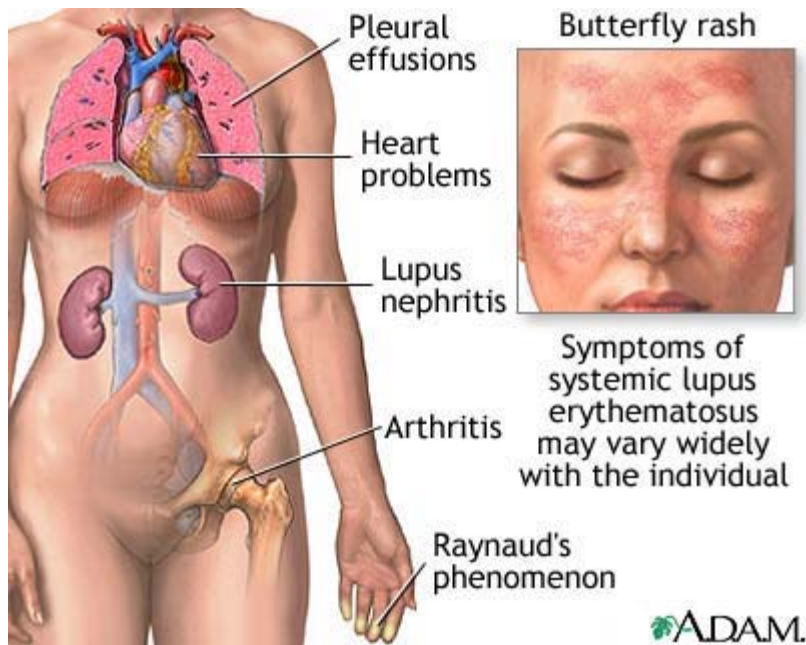


Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is a chronic, usually life-long, potentially fatal autoimmune disease characterized by unpredictable exacerbations and remissions.



- Systemic refers to Multisystem involvement
- Lupus is Latin for wolf.
- Erythematosus is from the Greek word for red.

Etiopatogenesis

SLE is a chronic inflammatory disease believed to be a type III hypersensitivity (serum sickness) response, which is characterised by the body's production of antibodies against the nuclear components of its own cells.

The exact cause of the disease is unknown and there is no consensus on whether it is a single condition or a group of related diseases.

Genetically predisposed immunologic influences, such as associations with HLA class II alleles DR2 and DR3, play a role, along with complement deficiencies (primarily C4a and C4b) and ethnic susceptibilities.

- **The Normal Immune System Response**

The inflammatory process is a byproduct of the activity of the body's immune system, which fights infection and heals wounds and injuries.

When an injury or an infection occurs, white blood cells are mobilized to rid the body of any foreign proteins, such as a virus.

The masses of blood cells that gather at the injured or infected site produce factors to fight any infections.

In the process, the surrounding area becomes inflamed and some healthy tissue is injured. The immune system is then called upon to repair wounds by clotting any bleeding blood vessels and initiating fiber-like patches to the tissue.

Under normal conditions, the immune system has special factors that control and limit this inflammatory process.

The Infection Fighters: B cells and T cells are two important components of the immune system that play a role in the inflammation associated with lupus. Both B cells and T cells belong to a family of immune cells called lymphocytes. Lymphocytes help fight infection.

For reasons that are still not completely understood, both the T cells and B cells become overactive in lupus patients.

In an immune response, it is normal for the antibody response to change over time, particularly if the first antibodies that are made do not eliminate the invading particles. Little by little, the types of antibodies being made undergo changes in an attempt to better recognize and fight an invader.

In lupus, a complex interaction between activated immune cells and an impaired antigen-elimination process leads to a greater than normal range of what the antibodies recognize.

Eventually, antibodies are made that recognize more of the body's own tissues in a stronger or more persistent manner than is healthy, and inflammatory responses are mounted in these tissues.

Autoantibodies :

In the majority of patients with SLE, antinuclear antibodies (ANA) are detectable.

Important research published in 2003 found that such autoantibodies may be present in individuals up to 7 years prior to their developing symptoms of lupus. Some subtypes of ANA are found in lupus patients and only rarely in people without lupus. These include:

Anti-ds DNA:

An autoantibody called anti-double stranded DNA (anti-ds DNA) may play an important role in some lupus patients. A 2001 study suggested that some of these antibodies specifically recognize a protein in the kidney called alpha-actinin, which researchers suspect may also occur in other tissues that are affected by SLE, such as in the skin, joints, and brain.

A subset of anti-DNA has also been found to target nerve-cell receptors in the brains of patients with SLE.

Anti-Sm antibodies:

This antibody is found most often in lupus patients of African descent and is almost never detected in people without lupus.

Although it is not usually seen in lupus patients, it almost always indicates SLE when it is detected.

Anti-Ro (SSA) and Anti-La (SSB):

These autoantibodies may be involved in the sun-sensitive rashes sensitivity experienced by patients with SLE and are also found in association with neonatal lupus syndrome, in which a pregnant mothers' antibodies cross the placenta and cause inflammation in the developing child's skin or heart.

Antiphospholipid antibodies:

A quarter to a half of patients with SLE may have these antibodies. They attack blood clotting regulator proteins which stick to phospholipids, fatty compounds found in cell membranes throughout the body.

They increase the risks for blood clots and may be responsible for narrowing of and irregularities in blood vessels.

Antiphospholipid antibodies are linked with miscarriages and other pregnancy complications, strokes, heart attacks and blood clots in almost any part of the body, including kidneys, legs, lungs, and eyes.

Cytokines:

Most immune cells secrete or stimulate the production of powerful immune factors called cytokines.

In small amounts, cytokines are indispensable for maintaining the balance of the body during immune responses, infections, injuries, tissue repair, blood clotting, clearing of debris from inflamed blood vessels, and other aspects of healing.

If overproduced, however, they can cause serious damage, including dangerous levels of inflammation and cellular injury.

Specific cytokines called interferons and interleukins play a critical role in SLE by regulating the secretion of autoantibodies by B cells.

Currently research is being done on role of interferon alpha; some evidence suggests high levels of this cytokine may underlie the autoimmune response in SLE.

Complement:

This is comprised of more than 30 proteins and is important for defending and regulating the immune response.

Inherited deficiencies in certain complement components (C1q, C1r, C1s, C4, and C2) have long been associated with SLE. Deficiencies may contribute to SLE in the following manner:

The complement system may protect against autoimmune disease by normalizing *apoptosis*, the natural process by which cells self-destruct.

This self-destruction process is an important part of the normal way in which the body cleans out damaged or no longer useful cells.

In healthy people, autoantibodies may also play a role in regulating apoptosis so that dangerous antigens are not left in the bloodstream long enough to trigger a more global (dysregulated) immune response.

Complement components are also necessary for clearing molecular rubble called immune complexes.

These are the end product of the battle between autoantibodies and antigens.

In the absence of complement, this debris accumulates and is deposited in the kidneys, blood vessels, joints, and other sites where it can cause the immune system to produce inflammation and tissue damage.

Triggers of the Immune Response

In genetically susceptible people, there are various external factors that can provoke an immune response. These include :

Viruses:

Blood tests reveal that patients with SLE are more likely to have been exposed to certain viruses than the general population. These viruses include the Epstein-Barr virus (the cause of mononucleosis), cytomegalovirus, and parvovirus-B1.

Results from a 2005 study suggested a strong association between Epstein-Barr virus (EBV) and increased risk of lupus, particularly for African Americans.

The study of 230 patients with lupus and matched controls assessed the seroprevalence of EBV antibodies.

One particular antibody, EBV-IgA, was linked to a five times greater risk of SLE in African Americans. The association was not as strong for whites, but increased with age (patients over 50 years of age had four times higher risk.)

The researchers also observed that a genetic variation in CTLA-4, a protein that helps regulate T-cell immune system response, appeared to modify the risk of lupus associated with EBV-IgA antibodies.

The Epstein-Barr virus settles into B cells after initial infection and can become dormant for long periods of time. T-cells trigger an immune response and help fight reactivation of infection.

Therefore, an individual's CTLA-4 genotype could determine the immune system's responsiveness in fighting repeat episodes of EBV infection.

Sunlight:

Ultraviolet (UV) rays found in sunlight are important SLE triggers.

When they bombard the skin, they can alter the structure of DNA in cells below the surface. The immune system may perceive these altered skin cells as foreign and trigger an autoimmune response against them.

UV light is categorized as UVB or UVA depending on the length of the wave.

UVB are short waves (280 to 320 nm). The shorter the wavelengths, the more damage they do.

UVA are longer waves (320 to 400 nm). Some research suggests that UVA wavelengths in the longest range, known as UVA1 (340 to 400 nm), may actually repair DNA and normalize immune responses.

Chemicals:

Clusters of SLE cases have occurred in populations with high exposure to certain chemicals.

For example, in a 2001 study, citizens in a small town in Arizona had two to seven times the prevalence of SLE, which was associated with a high exposure to chlorinated pesticides. Crystalline silica is another suspect.

Silicone breast implants have been under intense scrutiny as a possible trigger of autoimmune diseases, including SLE.

Hormones:

Cytokines, major immune factors that are active in SLE, are directly affected by sex hormones.

In general, estrogen enhances antibody production and testosterone reduces antibody production, although their exact role in SLE may be more complicated than that since there are various ways in which each hormone might influence various immune cells.

Women with SLE may have lower levels of several active male hormones (androgens), and some men who are affected by SLE may also have abnormal androgen levels.

Oral Contraceptives:

Female patients with SLE have long been cautioned against taking oral contraceptives due to the possibility that estrogen could trigger lupus flare-ups.

Studies presented at the 2004 annual meeting of the American College of Rheumatology suggested that oral contraceptives are safe for most women with lupus.

Women who were at high risk for blood clots due to antiphospholipid syndrome were excluded from these studies, and the researchers advised that such patients should not use oral contraceptives.

- **Gender**

About 90% of lupus patients are women, most of whom are diagnosed when they are in their childbearing ages, a fact that may be explained by hormones.

However after menopause, women are only 2.5 times as likely as men to contract SLE. Flares also become somewhat less common after menopause in women who have chronic SLE.

- **Genetics**

Research indicates that SLE may have a genetic link. Several genes need to be affected for lupus to occur, and the most important genes are located on chromosome 6. These mutations may occur randomly (*de novo*) or be inherited.

Researchers estimated that between 20 and 100 different genetic factors may be involved in the alterations of the immune system set point that could make a person susceptible to SLE.

Research published in 2003 identified a particular set of genes, now commonly called the "*interferon signature*," that is activated by interferon in patients with severe lupus.

This discovery may help doctors be able to identify patients at particular risk for severe disease before they develop symptoms.

A genetic risk factor for lupus in African American women was identified in 2003.

This defect causes increased production of nitric oxide, which may predispose individuals to lupus, and to severe disease in particular.

- **Other Autoimmune Disorders**

Rheumatoid Arthritis One study investigated the relationship between hormones, SLE, and rheumatoid arthritis, another autoimmune disease. Higher levels of estrogen are associated with SLE, while *lower* levels are associated with rheumatoid arthritis. The study found that some patients, in fact, progress from one disease to the other, and that such transitions occur during major hormonal shifts, such as the onset of menopause or pregnancy.

Fibromyalgia which some experts believe may be another autoimmune disorder, is also a common co-condition in patients with SLE.

Porphyrias The five major forms of dominantly inherited porphyrias (acute intermittent porphyria, porphyria cutanea tarda, hereditary coproporphyria, variegate porphyria and erythropoietic protoporphyria) have been detected in patients with SLE.

- **Drug-induced lupus**

Certain medications can cause temporary symptoms and signs of lupus. The symptoms go away when medication is stopped, generally within a few weeks. Symptoms are usually milder than in typical lupus, and the kidneys and central nervous system are rarely affected.

Common medications that may play a role in inducing lupus include:

- ACE inhibitors (captopril, lisinopril).
- Procainamide hydrochloride.
- Hydralazine hydrochloride.
- Isoniazid.

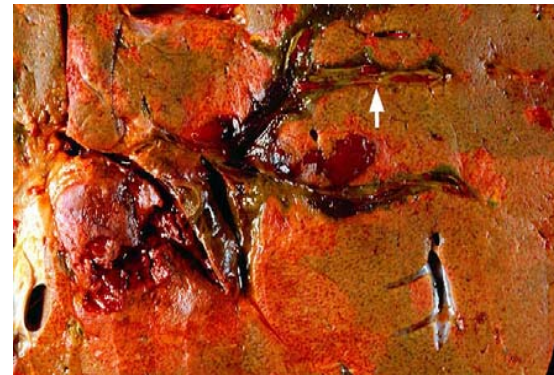
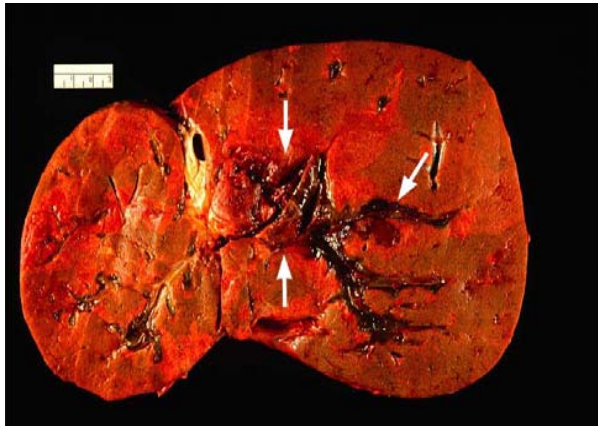
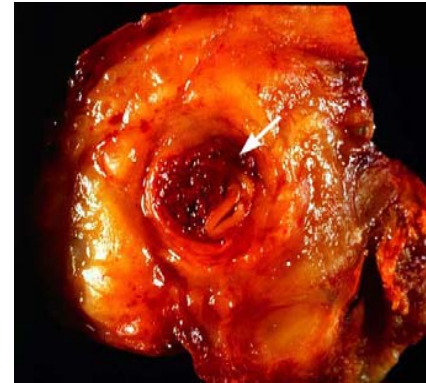
- Hydantoin group of anticonvulsants , such as phenytoin and ethotoin.
- Chlorpromazine hydrochloride.
- Methyldopa.
- Minocycline.
- Interferon alfa.
- D-penicillamine.

- **Lifestyle Factors**

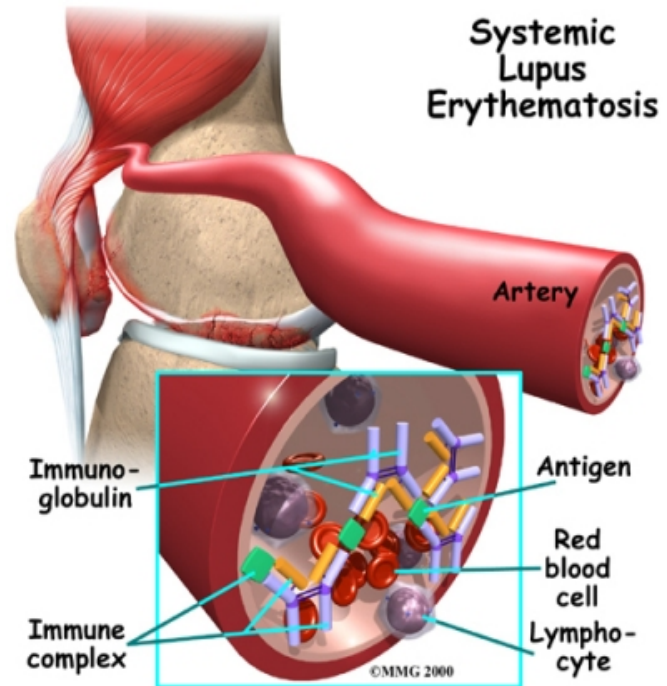
Smoking : A 2004 review found a small association between current smoking and SLE development. No association was observed for past cigarette use.

Pathology

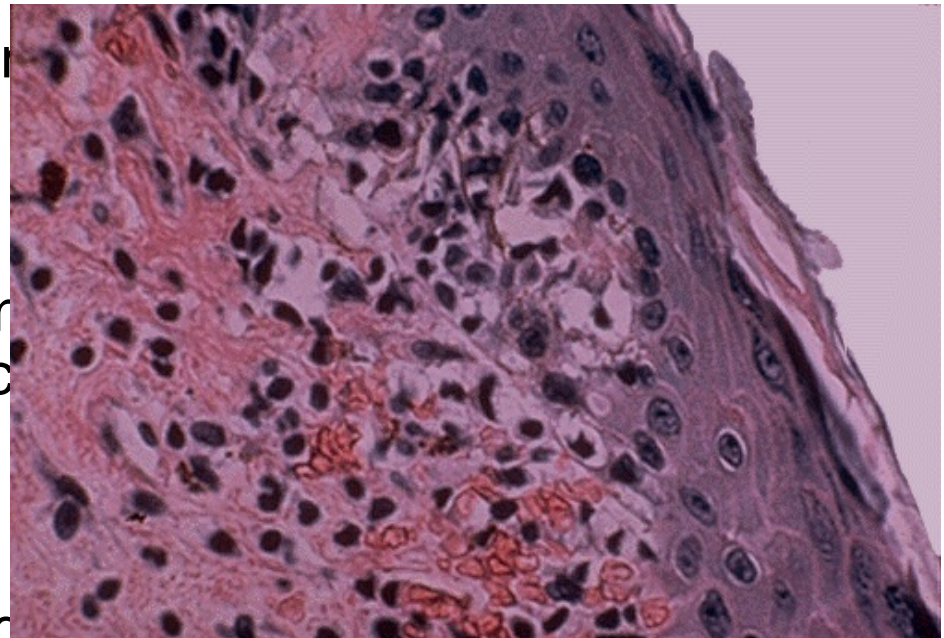
- The pathologic hallmark of the disease is recurrent, widespread, and diverse vascular lesions.



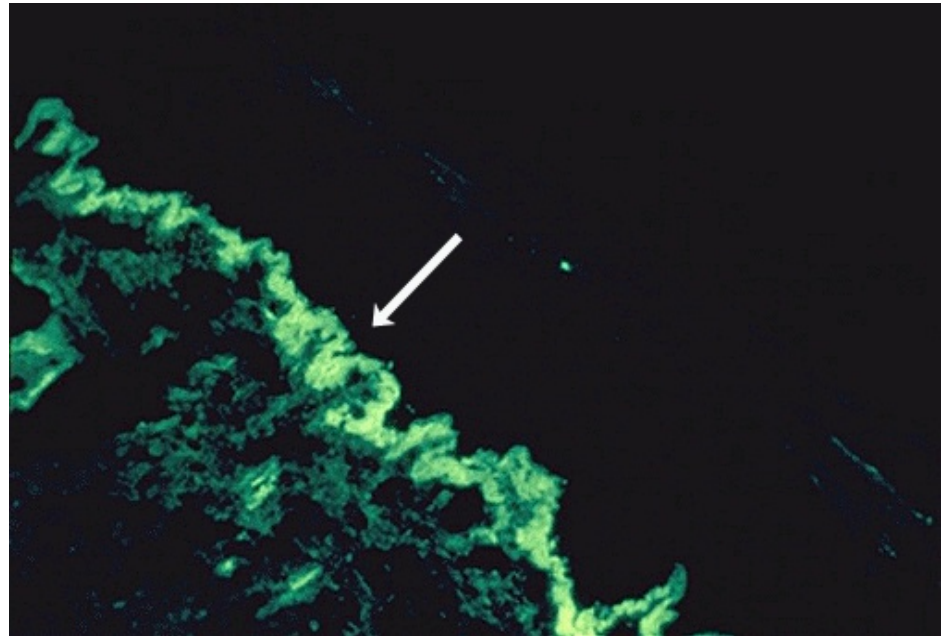
- Immune complexes can be deposited in glomeruli, skin, lungs, synovium, mesothelium, and other places.



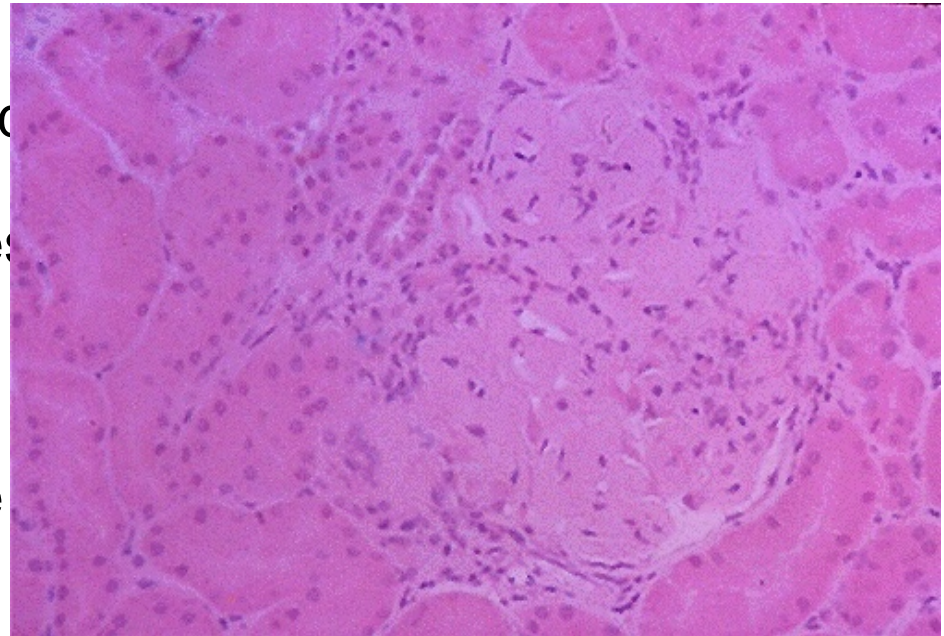
- A skin biopsy in the region of the rash reveals liquefactive necrosis of the basal layer at the dermal-epidermal junction along with dermal chronic inflammatory cell infiltrates (often perivascular) and extravasation of red blood cells (purpura) leading to the visible rash.



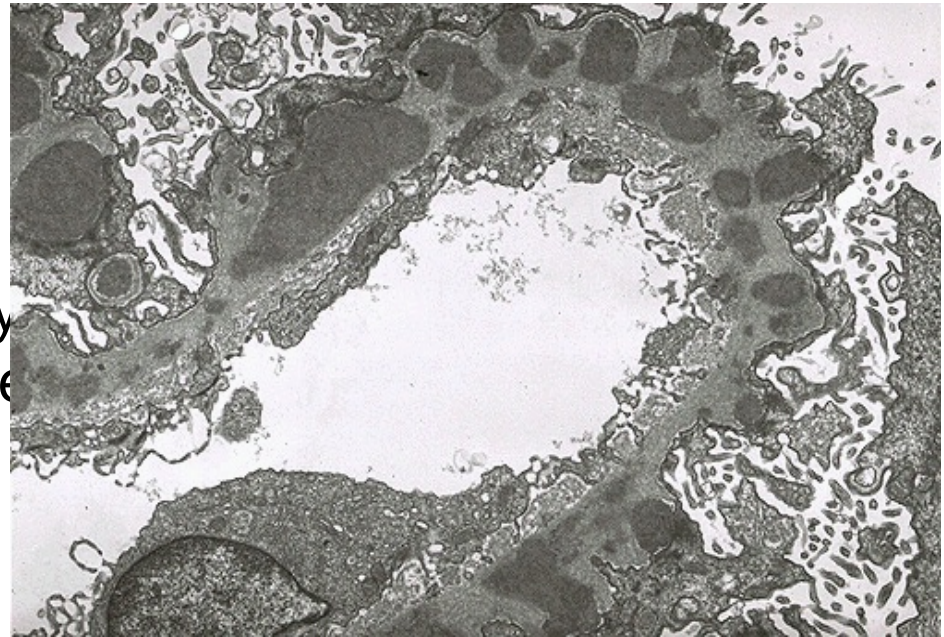
- Immunofluorescence of skin with antibody to IgG demonstrates a band-like deposition of immune complexes that is bright green at the dermal epidermal junction in this skin biopsy taken from an area with a visible rash.



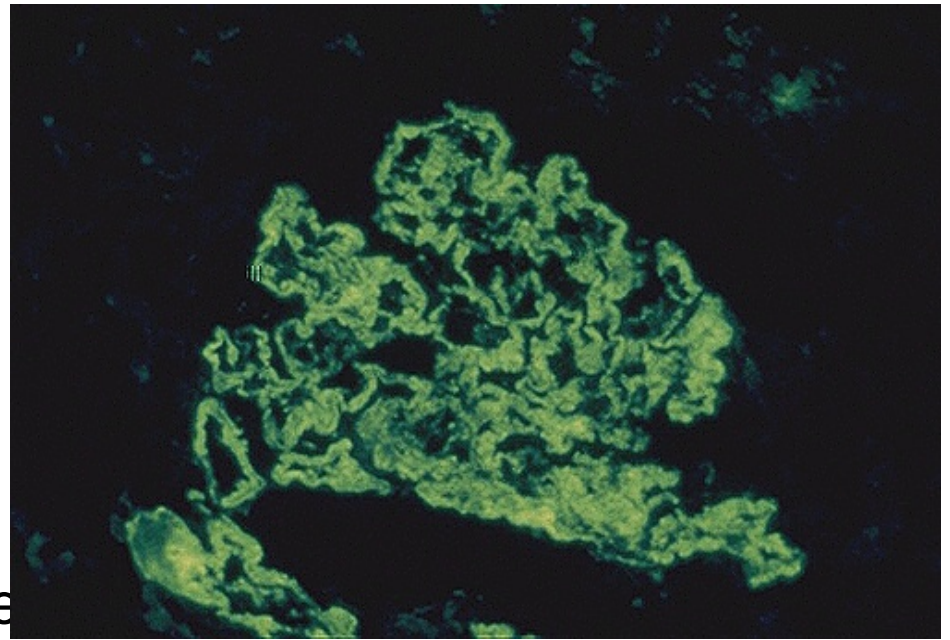
- A renal biopsy with H and E staining by light microscopy demonstrates a glomerulus that has markedly thickened capillary loops as a consequence of immune complex deposition.



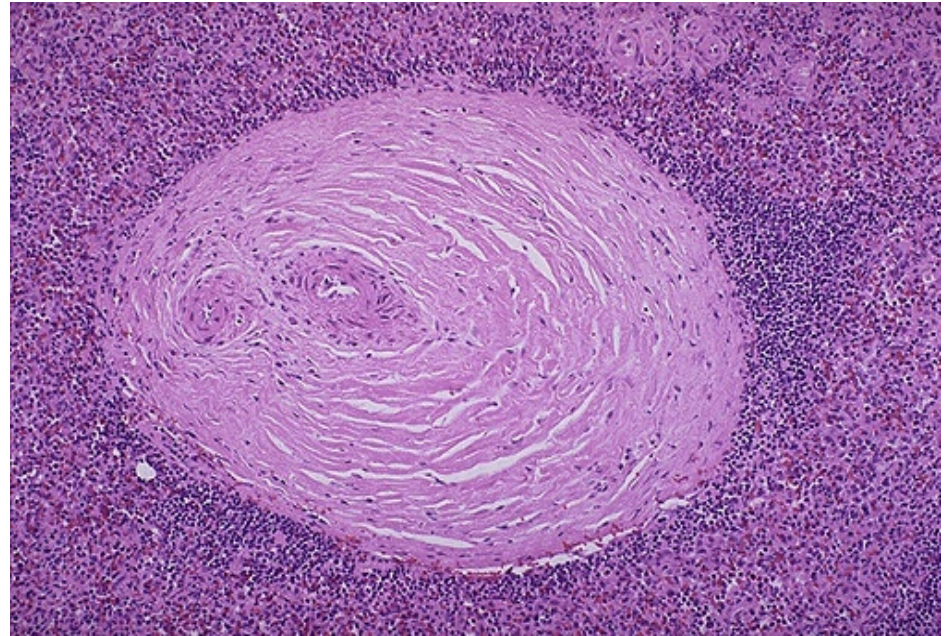
- Electron microscopy demonstrates thickening of the glomerular capillary loop basement membrane with scattered irregular electron dense deposits.



- A renal biopsy with immunofluorescence staining with antibody to C1q component of complement demonstrates extensive granular light green immunofluorescence in the glomerular capillary loops.



- SLE is associated with a peculiar periarteriolar fibrosis in the spleen.



- SLE can be associated with endocarditis (Libman-Sacks endocarditis) in which there are many fine reddish-tan vegetations spreading over the mitral valve and chordae.



All the best..