Corso di Laurea Magistrale in Biotecnologie Mediche
Università degli Studi di Napoli Federico II
Corso Integrato di Basi molecolari di patologie immunitarie e neurologiche

Systemic Vasculitis

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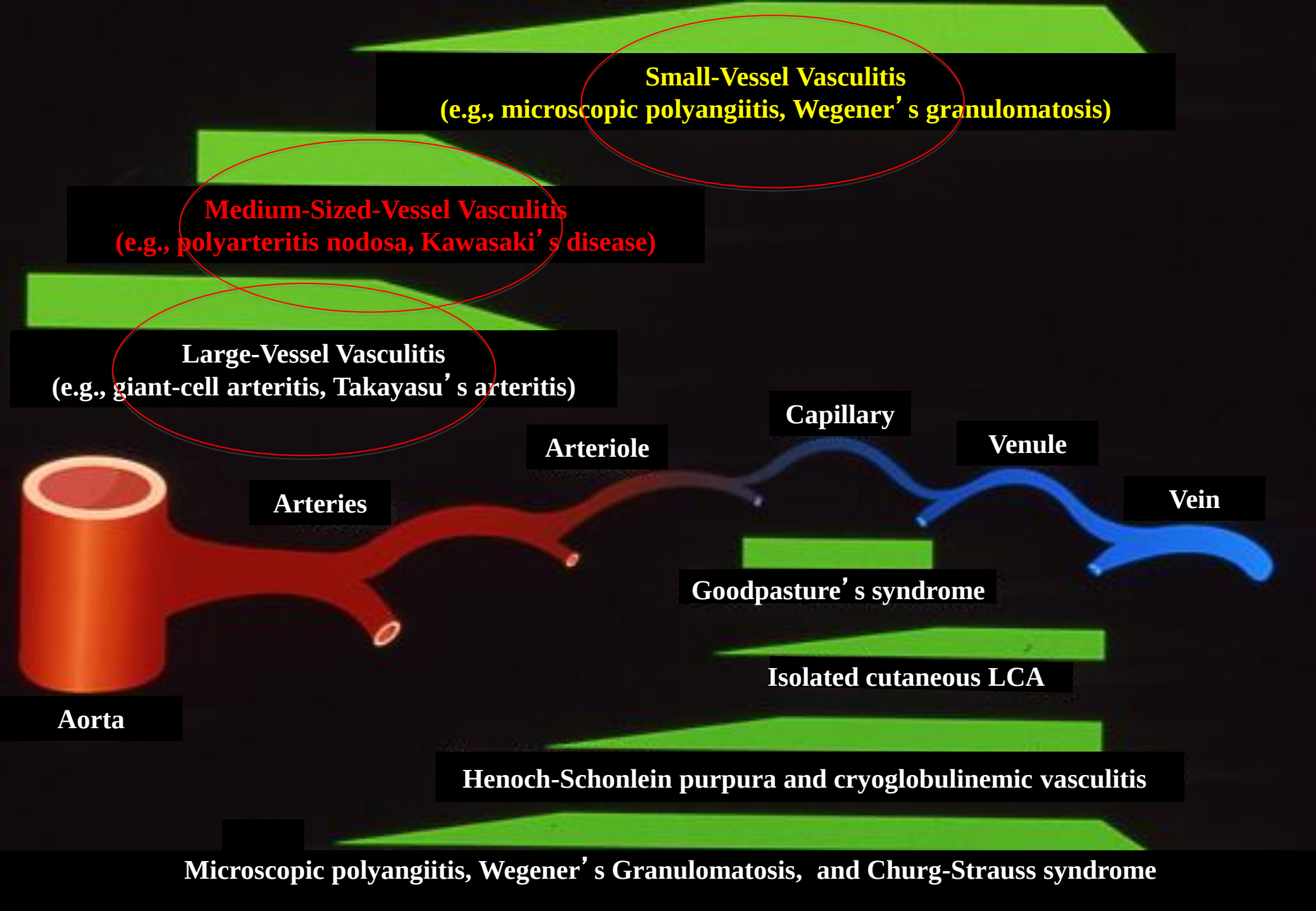
Vasculitis

Vasculitis are a group of heterogeneous clinical and pathogenetic conditions characterized by inflammation and necrosis of the blood vessels. This results in reduction or occlusion of the vessel lumen and ischemia of the tissues and organs involved in the vasculitic process.


Small-Vessel Vasculitis
(e.g., microscopic polyangiitis, Wegener's granulomatosis)
Medium-Sized-Vessel Vasculitis
(e.g., polyarteritis nodosa, Kawasaki's disease)
Large-Vessel Vasculitis
(e.g., giant-cell arteritis, Takayasu's arteritis)
Capillary
Arteriole
Venule
Arteries
Vein
Goodpasture's syndrome
Isolated cutaneous LCA
Aorta
Henoch-Schonlein purpura and cryoglobulinemic vasculitis
Microscopic polyangiitis, Wegener's Granulomatosis, and Churg-Strauss syndrome

Classification of Primary Vasculitis

	ANCA
• **Large Vessel Vasculitis**	
Giant Cell Arteritis (GCA) (Temporal Arteritis)	-
Takayasu's arteritis (TAK)	-
• **Medium Vessel Vasculitis**	
Panarteritis Nodosa (PAN)	-
Kawasaki's Disease (KD)	-
• **Small Vessel Vasculitis**	
Granulomatosis with Polyangiitis/GPA/Wegener's	+
Churg-Strauss Syndrome/EGPA	+
Microscopic polyangiitis (MPA)	+
Henoch-Schönlein purpura/IgA vasculitis	-
Cryoglobulinemic vasculitis (CV)	-
Leukocytoclastic vasculitis	-

ANCA – Associated Vasculitis

• **ANCA associated vasculitis** are a distinct form of autoimmune vasculitis characterized by necrotizing inflammation with a paucity of vessel wall Ig detectable. They affect predominantly **small vessels** in any organ of the body, including small arteries, arterioles, venules and veins.

• **ANCA (Anti-Neutrophil Cytoplasmic Antibodies)** bind to antigens in the primary granules of neutrophils

• On the basis of clinical and pathological features:

• **Granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis)**

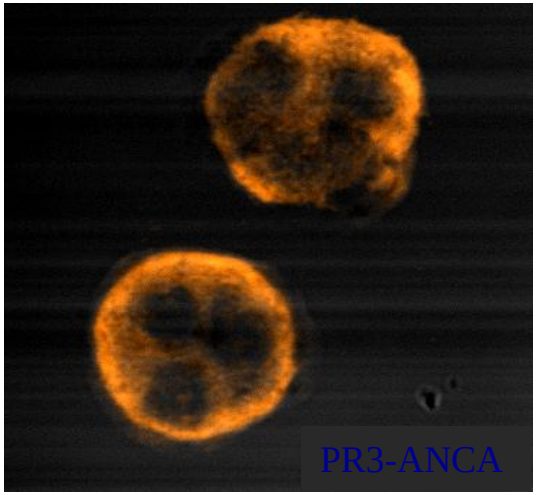
• **Eosinophilic Granulomatosis with polyangiitis (EGPA) (Churg-Strauss Syndrome)**

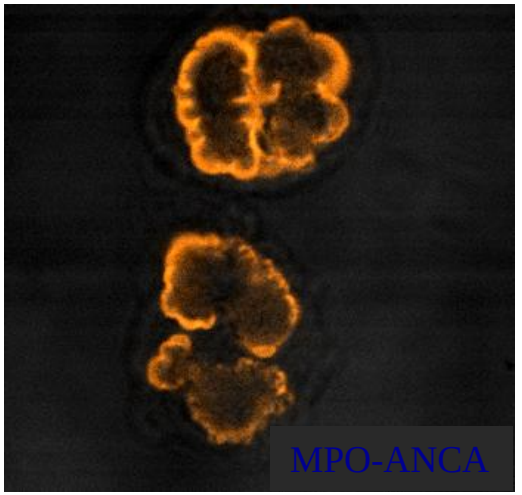
• **Microscopic Polyangiitis (MPA)**

Anti-Neutrophil Cytoplasmic Antibodies: ANCA

PR3-ANCA	**Citoplasm**	**Proteinase-3 (PR-3)** **α granules**	**Wegener Granulomatosis** **Sensitivity 92%** **Specificity 100%**
MPO-ANCA	**Perinuclear**	**Myeloperoxidase (MPO)** **Lactoferrin** **Elastase**	**Associated with MPA and EGPA**

The granular, cytoplasmic staining pattern of PR3-ANCA





Perinuclear staining typical of MPO-ANCA

ANCA Associated Vasculitis Pathogenesis

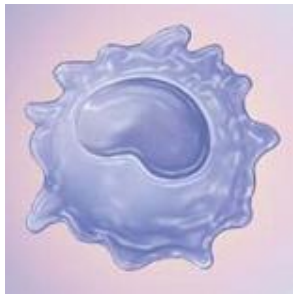
- **Unknown origin**
- **Genetic Factors (GPA: Allele DPB1*041; EGPA: HLA-DRB4)**
- **Environmental factors (infectious agents, environmental toxic agents, allergens)**
- **Both innate immune (macrophages, neutrophils and eosinophils) and adaptive immune cells (B and T cells) are involved.**
- **Pivotal role played by circulating soluble factors, such as autoantibodies, immunocomplexes, complement factors and inflammatory mediators**

Pathogenetic Role of ANCA

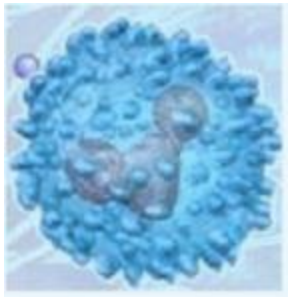
- The genesis of the ANCA autoimmune response is a **multifactorial** process that includes genetic predisposition, environmental adjuvant factors, an initiating **self antigen**, and **failure of T cell regulation**
- **ANCA activate primed neutrophils** (and monocytes) by binding to certain neutrophil antigens in specific inflammatory microenvironments
- ANCA-activated neutrophils activate the **alternative complement pathway**, establishing an inflammatory amplification loop
- The acute injury elicits an innate inflammatory response that recruits **monocytes and T lymphocytes**, which replace the neutrophils that have undergone **karyorrhexis** during acute inflammation

ANCA and Vasculitis: Much More than a Disease Marker

Monocyte

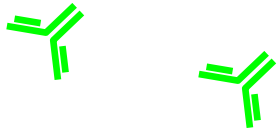


TNF-α



Cytokine-primed PMN
Traslocation of cytoplasmic primary granules

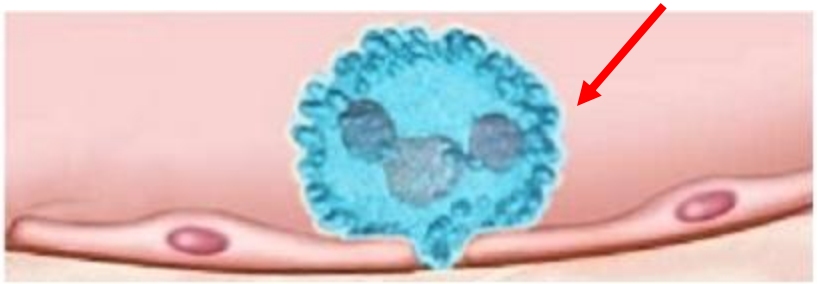
ANCA
Antibody anti-PR-3



Primed PMN activation:
Fc receptor engagement

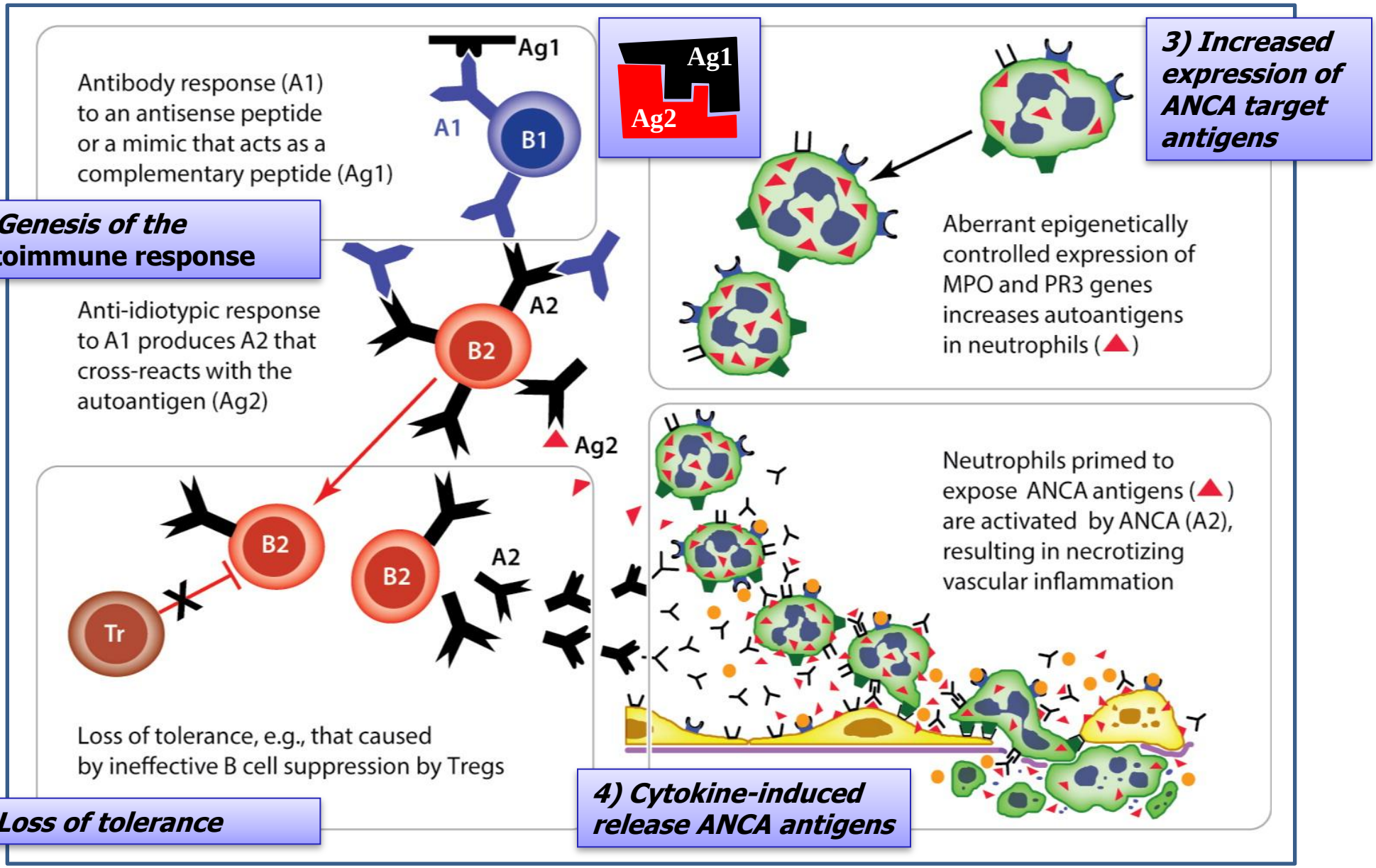
Release of
toxic oxygen
Radicals and NETs

Intercurrent viral or
bacterial infections of the
upper respiratory tract

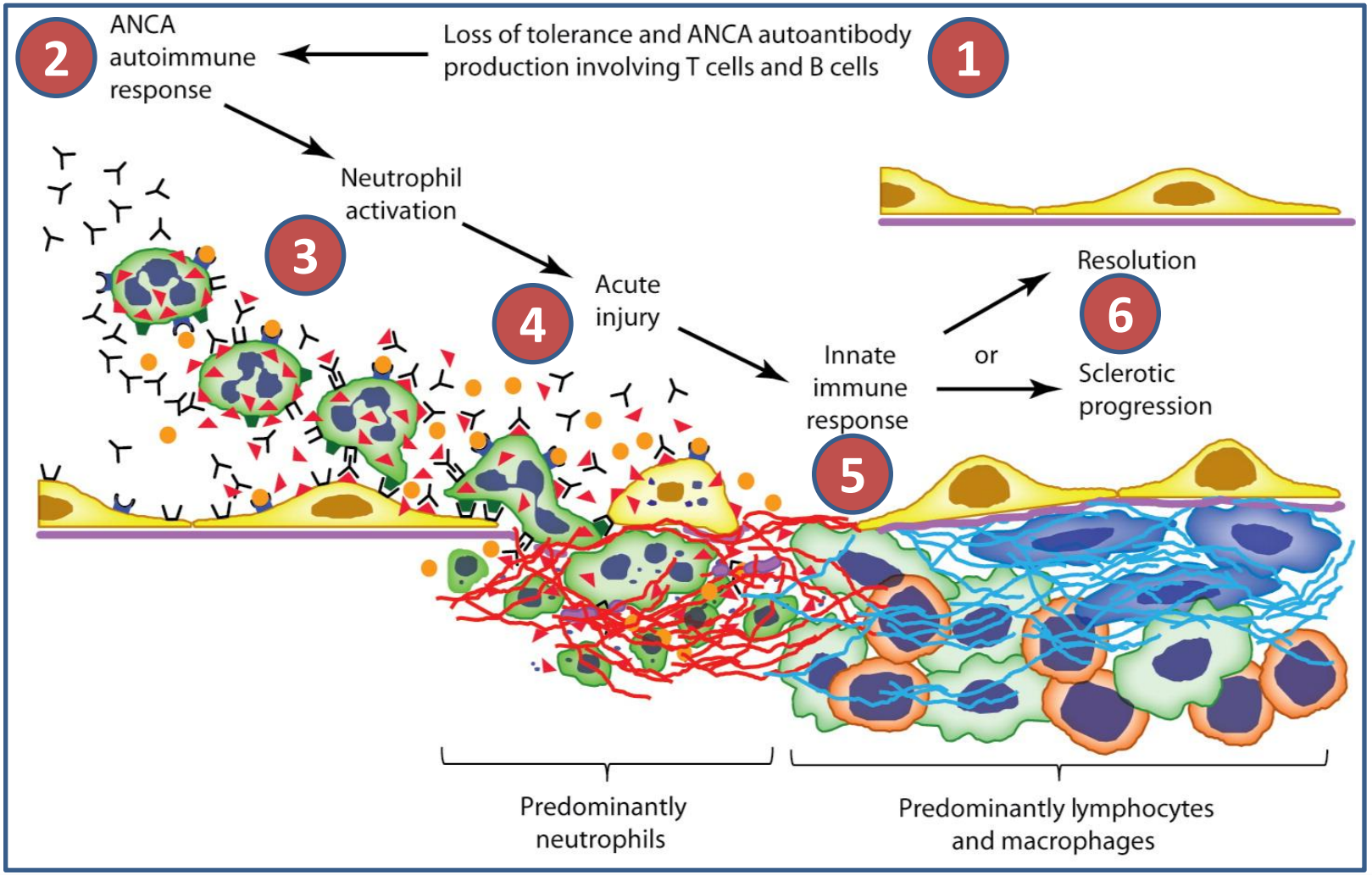


Endothelial Cells

Multiple Events Contributing to the Pathogenesis of ANCA-associated Vasculitis



Sequence of Events in ANCA-associated Vasculitis



1) Loss of tolerance allows for 2) production of pathogenic levels of ANCA. 3) ANCA activate primed neutrophils by binding to ANCA antigens at the surface of neutrophils and in the microenvironment of the inflammation. 4) ANCA-activated neutrophils mediate acute necrotizing injury with fibrinoid necrosis and leukocytoclasia. 5) The acute injury elicits an innate inflammatory response that recruits monocytes and T lymphocytes, which replace the neutrophils and lead to either 6) resolution of the injury or development of localized fibrosis/sclerosis.

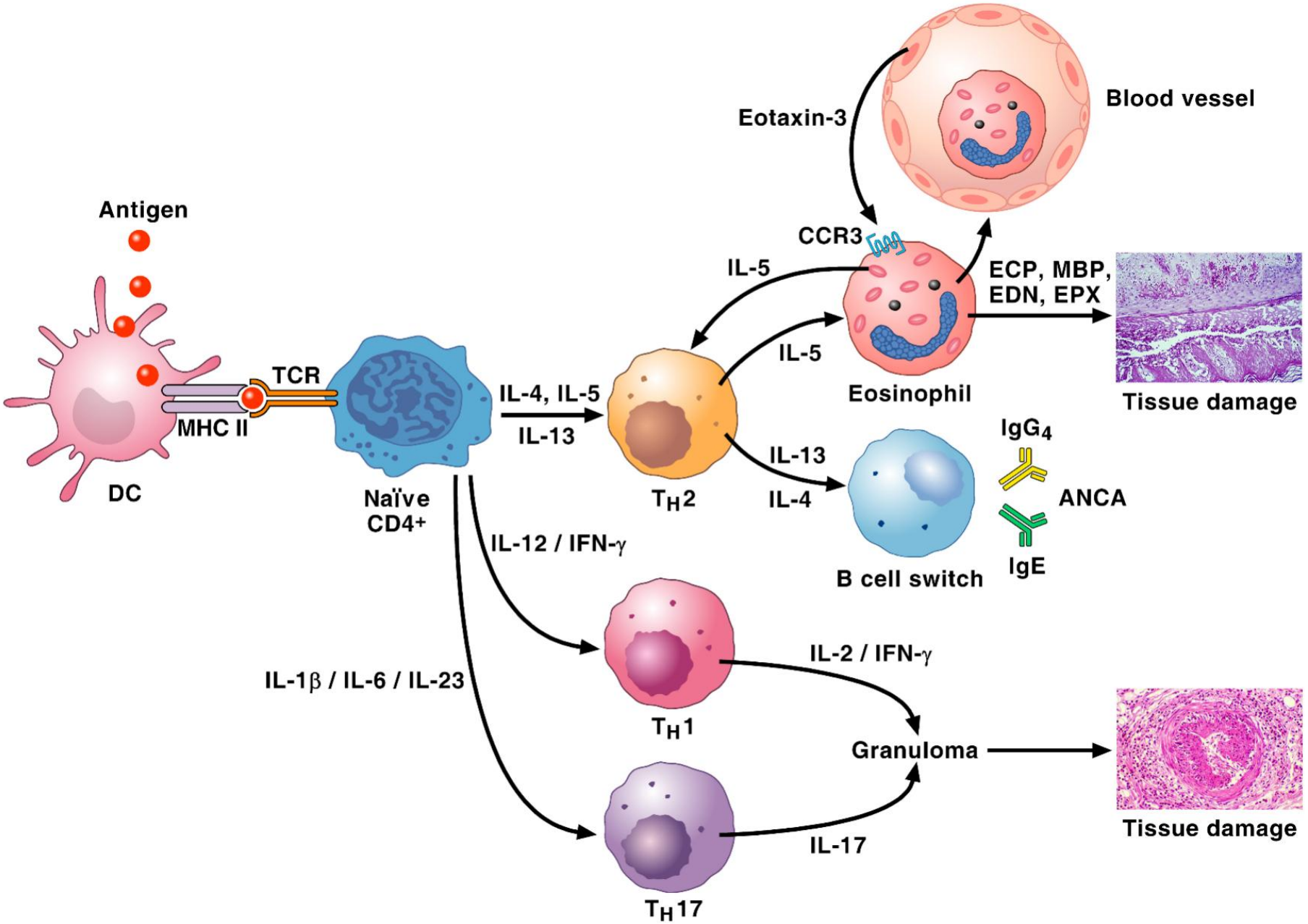
ANCA - associated Vasculitis

	EGPA/Churg-Strauss	Granulomatosis with polyangiitis/Wegener's
Eosinophilia	+++	+
Cardiac involvement	+++	±
Renal involvement	+	+++
MPO – ANCA	± 40%	-
PR3 – ANCA	-	± 90%
Genetic background	HLA-DRB4	
IL-5	↑↑	-
IL-10	↑↑	-
Eotaxin - 3	↑↑	

Eosinophilic Granulomatosis with Polyangiitis (EGPA)/Churg-Strauss Syndrome

- It is a necrotizing vasculitis of small and medium arteries and veins. It affects predominantly the vessels of the lung, bowel, heart and kidney with granuloma formation intra- and extravessel widely infiltrated by **eosinophils**
- It is twice more common among males
- The age of greatest incidence is in the 3rd and 4^{th} decade
- The etiology is unknown

Pathogenesis of EGPA



Churg-Strauss Syndrome: Clinical Manifestations

Apparatus	Signs or symptoms	Frequency %
Respiratory	Lung infiltrates	70
	Löffler syndrome	40
Genitourinary	Kidney impairment	50
Cardiovascular	Pericarditis	40
	Hypertension	40
Gastro-intestinal	Abdominal pain	60
	Dyarrhea	35
Nervous	Peripheral mononeuritis	65
	Stroke	25
Osteomuscular	Arthritis	50
	Artromyalgia	40
Cutaneous	Purpura	50
	Erythema/urticaria	35
	Nodules	30

Evolution of Clinical Course

Prodromal phase	**It can last for months or years and it is characterized by recurrent episodes of bronchial asthma, sinusitis, fever, weight loss and eosinophilia**
Intermediate phase	**It may appear with the Löffler's syndrome or eosinophilic gastroenteritis**
Full-blown phase	**Pulmonary and systemic vasculitis**

Diagnostic Criteria of EGPA

ACR, 1990

- Episodes of bronchial asthma
- Eosinophilia (> 1.500 / mm^3)
- Mono- or polyneuropathy
- Transient or migrant pulmonary infiltrates
- Symptoms and radiographic signs of sinusitis
- Eosinophils in perivascular, arterial or venous biopsies

The presence of at least 4 of 6 of the above parameters allows us to make the diagnosis with 85% of sensitivity and a specificity close to 100%

Therapy of EGPA

- **Prednisone (1 mg/Kg/day) for 3 weeks**

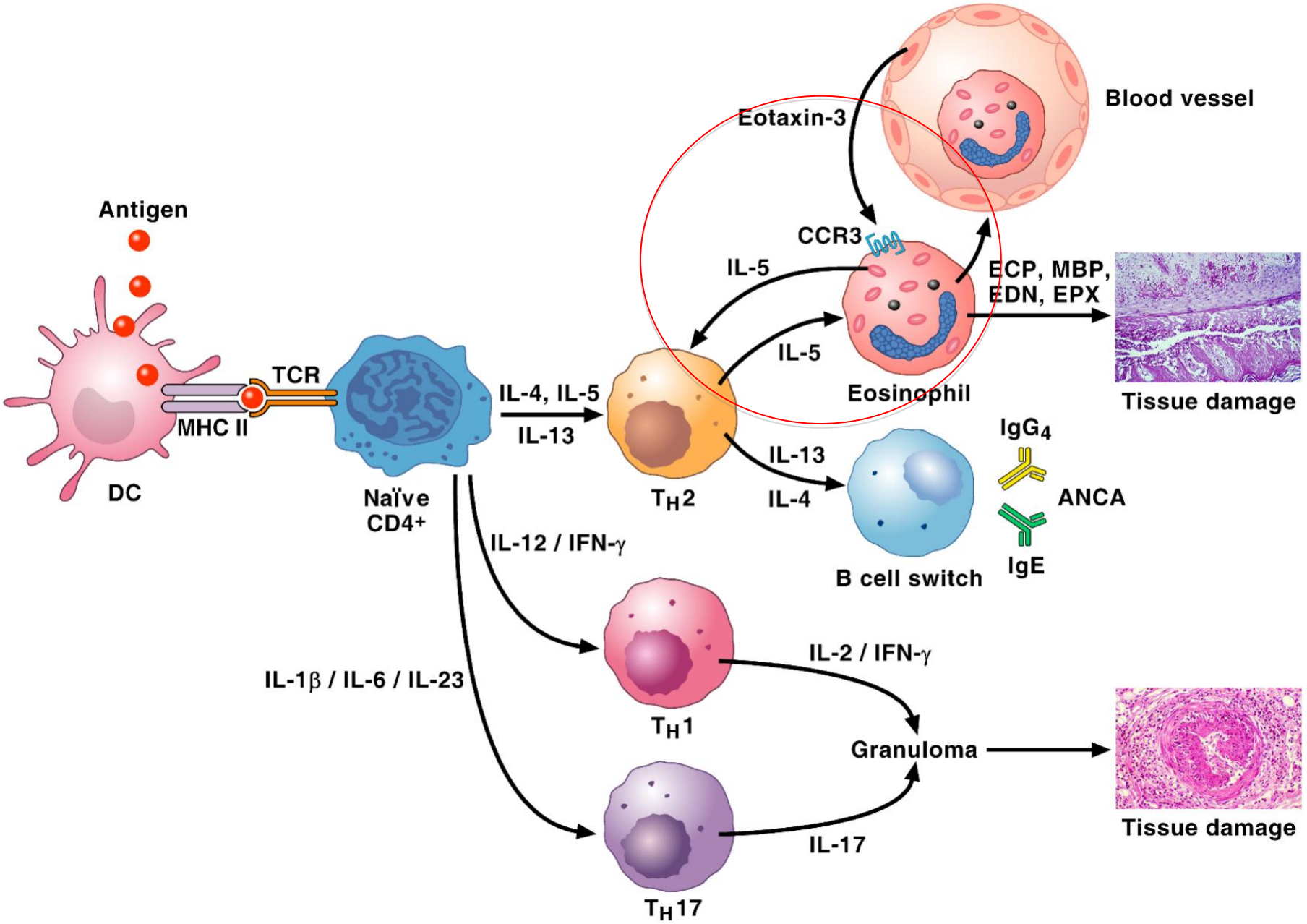
  Then tapered 10% every 10 days to the minimal effective dose

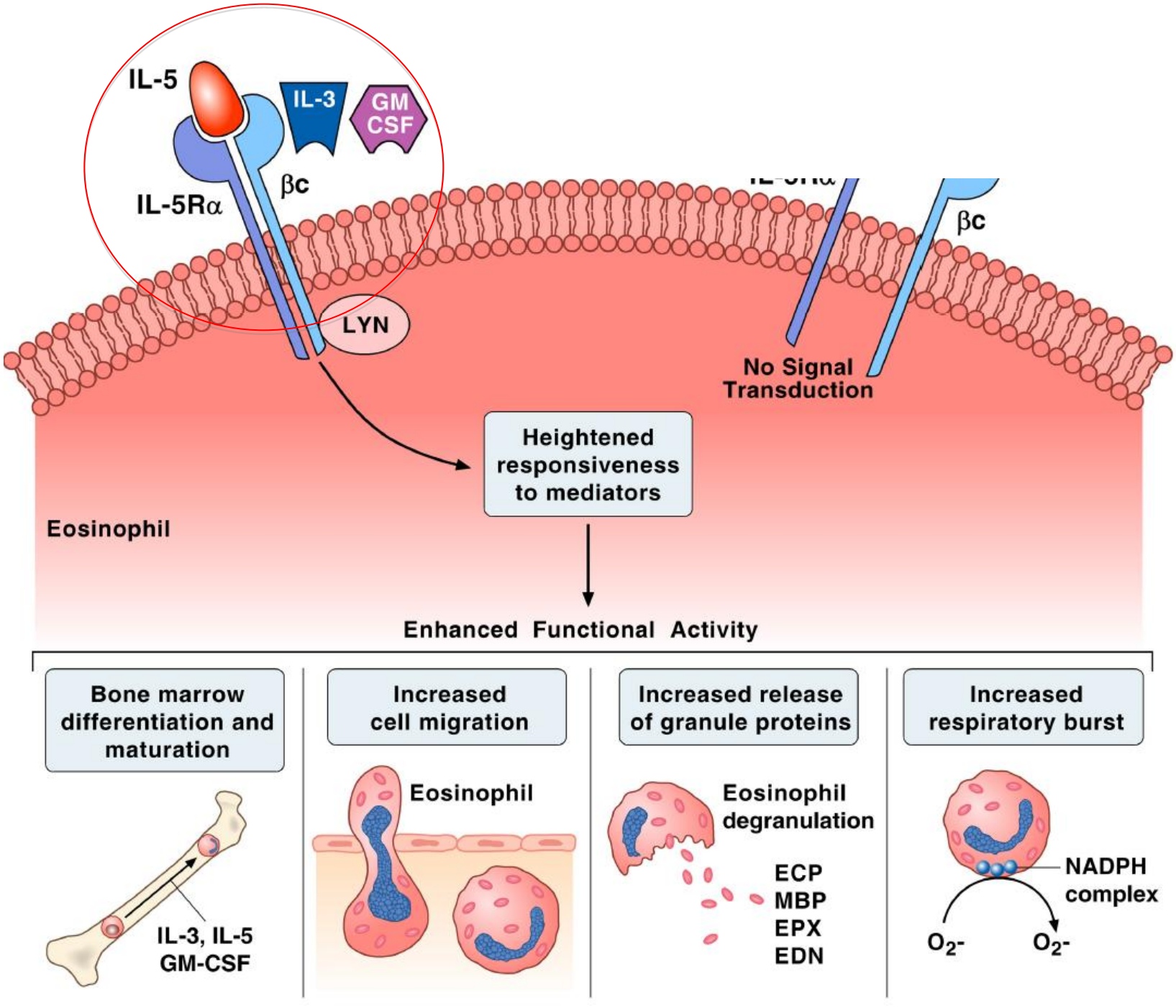
- **Cyclophosphamide (CYC) (600 mg/m^2) i.v. every 4 weeks for a maximum of 7 to 12 pulses + Mesna (Uromitexan®) 400 mg i.v. immediately before and 4 h after CYC**

- **Calcium + Vit. D_3 (Cacit®, 1 dose/day) and Bisphosphonates**

- **Hematologic monitoring every 2-4 weeks**

Pathogenesis of EGPA




IL-5
IL-3
GM CSF
βc
IL-5Rα
LYN
βc
No Signal Transduction
Heightened responsiveness to mediators
Eosinophil
Enhanced Functional Activity
Bone marrow differentiation and maturation
IL-3, IL-5 GM-CSF
Increased cell migration
Eosinophil
Increased release of granule proteins
Eosinophil degranulation
ECP
MBP
EPX
EDN
Increased respiratory burst
NADPH complex
O2-
O2-

Mepolizumab as a Steroid-sparing Treatment in Patients with Churg-Strauss Syndrome (CSS)

- **Levels of IL-5 can be increased in patients with CSS**
- **7 patients with CSS were treated with 4 monthly doses of Mepolizumab (750 mg i.v. in 30 min)**
- **Mepolizumab was well tolerated in all patients**
- **Mepolizumab reduced eosinophil counts and effectively served as corticosteroid-sparing therapy (≈ 60% reduction)**

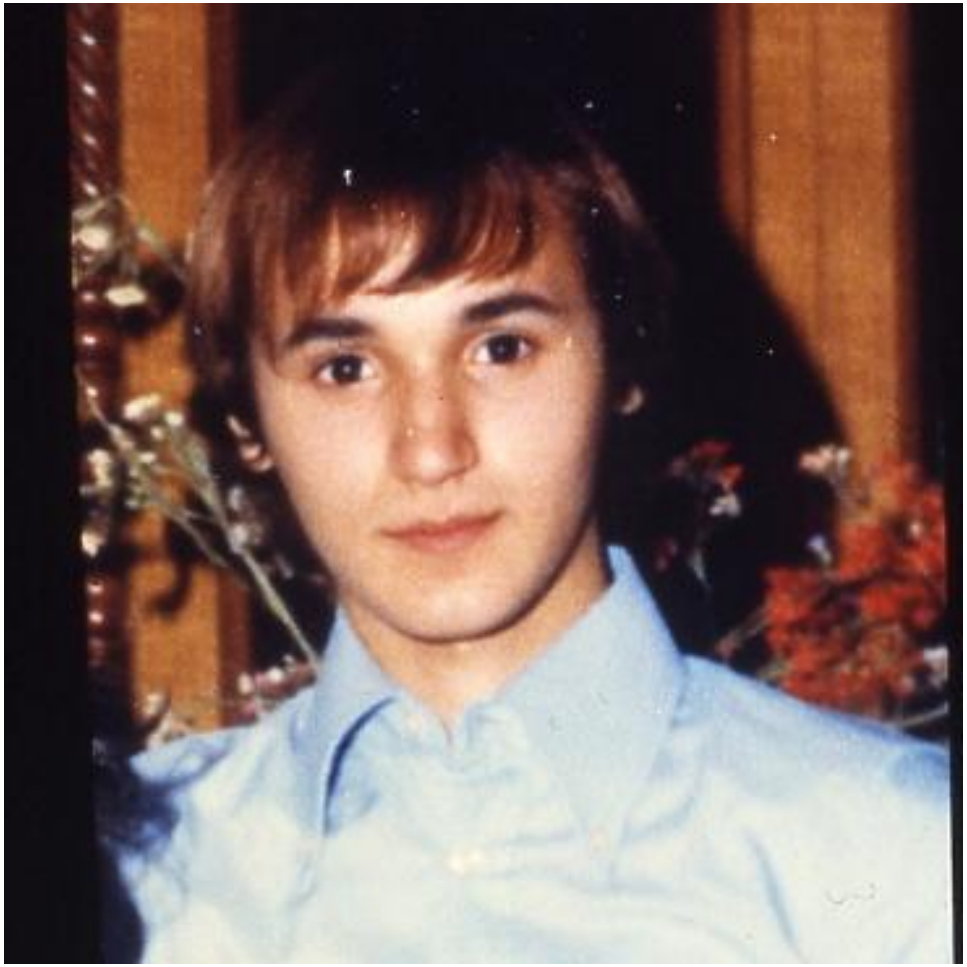
Granulomatosis with Polyangiitis/Wegener's

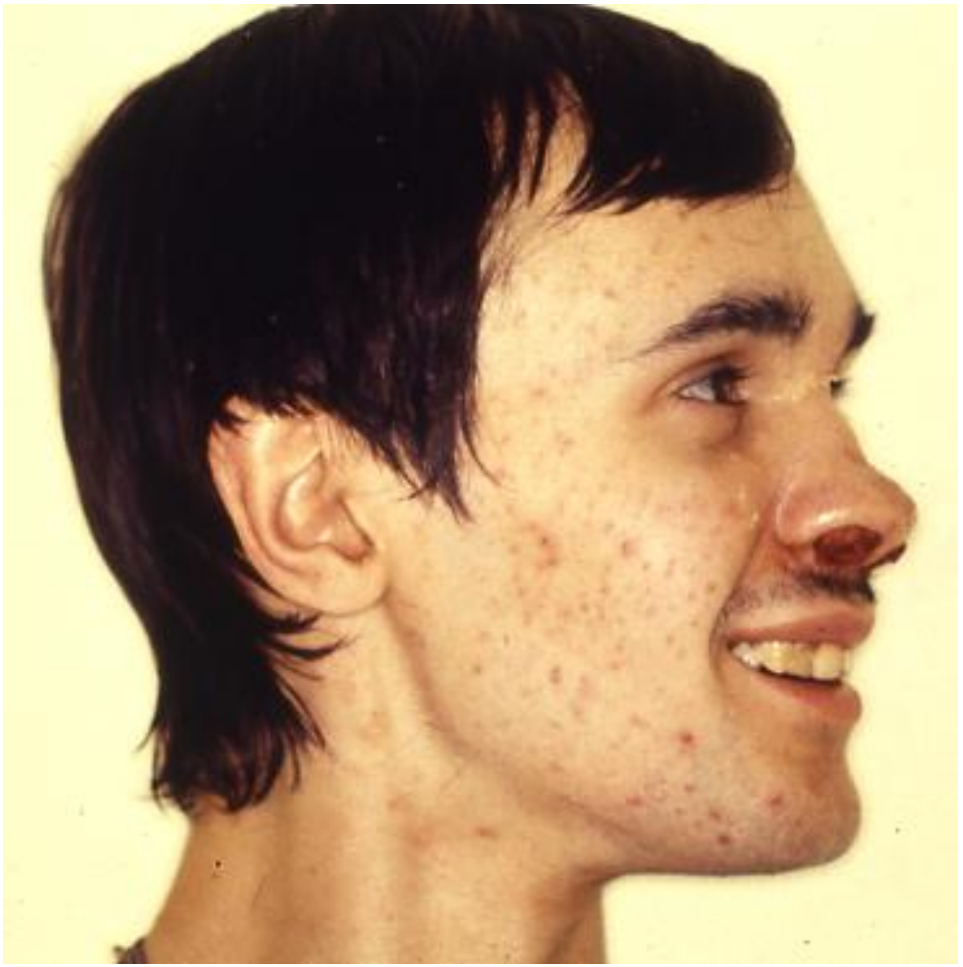
- Granulomatosis with Polyangiitis/Wegener's, described in 1936, is an inflammatory process of the respiratory tract with small and medium vessel necrotizing vasculitis
- It frequently coexists with a necrotizing glomerulonephritis
- The incidence is about 1/30.000 in the Caucasic population
- The disease manifests itself preferably in men (3: 2), usually after the third decade of life
- The etiology is unknown

Granulomatosis with Polyangiitis/Wegener's: Clinical Manifestations

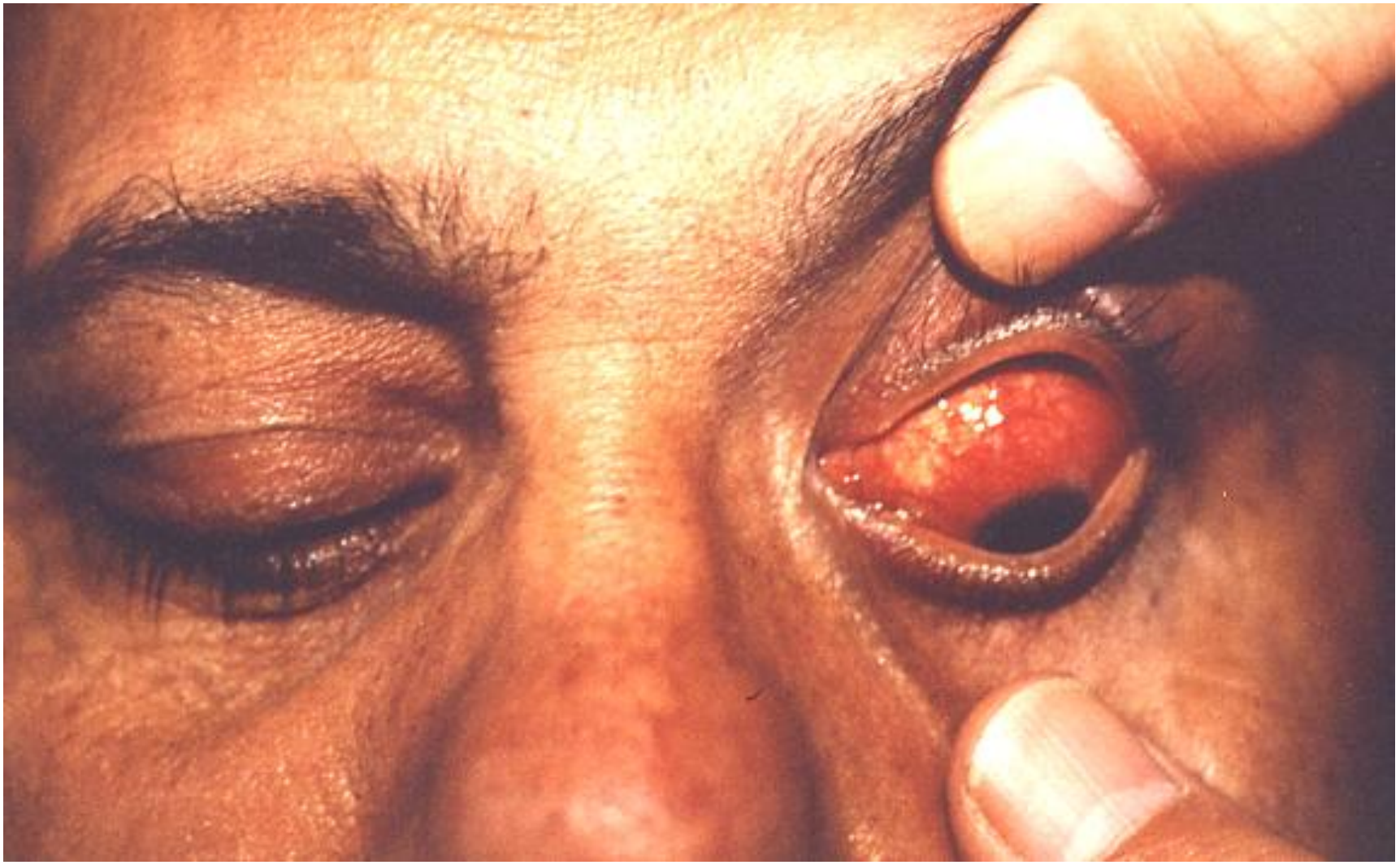
Involved Sites	Frequency %	Signs or symptoms
Upper respiratory tract	90-95	Sinusitis, otitis media, nasal ulcers, oral ulcers, deformities of the nose saddle
Lower respiratory tract	90-95	Cough, dyspnea, hemoptysis, pulmonary infiltrates, pleural effusion, endobronchial lesions, interstitial lung disease
Kidney apparatus	75	Hematuria and / or cylindruria with or without renal failure, nephrotic syndrome, hypertension
Osteomuscular apparatus	70-90	Polyarthralgias, mono- oligo- polyarthritis, myalgia or myositis
Eye	50-65	Conjunctivitis, scleritis / episcleritis, uveitis, proptosis, corneal scleral ulcerations, retinal vasculitis
Skin	50	Palpable purpura, subcutaneous nodules, petechiae, ulcers, Raynaud's phenomenon, livedo reticularis, papules necrotic
Heart	40	Pericarditis, arrythmias, coronaric arteritis
Nervous System	20-25	Mononeuritis plexus disorders, peripheral neuropathy, vasculitis of the central nervous system
Gastrointestinal tract	15-30	Granulomatous hepatitis, vasculitis of the small intestine, Ascites

Destruction of the cartilage of the nasal septum resulting in the “saddle nose” deformity

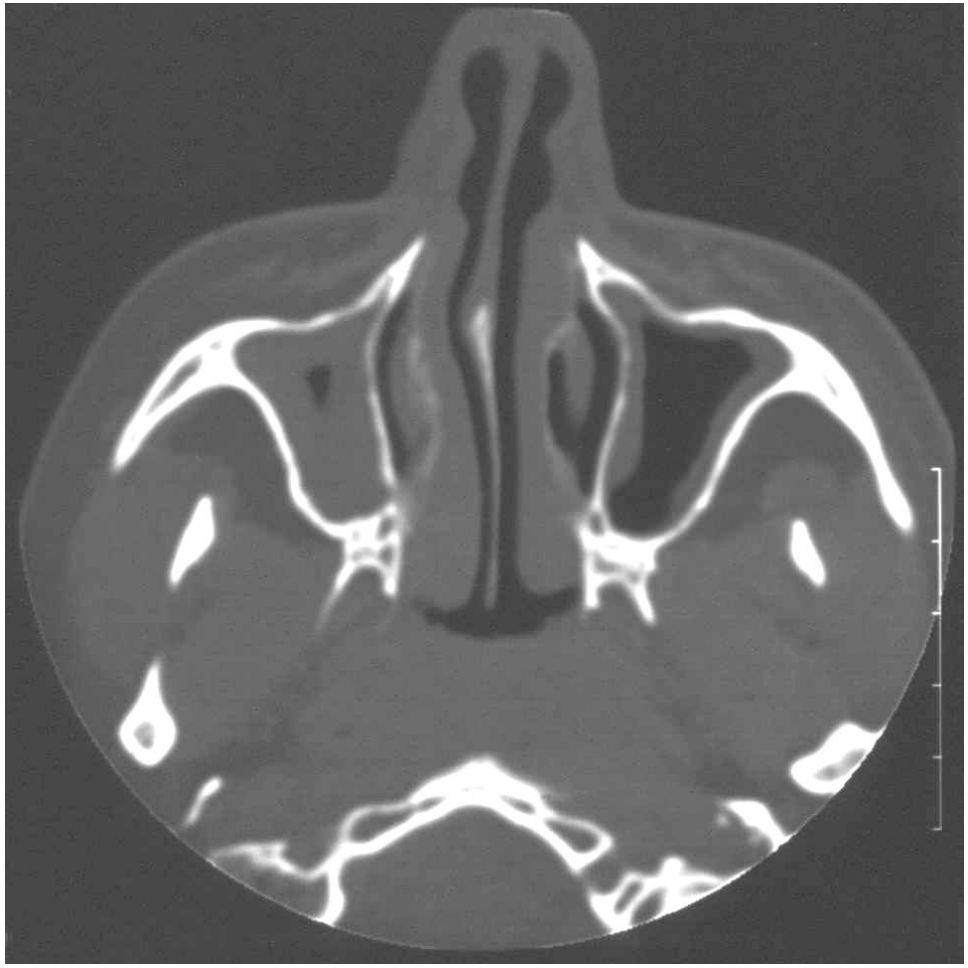


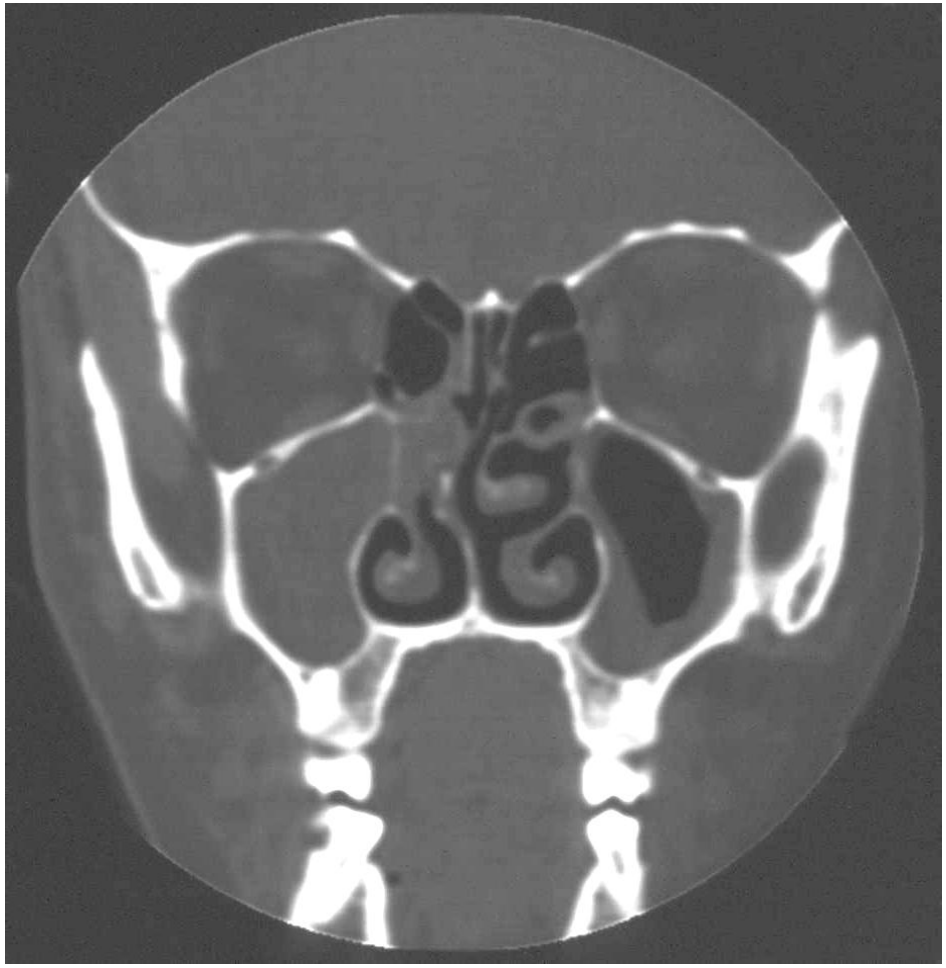


Ocular involvement with conjunctivitis

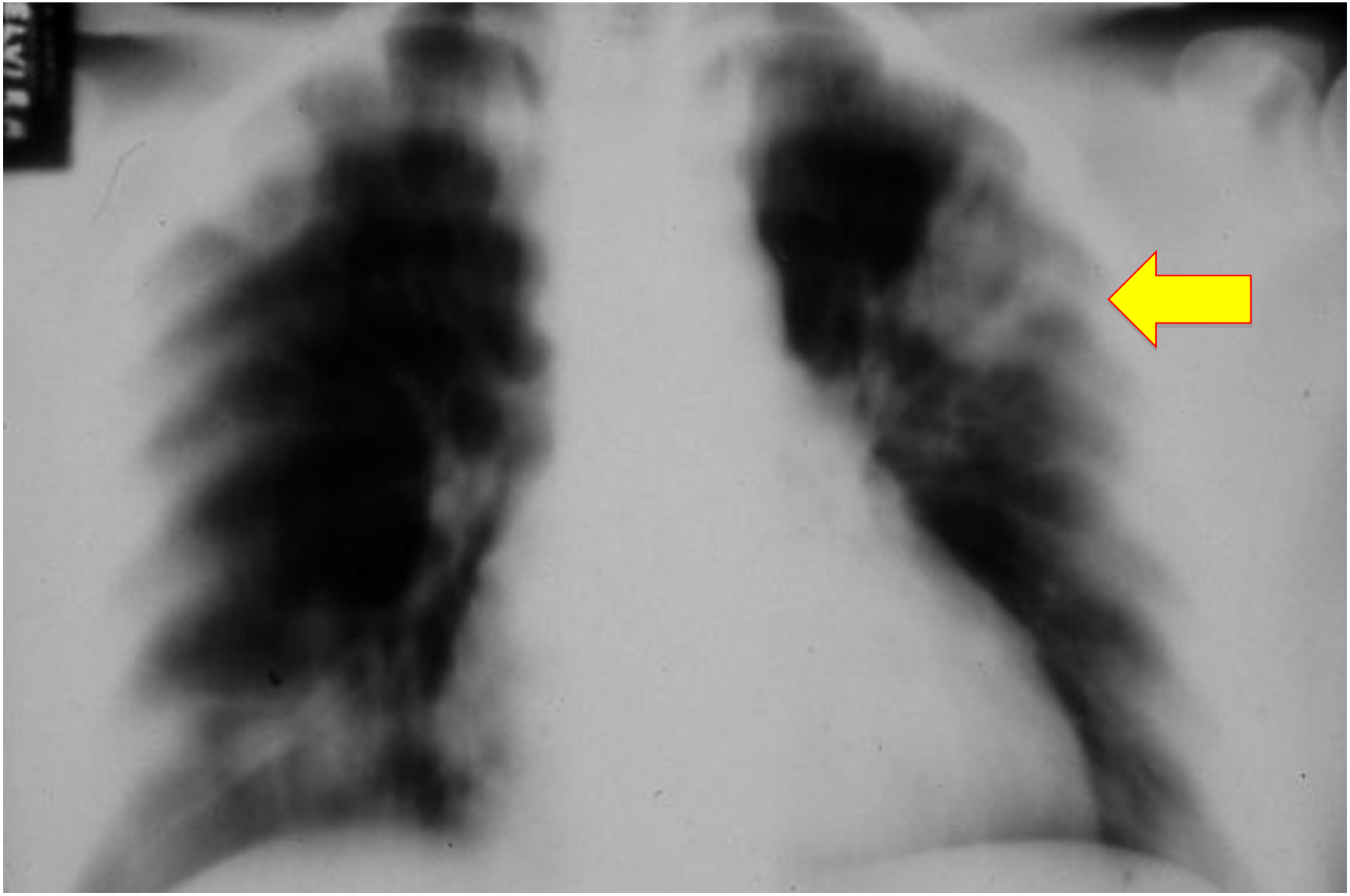


CT Scan evidence of sinusitis





Chest X-ray from a patient with cavitary lung lesion in the upper left field



Different Forms of Granulomatosis with Polyangiitis/Wegener's

Classic Form	**Lung and renal glomerular lesions**
Limited Form	**Lung lesions without kidney involvement**
Fulminant Form	**Association of rapidly progressive kidney, heart and lung failure**

Diagnostic Criteria of Granulomatosis with Polyangiitis/Wegener's

ACR, 1990 modified

- Nasal or oral ulcer, with epistaxis or purulent nasal secretion
- Chest X-ray abnormalities (nodules, infiltrates, cavitary infiltrates)
- Microematuria (> 5 red blood cells/field)
- Pathologic evidence of necrotizing granulomatous vasculitis
- Presence of PR3 – ANCA

The presence of at least 3 of the 5 above parameters allow us to make the diagnosis with a sensitivity and specificity of approximately 90%

Therapy of Granulomatosis with Polyangiitis/Wegener's

Form	Drug	Initial Dose	Lenght
Moderate and severe	Glucocorticoids	1 mg / kg / *die* of prednisone i.v. or *per os*	Taper to 10 - 5 mg / die
	Cyclofosphamide	600 mg /m^2 e.v. every 4 weeks for a maximum of 7 - 12 cycles	
Limited form without renal lesions	Methotrexate	Up to 15 - 25 mg i. m. once a week	Try to stop therapy one year after remission
Secondary bacterial infections	Antibiotics or Trimetoprim/ sulfametoxazolo		

Maintenance Therapy of Granulomatosis with Polyangiitis (GPA)/Wegener's

After at least 3 months of therapy with cyclophosphamide (600 mg / m^2 / month for 7-12 cycles) and prednisolone (1 mg / kg / day), the treatment with azathioprine (2 mg / kg / day) and prednisolone (0.25 mg / kg / day) is not associated with an increased risk of relapse

European Vasculitis Study Group *New Engl. J. Med.* 349: 36-44, 2003

Microscopic Polyangiitis (MPA)

- MPA affects small vessels (i.e. capillaries, venules or arterioles) causing pathological lesions
- It is more common in males
- The incidence is highest around age 50
- Lung involvement is common (25-55% of cases)
- Necrotizing glomerulonephritis is common
- Patients are HBsAg negative
- MPO-ANCA are present in 70% of patients, whereas PR3-ANCA are present in 15% of patients

Conclusions

- **Respiratory tract, kidney, skin and heart are frequently involved in ANCA-associated vasculitis.**
- **Some immunological evaluations (ANCA, IL-5, IL-10, Eotaxin-3, etc.), systemic (VES, PCR, etc.), imaging (ECHO, HR-CT, FDG-PET, PET-CT, etc.) and genetic (HLA-DRB4, etc.) are pivotal in the diagnosis and follow up in vasculitis patients**
- **Biopsy and angiography are central in the diagnosis of vasculitis**
- **Immunosuppressive therapy has dramatically changed the prognosis of patients**