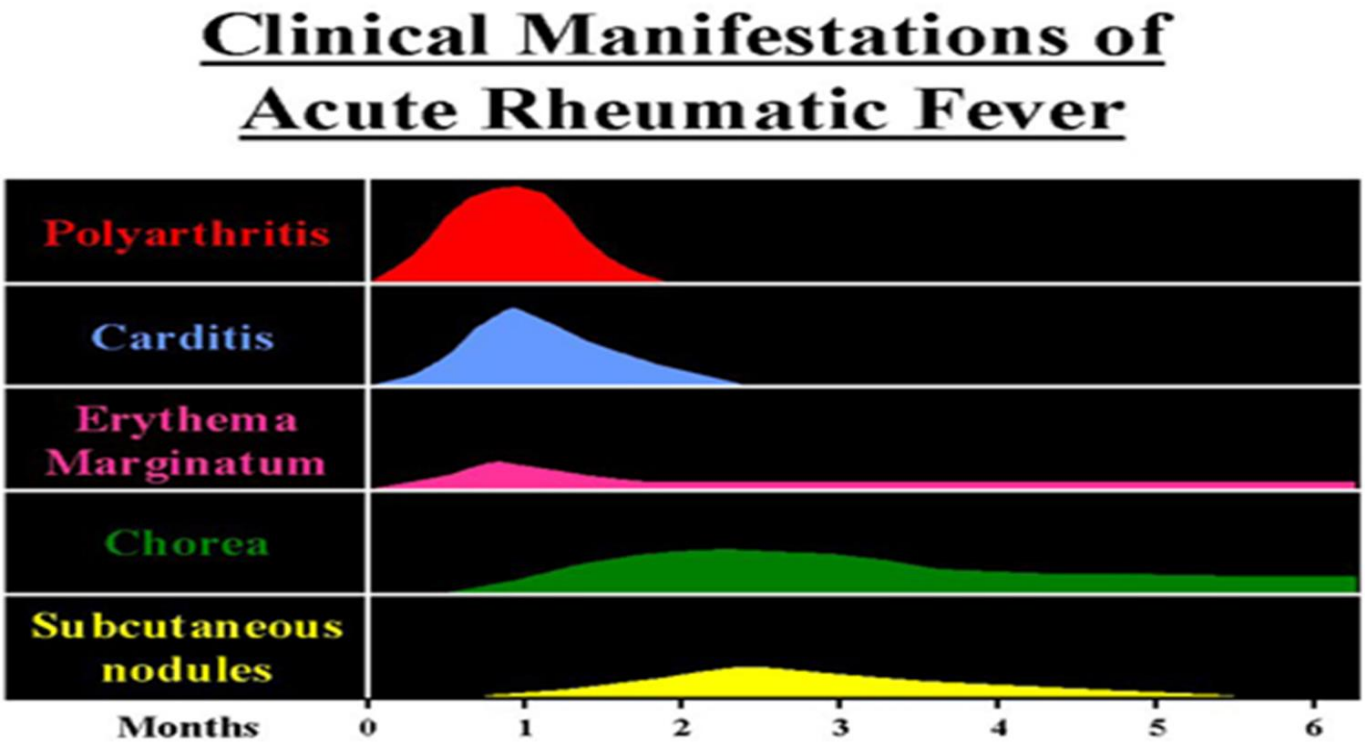


Diagram illustrating the process of initial mimicry which leads to granuloma formation, gamma interferon production and scarring in the valve. After the initial process has developed inflammation in the valve, other proteins in the valve may then be recognized by the immune system leading potentially to epitope spreading and responses against other valve proteins such as vimentin and collagen.

Epitope spreading: Release of sequestered antigens and more antigens are seen by the immune system. Epitope spreading is found in all autoimmune diseases not only RF.



Immunofluorescent staining of heart muscle with serum obtained from an acute rheumatic fever patients



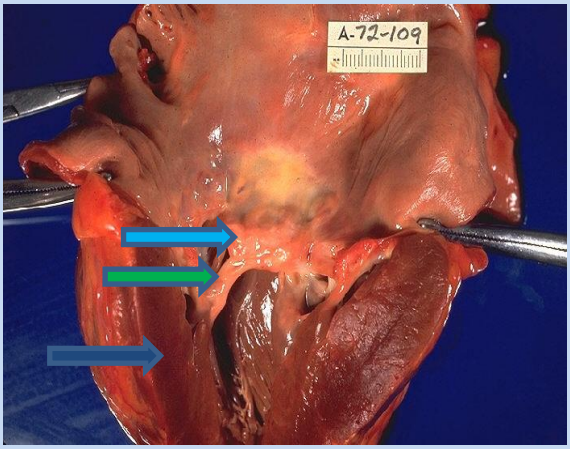
The first 3 appear early but chorea and subcutaneous they appear later but stay longer.

Clinical Presentation of Rheumatic Fever

Heart

*60% of patients with ARF progress to Rheumatic Heart Disease

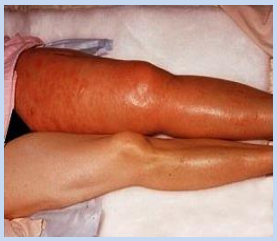
- The endocardium, pericardium, or myocardium may be affected Pancarditis
- Valvular damage (The mitral valve is almost always affected)
- Severe thickening of mitral valve, chordae tendineae and hypertrophied left ventricular



Joints

(arthritis)

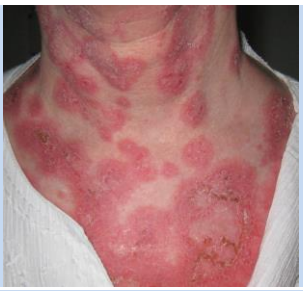
- Polyarthritis (migrate(flitting) from joint to joint)
- There is Swelling, redness and tenderness of the joint and occasionally joint effusion.
- affecting the larger joints more than the smaller ones.



Skin

(Erythema Marginatum)

- Skin lesions: The classical erythema marginatum—lesions with prominent margins slightly raised



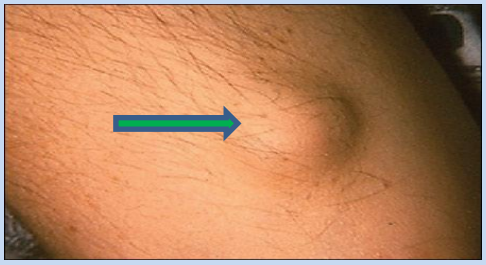
Central nervous system

(chorea)

- Sydenham's chorea (also known as saint vitus dance)
- (choreiform movements affect particularly the head and the upper limbs)
- They may be generalized or restricted to one side of the body (hemi-chorea)
- Chorea eventually resolves completely, usually within 6 weeks

Subcutaneous nodules

- Painless, round, firm lumps overlaid by normal looking skin
- (They range from a few millimeters to 1.5 cm in diameter, are localized over bony prominences like the elbow)
- They sometimes last longer than a month



Investigation of Rheumatic Fever	
1	**Anti-streptolysin O (ASO) titer** **At least 80% of patients with ARF have an elevated anti-streptolysin O titer at presentation** **Rising titer is more convincing**
2	**Anti-DNAse B (less used)**
3	**Anti-hyaluronidase test (less used)**
4	**Throat culture for group A streptococci (obtain 2 or 3 cultures)**

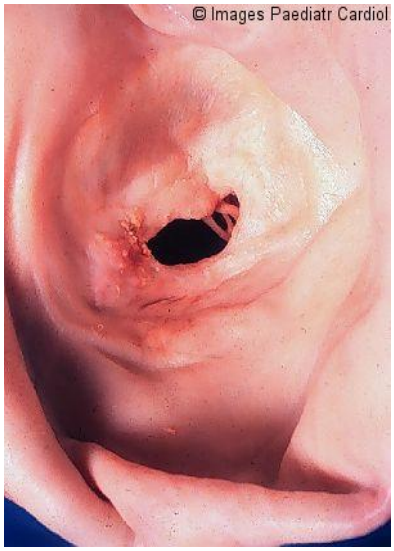
○ Clinical Course

- **Subsequent attacks**
  - **Increased vulnerability to reactivation of disease with subsequent strep infections**
  - **Same symptoms with each attack**
  - **Carditis worsens with each attack**
  - **Heart valves are frequently deformed (mitral)**
  - **Hear failure develops after decades**

○ Acute, recurring, chronic:

- **Symptoms prone to recur with subsequent Strep. infections**
- **Chronic disease leads to fibrosis (chordae of heart valves + valve cusps)**
- **We treat stenosis and incompetence valves by surgery but if damage was sever we use artificial valves.**

Opened stenotic mitral valve



Stenotic mitral valve seen from left atrium

○ Treatment of Rheumatic Fever

Treatment has 3 steps:

1) **Treat streptococcus throat infection with penicillin.**
2) **Treat other manifestations symptomatically.**
3) **Prophylactic long term anti-strep therapy given to anyone who has had rheumatic fever. (Penicillin is given as a prophylactic drug for about20 to 25 years)**

○ Take home message

- Rheumatic heart disease results from cross reacting antibodies binding the heart valves
- Repeated attacks of Streptococcal throat infection over the years damage heart valves resulting in either stenotic or incompetent heart valves
- Treatment involves surgical replacement of the damaged heart valves
- In patients with rheumatic fever long term administration of penicillin is recommended for prevention of future infections by group A Streptococcus

○ MCQs

Q1: **Rheumatic fever** is an inflammatory disease that may occurs following a _____.

A- Certain parasitic diseases.
B- Enterococcus infection.
C- Corynebacterium infection.
D- Group A streptococcal infection.

Q2: Which one of the following valves is most commonly affected by **rheumatic heart disease**?

A- The heart valve between the left chambers of the heart.
B- The pulmonary valve.
C- The heart valve between the right chambers of the heart.
D- The aortic valve.

Q3: Which one of the following causes the platelets to undergo lysis in **rheumatic fever**?

A- Pyrogenic toxins.
B- Peptidases.
C- Streptolysins.
D- M proteins.

Q4: Which one of the following is considered as an important clinical investigation of rheumatic fever?

A- ASO titer.
B- Platelet antibody testing.
C- ELISA.
D- Agglutination test.

Q5: Which one of the following is **NOT** a clinical manifestation of acute rheumatic fever?

A- Carditis.
B- Erythema marginatum.
C- Sydenham's chorea.
D- Parkinsonian syndrome.

Q6: Group A-Streptococcus has antigen that is responsible for Attachment & interferes with host immune response

A. Peptidases
B. Streptokinases
C. Streptolysins
D. M proteins

ANSWERS:
Q1-D Q2-A Q3-C Q4-A Q5-D Q6-D