INTRODUCTION TO MEDICAL

IMMUNOLOGY

SLIDE SHEET

NUMBER	17
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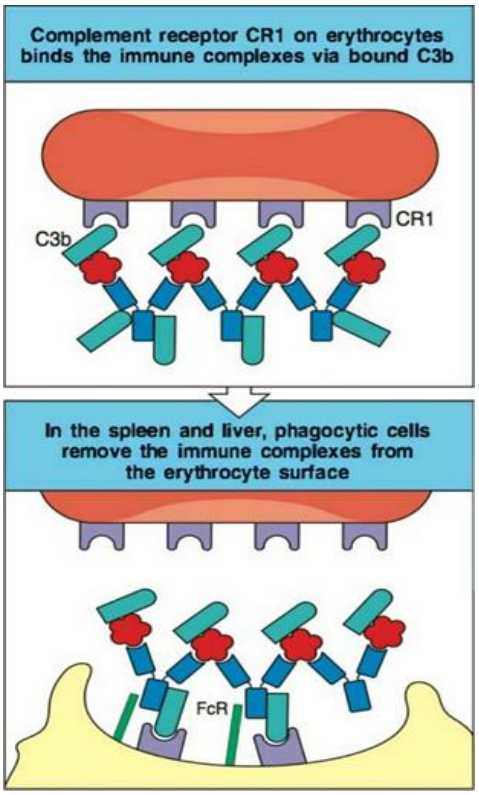
Systemic Lupus Erythematosus

The disease is called “systemic” as it affects multiple organs in the body, “erythematosus” since it causes redness of the skin, “lupus” – which means wolf – as it has symptoms thought to be similar to those caused by wolf bite.

Normally, the immune system functions in fighting foreign invaders and protecting our bodies. SLE is an autoimmune disease, as in many other autoimmune diseases the immune system attacks our own organs and tissues.
Genetic and environmental factors are involved in the pathogenesis of SLE. Some patients have **susceptibility genes**, when those patients are exposed to UV light some skin cells will encounter DNA damage, these cells will commit suicide (apoptosis), forming apoptotic bodies and releasing cellular components and nuclear antigens (DNA, histones, and others).
Normally the immune system doesn’t exist inside our cells, so when cellular (nuclear) components are expelled outside the cell the immune system will recognize them as foreign antigens and start producing antibodies against them. Since these antibodies are against nuclear “antigens” they’re called **Anti-Nuclear Antibodies (ANA).**



Clearance: when an immune response takes place, antigen-antibody complexes are formed. These complexes deposit at the site of invasion then the complement system recognizes them and binds them, complement system has receptors on erythrocytes called CR1. After that, erythrocytes travel to secondary lymphoid organs where phagocytes recognize Fc portion in the complex (because phagocytes have receptors for the Fc portion) and phagocytose them.

If **clearance fails**, antigen-antibody complexes will **accumulate** at the site of invasion, they might also be **transported** to other distant sites in the body. Wherever these complexes go, the compliment proteins will recognize them and bind them eliciting an **inflammatory reaction**. This widespread inflammation will cause **tissue damage**.
(Also people with **complement deficiency** are susceptible to develop SLE because they have a defective clearance).

SLE is one of the autoimmune diseases caused by antigen-antibody complexes, a mechanism known as **type III hypersensitivity** . Two other diseases belong to this group:

- Sub-acute bacterial endocarditis:
  In this disease bacteria are present on the **heart valves** for a long period of time, producing antigens that **mimic auto-antigens**, resulting in autoimmune diseases associated with **immune-complexes** that usually cause **glomerulonephritis**
- Cryoglobulinemia:
  Cryo- means "cold", **Cryoglobulins** are **auto-antibodies** (mainly **IgM**) precipitating under cold temperature. This explains the manifestation of certain immune diseases in cold weather, like **Reynaud's phenomenon** for example.
  Certain viral infections, like **Hepatitis C**, can cause the body to produce cryoglobulins, and their main consequence is **vasculitis**

From its name, SLE is a **systemic** disease so it causes wide variety of symptoms in many organs (skin, mucosa, etc.), which makes diagnosis of SLE **difficult**.
The American College of Rheumatology made 11 diagnostic criteria for SLE, **4 of them** should be met to diagnose a patient as SLE patient:

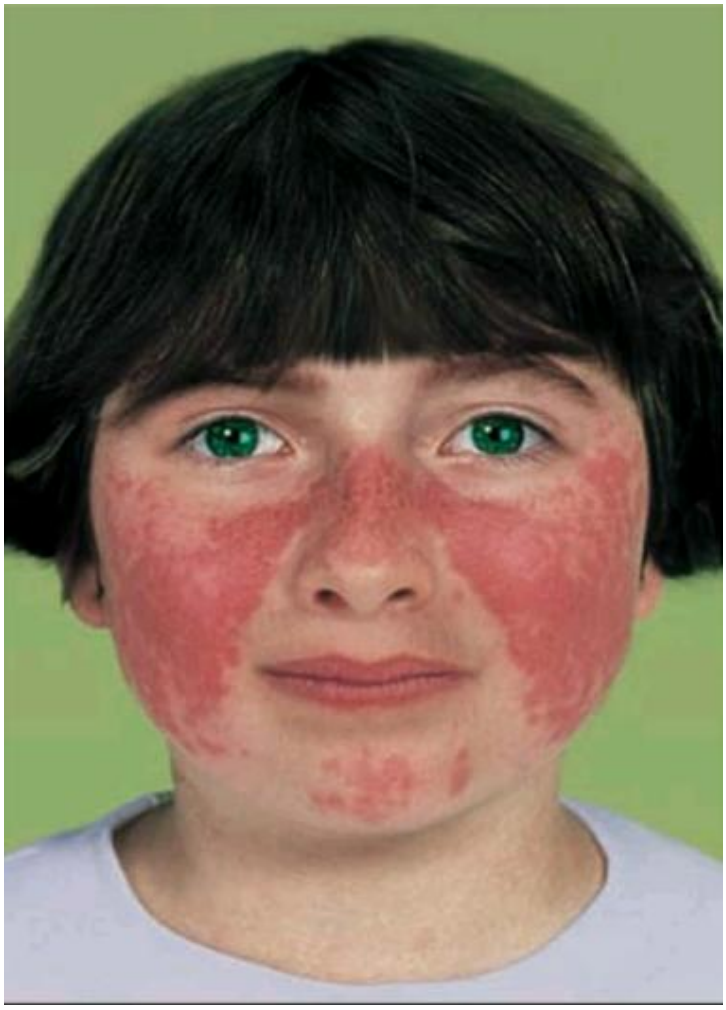
- **S**erositis (Pleuritis or Pericarditis)
- **O**ral ulcers
- **A**rthritis (more than 2 joints)
- **P**hotosensitivity
- **B**lood: Hemolytic anemia, leukopenia, lymphopenia or thrombocytopenia
- **R**enal: proteinuria and hematuria
- **A**NA
- **I**mmunologic(Antibodies to dsDNA or anti-phospholipids antibodies)

- **N**eurologic (psychosis, seizures)

- **M**alar (butterfly) rash

- **D**iscoid rash

SOAP BRAIN MD



The case of Nicole Chawner:

A 16 years old experienced excessive exposure to sunlight presented with **butterfly rash** and **stiff** joints and hips. SLE is suspected, so she was tested for the presence of **ANA** (with 1:1280 titer) and the test was positive. Further tests were done and they found that **anti-double-stranded-DNA antibodies** are present.
4 diagnostic criteria were met so Nicole was diagnosed as SLE patient.

Nicole's serum levels of C3 and C4 were low as a result of continuous consumption of complement components, while IgG level was high due to the persistent immune response, these two results correlate with SLE.
But she had normal platelet count (no thrombocytopenia), negative direct and indirect coombs test (no autoimmune hemolytic anemia), negative antiphospholipid antibodies, and normal urine tests (no proteinuria, no hematuria).

Since Nicole's case already met 4 of the diagnostic criteria, the doctors prescribed her an **anti-malarial** agent (Hydroxychloroquine sulfate) and asked her to **avoid direct sunlight because SLE patients have photosensitivity.**

Note: anti-malarial agents were found effective in treating SLE.

After a period of time, Nicole suffered from fever and chills every evening. She also had enlarged lymph nodes and unintended weight loss, and the tests showed anti-dsDNA titers increased and C3 levels were further decreased. So the anti-malarial agent made the situation even worse and the doctors replaced it with NSAIDs and steroids.

Note: ANA test is sensitive for SLE (Almost always positive in SLE, however, it can be positive in other autoimmune diseases"), while anti-dsDNA is specific for SLE(Positive only in SLE, however, false negative can occur in about 40% of SLE cases).

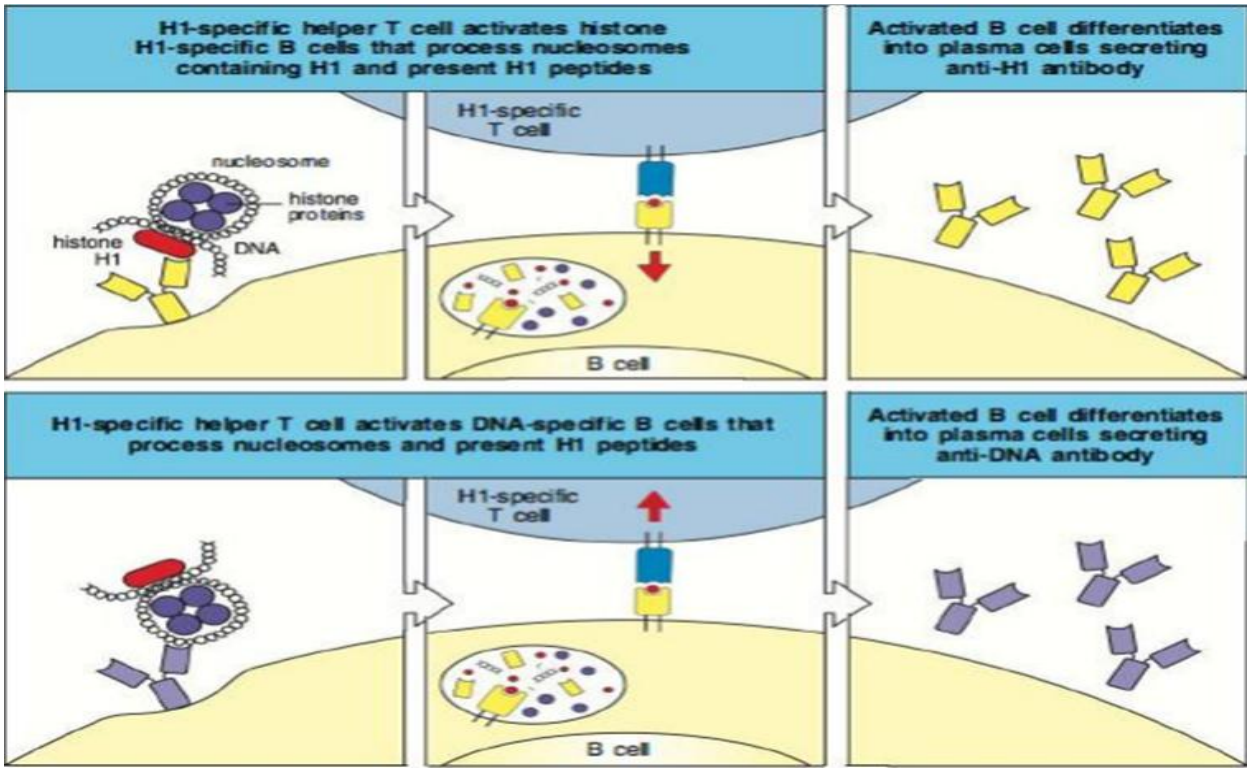
Note: Sometimes when we find two criteria of SLE and the disease is strongly suspected we treat it like SLE even without meeting the 4 criteria rule. We do so because the 4 criteria are **not necessarily present at the same time**, so we don't wait for another two criteria to show up, instead we act immediately. But still we don't label it as SLE unless 4 criteria are met.

Induction of SLE symptoms in patients with SLE susceptibility is not exclusively caused by sunlight, some drugs can induce SLE, e.g: Interferon-alpha which is used in cases of viral infections. In drug-induced SLE, symptoms are relieved after discontinuation of the medication.
in our bodies, the production of interferon-alpha is induced by the transcription factor IRF-5, Some people have certain haplotypes of IRF-5 that make them genetically predisposed to SLE.

- ***What is the significance of multiple measurements C3 levels?***
  C3 levels (and some other complement system components) are decreased in SLE patients due to their progressive interaction with the complexes, they are cleaved and consumed increasingly. C3 levels are used **as prognostic tool**, if the treatment is successful, C3 will increase back to normal, if treatment fails, C3 levels will remain low or further decrease.

- ***Why IgG levels were high?***
  Because of the constant stimulation by auto-antigens to the B cells that produce these antibodies.
- ***What was the significance of Nicole's normal urine tests?***
  To rule out the presence of glomerulonephritis.

SLE is not caused by reaction toward one auto-antigen, instead it's caused by a complex of auto-antigens, if one component of this complex is identified, antibodies can be produced against every component in the complex, how?
A nuclear fragment is released after apoptosis, one T helper cell recognizes histones as foreign antigens and stimulate B cells to react to it and differentiate into a plasma cells that produce antibodies, those antibodies are specific for histones, once the antibody binds to its antigen (histones) **the whole complex (nuclear fragment) is taken into the cell, then it's chopped into smaller pieces and presented on the surface**, now each peace (component of the complex; DNA, RNA, etc.) will be recognized by cognate T helper cell that will stimulate B cells and so on..



NOTE: Th1 cells mediate a cellular response whereas Th2 cells potentiate a humoral response, polarization toward Th2 response is higher in females making autoimmune diseases more frequent. **As for SLE, the male to female ratio 1:9.**

The rest of the lecture was about autoimmune diseases and the doctor read the slides. He only mentioned some notes about The HLA association with AID – table in slide 34:

HLA type is one of the genetic factors that play a role in the development of AID

This table shows many AID with their respective HLA type association

Most important ones to know are:

- Ankylosing Spondylitis and HLA type - B27, it will increase the risk of development of Ankylosing spondylitis by 150 times.
- Graves Disease and HLA type – DR3.
- Type 1 diabetes is also negatively associated with DQ6; patients with DQ6 HLA type are less susceptible to develop Type 1 diabetes , but it is positively associated with DQ8 .

Note: type 2 hypersensitivity rxn is mainly organ specific

Whereas immune complex hypersensitivity rxn is mainly systemic.

Thanks to Sura A-Kkhalili