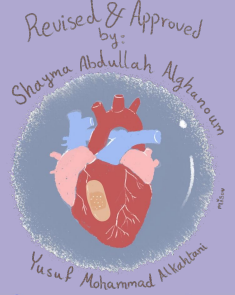
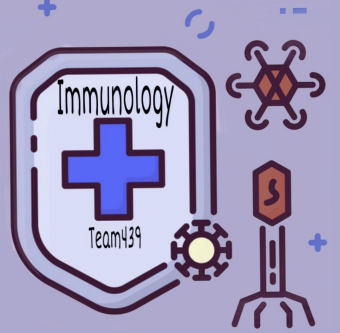
Autoimmune Diseases



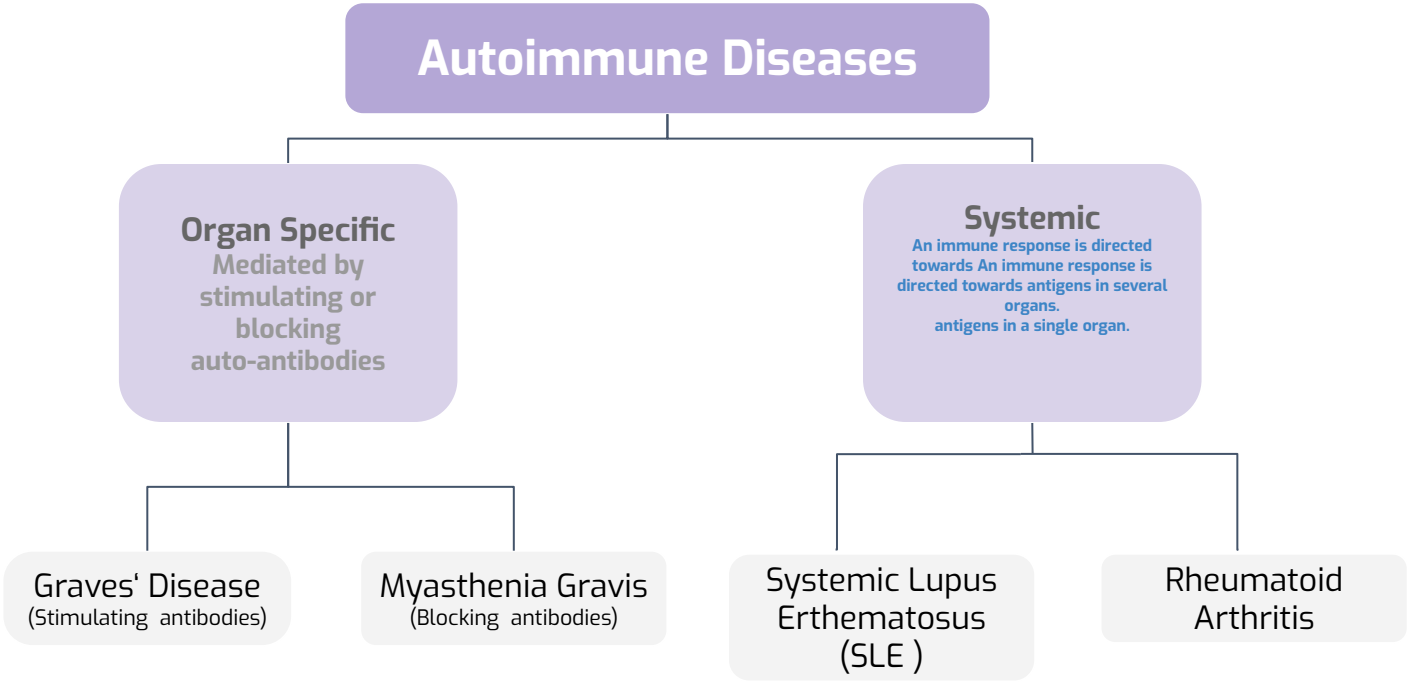


Objectives

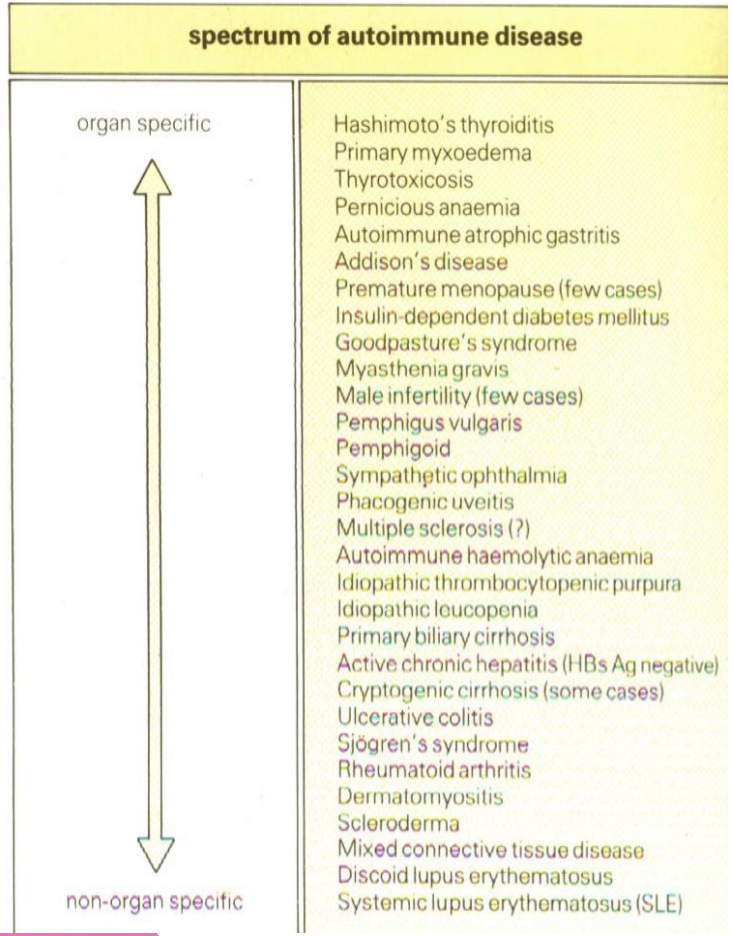
1- To know that the inflammatory processes in autoimmune diseases are mediated by hypersensitivity reactions (type II, III and IV).

2- To know that autoimmune diseases can be either organ specific or may be generalized involving many organs or tissues.

3- To understand that the manifestations of autoimmune diseases depend upon the organ and the degree of damage inflicted on the target tissues.



- Disease processes and tissue damage are due to Type II, Type III, and Type IV hypersensitivity reactions.



SOME AUTOIMMUNE DISEASES IN HUMANS

Disease	Self-antigen	Immune response
Organ-specific autoimmune diseases		
Addison's disease	Adrenal cells	Auto-antibodies
Autoimmune hemolytic anemia	RBC membrane proteins	Auto-antibodies
Goodpasture's syndrome	Renal and lung basement membranes	Auto-antibodies
Graves' disease	Thyroid-stimulating hormone receptor	Auto-antibody (stimulating)
Hashimoto's thyroiditis	Thyroid proteins and cells	T_{DTH} cells, auto-antibodies
Idiopathic thrombocyopenia purpura	Platelet membrane proteins	Auto-antibodies
Insulin-dependent diabetes mellitus	Pancreatic beta cells	T_{DTH} cells, auto-antibodies
Myasthenia gravis	Acetylcholine receptors	Auto-antibody (blocking)
Myocardial infarction	Heart	Auto-antibodies
Pernicious anemia	Gastric parietal cells; intrinsic factor	Auto-antibody
Poststreptococcal glomerulonephritis	Kidney	Antigen-antibody complexes
Spontaneous infertility	Sperm	Auto-antibodies
Systemic autoimmune disease		
Ankylosing spondylitis	Vertebrae	Immune complexes
Multiple sclerosis	Brain or white matter	T_{DTH} and T_C cells, auto-antibodies
Rheumatoid arthritis	Connective tissue, IgG	Auto-antibodies, immune complexes
Scleroderma	Nuclei, heart, lungs, gastrointestinal tract, kidney	Auto-antibodies
Sjogren's syndrome	Salivary gland, liver, kidney, thyroid	Auto-antibodies
Systemic lupus erythematosus (SLE)	DNA, nuclear protein, RBC and platelet membranes	Auto-antobidies, immune complexes

Similar to

Primary example of multiple organs

Examples of Autoimmune Diseases Affecting Different Systems:

Nervous System:
Multiple sclerosis
Myasthenia gravis
Autoimmune neuropathies such as:
- Guillain-Barré Syndrome (GBS)

Autoimmune uveitis

Blood:
Autoimmune hemolytic anemia
Pernicious anemia
Autoimmune thrombocytopenia

Blood Vessels:
Temporal arteritis
Anti-phospholipid syndrome
Vasculitides such as
Wegener's granulomatosis
Behcet's disease

Skin:
Psoriasis
Dermatitis herpetiformis
Pemphigus vulgaris
Vitiligo

Gastrointestinal System:
Crohn's Disease
Ulcerative colitis
Primary biliary cirrhosis
Autoimmune hepatitis

Endocrine Glands:
Type 1 or immune-mediated diabetes mellitus
Grave's Disease
Hashimoto's thyroiditis
Autoimmune oophoritis and orchitis
Autoimmune disease of the adrenal gland

Multiple Organs, Musculoskeletal System
Rheumatoid arthritis
Systemic lupus erythematosus
Scleroderma
Polymyositis, dermatomyositis
Ankylosing spondylitis
Sjogren's syndrome

Organ specific autoimmune diseases

1.Graves' diseases (Thyrotoxicosis):

Normal state

- Production of thyroid hormones is regulated by **thyroid-stimulating hormones (TSH).**

Which produced by pituitary gland

- The binding of TSH to a receptor on thyroid cells stimulates the synthesis of two **thyroid hormones: Thyroxine** and **Triiodothyronine**

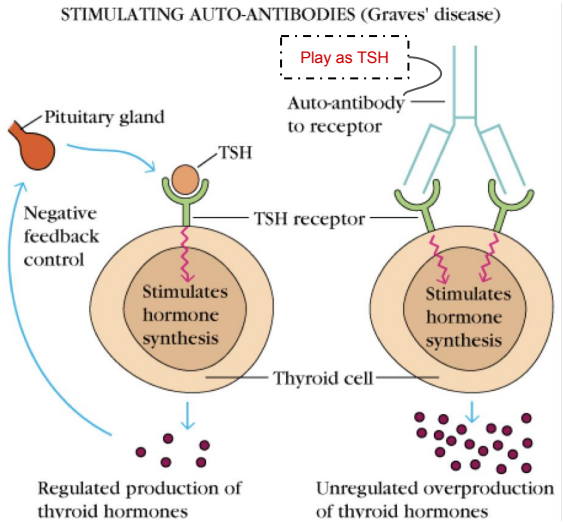
Graves' patient

-A person with Graves' Disease makes **auto-antibodies** to the receptor for TSH.

-Binding of these auto-antibodies to the receptor **mimics** the normal action of TSH leading to over stimulation of the thyroid gland (hyperthyroidism).

Clinical signs

Visible tremor
High blood pressure
Weight loss
Sclera is visible above pupil
Exophthalmos (eye pushed out)



Only disease with stimulating antibodies

2.Myasthenia Gravis

Normal state

An action potential arrives at NMJ, ACh is released and then binds to receptors and opens Na ion channels, leading to muscle contraction.

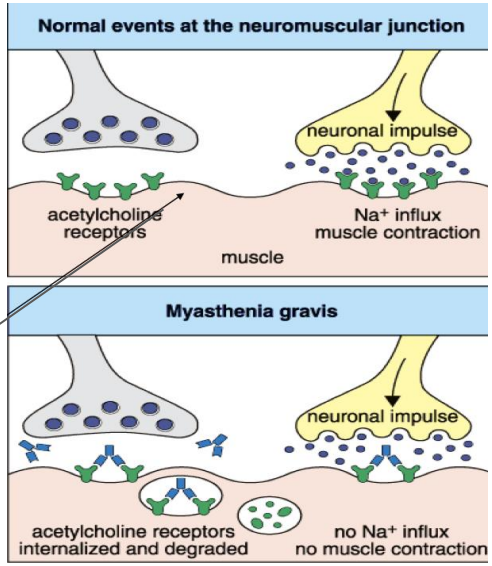
Myasthenia Gravis Patient (Pathophysiology)

Thanks to #med438

(Blocking Antibodies)

- Antibody (IgG) directed against (ACh) receptor by interacting with postsynaptic AChR at the nicotinic NMJ.
- Reduction in the number of functional AChR by increasing degradation (complement mediated) of receptor.

characterised By :weakness and fatigability on sustained effort



Motor end-plates of muscles

Systemic autoimmune diseases :

1. Systemic lupus erythematosus (SLE)

Definition

- Systemic lupus erythematosus is the prototype of systemic autoimmune disorder.
- It's a potentially fatal autoimmune disease.
(disease where the body attacks its own tissues)
When it becomes a fetal disease?
During infection and kidney involvement which make it sever disease.

complication

Affects patients with sun-sensitive (photo-sensitive) butterfly rash.

Treatment

-NSAIDs (Non-steroidal anti-inflammatory drugs).
-Antimalarials (Hydroxychloroquine)
-Immunosuppressive agents

Women are 90% more prevalent to the disease.

Pathophysiology of SLE

Genetic + environmental factors

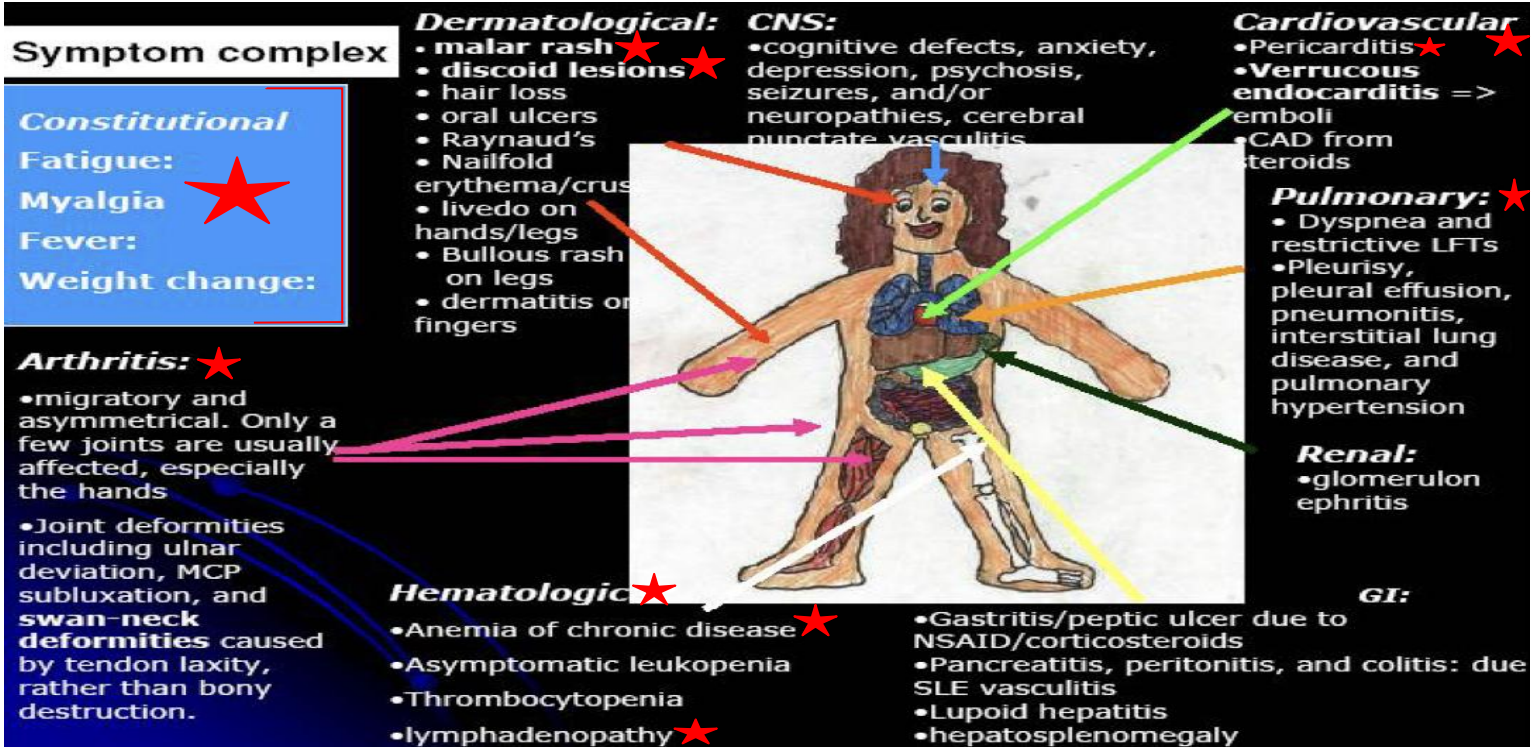
Pathogenic autoantibodies
DNA/RNA protein complexes

Immune complexes

Complement activation

IL-4, IL-6, and IL-10 released | Destruction of cells | Chemotaxins | Leukocytes

- Symptoms Complex :



Important

SLE test

-Anti-nuclear antibody(ANA) test
best screening test for SLE) it's determined by immunofluorescence
- The ANA is positive in significant titer (usually 1:160 or higher) in virtually all patients with SLE

Screening test

If we think of SLE as a diagnosis
First we use **ANA (anti-nuclear antibody)** because it's a screening test
Result:
- > these is **no** anti nuclear antibody
+ > there is anti-nuclear antibody ⟶ We should do another investigation to know the target of antibody
There are three important target :
Double-stranded DNA, **SM antigen** and **antiphospholipid**

Sensitive

(most specific)
SM : Smith (name of the patient)

-decrease Complement Levels (CH50, C3, C4)
-Complement Split products

-ESR (high) -CRP (high)
-Decreased complement C1q

Targeting test

Antigen	Clinical associations
Double stranded DNA	Nephritis (and flare)
Anti RNP	Scleroderma, myositis
Histones	Drug-Induced lupus
SM antigen (specific for SLE)	Severe SLE
Anti ribosomal	Psychosis (الذهان), Depression
Antiphospholipid	fetal loss, Clotting
Anti neuronal	Active CNS lupus
SSA/Ro	SCLE, SJOGREN's, NLS
SSB/La	SCLE, SJOGREN's, NLS

Not specific for SLE

Important

Because it involves the kidney

Can affect platelets phospholipid > coagulation process affected > risk of thrombosis

مرض SLE مثل ماقلنا يصيب النساء أكثر شيء وايضًا له فترات يكون المرض نشط ومرات خامل، إذا صدف وحملت المصابة فراح يتعرض جنينها للخطر بانتقال Autoantibodies أو من التجلط او من SSA/Ro or SSB/La
لأنهم إذا انتقلوا للجنين يسببون له Cardiovascular blocking فلازم يكون فيه تخطيط للحمل يكون في المرحلة الخاملة مو النشطة

2. Rheumatoid Arthritis

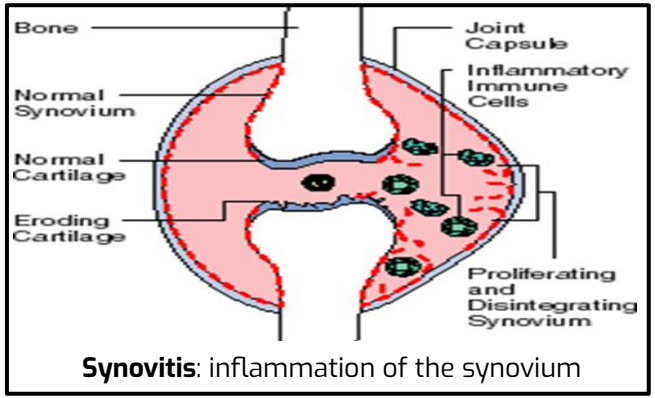
Rheumatoid arthritis (RA) that affects peripheral joints is characterized by synovitis that may cause destruction of both cartilage and bone.

Definition

it's a common **autoimmune disease** in which the normal immune response is directed against an individual's own tissue, including the: **Joints, Tendons and Bones.** Resulting in inflammation and destruction of these tissues with progressive disability.

Systemic complication

1-Cardiovascular
2-Pulmonary
Leading to early death



Synovitis: inflammation of the synovium

Prevalence & incidence

Both prevalence and incidence are 2-3 times greater in **women** than in men.

Cause

The cause of rheumatoid arthritis is not known:

- **complex interplay among genotype**
- **environmental triggers**

Genetic factors

HLA-DR B1 locus alleles which contain the amino acid motif (QKRAA) are termed the **shared epitope**, confer particular susceptibility.

There is sequence found on "HLA-DRB1" gene , shared on all Rheumatoid arthritis patients, but it doesn't mean that everyone has this sequence must have Rhematoid arthritis.

Pathogenesis
(Type III hypersensitivity reaction)

1

Lack of tolerance to **citrullinated proteins** or **immune complexes** leads to activation of immune system(inflammatory cells).

2

Inflammatory cells(macrophages) will engulf the immune complexes and produce pro inflammatory cytokines: TNF-α,IL-1, and IL-17. These cytokines induce the secretion of **metalloproteinases**.

3

T cell activation due to unknown antigens also contributes to the inflammation in RA.

4

Activation of B cells which synthesize **ACP** and rheumatoid factor.

Citrullinated proteins: convert of the amino acid arginine in a protein into the amino acid citrulline
Immune complex: integral binding of ab with an antigen
Metalloproteinases: cause joint destruction
Anti-citrullinated proteins antibodies(ACP) : Antibodies that attack the citrullinated proteins

Rheumatoid arthritis

Diagnosis

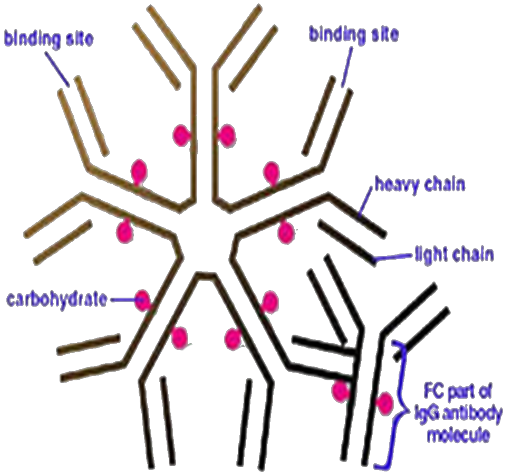
Important

- Anti–citrullinated protein/peptides(ACP) antibodies/ anti-CCP : specific markers
- Rheumatoid factor

Treatment

- NSAIDS (Non-steroidal anti-inflammatory drugs)
- Disease-modifying drugs (eg, gold (injectable), hydroxychloroquine, sulfasalazine, penicillamine)
- Immunosuppressive therapy:
  -Corticosteroids
  -Methotrexate
- Surgery
- Physical therapy

Rheumatoid factor:
-In RA many individuals produce this type of auto-antibodies.
-The IgM ab is directed against the Fc region of the IgG ab forming the IgM-IgG complexes (Rheumatoid factor).
-this complex may be deposited in joints leading to activation of synovial macrophage(inflammatory cells).



Take Home Messages :

- The spectrum of autoimmune disorders is wide ranging from single organ involvement to a systemic disease.
- The disease process is usually prolonged and is generally associated with significant morbidity and mortality.
- The mainstay of the treatment is to maintain immunosuppression.

Quiz

Question 1: Which of the following is the disease associated with <u>stimulating</u> antibodies?
A - SLE **B-** Rheumatoid Arthritis **C-** Graves' **D-** Myasthenia Gravis
Question 2: Which of the following is the disease associated with <u>blocking</u> antibodies?
A - SLE **B-** Rheumatoid Arthritis **C-** Graves' **D-** Myasthenia Gravis
Question 3: What's the best screening test for SLE disease?
A - Anti-nuclear antibody(ANA). **B-**Complement Split products **C-**Anti-double-stranded DNA titers **D-**ESR
Question 4: which antibodies are secreted in RA
A - Anti-citrullinated proteins abs **B-** Rheumatoid factor **C-** IgG **D-** A and B
Question 5: which of the following is not a treatment for RA
A - NSAIDs **B-** Surgery **C-** Antimalarias **D-** Immuno suppressive therapy

1:C
2:D
3:A
4:D
5:C

team leaders

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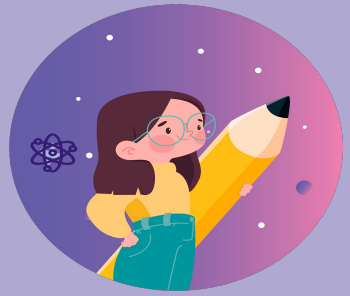

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