The Delicate Balance: Immunodeficiency & Autoimmunity

From Developmental Failures to Systemic Betrayal

Hypo-activity: The failure of development (Primary Immunodeficiency)

The immune system is a narrative of regulation. Pathology arises when the system deviates from the center:

Hyper-activity: The loss of tolerance (Autoimmune Disorders)

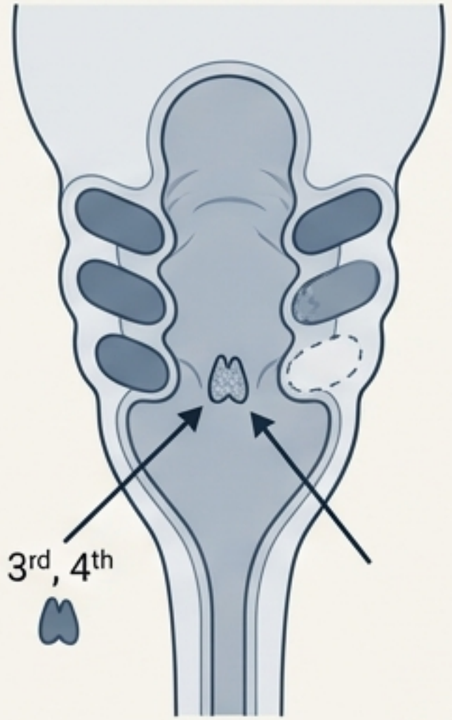
The Spectrum of Dysfunction

Defined by what is missing.
Key indicator: Recurrent infections, opportunistic pathogens, reaction to live vaccines.

Defined by loss of tolerance.
Key indicators: Female predominance, HLA HLA genetic susceptibility, Environmental triggers.

The Foundation Crumbles: T-Cell & Combined Defects

DiGeorge Syndrome (22q11 Deletion)



CATCH-22

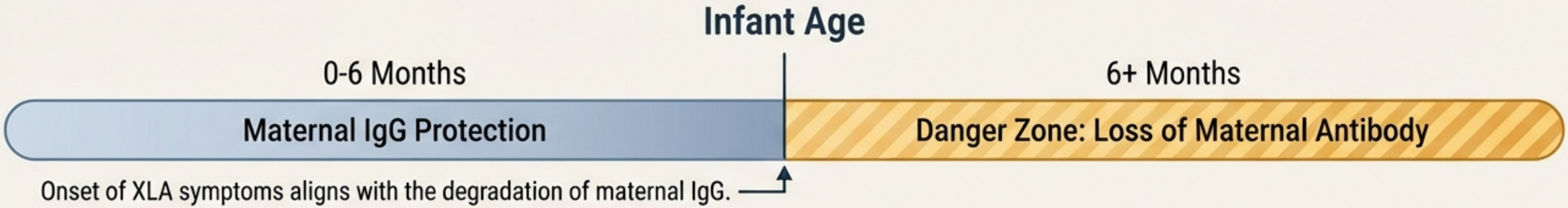
- Cardiac Abnormalities
- Abnormal Face
- Thymic Aplasia
- Cleft Palate
- Hypocalcemia

Severe Combined Immunodeficiency (SCID)

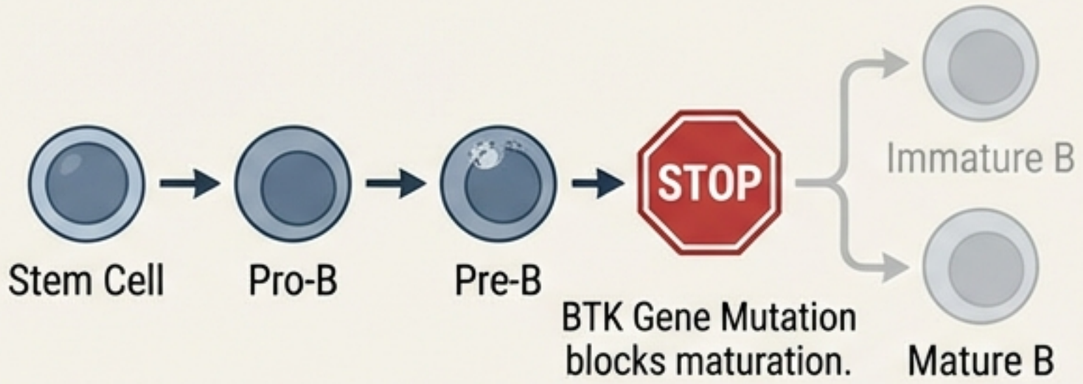
- **Cytokine Receptor Defects:** Signaling failure prevents maturation.
- **ADA Deficiency:** Toxic buildup of adenosine in lymphocytes.
- **MHC Class II Deficiency:** CD4+ helper T-cells cannot activate.

Systemic Failure: Loss of both Humoral and Cell-Mediated immunity. Susceptible to ALL pathogens.

The Antibody Drought: B-Cell Maturation Disorders



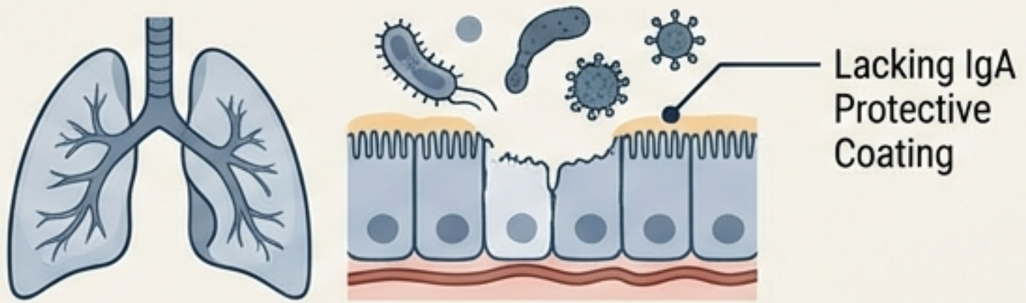
X-Linked Agammaglobulinemia (XLA)



Complete lack of Ig. Recurrent bacterial/enterovirus infections.
Contraindication: Live Vaccines.

IgA Deficiency

Most common immunoglobulin deficiency.



Often asymptomatic. Risk of Anaphylaxis if given blood products containing IgA.

Failure of Signaling: Hyper-IgM & CVID

Hyper-IgM Syndrome

Zoom-In: T-Cell to B-Cell Interaction

No Second Signal

No Class Switching

IgM stays High

IgG, IgA, IgE very Low

Recurrent pyogenic infections due to poor opsonization.

Common Variable Immunodeficiency (CVID)

The Late-Onset Failure

Defect: Low immunoglobulin due to B-cell or Helper T-cell defects.

Key Distinction: Diagnosis typically in late childhood (vs. infancy).

High Yield Associations

- Increased risk of Autoimmune Disease

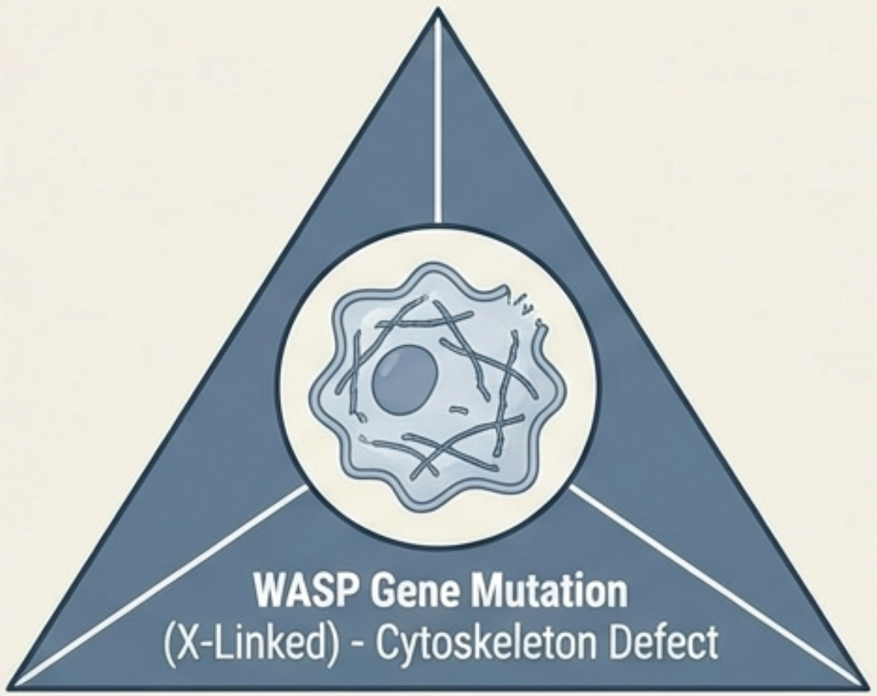
- Increased risk of Lymphoma

- Susceptibility to *Giardia lamblia*

Structural Integrity & The Complement Cascade

Wiskott-Aldrich Syndrome

Eczema

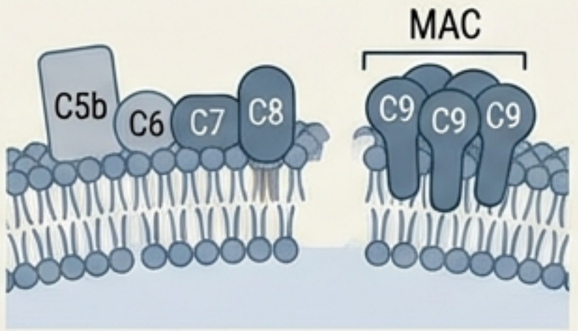


WASP Gene Mutation
(X-Linked) - Cytoskeleton Defect

Thrombocytopenia
(Bleeding is major cause of death)

Recurrent Infections

Terminal Complement Deficiency (C5-C9)



Clinical Consequence:
Inability to lyse bacteria → High risk for Neisseria (Gonorrhea/Meningitis).

C1 Inhibitor Deficiency

Hereditary Angioedema
(Unregulated Kallikrein → Bradykinin).

The Mechanics of Betrayal: Loss of Tolerance

Bone Marrow & Thymus (The Academy)

Central Tolerance

Self-Reactive T-Cells

Failure of Selection

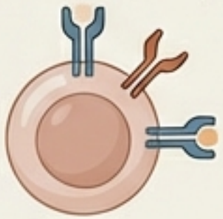
AIRE Mutation → **Autoimmune Polyendocrine Syndrome**

Peripheral Tissue (The Real World)

Peripheral Tolerance

Apoptosis
(Negative Selection)

Anergy
(Inactivation)

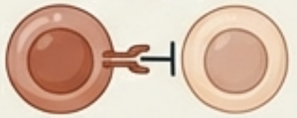


Apoptosis via Fas Pathway

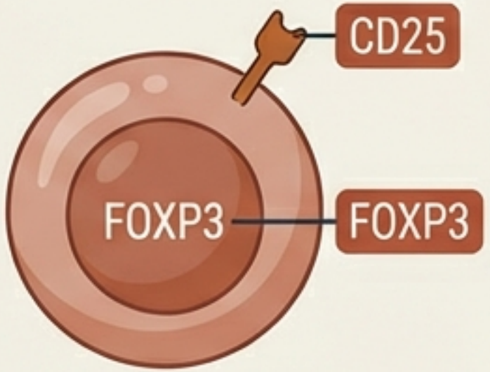
Fas

(Note: Fas mutation = ALPS)

Suppression by Regulatory T-Cells (Tregs)

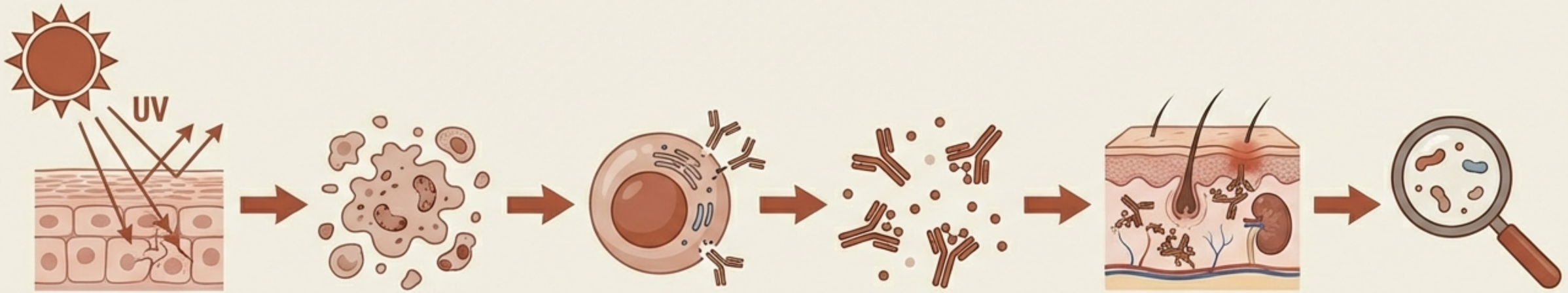


Treg Detail



FOXP3 Mutation → IPEX Syndrome.

Systemic Lupus Erythematosus (SLE): The Pathogenesis



Trigger:
UV Damage / Apoptosis

Nuclear Debris
(Poor clearance)

Self-Reactive Lymphocytes
produce ANA

Antigen-Antibody Complexes Form

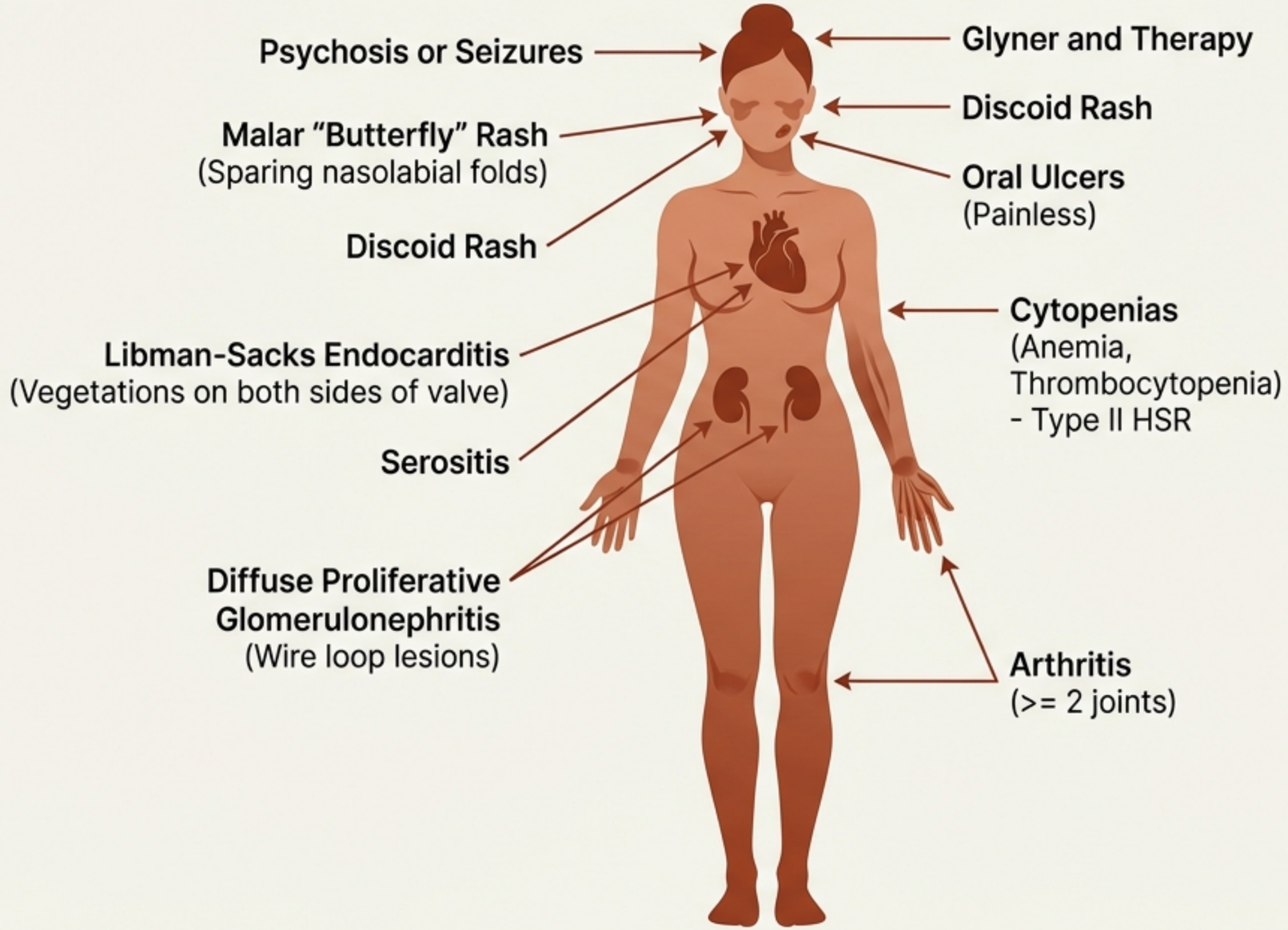
Type III Hypersensitivity:
Complexes deposit in Skin, Joints, Kidneys

Complement Activation
(Low C3/C4)

Highlight

Epitope Spreading: The immune response expands to include more self-antigens over time, worsening the disease.

SLE: The Clinical Body Map



Diagnostic Antibodies

ANA
(Sensitive, Screening)

Anti-dsDNA
(Specific, Renal prognosis)

Anti-Sm
(Specific)

SLE Variants & Complications

Antiphospholipid Syndrome

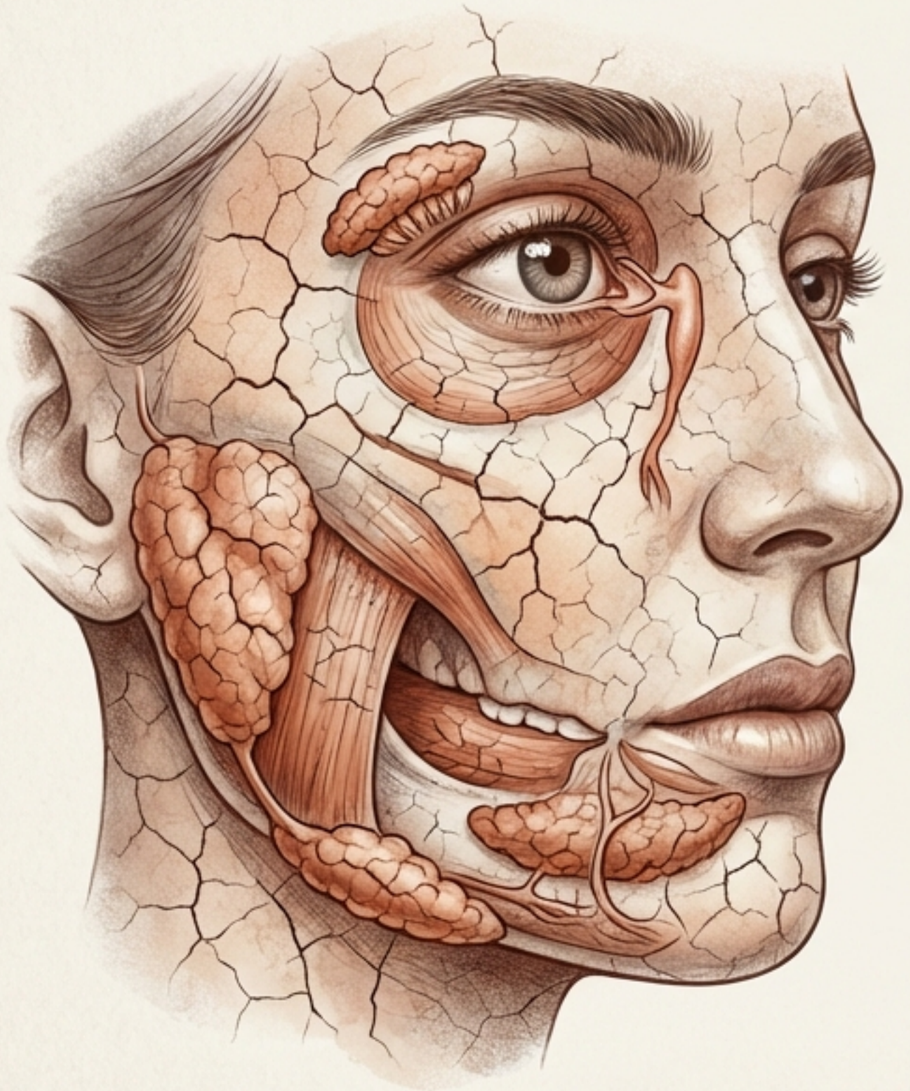
- **The Paradox:** High PTT (Lab artifact) but Hypercoagulable State (Clinical reality).
- **Antibodies:** Lupus Anticoagulant, Anti-Cardiolipin (False Positive VDRL/Syphilis), Anti-B2-Glycoprotein.
- **Outcomes:** DVT, Stroke, Recurrent Miscarriage.
- **Tx:** Lifelong Anticoagulation.

Drug-Induced Lupus

- **Key Marker:** Anti-Histone Antibodies.
- **The Culprits:** Procainamide, Hydralazine, Isoniazid.
- **Differentiation:** Renal and CNS involvement is RARE. Symptoms remit when drug is stopped.

Sjogren Syndrome

"Can't chew a cracker, dirt in my eyes."



Mechanism

Lymphocyte-mediated destruction (Type IV HSR) leading to fibrosis of exocrine glands.

Clinical Features

Keratoconjunctivitis sicca (Dry eyes -> Corneal damage)
Xerostomia (Dry mouth -> Cavities)
Parotid Gland Enlargement

Key Markers

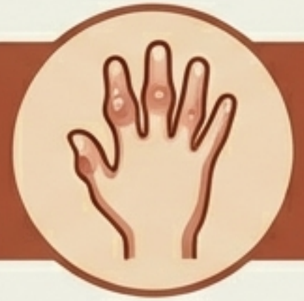
ANA positive
Anti-SSA (Ro) & Anti-SSB (La)

⚠ **Pregnancy Risk:** Anti-SSA crosses placenta -> Neonatal Lupus (Congenital Heart Block).

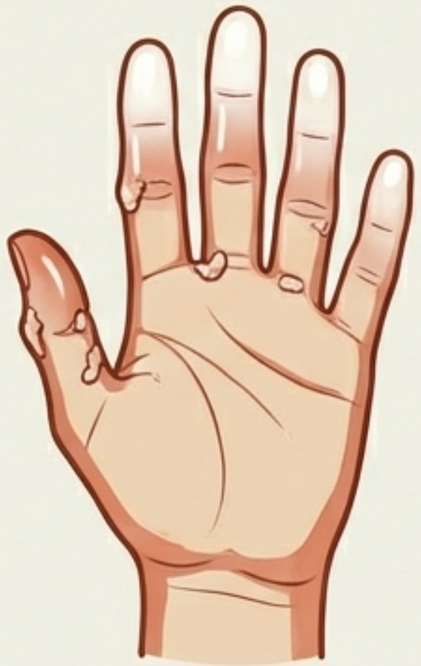
⚠ **Cancer Risk:** Unilateral parotid growth -> B-Cell Lymphoma.

Systemic Sclerosis (Scleroderma): The Fibrosis Triad

Endothelial Dysfunction -> Vasoconstriction -> Fibroblast Activation -> Collagen Deposition

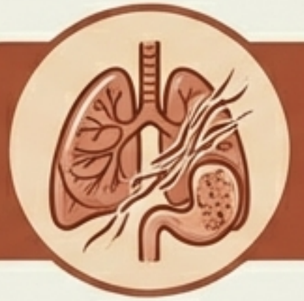


Limited Type (CREST)



Antibody: Anti-Centromere

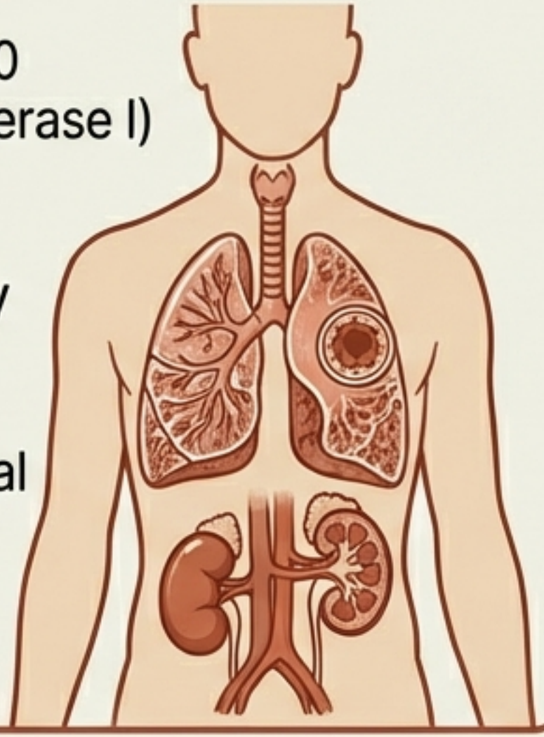
- Calcinosis
- Raynaud phenomenon
- Esophageal dysmotility
- Sclerodactyly
- Telangiectasia



Diffuse Type

Antibody: Anti-Scl-70 (Anti-DNA Topoisomerase I)

- Widespread skin involvement. Early visceral damage: Pulmonary Fibrosis (Interstitial Lung Disease) and Scleroderma Renal Crisis.



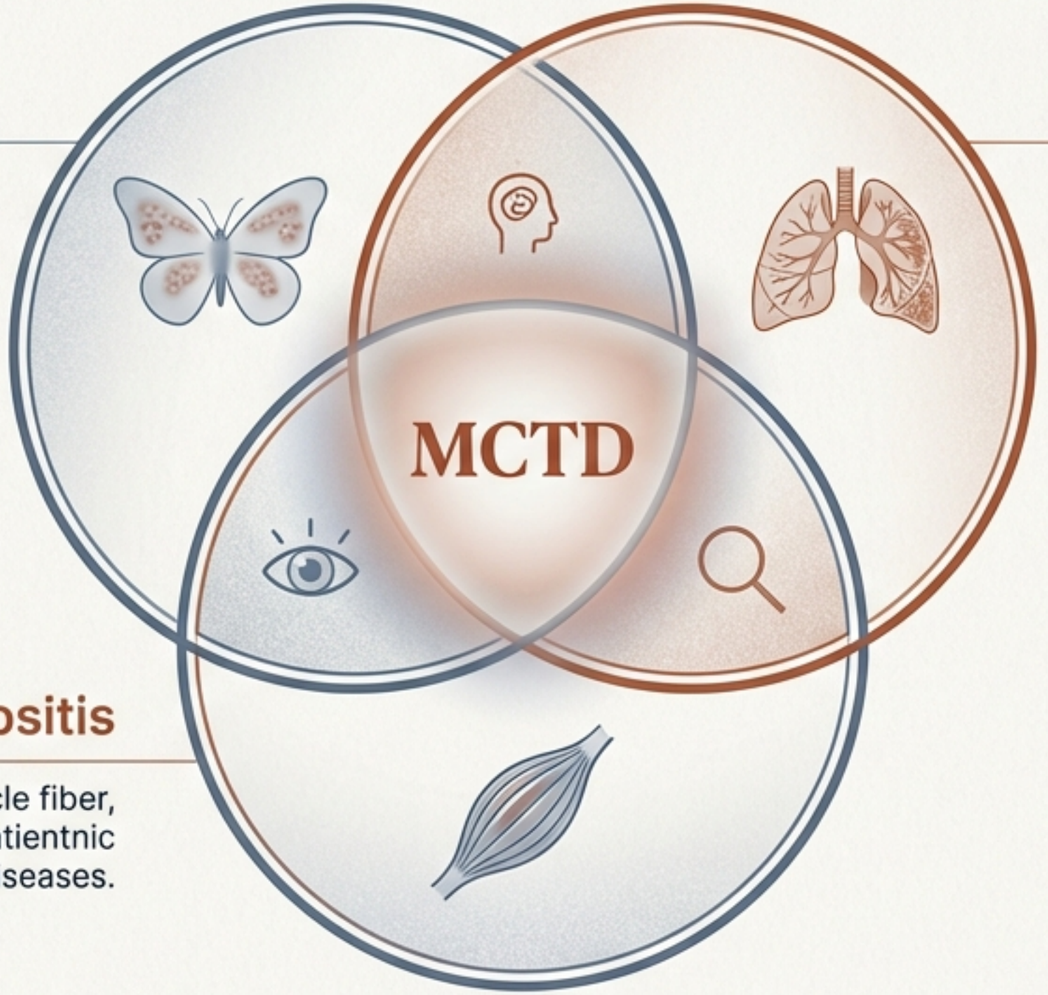
Mixed Connetive Tissue Disease (MCTD)

SLE (Lupus)

Butterfly rash is reponsible butterfly rash in the soottnesis, and medical diseases.

Systemic Sclerosis

Fibrotic lung is anonotomic category with fibrotic coters anothemic scleɐory.



Polymyositis

Polymyositis is usen muscle fiber, muscle muscle and patientnic fibrored dimina diseases.

Anti-U1-RNP Antibody

Patients do not fit clearly into one specific category.

Autoimmune-mediated tissue damage presenting with overlapping features of the three distinct diseases.

High-Yield Autoimmunity Summary Matrix

Disease	Target / Mechanism	Key Antibodies	Classic Presentation
SLE	Nuclear Antigens (Type III HSR)	ANA, Anti-dsDNA, Anti-Sm	Malar Rash, Renal Failure, Joint Pain
Drug-Induced Lupus	Histone Proteins	Anti-Histone	Linked to Hydralazine/Procainamide. No Renal/CNS issues.
Sjogren Syndrome	Exocrine Glands (Type IV HSR)	Anti-SSA/Ro, Anti-SSB/La	Dry eyes, Dry mouth, Dental caries
Scleroderma (Limited)	Microvasculature	Anti-Centromere	CREST Syndrome, Sclerodactyly
Scleroderma (Diffuse)	Systemic Fibrosis	Anti-Scl-70	Visceral involvement (Lung/Kidney), Diffuse skin hardening
MCTD	Overlap	Anti-U1-RNP	Mixed features of SLE, Sclerosis, Polymyositis