Pathophysiology of Rheumatic Fever

Rheumatic fever is an acute immune-mediated, multi-system inflammatory disease that occurs after an untreated group A (-hemolytic) streptococcal (GAS) pharyngitis.

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Rheumatic fever is an inflammatory condition associated with Group A beta-hemolytic (GABS). In 97 percent of the individuals respond properly to it by producing antibodies against bacteria itself but in the remaining 3 percent, they produce antibodies directed not only to the bacteria but also to the body tissues which have antigens that mimic the bacteria.

The associated bacteria is GABS, specifically the streptococcal pyogenes which is pus forming.

What is meant by beta hemolyticus?

To understand what beta hemolyticus lets look at this case.

When bacteria are put in a blood agar with red blood cells and properly incubated some white spots will appear on the surface. This is because the bacteria produces a protein known as streptolysin. Streptolysin protein causes hemolysis of the cells particularly beta hemolysis.

When a normal individual becomes infected with the streptococcus bacteria, the bacteria have some antigens or proteins known as **M proteins** which are the ones that activate the immune system. The tissue damage by the bacteria signals the production of immune cells such as the leukotrienes, prostaglandins, and activation of mast cells producing histamines. All this causes an inflammatory response.

As a result of this response, there will be increased blood flow to the area and increased permeability of the capillaries. All this is to eliminate the bacteria since more white blood cells will increase at the area specifically macrophages and neutrophils to phagocytose or engulf the bacteria and killing them.

Neutrophils after phagocytosing the bacteria, will kill the bacteria with lysosomes and exocytose or release the antigens which then freely circulate into the lymphatic system and the regional lymph nodes. In this case, the ones located in the throat.

On the other hand, when macrophages phagocytose the bacteria they activate the gene on chromosome number six to MHC II molecules. As a result, the HLA II genes on chromosome number six are activated and causing it to produce the MHC II complex which will present the antigen to the T-cells. T cells have a molecule CD4 which is able to react with MHC II and TCR which will react and eliminate the bacteria.

A number of cytokines are massively produced by the T cells when activated by interleukin I,11, IV, V. These cytokines activate B cells in the lymph nodes. The B cells undergo clonal expansion and differentiate to plasma cells which have a lot of rough endoplasmic reticulum.

Usually, self-reactive B cells remain anergic in the periphery without T cell co-stimulation. During a Streptococcus infection, mature antigen-presenting cells such as B cells present the bacterial antigen to CD4-T cells which differentiate into helper T2 cells.

Helper T2 cells subsequently activate the B cells to become plasma cells and induce the production of antibodies against the cell wall of Streptococcus.

The cytokines will also stimulate antibody production by the B cells which are to attack the actual antigens enhancing more inflammation and inflammatory mediators to clear the bacteria.

However, in 3% of the patients, the antibodies are produced and directed to body tissues. This is specifically common in children at the age bracket of 5 to 15 years, the ones living in poverty and overcrowded populations.

Some proteins in the body mimic the bacterial proteins this phenomenon is known as molecular mimicry. Examples of these proteins are found in the following issues;

In the Skin

Keratin in the skin is one of these proteins

In the CNS

The basal ganglia which coordinates the movement have proteins known as gangliocytes specifically.

Heart

In the heart tissues, there are three layers we have **laminin** protein, muscle cell protein **tropomyosin**, **actin**, **troponin.** When all these layers are involved it is known as pancarditis.

Joints

In the large synovial joints, we have a protein known as **vimentin,** when involved it will lead to polyarthritis.

The heart

50 to 60 percent of the symptoms are with respect to carditis or heart disease-causing rheumatic heart disease.

As you know the outer layer is the **pericardium**. It has a **visceral** and **parietal** layer. In between these, there is a potential space with a serous fluid known as pericardium fluid. In the case of inflammation, these layers will be rubbing against each other causing pericardial friction rub when the heart is relaxing and contracting. On auscultation, you will hear this as a scratchy sound.

The **myocardium** is the muscular inner layer. When it is damaged by the tissues of the myocardium will undergo fibrinoid necrosis due to excess fibrinogen deposit. The part of the myocardium that has undergone fibrinoid necrosis will have a lot of fibrinogen.

Histologically characteristic Aschoff bodies, composed of swollen eosinophilic collagen surrounded by lymphocytes and macrophages can be seen on light microscopy. The larger macrophages may become **Anitschkow cells or Aschoff giant cell**s.

This tissues once destroyed is unable to contract enough reducing the degree of stretch known as cardiac pre-load, this, in turn, reduces the stroke volume and cardiac output causing congestive heart failure.

The endocardium is no exception. In rheumatic fever, valves are the most vulnerable. Rheumatic vegetations and a lot of inflammation will cause edema and inflammatory infiltration into the valvular surface. As this process occurs the fibroblasts are activated and produce fibrous tissue which is deposited on the surface of the valves thickening them.

If the process is recurrent it will lead to **stenosis** of the valve and **regurgitation**. *The primarily affected valves are of the left heart the mitral and the aortic semilunar valve.*

Commissural fusion at the edges of the valves can also arise. If this is extensive it can lead to impaired opening and closure of the valves. The cordae tendinae can also be thickened.

Sub-acute bacterial endocarditis can also arise over time. With repeated inflammation, the valves may be extensively affected and destroyed. This may dislodge off the septic vegetations to the brain vessels and pulmonary vessels which will be more dangerous to the patient.

In the central nervous system, we have the *lentiform nucleus* which is made up of the *putamen* and *globus pallidus.* The globus pallidus is divided into two parts by the medial medullary lamina. These are the internal globus pallidus (GPi) and the external globus pallidus [GPe]), the caudate nucleus and the subthalamus.

The globus pallidus is a structure in the brain involved in the regulation of voluntary movement. It is part of the basal ganglia, which, among many other things, regulates movements that occur on the subconscious level. the globus pallidus has a primarily inhibitory action that balances the excitatory action of the cerebellum.

These two systems evolved to work in harmony with each other to allow smooth and controlled movements. If there is damage to this area it will cause Sindehans chorea which is an uncontrolled jerky movement that occurs very rapidly. The areas involved are the face, the tongue, and the upper limbs.

Joints

When the joints are involved; 75 percent of the patients present with polyarthritis, you remember the protein vimentin?

The larger synovial joints specifically the hip joints and shoulder joints are involved. This polyarthritis is migratory in nature, unlike just arthralgia.

Skin lesions.

These patients present with some kind of rash which is a painless, nonpruritic, red annular

macules with concentric ring and is known as **erythema marginatum** shown in the image below. This kind of rash occurs on the extremities and upper trunk.

Collagen deposits can be deposited along the subcutaneous known as s**ubcutaneous nodules**. They usually appear on the extensor parts of the arms like the elbows and the knees.