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ראומטולוגיה - שיבא
Sheba Rheumatology

האיגוד הישראלי לראומטולוגיה
ISR
The Israeli Society Of Rheumatology

# CAR-T CELL THERAPY
## AUTOIMMUNE RHEUMATIC DISEASES


**Prof. Merav Lidar**

- **H**ead of Rheumatology Sheba Medical Center
- President of the Israeli Society of Rheumatology

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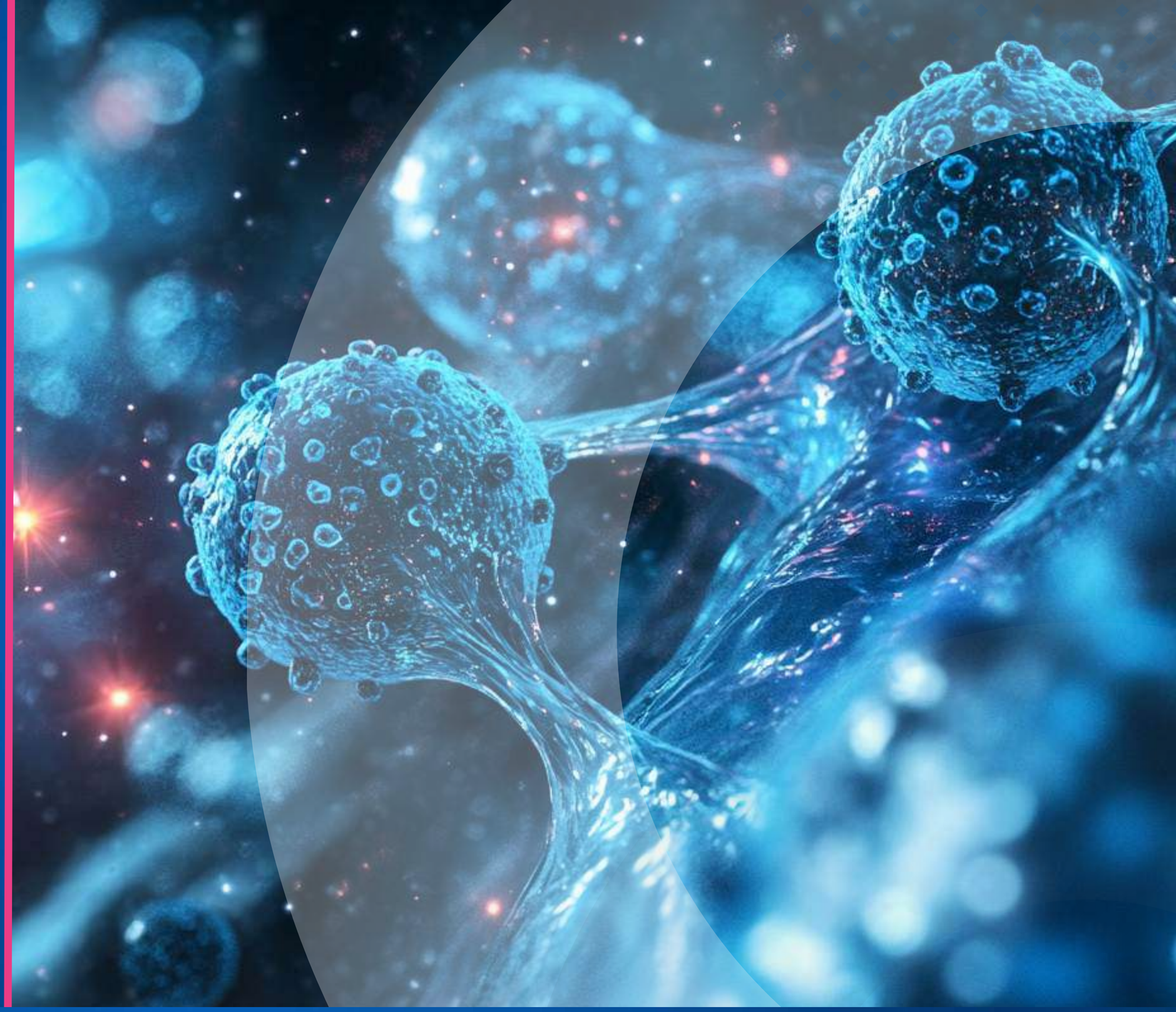
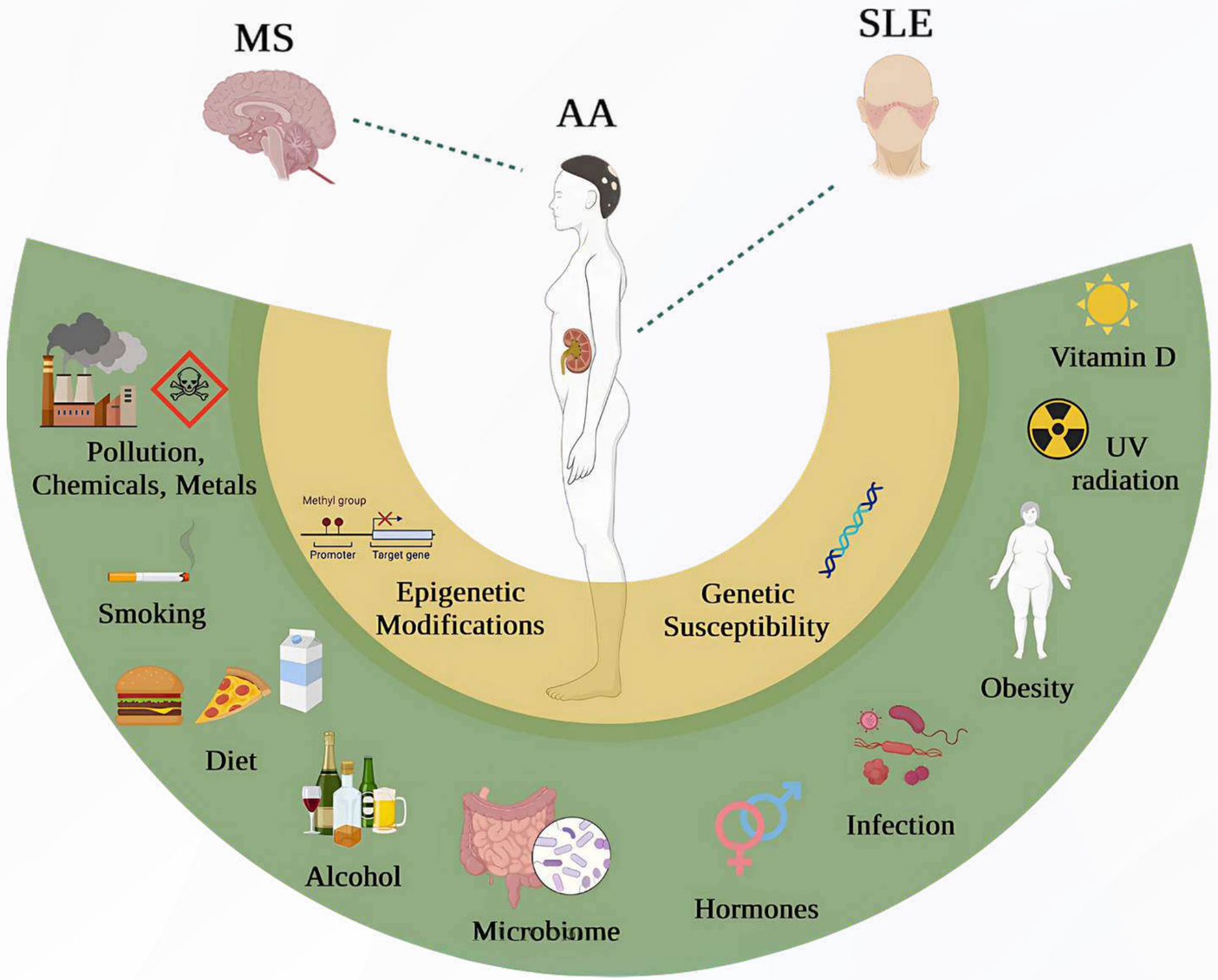
# How does an **autoimmune disease develop?**



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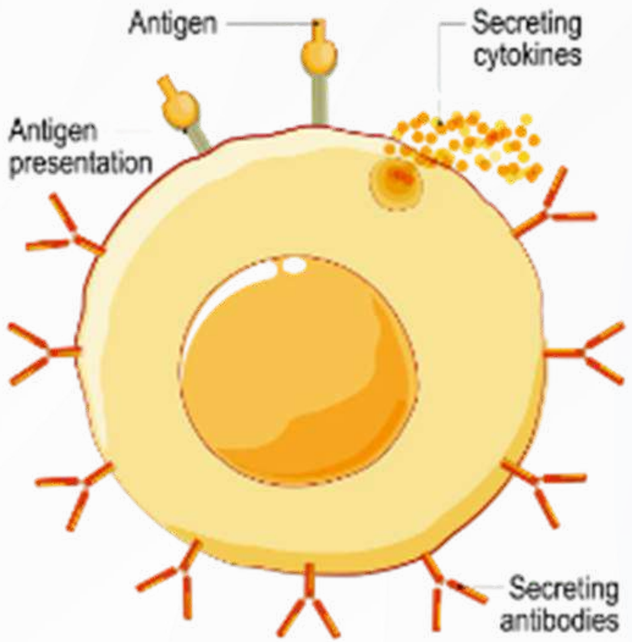
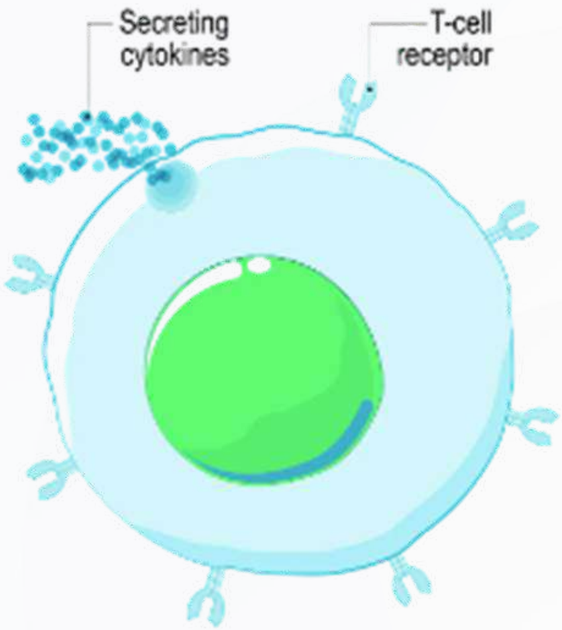
# Cells of the adaptive immune system

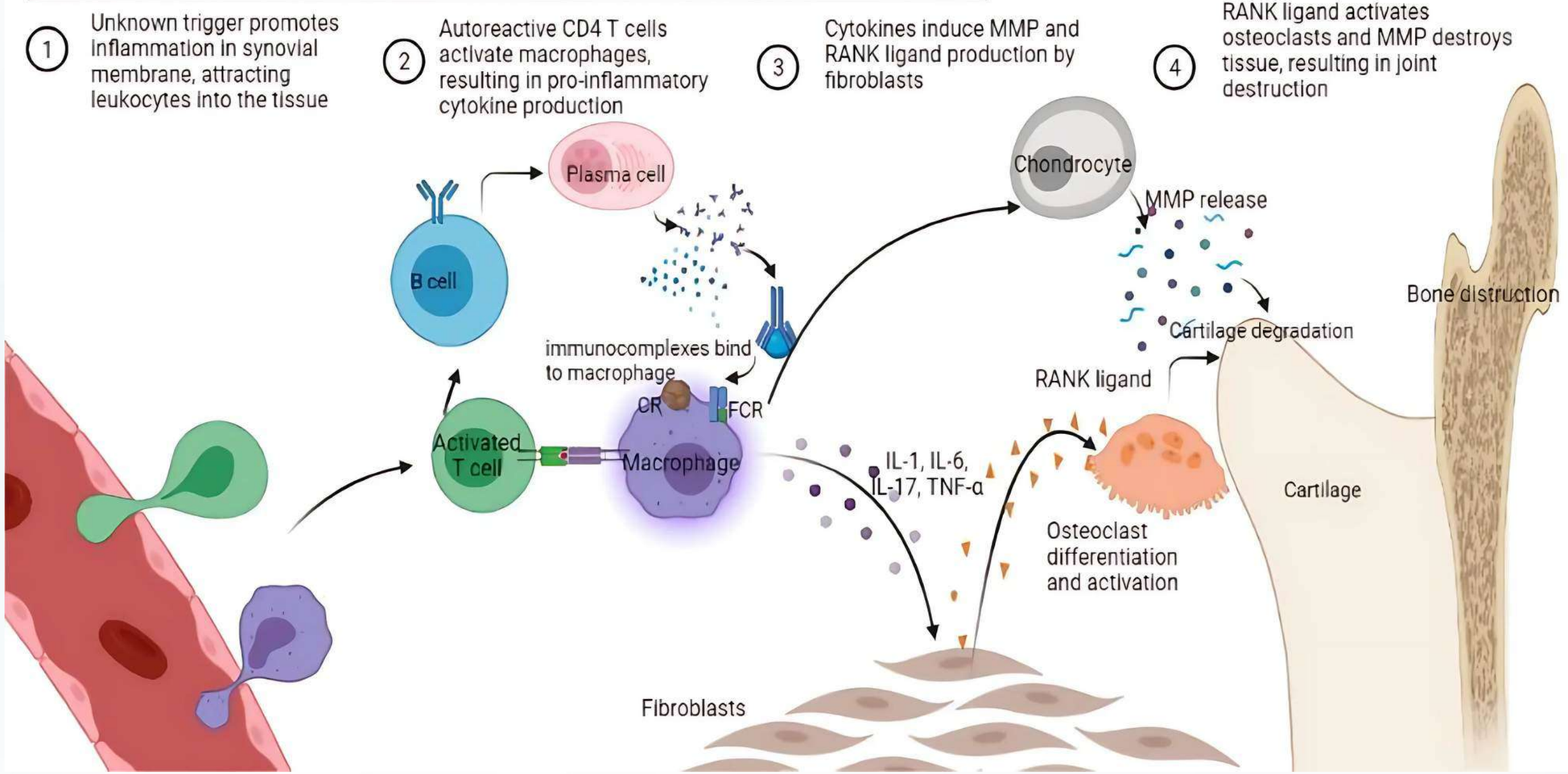



B-cell

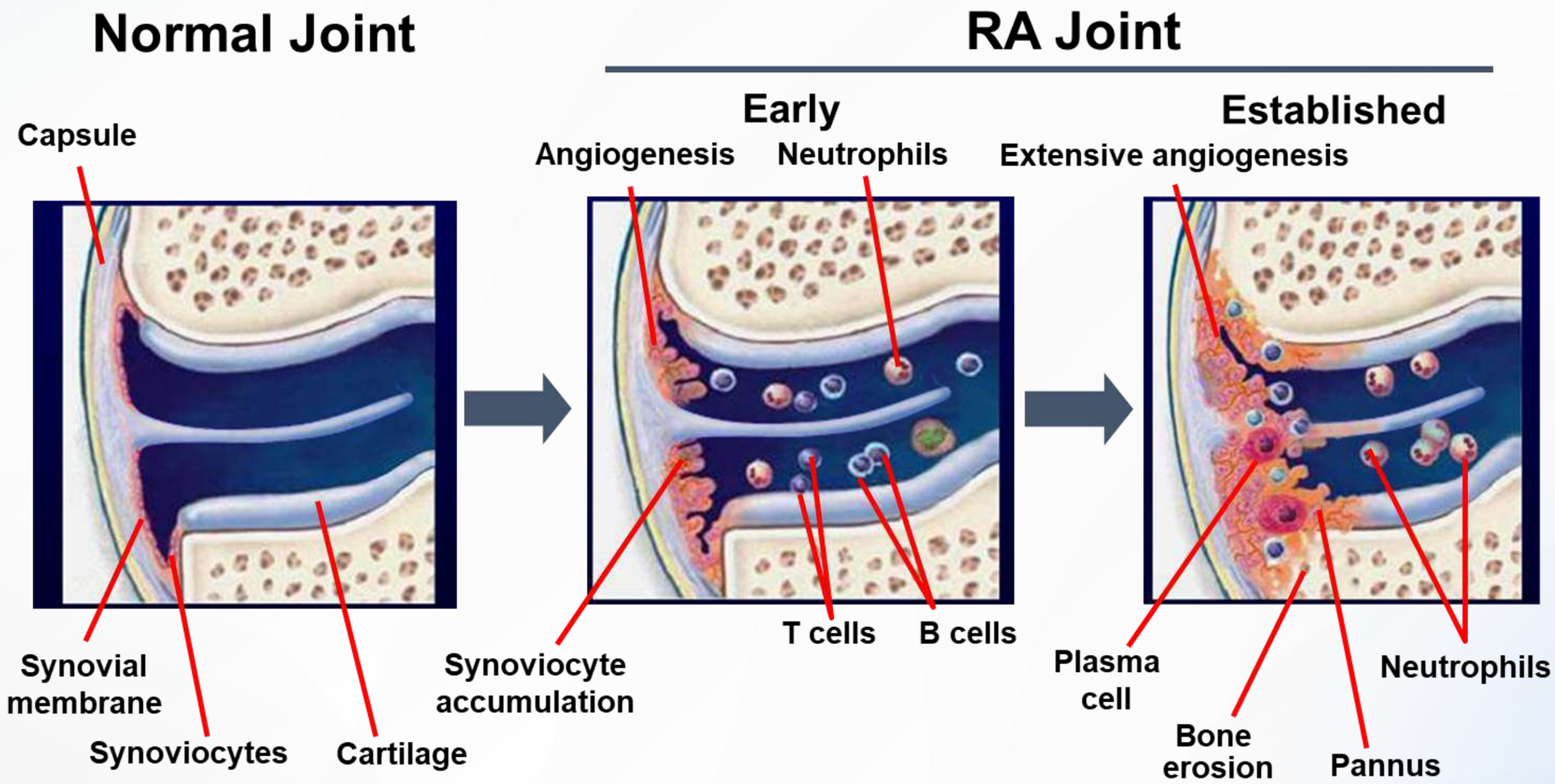



T-cell

# Pathogenesis of Rheumatoid Arthritis



# Pathophysiology of RA

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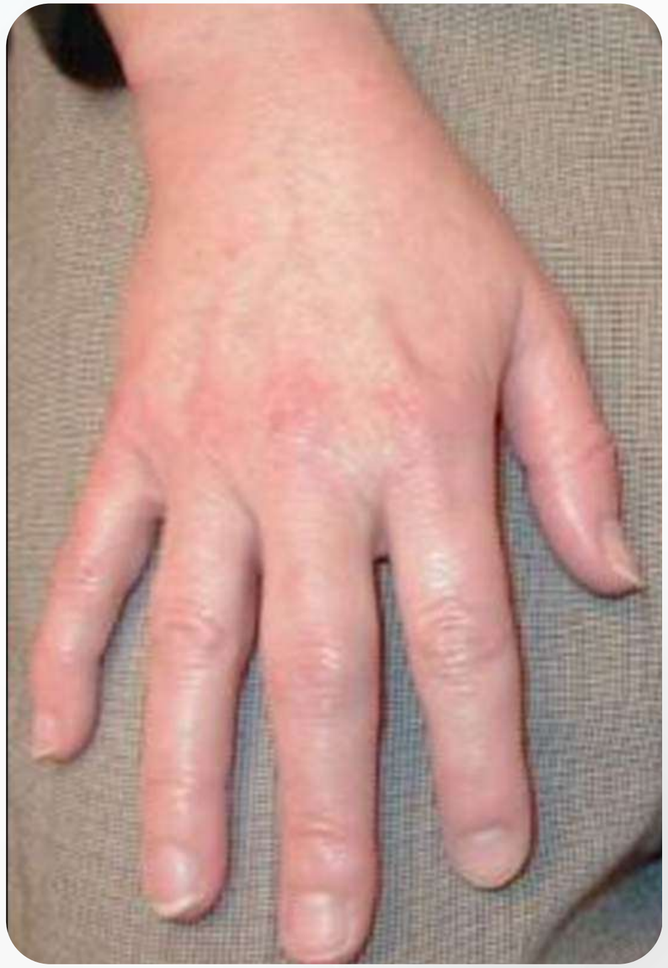

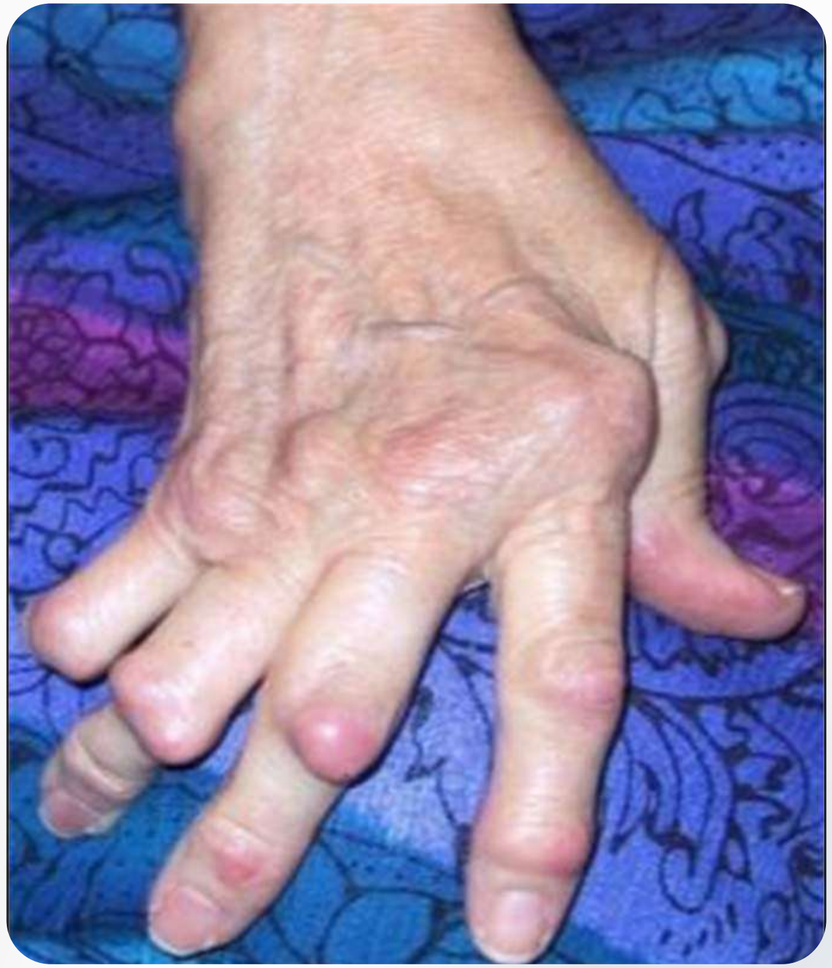

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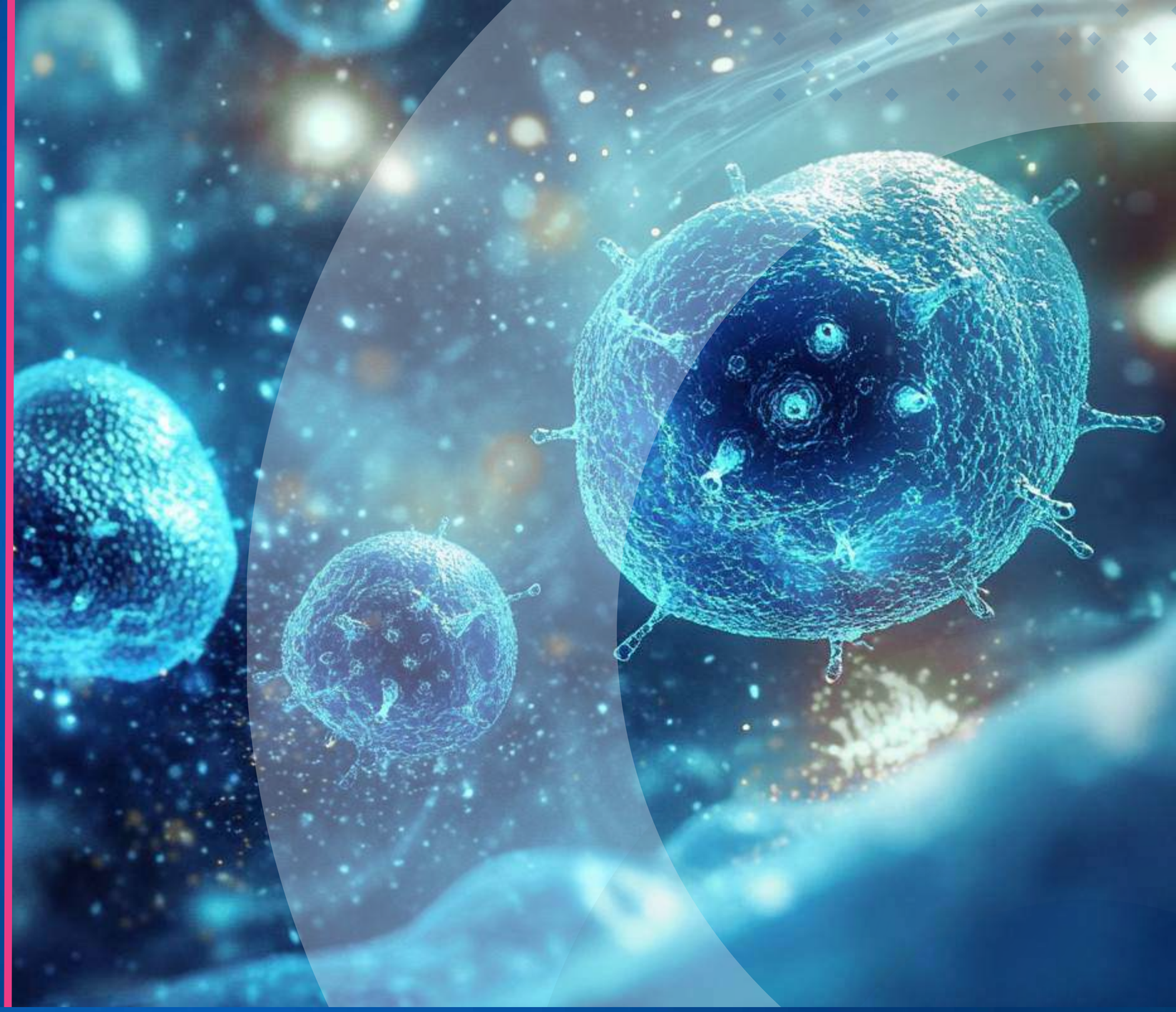
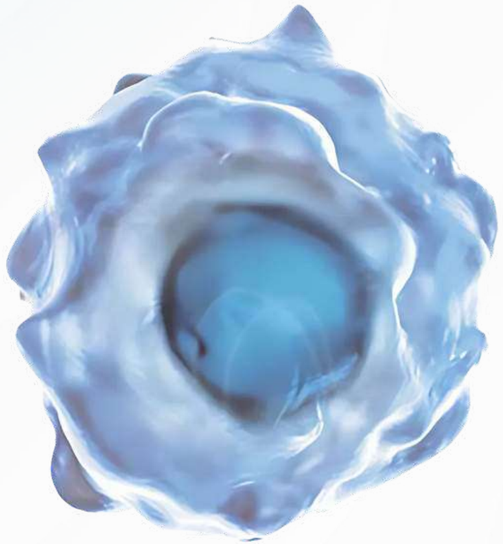
# **CAR T-cell therapy:**
# A "living drug"



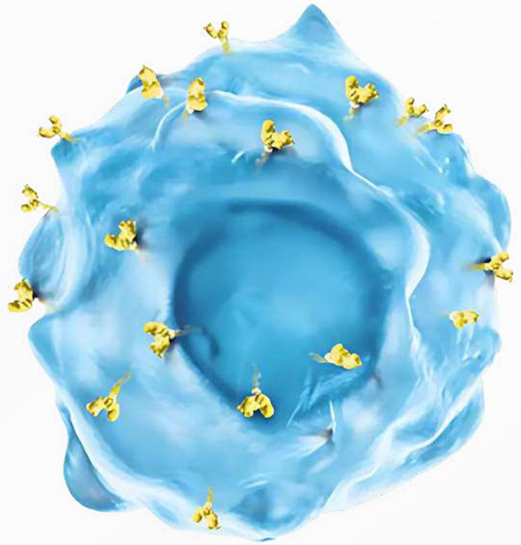


## T CELL

A key fighter in your immune system

## CAR

A specific receptor is added to the T cell



## CAR T CELL

The T cell with the CAR added helps find and fight specific targeted cells

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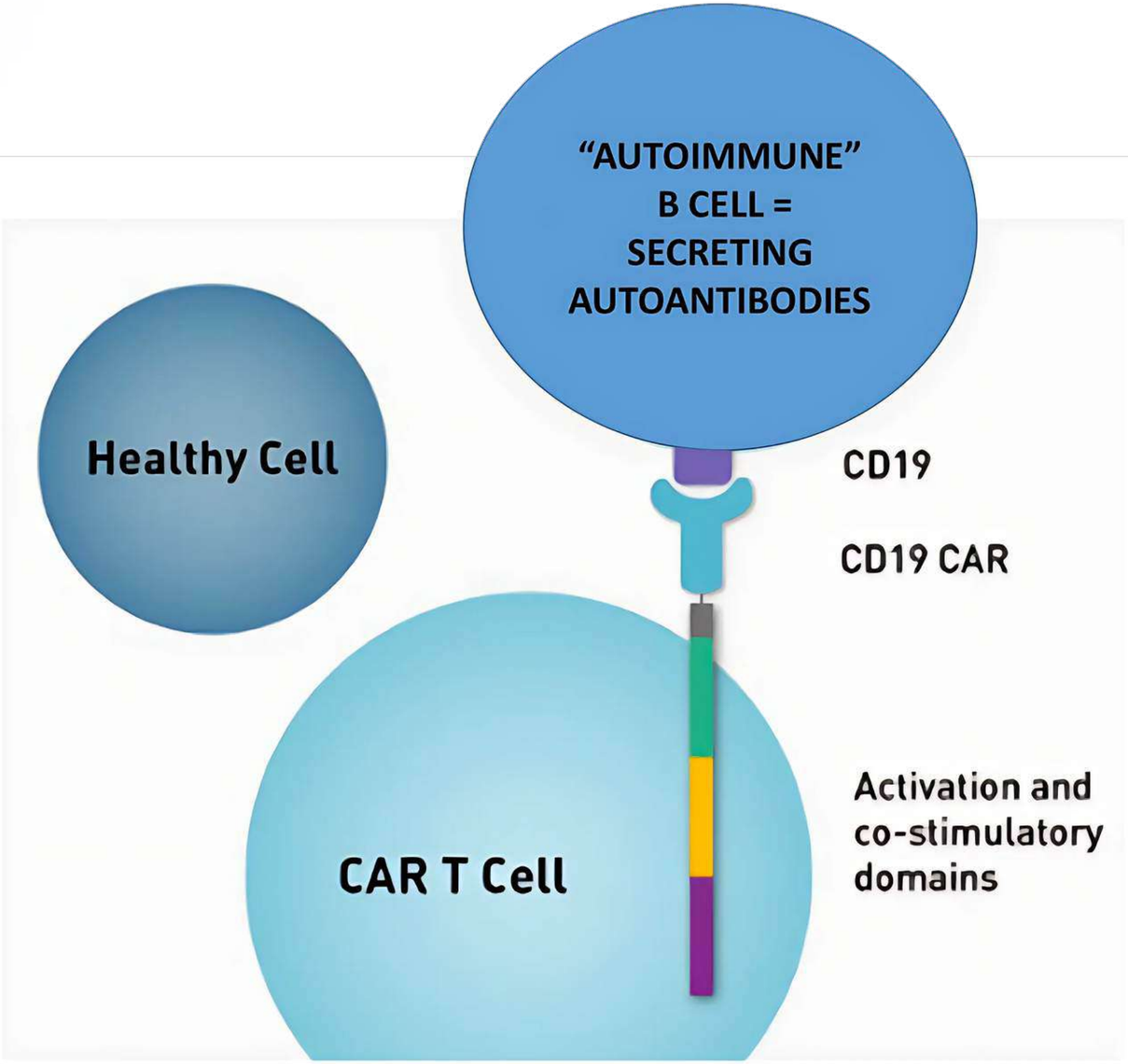
"AUTOIMMUNE"
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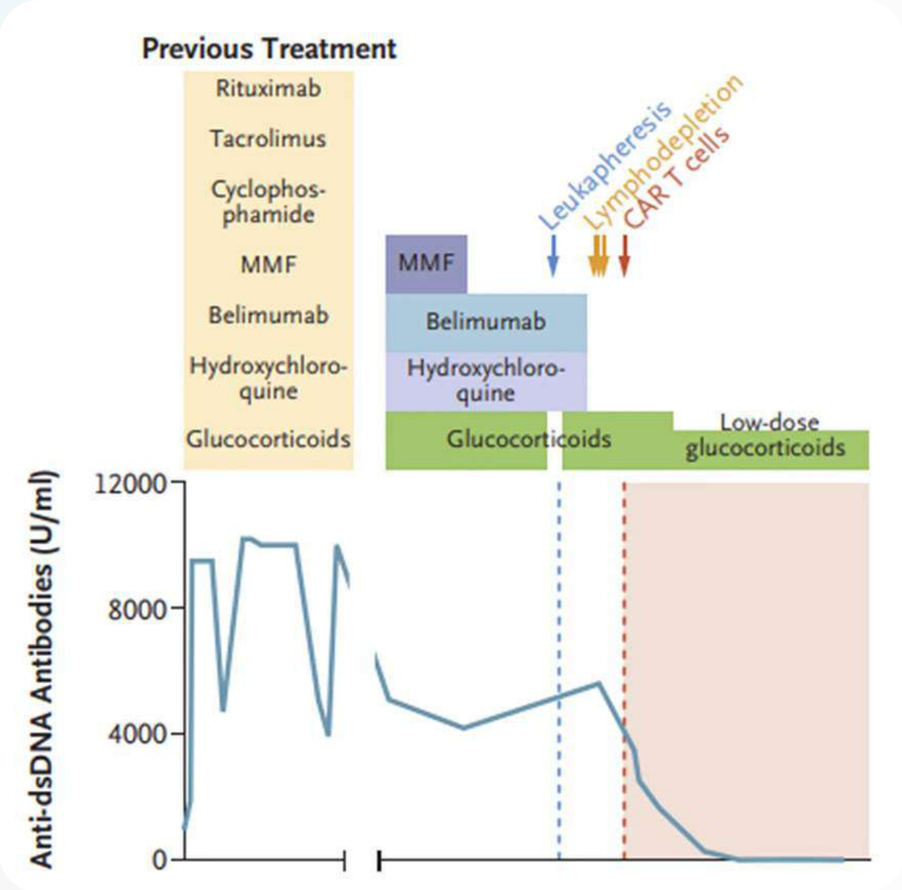
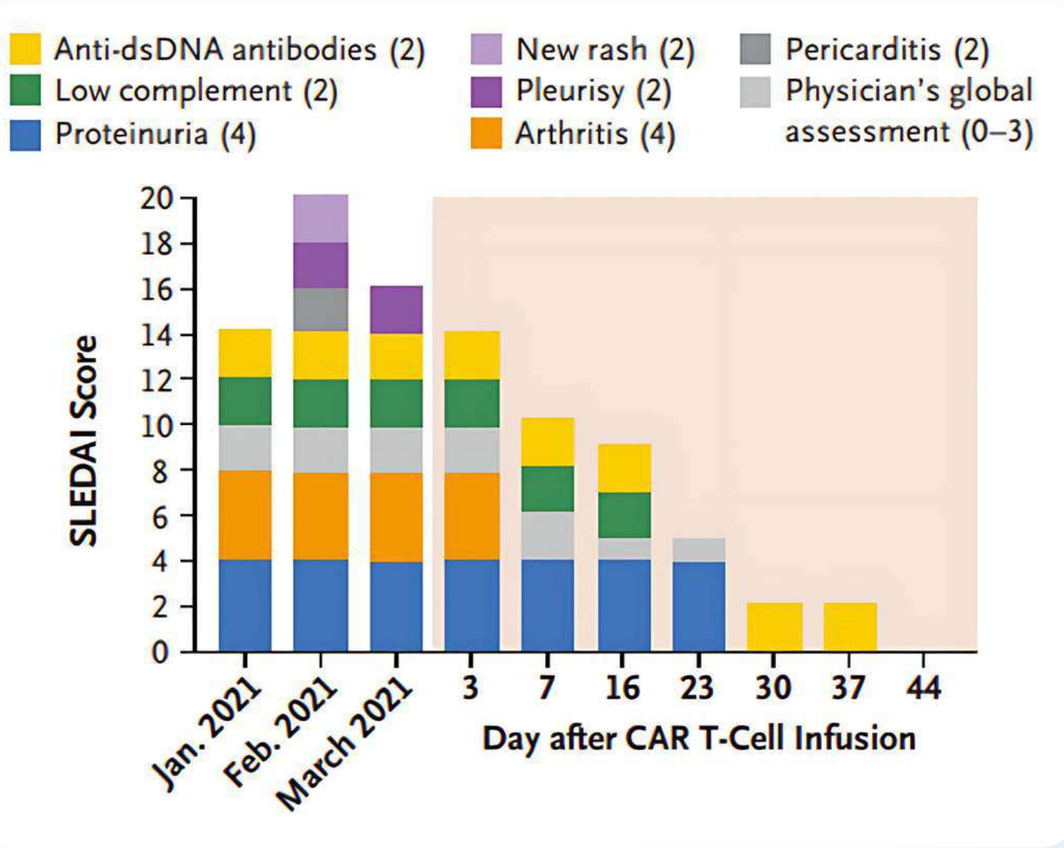
SECRETING
AUTOANTIBODIES
Healthy Cell
CD19
CD19 CAR
CAR T Cell
Activation and
co-stimulatory
domains

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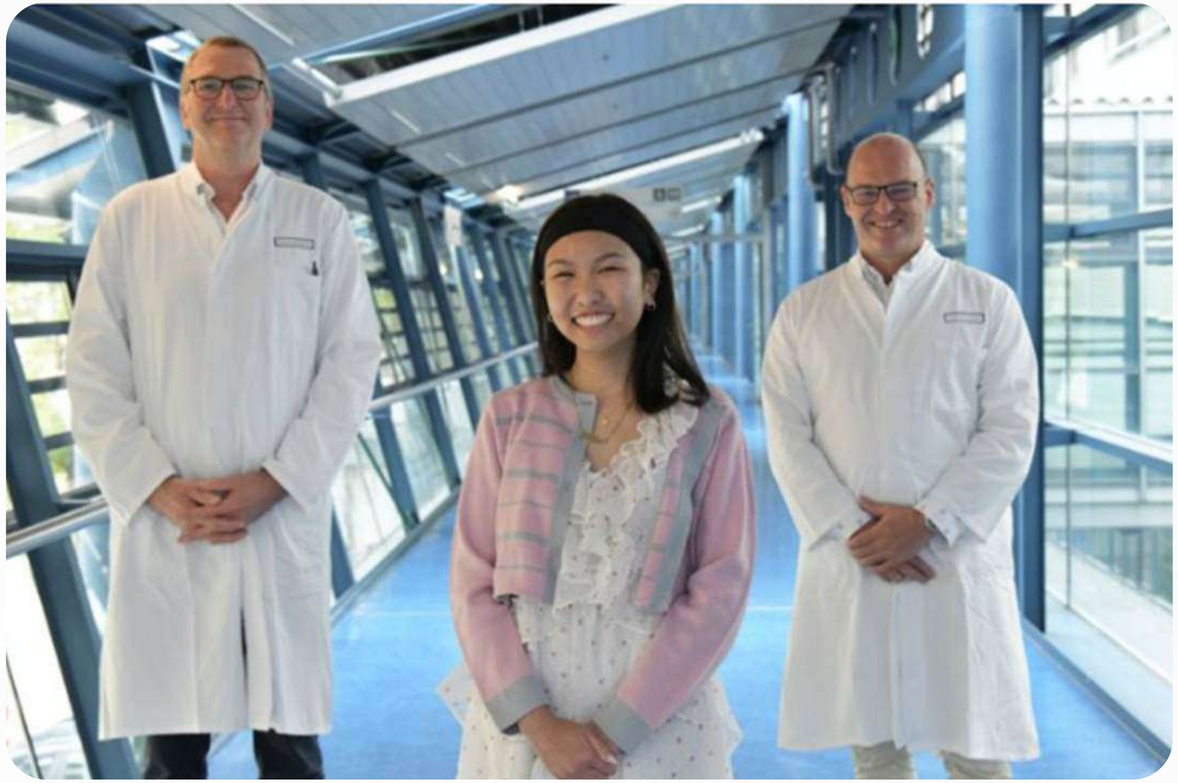

Prof. Dr. Andreas Mackensen (Director/Department of Medicine 5, 1.) and Prof. Dr. med. univ. Georg Schett (Director/Department of Medicine 3, right) are pleased that the CAR-T cell therapy has worked so well for their patient Thu-Thao V. (Image: Michael Rabenstein/Universitätsklinikum Erlangen)

The NEW ENGLAND JOURNAL of MEDICINE

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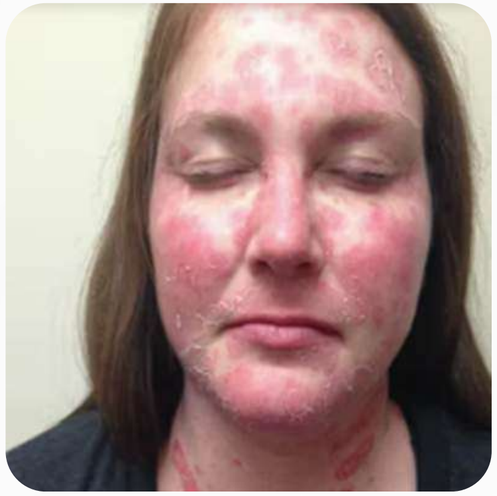
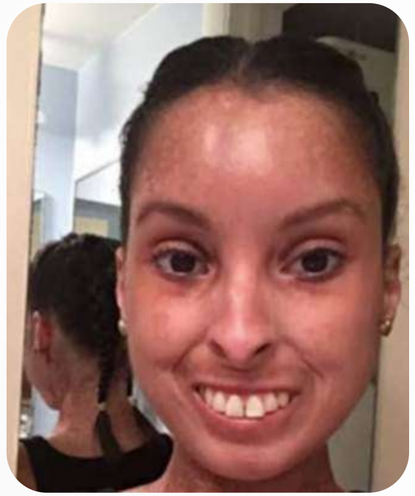
# CD19 CAR T-Cell Therapy in Autoimmune Disease — A Case Series with Follow-up

Fabian Müller, M.D., Jule Taubmann, M.D., Laura Bucci, M.D., Artur Wilhelm, Ph.D., Christina Bergmann, M.D., Simon Völkl, Ph.D., Michael Aigner, Ph.D., Tobias Rothe, Ph.D., Ioanna Minopoulou, M.D., Carlo Tur, M.D., Johannes Knitza, M.D., Soraya Kharboutli, M.D., Sascha Kretschmann, Ph.D., Ingrid Vasova, M.D., Silvia Spoerl, M.D., Hannah Reimann, Ph.D., Luis Munoz, M.D., Roman G. Gerlach, Ph.D., Simon Schäfer, Ph.D., Ricardo Grieshaber-Bouyer, M.D., Anne-Sophie Korganow, M.D., Dominique Farge-Bancel, M.D., Dimitrios Mougiakakos, M.D., Aline Bozec, Ph.D., Thomas Winkler, Ph.D., Gerhard Krönke, M.D., Andreas Mackensen, M.D., and Georg Schett, M.D.





# 15 PATIENTS:

- SLE (8 patients)
- Idiopathic inflammatory myositis (3 patients)
- Systemic sclerosis (4 patients)

**A single infusion of CD19 chimeric antigen receptor (CAR) T cells** after preconditioning with fludarabine and cyclophosphamide

**Efficacy up to 2 years** after CAR T-cell infusion

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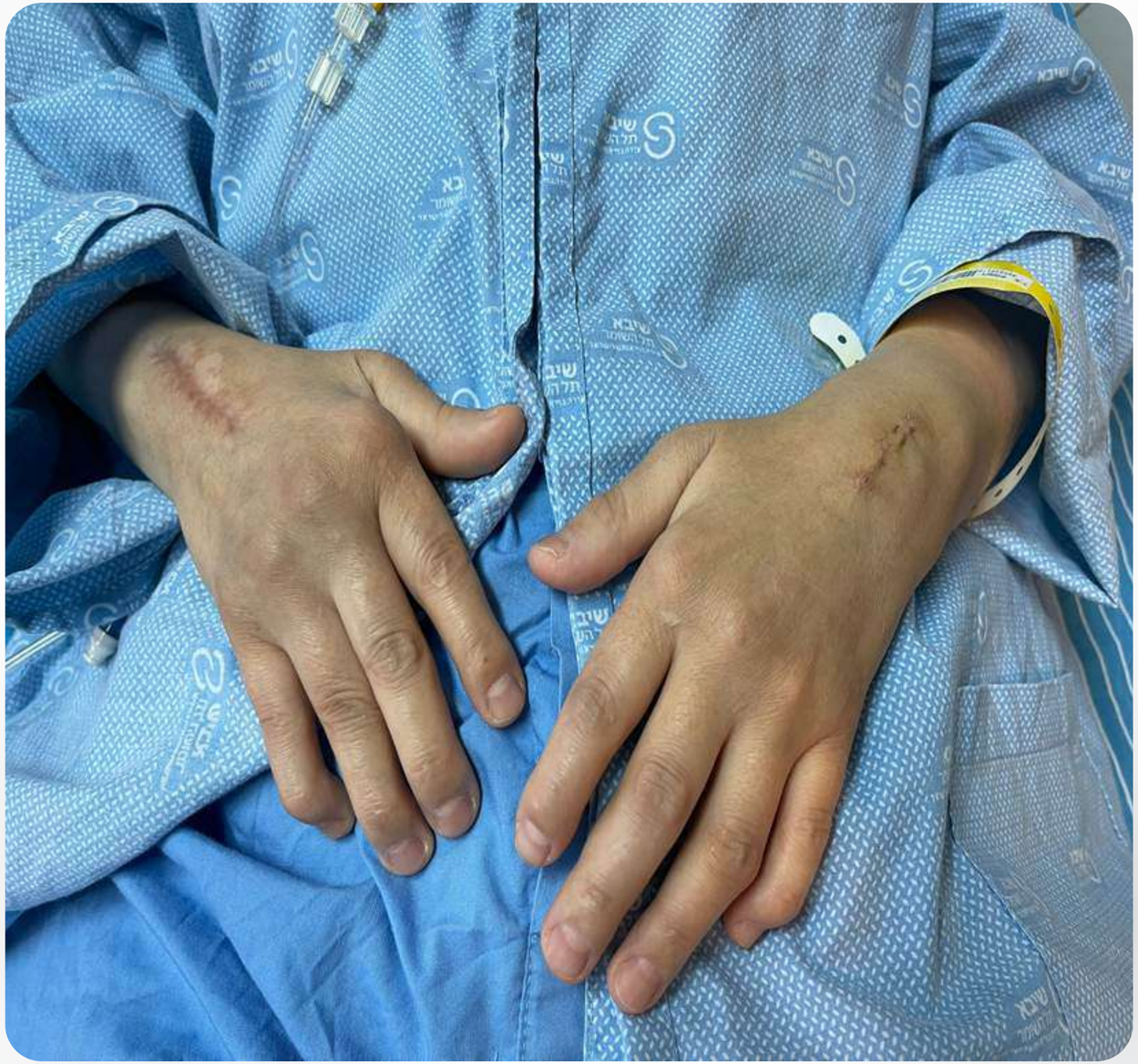

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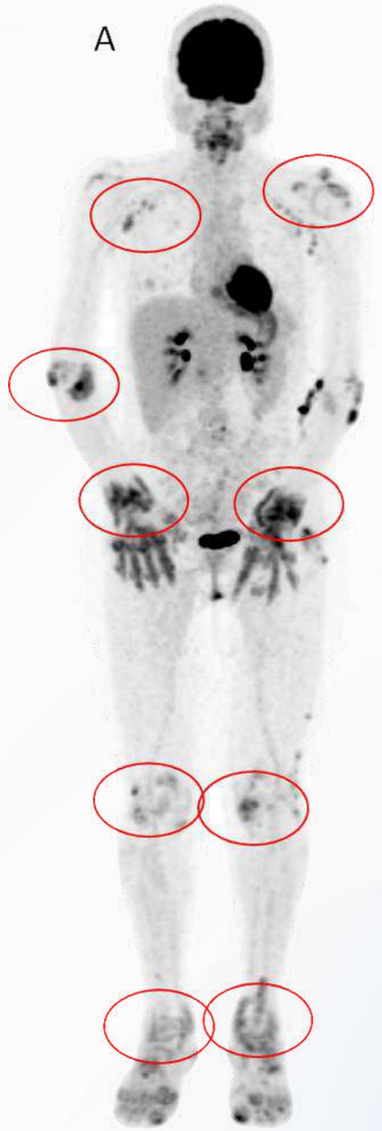
# FDG PET/CT MIP images before treatment

Symmetrically increased FDG uptake in the knee, hip, carpal, wrist, elbow, shoulder, and atlantoaxial joints, in bilateral axillary lymph nodes and in subcutaneous rheumatoid nodules, consistent with active rheumatoid arthritis.

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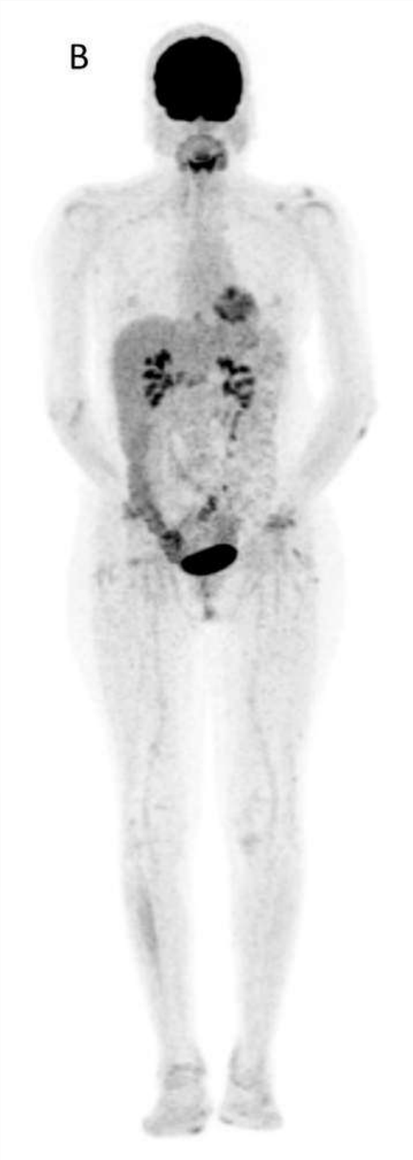
# FDG PET/CT MIP images  after treatment

Near complete metabolic response two months after CAR-T treatment initiation, with residual uptake in the right carpal and acromioclavicular joints, ΔSUVmax = 3.5.

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# CD-19 CAR-T cells for polyrefractory rheumatoid arthritis

'Poly-refractory' disease affects 2.7% of patients with rheumatoid arthritis (RA) who have failed different groups of biologic disease-modifying antirheumatic drugs (b-DMARDS) and targeted synthetic DMARDs (ts-DMARDS).[1] Recently, chimeric antigen receptor T-cell (CAR-T) therapy has emerged as a promising approach in autoimmune diseases.[2]

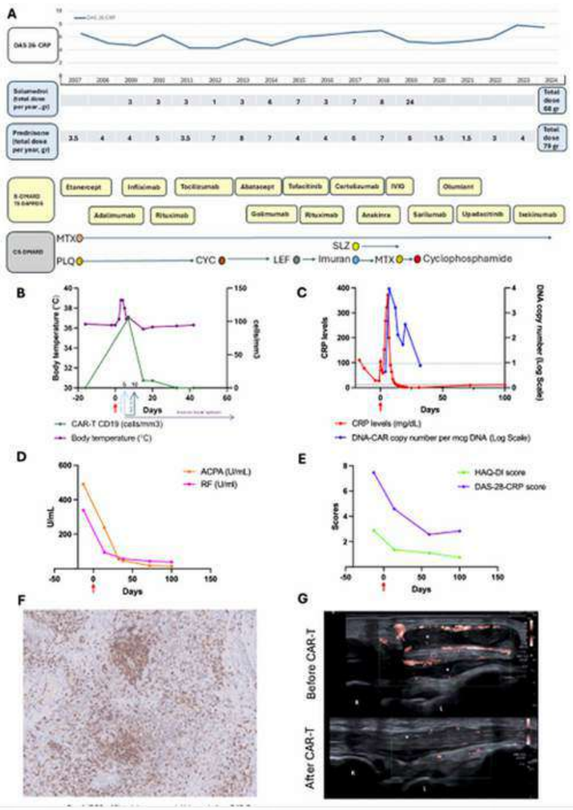
We present a 39-year-old woman with erosive seropositive RA who had failed all available biologic and ts-DMARDS therapies over a 20-year disease course (figure 1).

She remained corticosteroid-dependent with persistently active disease manifested on ultrasound and MRI, a Disease Activity Score (DAS)-28-C reactive protein (CRP) of 7.46 and a CRP level of 104 mg/L (normal <5 mg/L). Rheumatoid factor (RF) 339/mL (normal <14 U/mL) and anticitrullinated protein antibodies (ACPA) 489.68 U/mL (normal <2.99 U/mL) were significantly elevated. Health Assessment Questionnaire Disability Index score (HAQ-DI) of 2.88 correlated with severe impairment of daily activities. Given the failure of all classes of therapies that had resulted in persistent peripheral B cell depletion (6 CD19+ cells/$\mu$L) yet with an abundance of CD19+ B cells (>70%) on synovial biopsy, CAR-T therapy was proposed.

Anti-CD-19 CAR-T were produced on our institutional platform using an FMC63-28-CD3$\zeta$ CAR.[3] Following lymphodepletion with fludarabine (total 75 mg/m$^2$) and cyclophosphamide (900 mg/m$^2$), $1\times10^6$ CAR-T/kg were infused. The patient developed grade 3 cytokine release syndrome (CRS) on day 2 and grade 4 immune effector cell-associated neurotoxicity (ICANS) on day 5, which necessitated tocilizumab, anakinra and high-dose corticosteroids for resolution.

100 days post-therapy, the patient was in drug-free remission with a DAS-28-CRP score of 2.5 with no neurological sequelae. Imaging findings have shown improvement; inflammatory markers normalised, and RF/ACPA levels decreased by more than 80% (figure 1).

This is the first documented case of CAR-T therapy in polyrediseases following CAR-T therapy.[2] This can be attributed to the high burden of CD19 B cells within the synovium despite the low level in the periphery, to the potency of the CAR construct in use (having CD28 co-stimulation), to the number of cells given or to our patient's extreme inflammatory state at baseline with a CRP 20-fold higher than the upper limit of normal.




Merav Lidar,[1,2] Doron Rimar ,[3,4] Paula David ,[2,5] Elad Jacoby,[2,6] Ronnie Shapira-Frommer,[2,7] Orit Itzhaki,[7] Gleb Slobodin,[3,4] Myriam D Stern,[2,8] Iris Eshed,[2,8] Tamer Sanalla,[2,9] Ronit Marcus,[2,10] Avichai Shimoni,[2,10] Ronit Yerushalmi,[2,10] Noga Shem Tov,[2,10] Ivetta Danylesko,[2,10] Abraham Avigdor[2,10]



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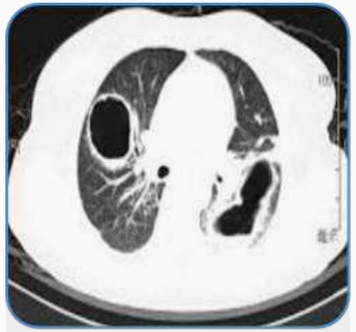
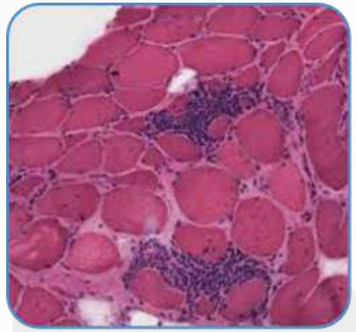
# WHAT AUTOIMMUNE DISEASES CAN BE TREATED WITH CAR-T CELL THERAPY?

LUPUS

SCLEORO-DERMA

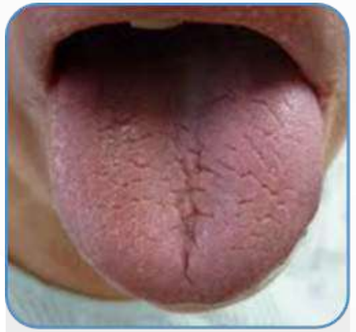


ANCA ASSOCIATED VASCULITIS



MYOSITIS

RHEUMATOID ARTHRITIS



SJOGREN's DISEASE

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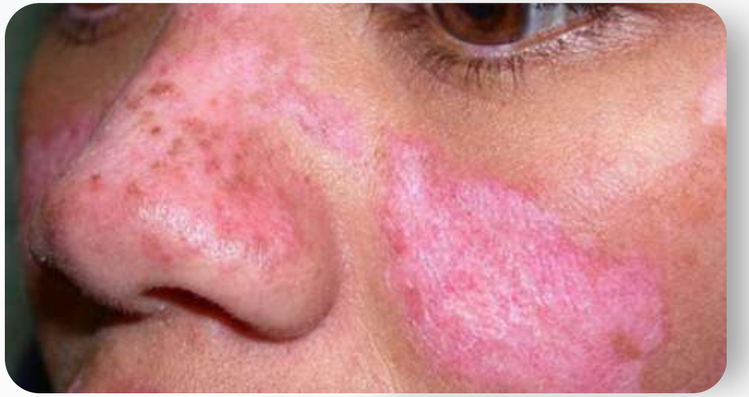
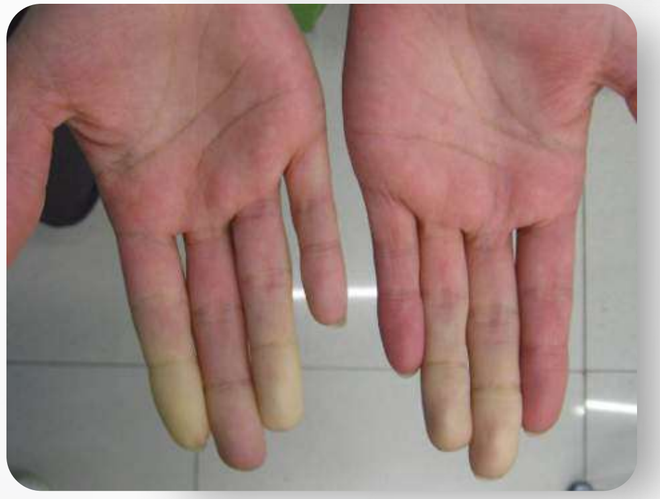
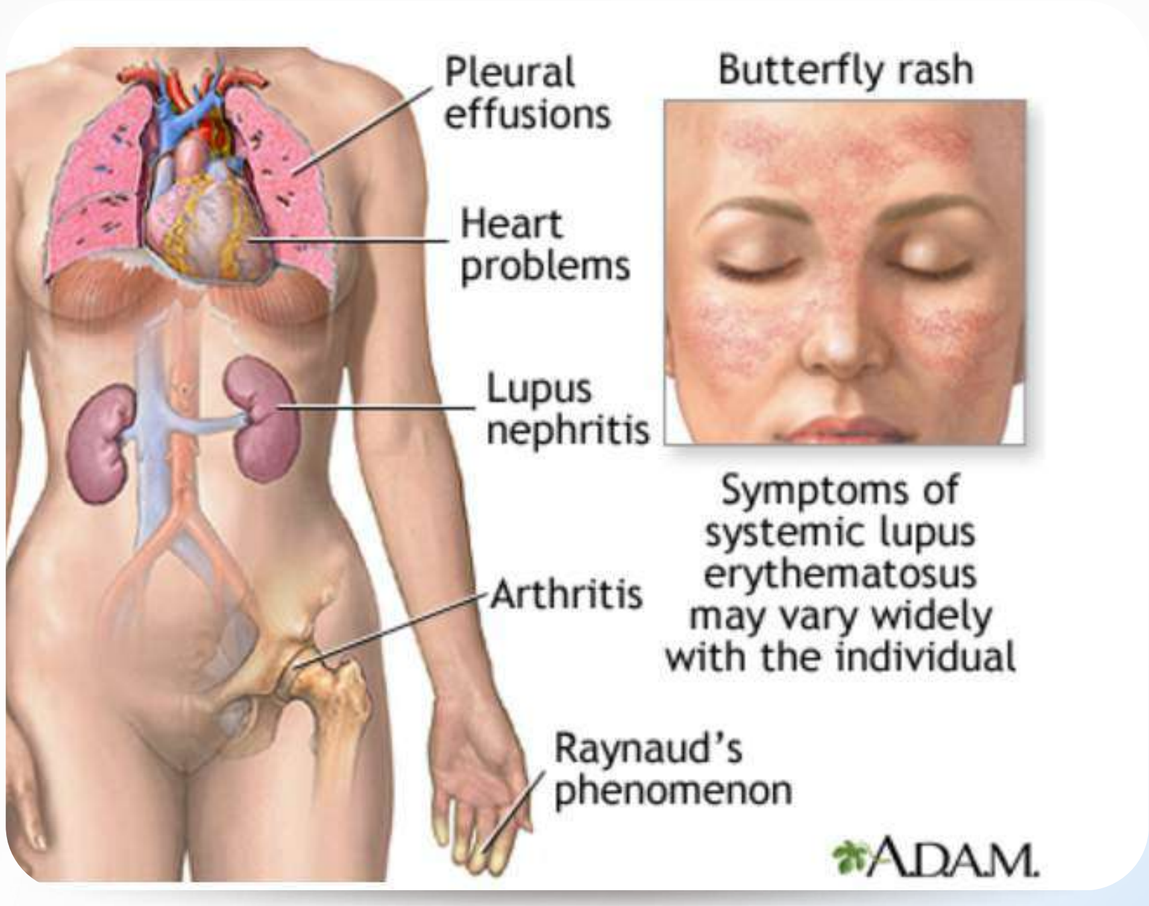
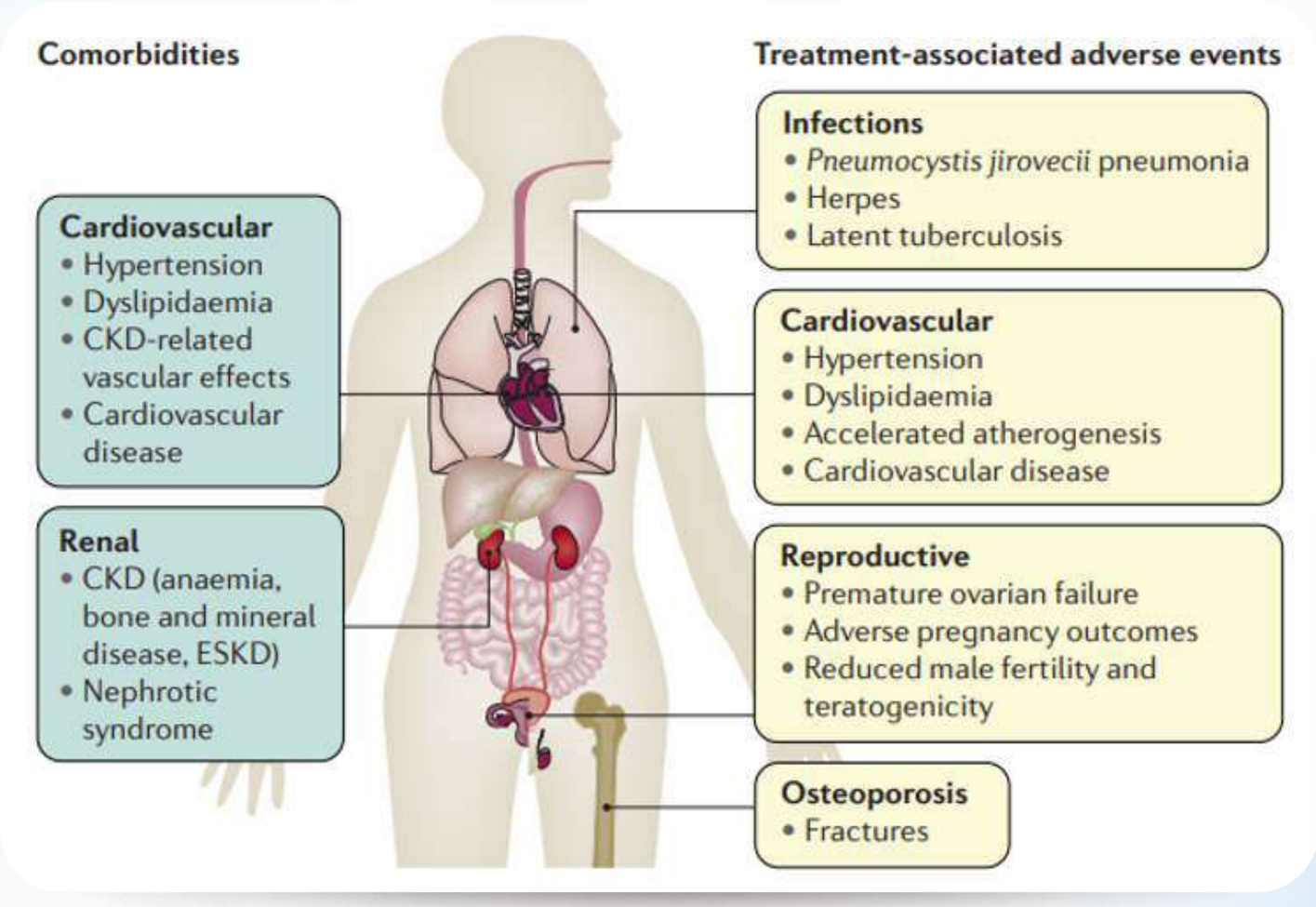
# Systemic Lupus Erythematosus







# Need for better therapies: Time is damage accrual

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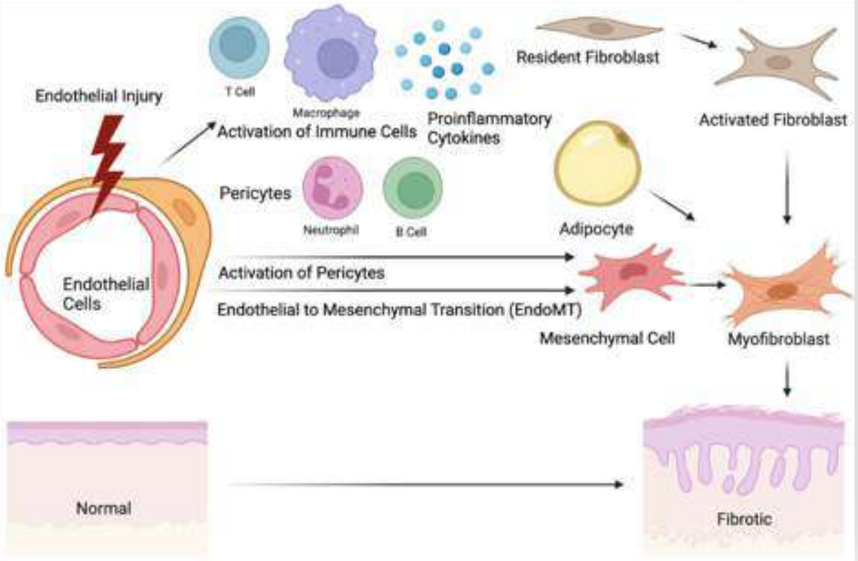
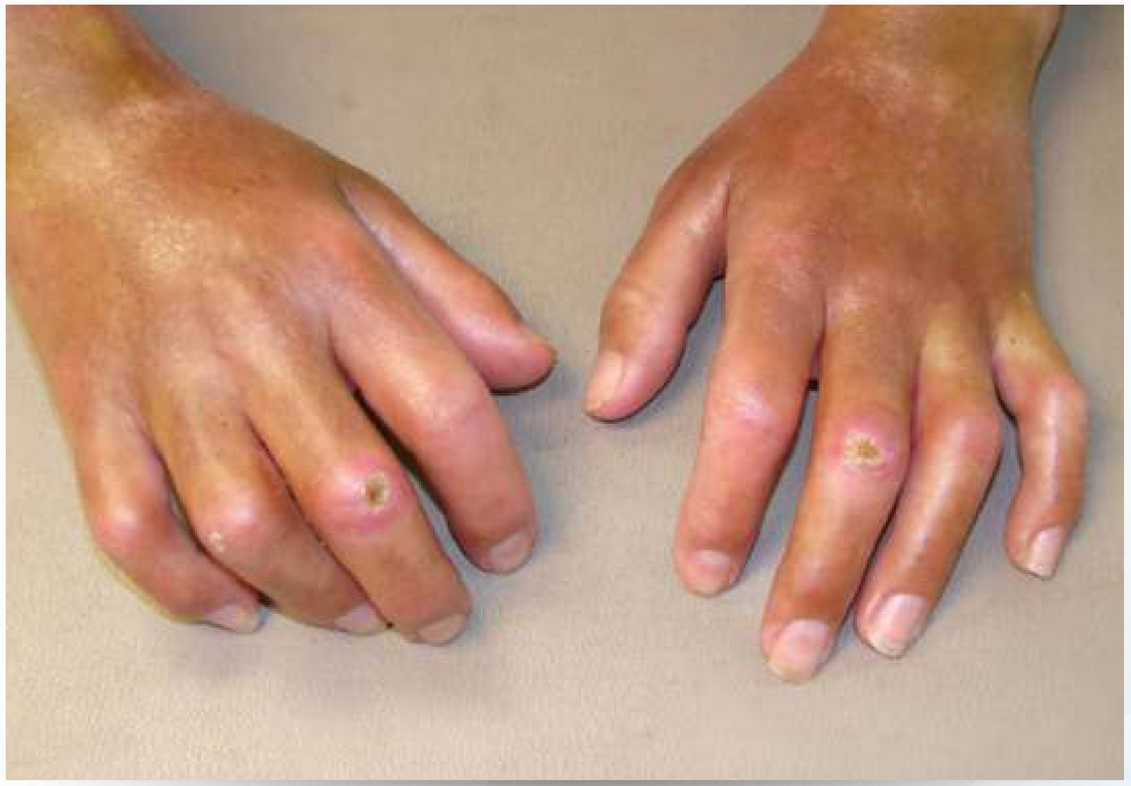
# SCLERO/DERMA

**Figure 1.** The origin of skin fibrosis in systemic sclerosis. Initial injuries in endothelial cells lead to the recruitment and activation of immune cells, including T cells, B cells, macrophages, and neutrophils. The activation of the immune cells promotes the production of proinflammatory cytokines, which subsequently activate the potential precursors of extracellular matrix (ECM)-producing myofibroblasts, such as pericytes, resident fibroblasts, endothelial cells, or adipocytes. The morphological change in the myofibroblasts and ECM production induce tissue remodeling and skin thickening. The image was created with **BioRender.com**.



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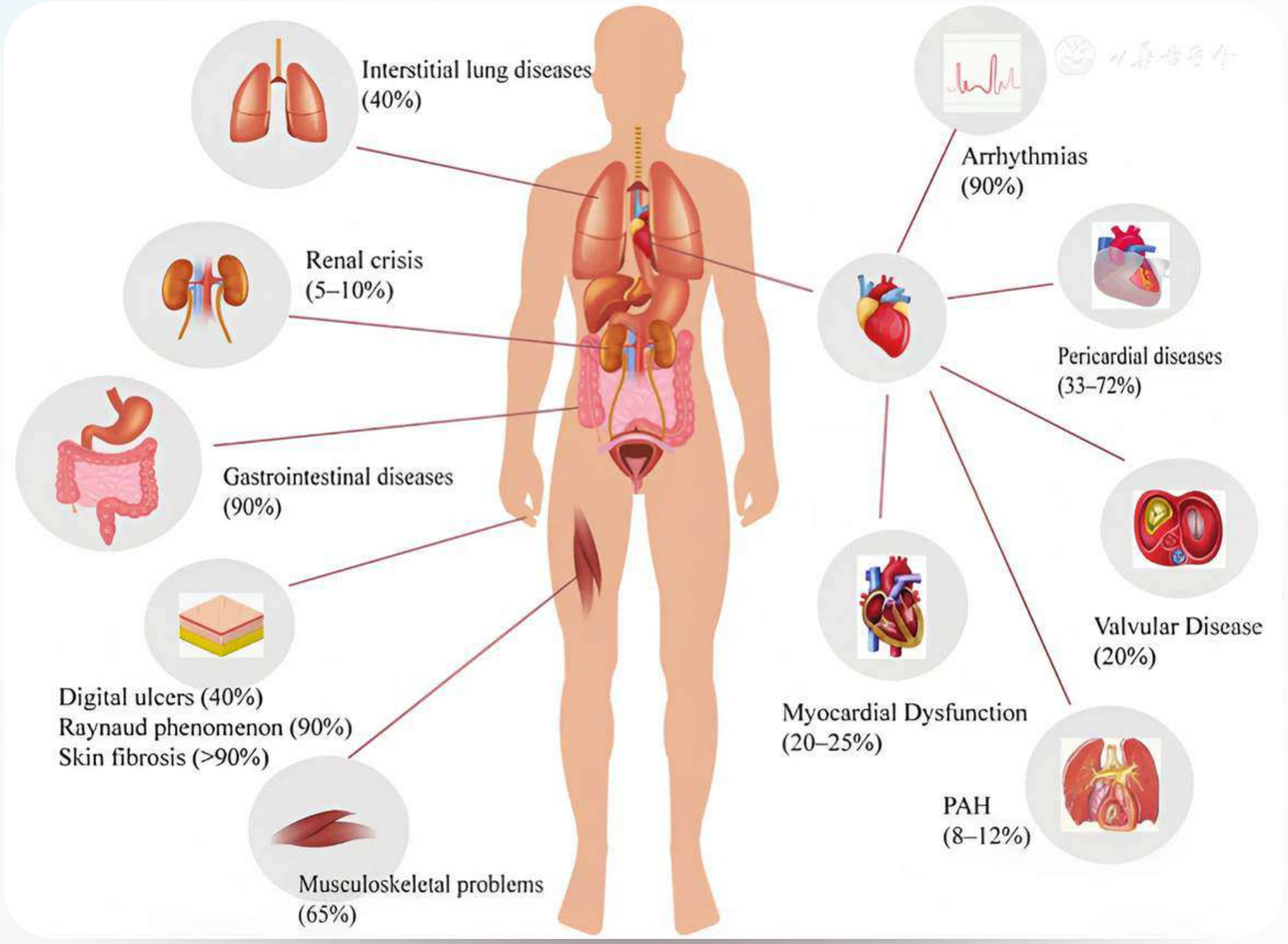


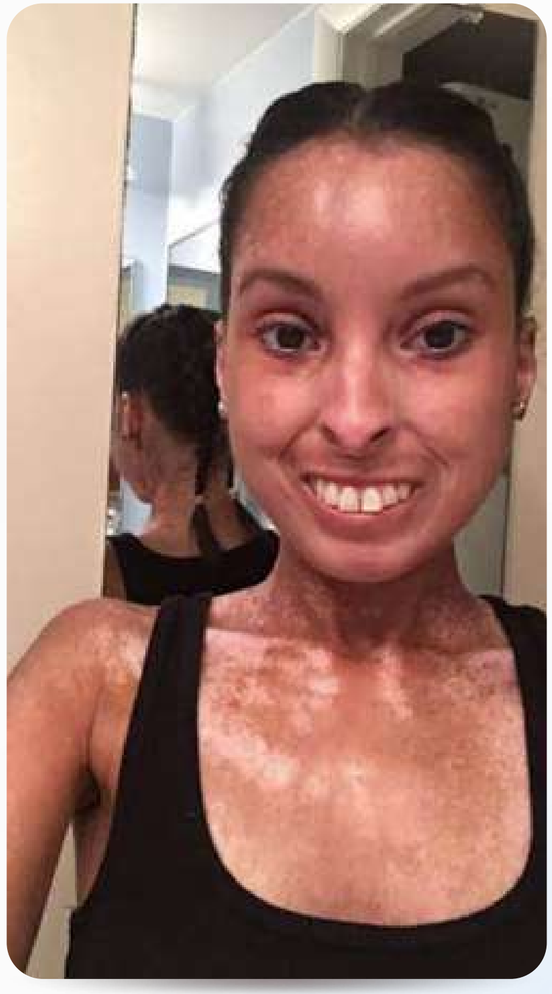

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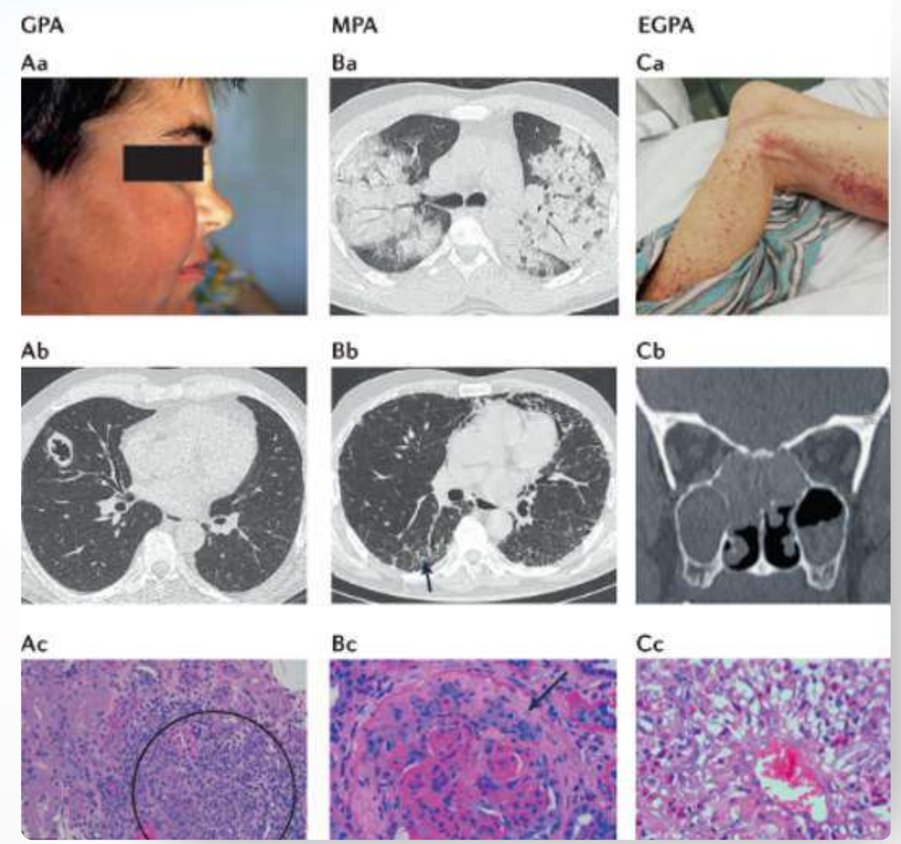
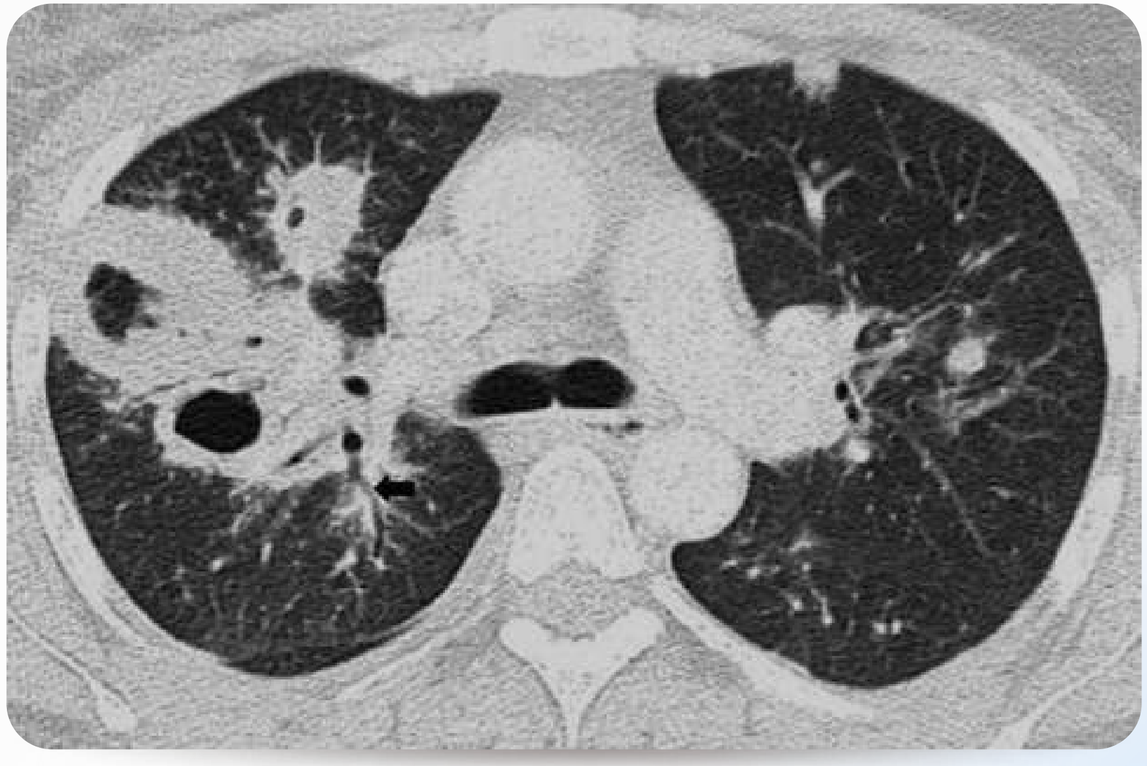
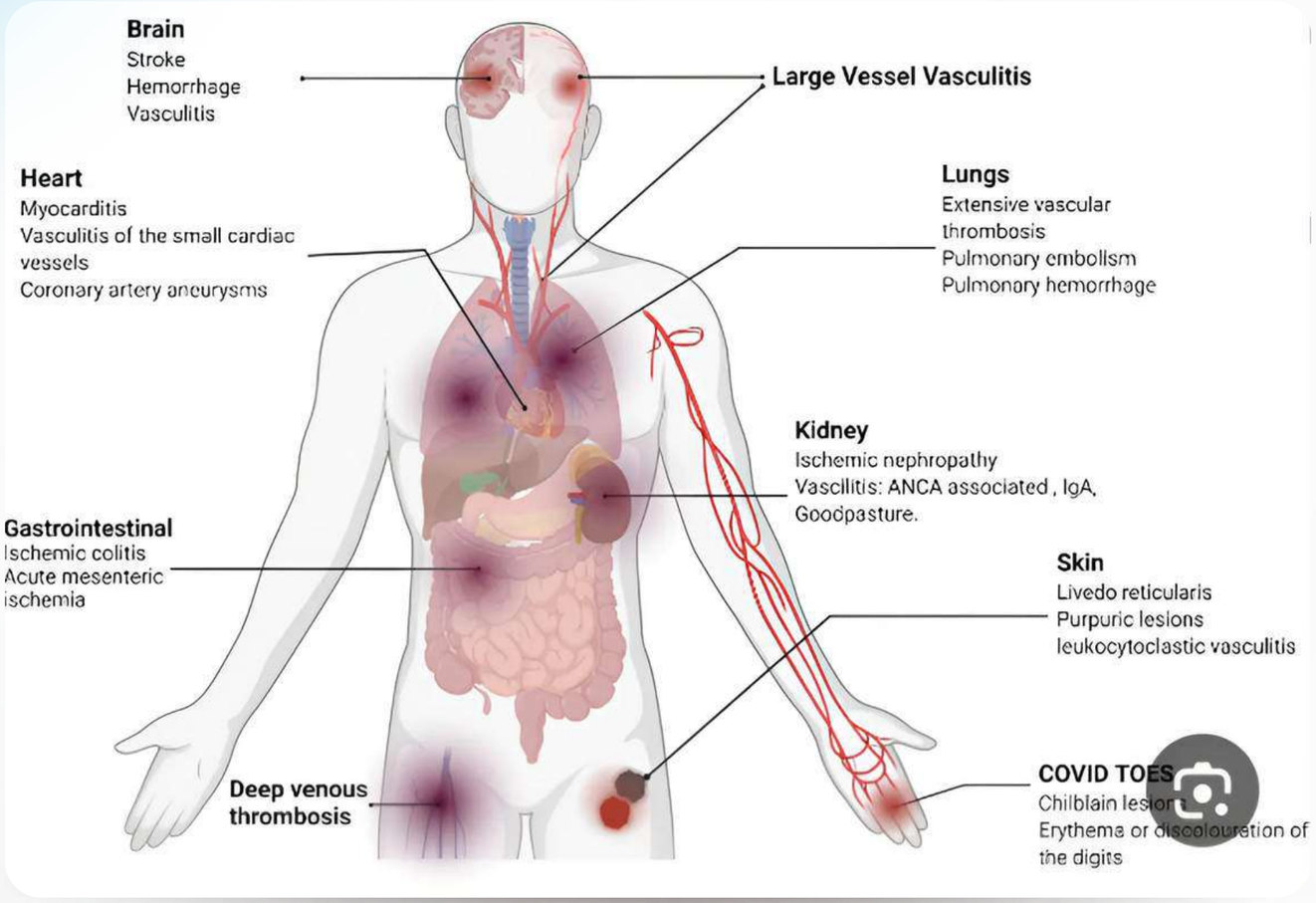
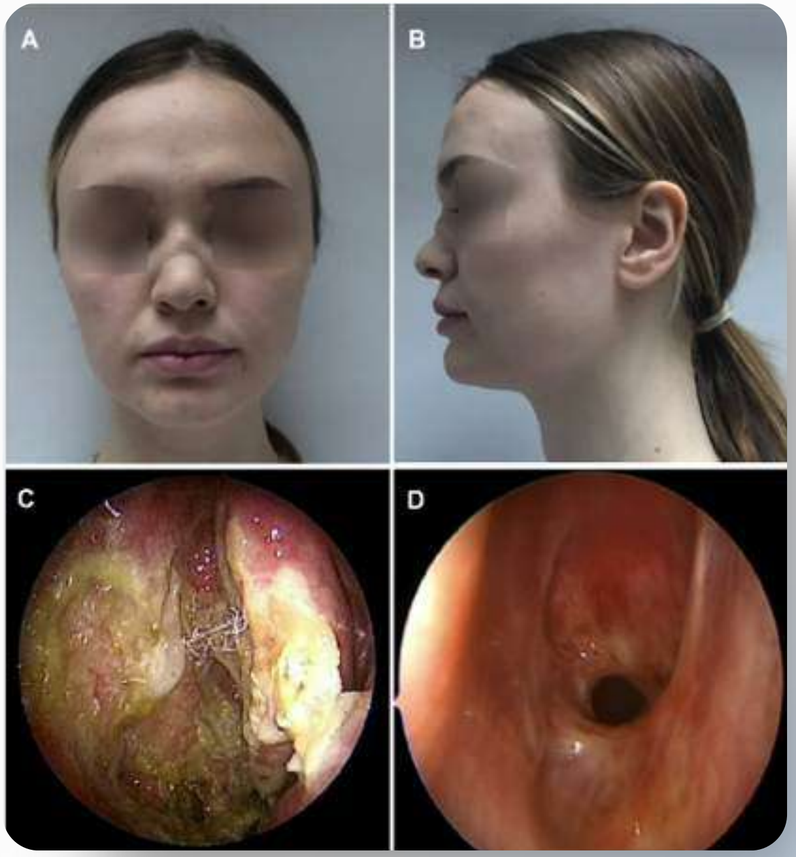
# ANCA Associated Vasculitis

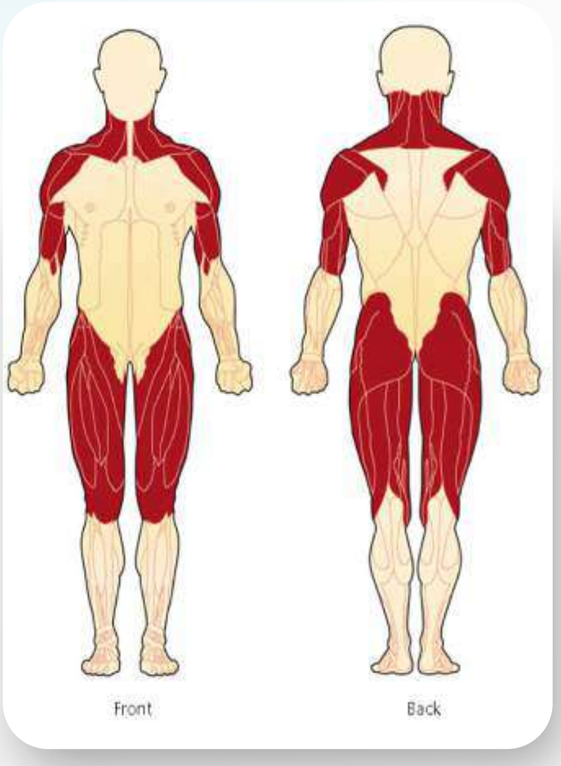


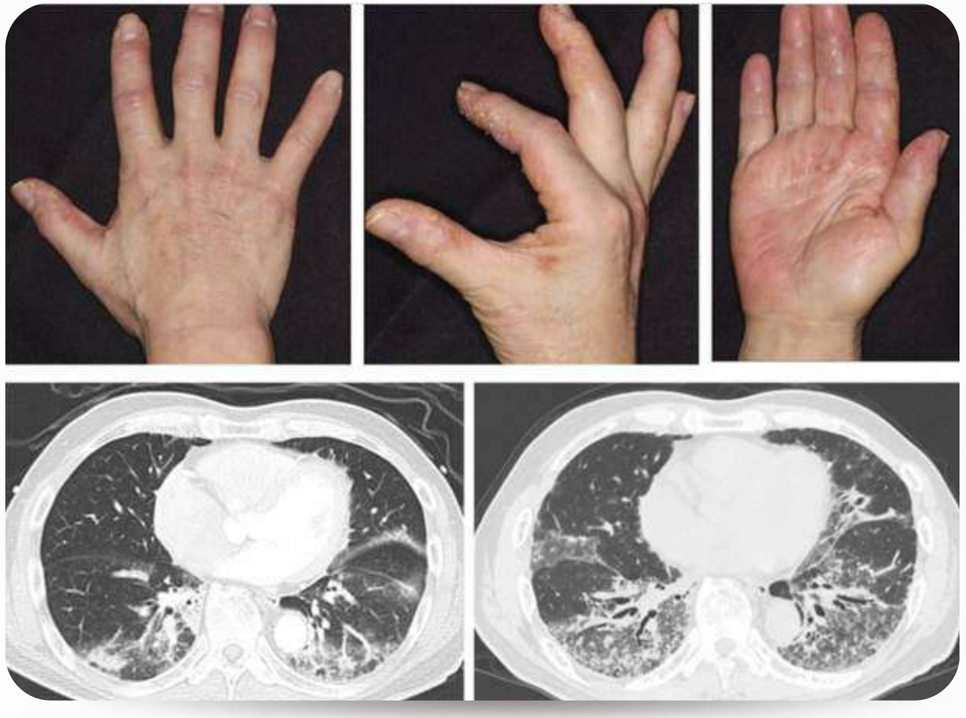




Brain
Stroke
Hemorrhage
Vasculitis
Large Vessel Vasculitis
Heart
Myocarditis
Vasculitis of the small cardiac vessels
Coronary artery aneurysms
Lungs
Extensive vascular thrombosis
Pulmonary embolism
Pulmonary hemorrhage
Kidney
Ischemic nephropathy
Vascilitis: ANCA associated , IgA, Goodpasture.
Gastrointestinal
Ischemic colitis
Acute mesenteric ischemia
Skin
Livedo reticularis
Purpuric lesions
leukocytoclastic vasculitis
Deep venous thrombosis
COVID TOES
Chilblain lesion
Erythema or discolouration of the digits


A
B
C
D

# Immune Mediated Myopathy (IMM)



# APPROACH TO MYOSITIS

## *Idiopathic Inflammatory Myopathies*

RHEUM ONE PAGERS

## PATHOPHYSIOLOGY

- **DM** → immune complex disease, mixed B-cell and CD4+ T-cells > perivascular damage; perifascicular atrophy
- **PM** → CD8+ T-cell mediated disease with direct myocyte injury; endomysial inflammation

## WORKUP / EVALUATION

**LABS**
- muscle enzymes (CK, AST/ALT, aldolase, LDH)
- myositis antibody panel (e.g. Myomarker)
- anti-HMGCoA (if clinical concern, ↑↑ CK)

**STUDIES**
- **EMG/NCS** or **MRI** myositis protocol
- CT Chest ILD protocol, PFTs (for ILD)
- PFTs (for ILD): ↓FVC, ↓DLCO
- malignancy screening (↑ cancer risk)

**BIOPSY**
- **muscle biopsy**
- +/- skin biopsy

★ Muscle Bx → critical to confirm dx (esp non-DM)

## TREATMENT

- high-dose steroids at diagnosis → taper
- methotrexate, azathioprine, mycophenolate
- refractory: Rituximab, CNI (e.g. tacrolimus)
- others: IVIg, cyclophosphamide (RP-ILD), JAKi

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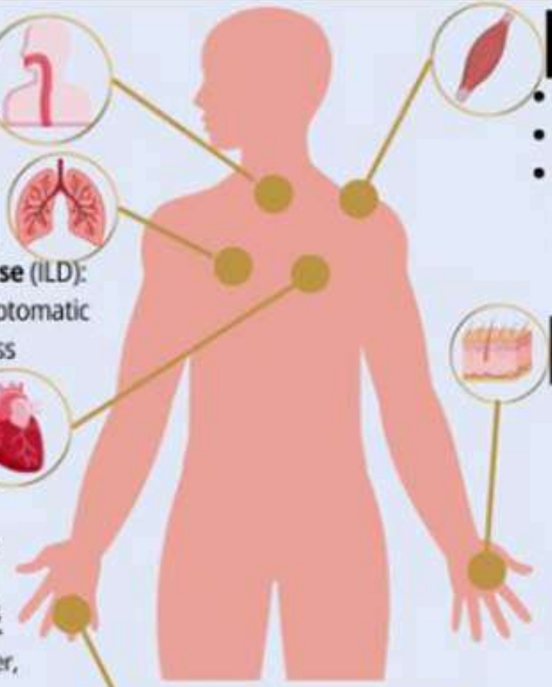
## CLINICAL PRESENTATION

### ESOPHAGEAL
- **dysphagia**, aspiration
- nasal regurgitation

### PULMONARY
- **interstitial lung disease** (ILD): dyspnea, may be asymptomatic
- diaphragmatic weakness

### CARDIAC
- usually subclinical / **asymptomatic**
- may cause arrhythmia



### MUSCLE WEAKNESS
- **proximal**, symmetric muscle **weakness**
- e.g. hips, buttocks, deltoids, neck
- s/sx: trouble combing hair, getting out of a chair, climbing stairs, lifting hands above head

### CUTANEOUS
- **Gottron papules**: raised erythematous scaly rashes over joints (MCP, DIP, PIP)
- **Gottron sign**: on dorsal elbows/knees
- **heliotrope rash**: purple discoloration around eyelids, +/- edema
- **V-neck sign**: erythema over neck and anterior chest
- **shawl sign**
- **holster sign**: on upper outer thigh
- **poikiloderma**
- **calcinosis cutis** (especially NXP2+)
- malar-like rash

★ Biopsy → shows interface dermatitis

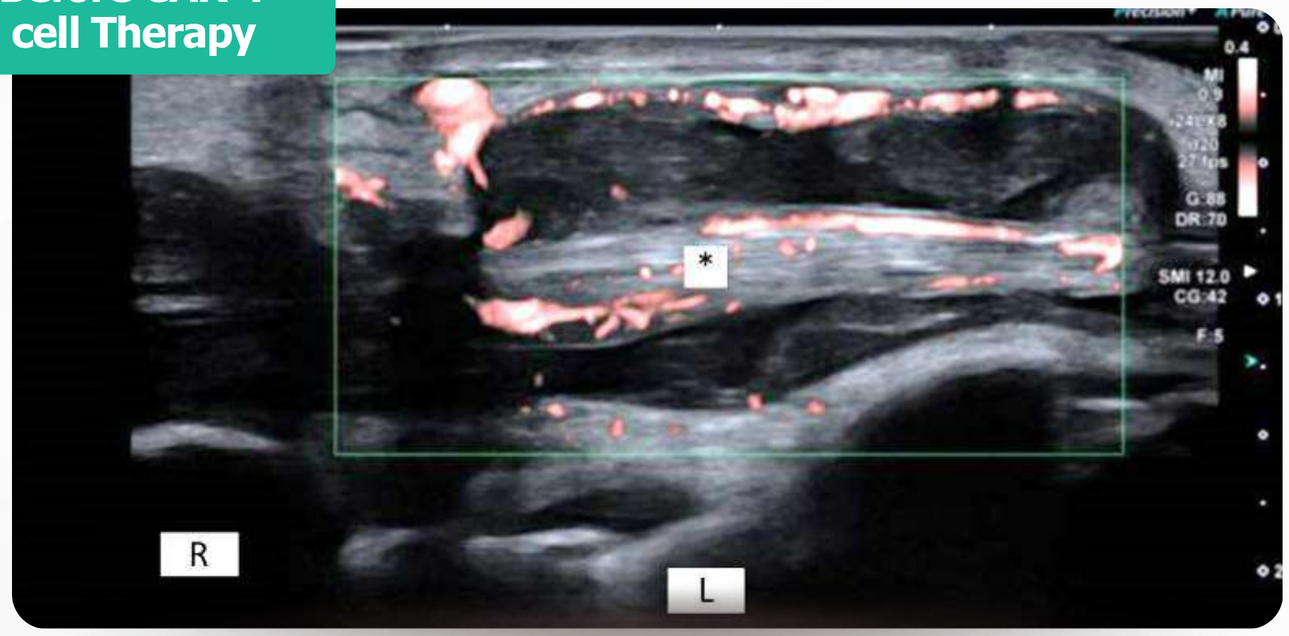
### VASCULAR
- **Raynaud's phenomenon** (RP)
- nailfold capillary changes

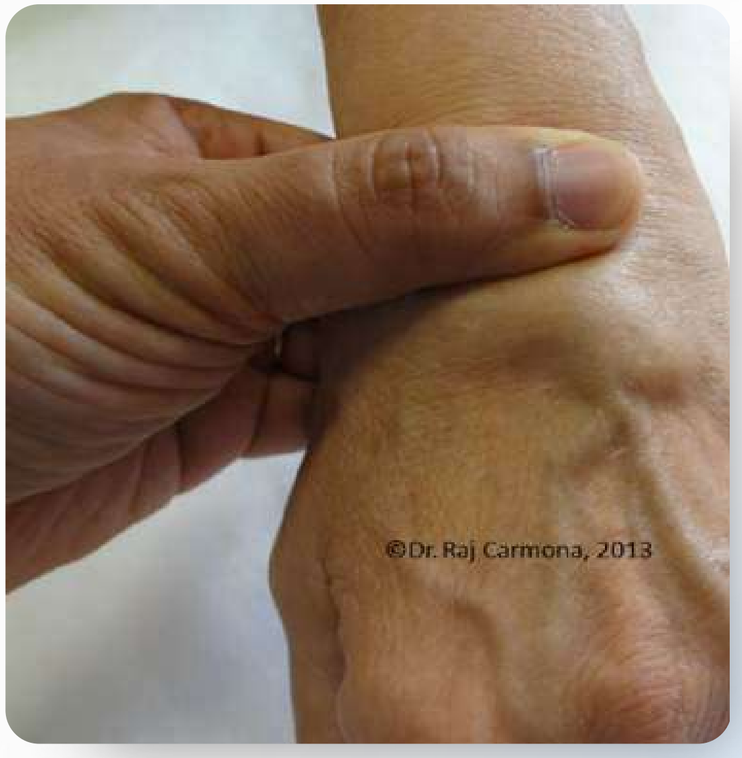
## Specific Subtypes of Myositis

- **Antisynthetase Syndrome**: myositis, ILD, fever, inflammatory arthritis, mechanic's hands, RP
- **Amyopathic DM**: no muscle weakness, +cutaneous
- **MDA-5**: ulcerative lesions, palmar papules, rapidly progressive ILD, pneumomediastinum
- **IMNM**: immune-mediated necrotizing myopathy; ↑ CK

# Rheumatoid Arthritis

**Before CAR-T cell Therapy**

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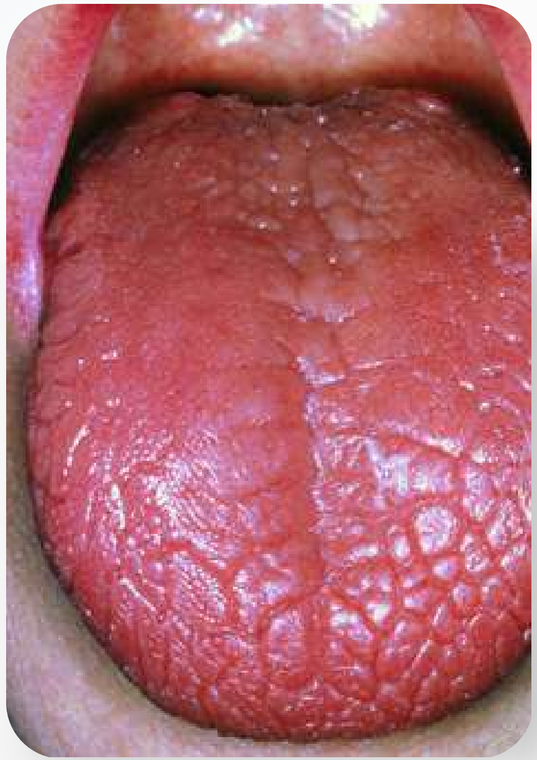
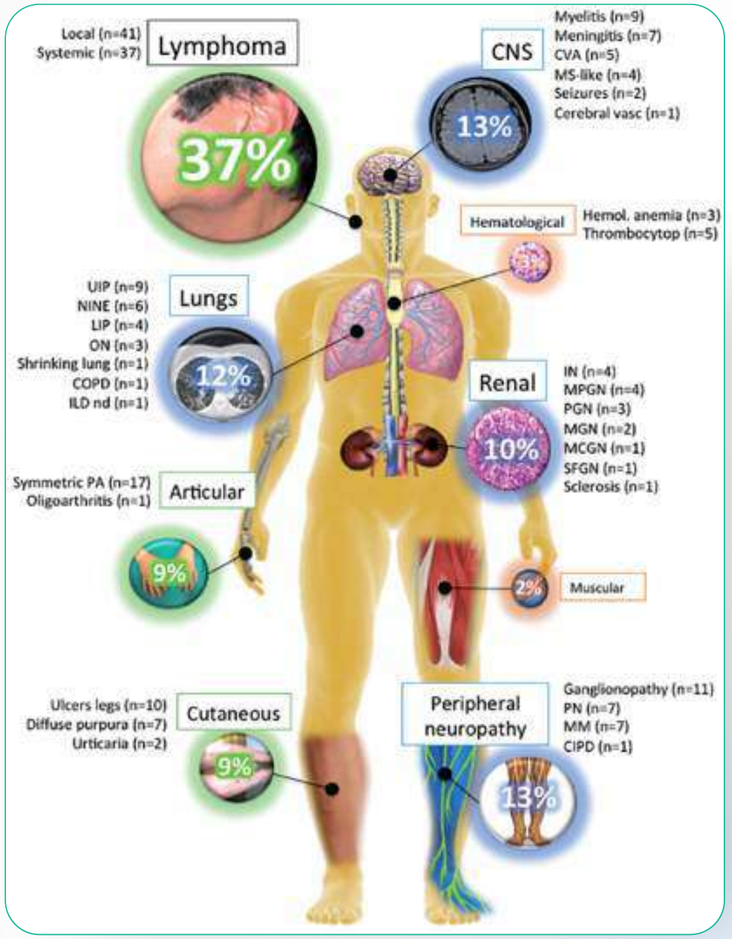
# Sjogren’s Disease



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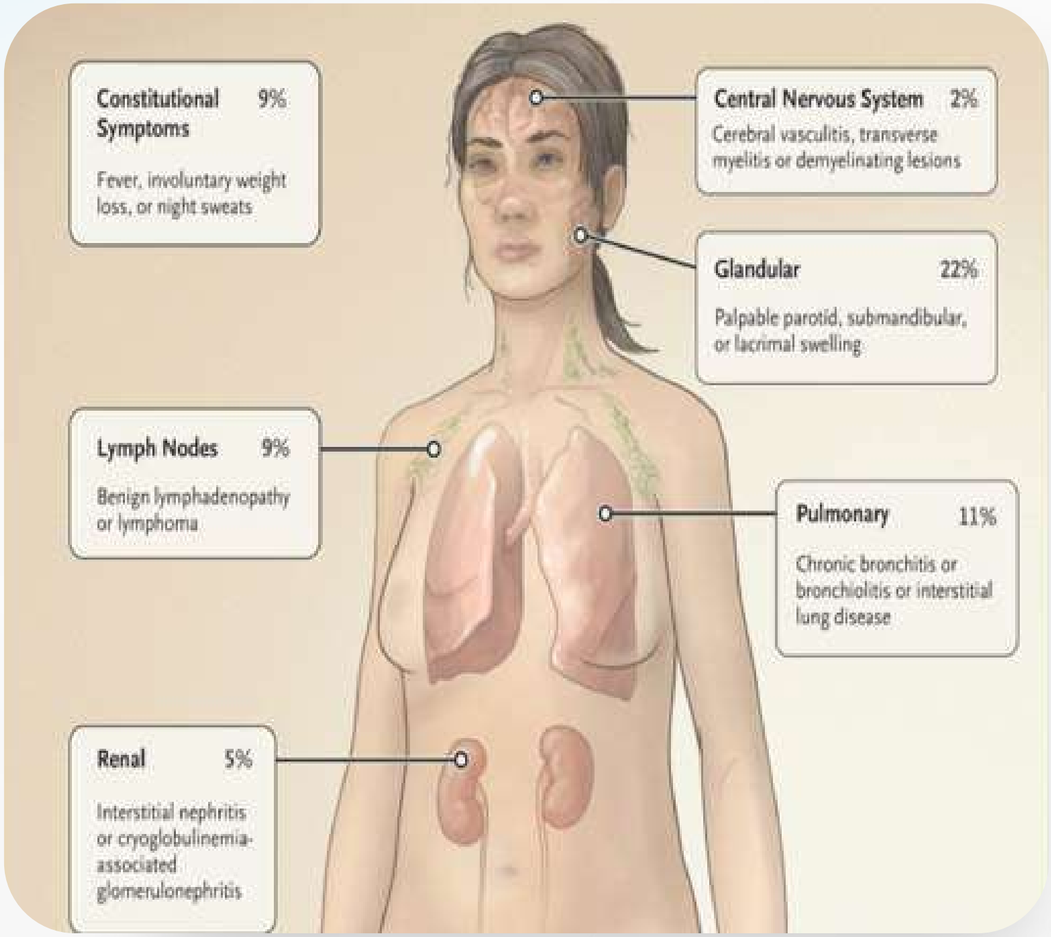
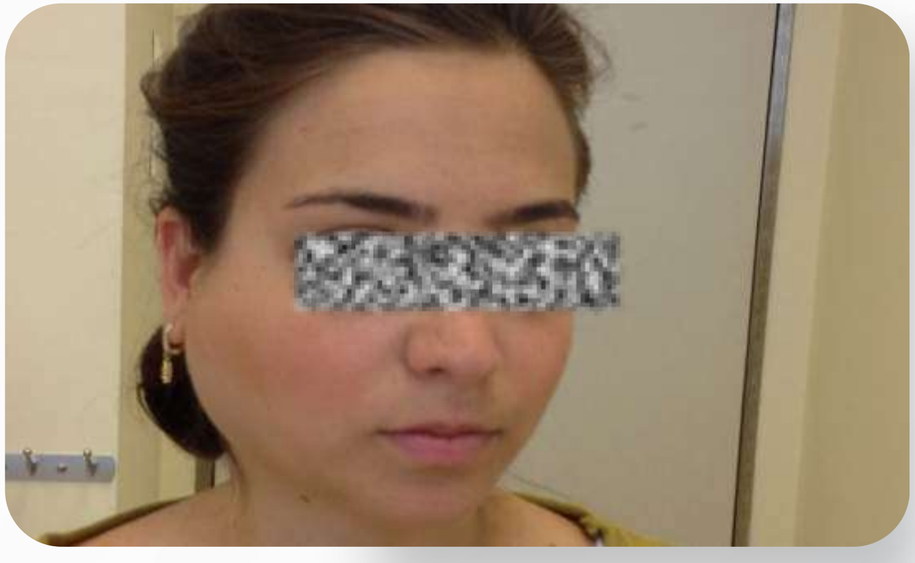
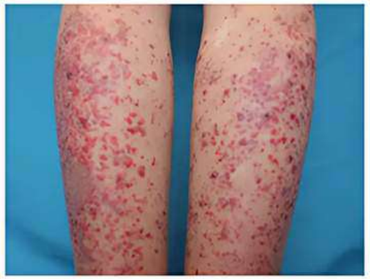
# Sjogren’s Disease

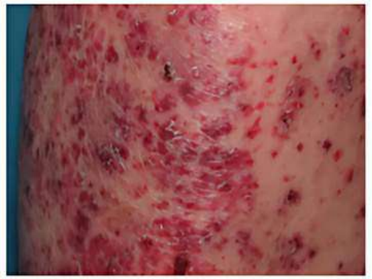


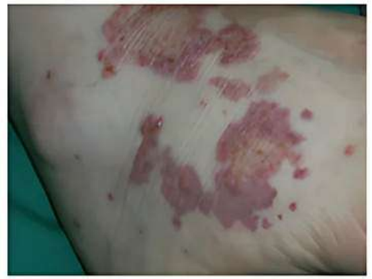
Sjogren syndrome – cutaneous vasculitis



Sjogren vasculitis



Sjogren vasculitis



Sjogren vasculitis

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# THANK YOU

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