

Аутоиммунные заболевания

## **TABLE 377e-1** MECHANISMS PREVENTING AUTOIMMUNITY

1. Sequestration of self-antigens
2. Generation and maintenance of tolerance
  - a. Central deletion of autoreactive lymphocytes
  - b. Peripheral anergy of autoreactive lymphocytes
  - c. Receptor replacement in autoreactive lymphocytes
3. Regulatory mechanisms
  - a. Regulatory T cells
  - b. Regulatory B cells
  - c. Regulatory mesenchymal cells
  - d. Regulatory cytokines
  - e. Idiotype network

- I. Exogenous
  - A. Molecular mimicry
  - B. Superantigenic stimulation
  - C. Microbial and tissue damage–associated adjuvanticity
- II. Endogenous
  - A. Altered antigen presentation
    1. Loss of immunologic privilege
    2. Presentation of novel or cryptic epitopes (epitope spreading)
    3. Alteration of self-antigen
    4. Enhanced function of antigen-presenting cells
      - a. Costimulatory molecule expression
      - b. Cytokine production
  - B. Increased T cell help
    1. Cytokine production
    2. Costimulatory molecules
  - C. Increased B cell function
    1. B cell activating factor
    2. Costimulatory molecules
  - D. Apoptotic defects or defects in clearance of apoptotic material
  - E. Cytokine imbalance
  - F. Altered immunoregulation
  - G. Endocrine abnormalities

**TABLE 377e-5 DISEASES ON THE AUTOIMMUNE SPECTRUM****Organ Specific**

|                                     |                                     |
|-------------------------------------|-------------------------------------|
| Graves' disease                     | Vitiligo                            |
| Hashimoto's thyroiditis             | Autoimmune hemolytic anemia         |
| Autoimmune polyglandular syndrome   | Autoimmune thrombocytopenic purpura |
| Type 1 diabetes mellitus            | Pernicious anemia                   |
| Insulin-resistant diabetes mellitus | Myasthenia gravis                   |
| Immune-mediated infertility         | Multiple sclerosis                  |
| Autoimmune Addison's disease        | Guillain-Barré syndrome             |
| Pemphigus vulgaris                  | Stiff-man syndrome                  |
| Pemphigus foliaceus                 | Acute rheumatic fever               |
| Dermatitis herpetiformis            | Sympathetic ophthalmia              |
| Autoimmune alopecia                 | Goodpasture's syndrome              |

**Organ Nonspecific (Systemic)**

|                                 |                                  |
|---------------------------------|----------------------------------|
| Systemic lupus erythematosus    | Granulomatosis with polyangiitis |
| Rheumatoid arthritis            | Antiphospholipid syndrome        |
| Systemic necrotizing vasculitis | Sjögren's syndrome               |

# Васкулиты



Pathogenic immune-complex formation and/or deposition

IgA vasculitis (Henoch-Schönlein)

Lupus vasculitis

Serum sickness and cutaneous vasculitis syndromes

Hepatitis C virus–associated cryoglobulinemic vasculitis

Hepatitis B virus–associated vasculitis

Production of antineutrophilic cytoplasmic antibodies

Granulomatosis with polyangiitis (Wegener's)

Microscopic polyangiitis

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

Pathogenic T lymphocyte responses and granuloma formation

Giant cell arteritis

Takayasu arteritis

Granulomatosis with polyangiitis (Wegener's)

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

## **TABLE 87-3** Considerations in the Classifications of Systemic Vasculitis

Size of predominant blood vessels affected

Epidemiologic features

Age

Sex

Ethnic background

Pattern of organ involvement

Pathologic features

Granulomatous inflammation

Immune complex deposition versus pauci-immune histopathology

Linear staining along glomerular basement membrane

Presence of ANCA, anti-GBM antibodies, or rheumatoid factor in serum

Demonstration of a specific associated infection (hepatitis B or hepatitis C)

ANCA, Anti-neutrophil cytoplasmic antibody; GBM, glomerular basement membrane.

**TABLE 385-1 VASCULITIS SYNDROMES**

| <b>Primary Vasculitis Syndromes</b>                           | <b>Secondary Vasculitis Syndromes</b>                    |
|---|--|
| Granulomatosis with polyangiitis (Wegener's)                  | Vasculitis associated with probable etiology             |
| Microscopic polyangiitis                                      | Drug-induced vasculitis                                  |
| Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) | Hepatitis C virus–associated cryoglobulinemic vasculitis |
| IgA vasculitis (Henoch-Schönlein)                             | Hepatitis B virus–associated vasculitis                  |
| Cryoglobulinemic vasculitis                                   | Cancer-associated vasculitis                             |
| Polyarteritis nodosa  | Vasculitis associated with systemic disease              |
| Kawasaki disease  | Lupus vasculitis   |
| Giant cell arteritis  | Rheumatoid vasculitis                                    |
| Takayasu arteritis  | Sarcoid vasculitis                                       |
| Behçet's disease  |  |
| Cogan's syndrome  |  |
| Single-organ vasculitis                                       |  |
| Cutaneous leukocytoclastic angiitis                           |  |
| Cutaneous arteritis   |  |
| Primary central nervous system vasculitis                     |  |
| Isolated aortitis   |  |

**Source:** Adapted from JC Jennette et al: Arthritis Rheum 65:1, 2013.



**TABLE 87-1** Names for Vasculitides Adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides

**Large-Vessel Vasculitis**

Takayasu's arteritis  
Giant cell arteritis

**Medium-Vessel Vasculitis**

Polyarteritis nodosa  
Kawasaki's disease

**Small-Vessel Vasculitis**

**Anti-neutrophil Cytoplasmic Antibody–Associated Vasculitis**

Microscopic polyangiitis  
Granulomatosis with polyangiitis  
Eosinophilic granulomatosis with polyangiitis

**Immune Complex Small Vessel Vasculitis**

Anti-glomerular basement membrane disease  
Cryoglobulinemic vasculitis  
IgA vasculitis (Henoch-Schönlein purpura)  
Hypocomplementemic urticarial vasculitis

**Variable Vessel Vasculitis**

Behçet's disease  
Cogan's syndrome

**Single-Organ Vasculitis**

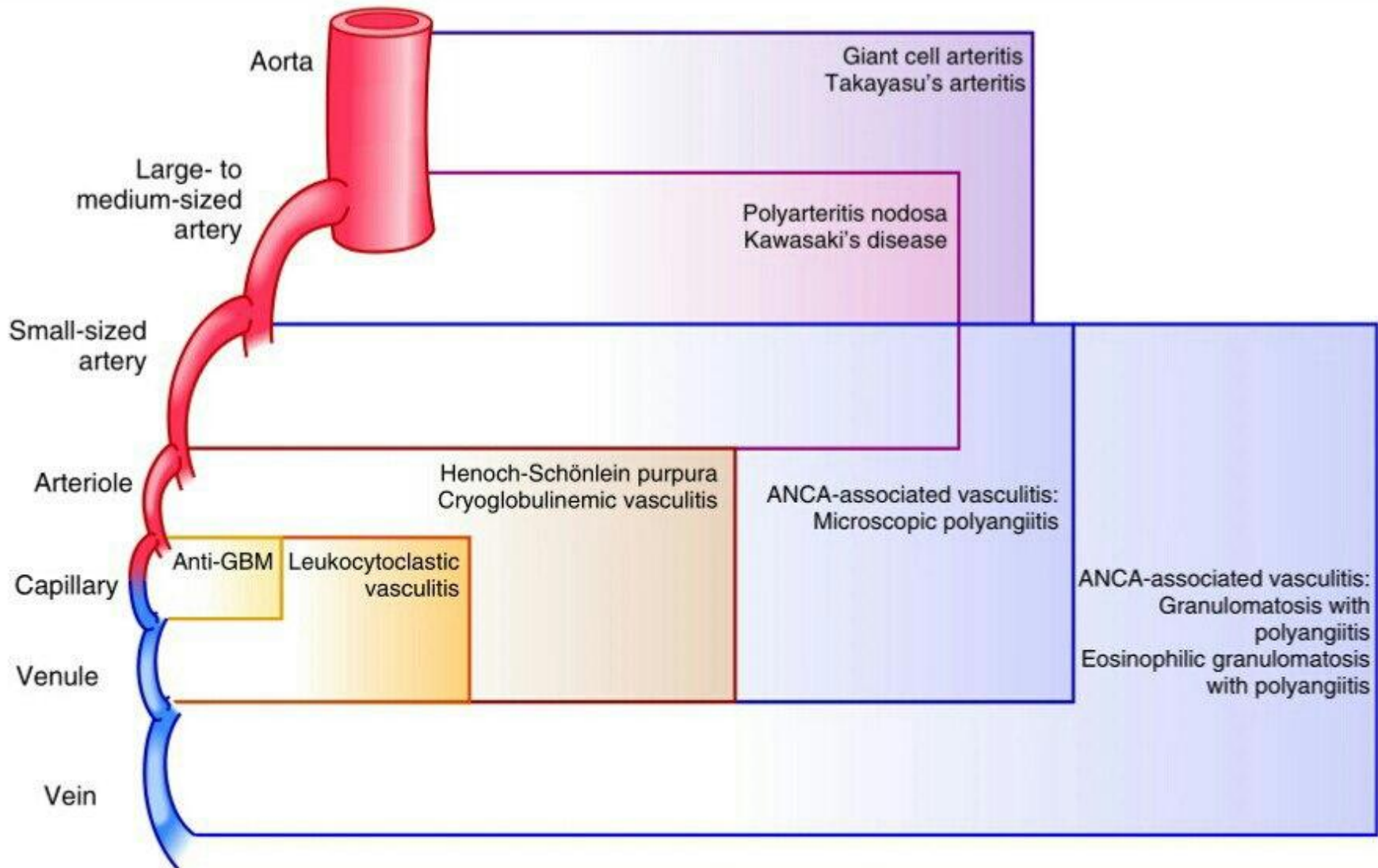
Cutaneous leukocytoclastic angiitis  
Cutaneous arteritis  
Primary central nervous system vasculitis  
Isolated aortitis

**Vasculitis Associated with Systemic Disease**

Lupus vasculitis  
Rheumatoid vasculitis  
Sarcoid vasculitis  
Others (e.g., IgG<sub>4</sub>-related aortitis)

**Vasculitis Associated with Probable Etiology**

Hepatitis C virus–associated cryoglobulinemic vasculitis  
Hepatitis B virus–associated vasculitis  
Syphilis-associated aortitis  
Drug-associated immune complex vasculitis  
Drug-associated ANCA-associated vasculitis  
Cancer-associated vasculitis  
Others



**Figure 87-1** Classification by blood vessel size. ANCA, Anti-neutrophil cytoplasmic antibody; GBM, glomerular basement membrane.

**TABLE 87-2** Typical Clinical Manifestations of Large-, Medium-, and Small-Vessel Involvement by Vasculitis

**Large**

Limb claudication  
Asymmetric blood pressures  
Absence of pulses  
Bruits  
Aortic dilation  
Renovascular hypertension

**Medium**

Cutaneous nodules  
Ulcers  
Livedo reticularis  
Digital gangrene  
Mononeuritis multiplex  
Microaneurysms  
Renovascular hypertension

**Small**

Purpura  
Vesiculobullous lesions  
Urticaria  
Glomerulonephritis  
Alveolar hemorrhage  
Cutaneous extravascular necrotizing granulomas  
Splinter hemorrhages  
Uveitis/episcleritis/scleritis

Constitutional symptoms: fever, weight loss, malaise, arthralgias/arthritis (common to vasculitides of all vessel sizes).

**TABLE 89-1** Names and Definitions of Small Vessel Vasculitides as Presented by the 2012 Chapel Hill Consensus Conference

| Name   | Definition and Comments   |
|--|---|
| Small-vessel vasculitis  | Vasculitis predominantly affecting small vessels, defined as small intraparenchymal arteries, arterioles, capillaries, and venules. Medium-sized arteries and veins may be affected.  |
| ANCA-associated vasculitis   | Necrotizing vasculitis with few or no immune deposits predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries), associated with MPO ANCA or PR3 ANCA. Not all patients have ANCA. Add a prefix indicating ANCA reactivity (e.g., MPO-ANCA, PR3-ANCA, ANCA-negative).                                      |
| Granulomatosis with polyangiitis                                       | Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small- to medium-sized vessels (e.g., capillaries, venules, arterioles, arteries and veins). Necrotizing glomerulonephritis is common.   |
| Microscopic polyangiitis   | Necrotizing vasculitis with few or no immune deposits predominantly affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small- and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent. |
| Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) | Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small- to medium-sized vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present.   |
| Immune complex vasculitis  | Vasculitis with moderate to marked vessel wall deposits of Ig and/or complement components predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries). Glomerulonephritis is frequent.  |
| Anti-glomerular basement membrane disease                              | Vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with GBM deposition of anti-GBM autoantibodies. Lung involvement causes pulmonary hemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents.   |
| Cryoglobulinemic vasculitis  | Vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with serum cryoglobulins. Skin, glomeruli, and peripheral nerves are often involved.  |
| IgA vasculitis (Henoch-Schönlein purpura)                              | Vasculitis, with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles). Often involves skin and gastrointestinal tract, and frequently causes arthritis. Glomerulonephritis indistinguishable from IgA nephropathy may occur.  |
| Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)         | Vasculitis accompanied by urticaria and hypocomplementemia affecting small vessels (i.e., capillaries, venules, or arterioles), and associated with anti-C1q antibodies. Glomerulonephritis, arthritis, obstructive pulmonary disease, and ocular inflammation are common.  |

ANCA

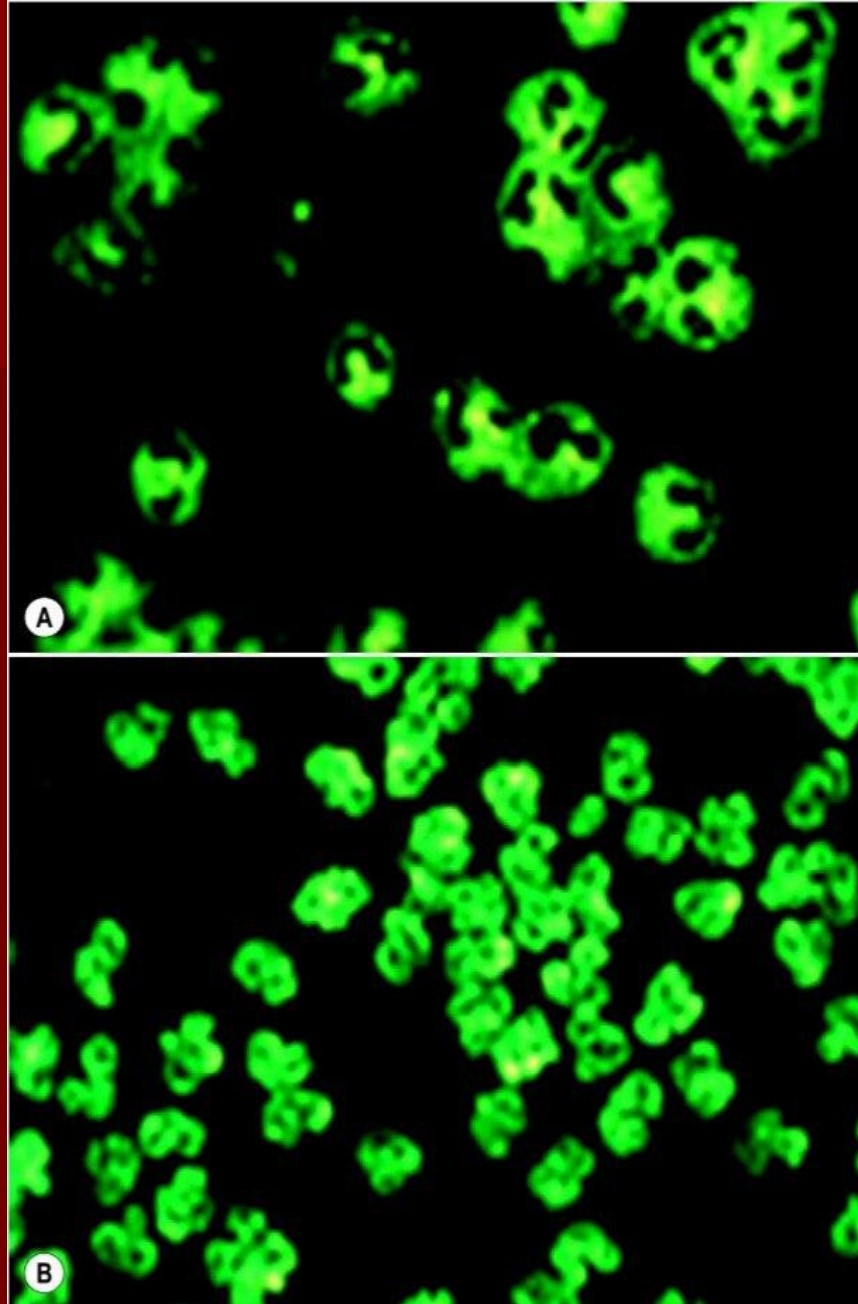


## **Vasculitides associated with antineutrophil cytoplasmic antibodies (ANCA)**

- Granulomatosis with polyangiitis (formerly Wegener's), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis/Churg–Strauss syndrome (EGPA (Churg–Strauss)) have become recognized as the types of vasculitis associated with ANCA.
- Shortcomings of reliance upon ANCA to define this group of complex diseases:
  - The role (if any) of ANCA in the pathogenesis of these conditions is unclear.
  - Not all patients with these diseases have a positive test for ANCA.
  - A variety of systemic illnesses, including infections, malignancies, and other conditions may be associated with a positive ANCA test, particularly when positive immunofluorescence tests are not confirmed by enzyme immunoassay.
  - Even when ANCA are present, they are unreliable indicators of disease activity. They are poor predictors of disease flares.

# ANCA

- Anti-neutrophil cytoplasmic antibody – антинейтрофильные цитоплазматические антитела – вид патологических антител к ферментам, содержащихся в гранулах нейтрофилов и макрофагов.
- Самые важные ANCA при аутоиммунных заболеваниях – это C-ANCA (cytoplasmic pattern) и P-ANCA (perinuclear pattern).
- C-ANCA связывается преимущественно с сериновой протеазой 3 (PR-3)
- P-ANCA связывается с миелопероксидазой (MPO)



**Fig. 57.1 ANCA patterns.** (A) Immunofluorescence study of serum on the substrate of human neutrophils, demonstrating cytoplasmic immunofluorescence (a positive ANCA assay, C-ANCA pattern). (B) Perinuclear immunofluorescence (P-ANCA pattern).



### Table 3

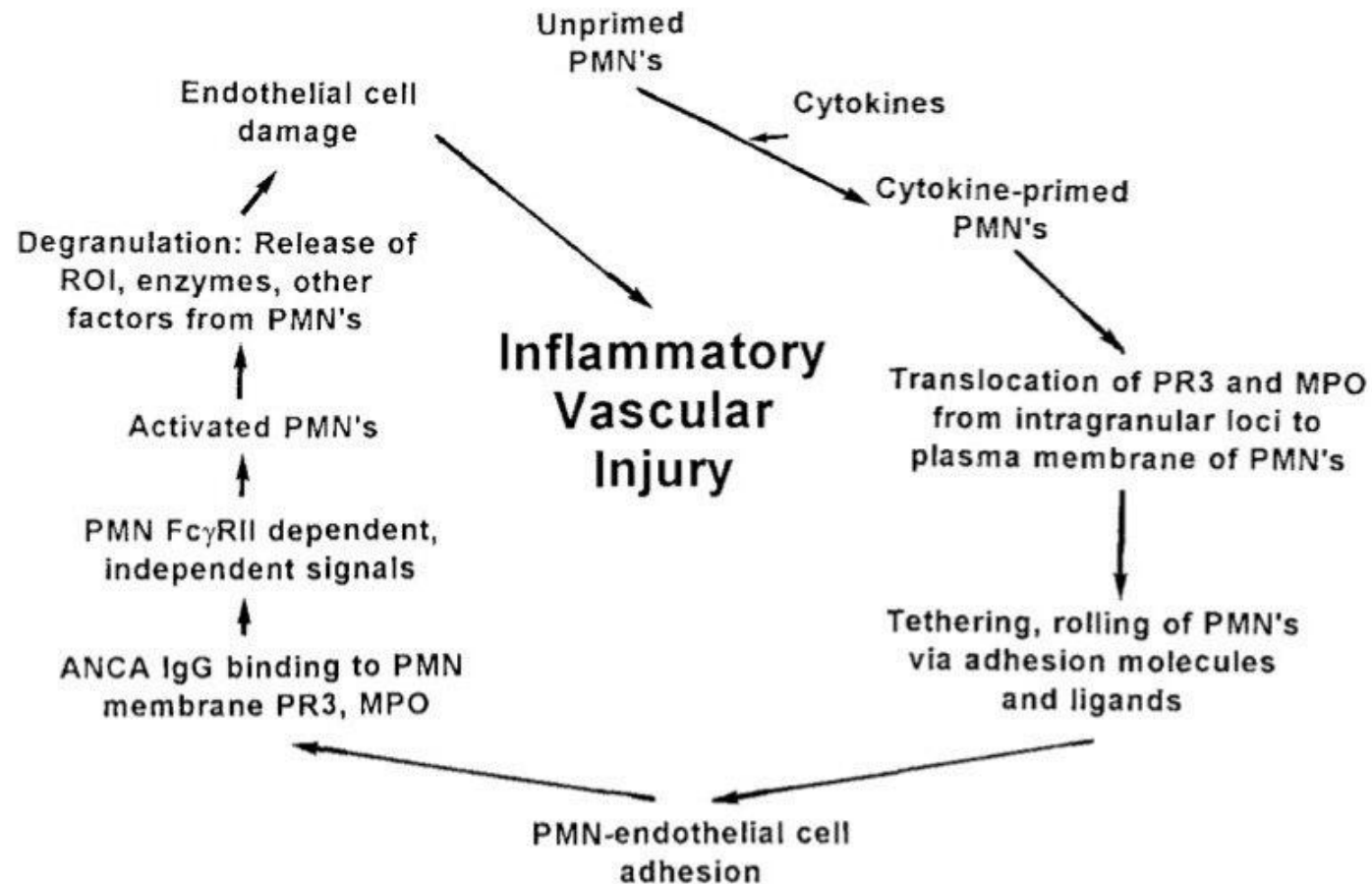
#### Spectrum of ANCA positive diseases.

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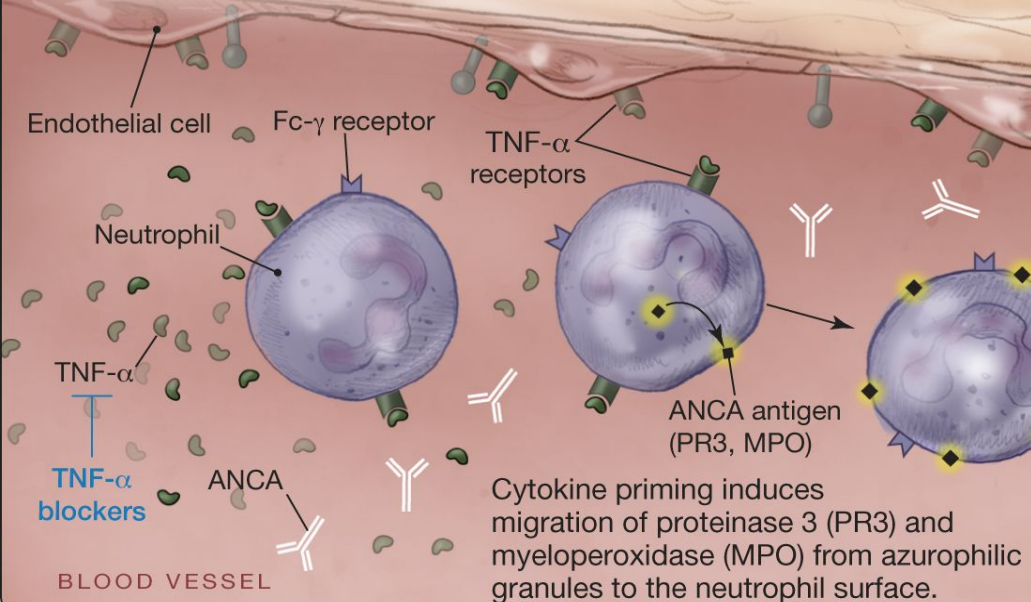
- ANCA-associated vasculitides (GPA, MPA, EGPA)
- Non-ANCA-associated vasculitis (i.e., Takayasu, GCA, polyarteritis nodosa)
- Connective tissue disorders (i.e., SLE, systemic sclerosis, RA)
- Gastrointestinal disorders (i.e., UC, Crohn disease, PSC)
- Infectious disorders (i.e., TBC, leprosy, HIV, infective endocarditis)
- Neoplasia (i.e., lymphoid neoplasia, myeloproliferative disorders, carcinomas)
- Miscellaneous disorders (sarcoidosis, IgA nephropathy, sweet syndrome)
- Drugs-induced autoimmunity (i.e., thiamazole, PTU, hydralazine, cocaine, etc.)

- 1) Quiescent neutrophils + cytokines (TNF- $\alpha$ ), infections, inflammation  $\rightarrow$  *primed* neutrophils.
- 2) *Primed* neutrophils  $\rightarrow$  membrane expression of azurophilic granule contents by translocation (e.g., proteinase-3).
- 3) Proteinase-3 + ANCA ( $\alpha$ -proteinase-3)  $\rightarrow$  proteinase-3-IgG complex.
- 4) Proteinase-3-IgG complex + Fc $\gamma$ R bridging  $\rightarrow$  cell signaling events, neutrophil *activation*. Reaction is amplified by 5-lipoxygenase pathway leukotrienes.
- 5) At surface of endothelial cells: *activated* neutrophils  $\rightarrow$  respiratory burst, degranulation  $\rightarrow$  VASCULITIS.

**Fig 2: Hypothetical sequence of events of ANCA IgG-activation of PMNs and endothelial cell damage, leading to inflammatory vascular injury. The diagram was compiled from data in references 20, 96, 100, 101, and 103.**

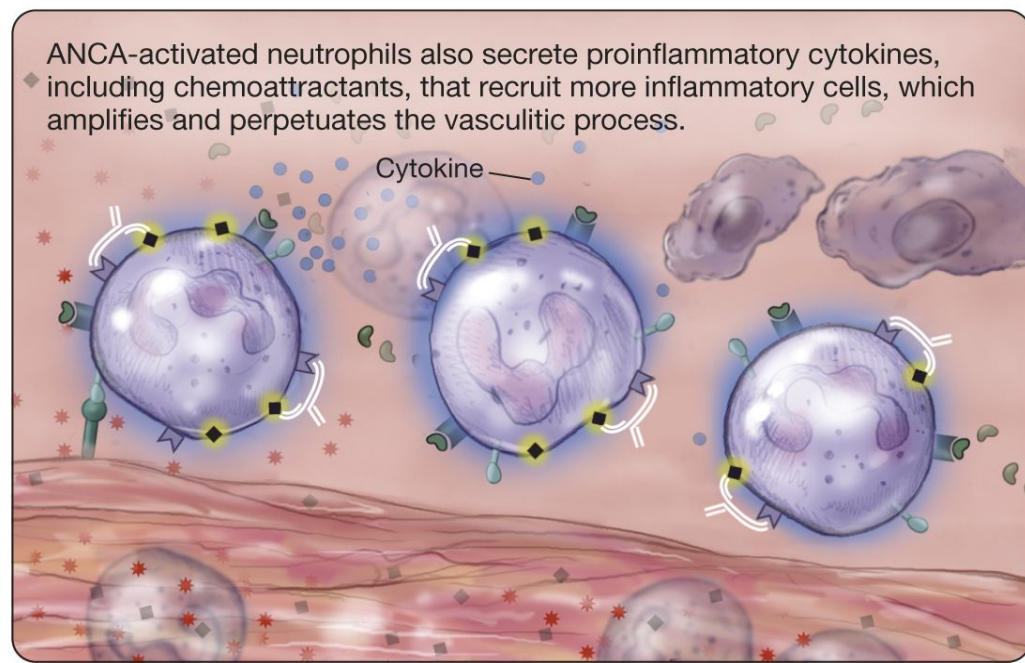
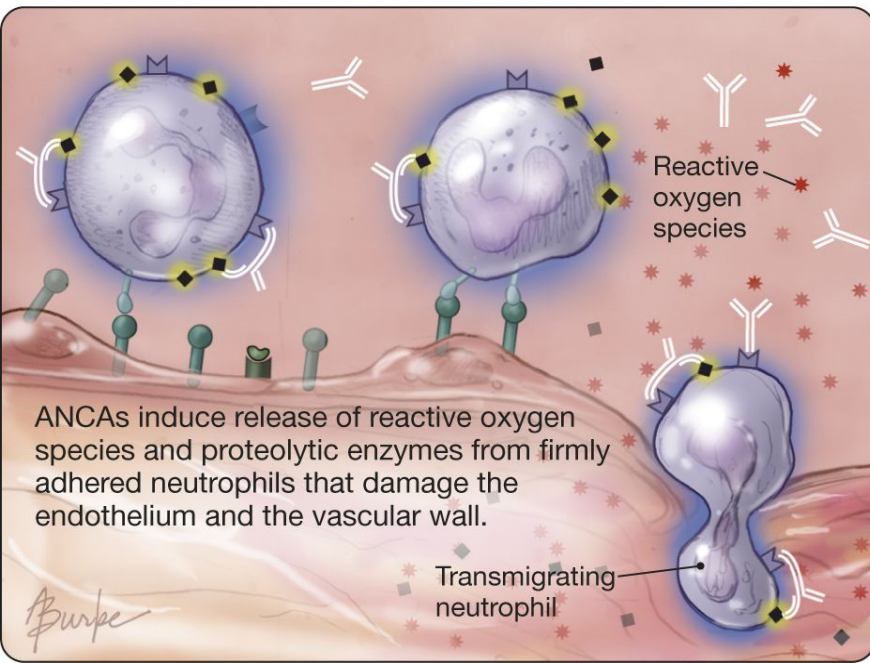
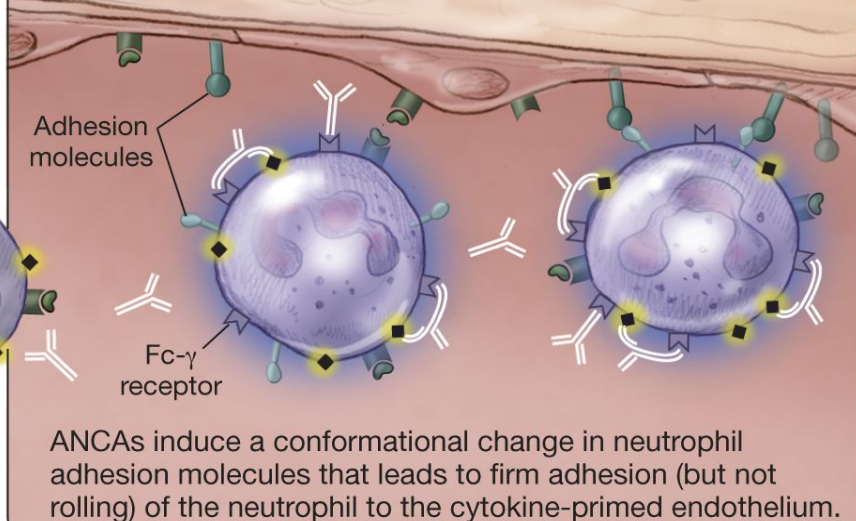


Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and other cytokines, secreted in response to infection or other inflammatory stimuli, prime neutrophils and endothelial cells.

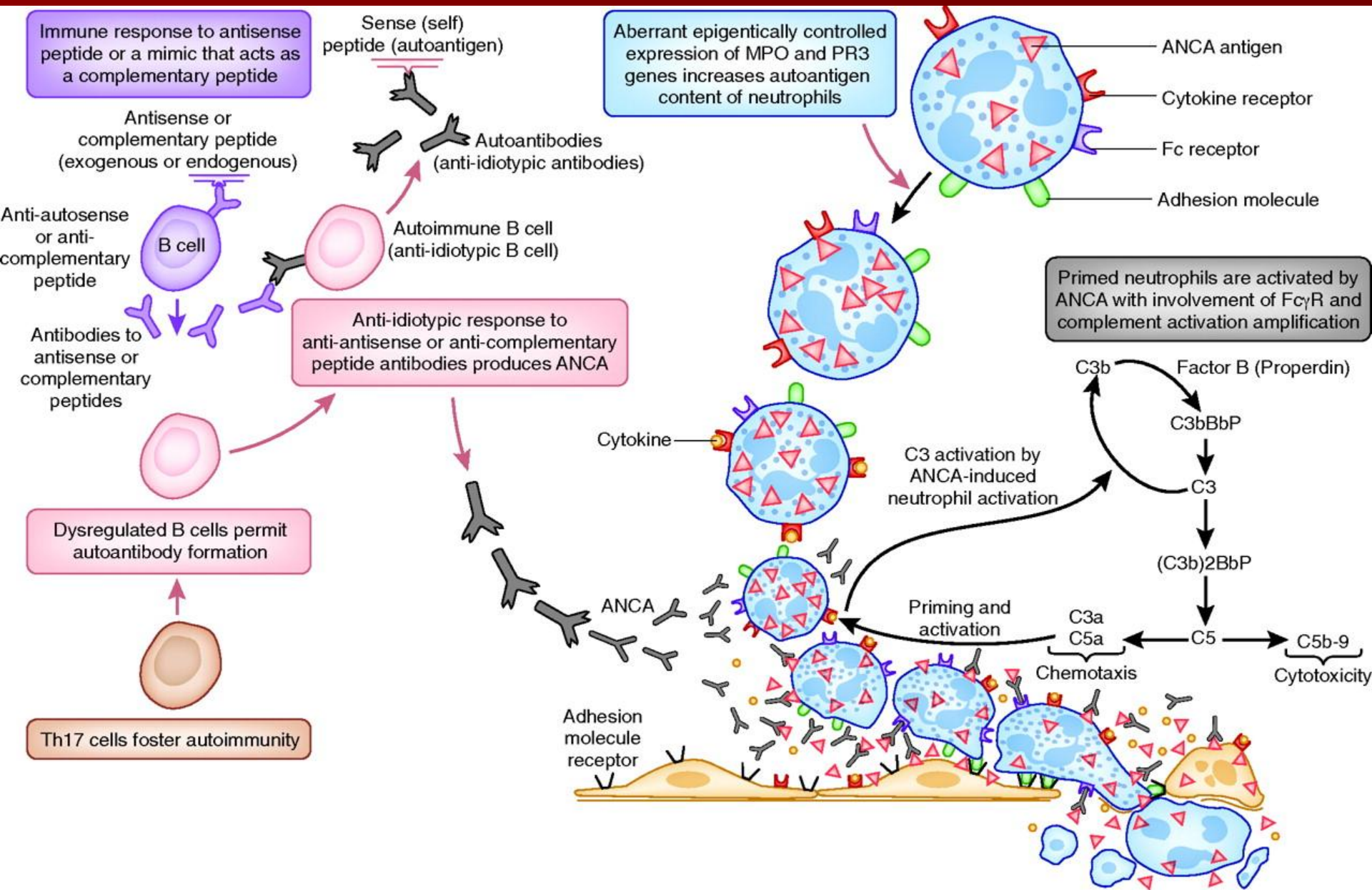


Simultaneous interaction of circulating antineutrophil cytoplasmic antibodies (ANCA) with their antigens (PR3 or MPO) and Fc- $\gamma$  receptors triggers neutrophil activation.

Cytokine priming induces neutrophils and endothelial cells to increase expression of adhesion molecules.



Burke



Immune response to antisense peptide or a mimic that acts as a complementary peptide

Aberrant epigenetically controlled expression of MPO and PR3 genes increases autoantigen content of neutrophils

Primed neutrophils are activated by ANCA with involvement of Fc $\gamma$ R and complement activation amplification

Anti-idiotypic response to anti-antisense or anti-complementary peptide antibodies produces ANCA

Dysregulated B cells permit autoantibody formation

Th17 cells foster autoimmunity

C3 activation by ANCA-induced neutrophil activation

Priming and activation

Chemotaxis

Cytotoxicity

Adhesion molecule receptor

Cytokine

ANCA

ANCA antigen

Cytokine receptor

Fc receptor

Adhesion molecule

Antisense or complementary peptide (exogenous or endogenous)

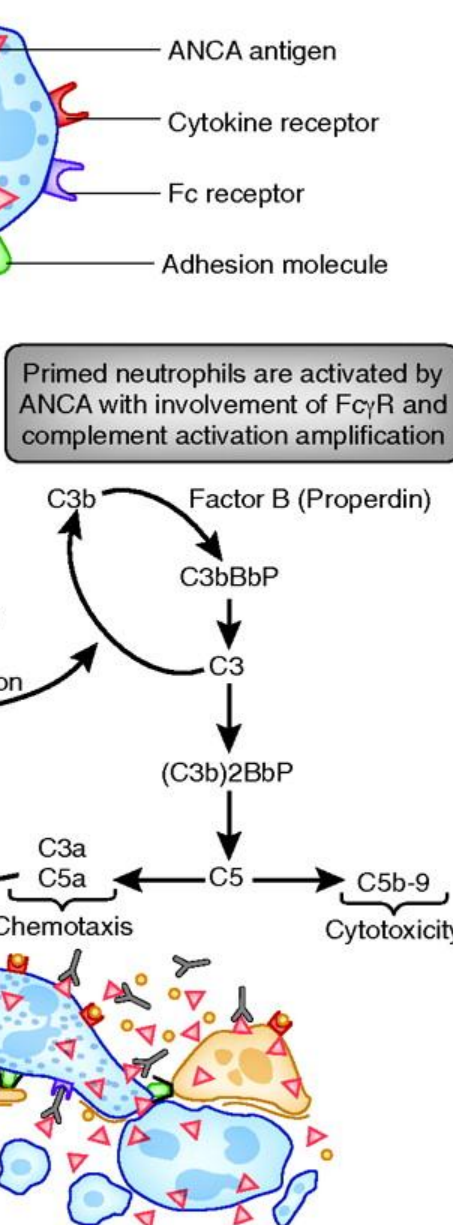
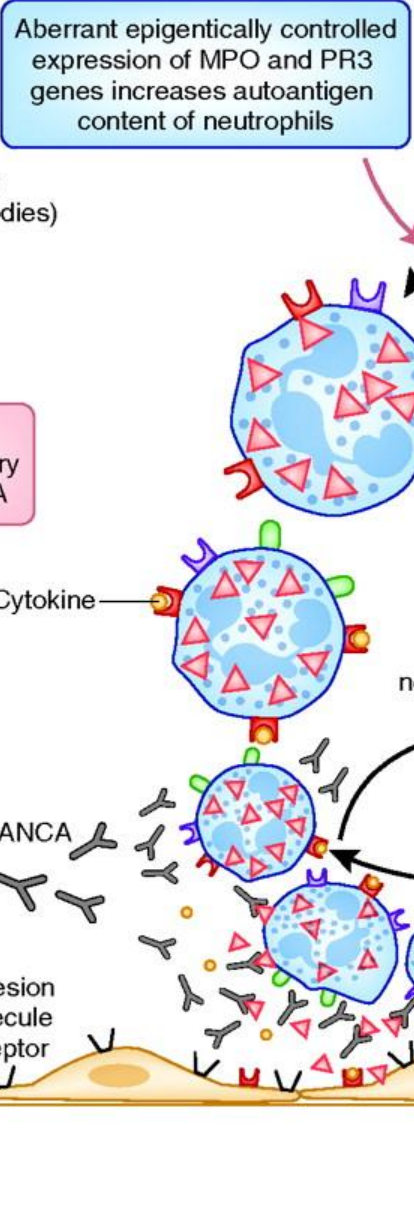
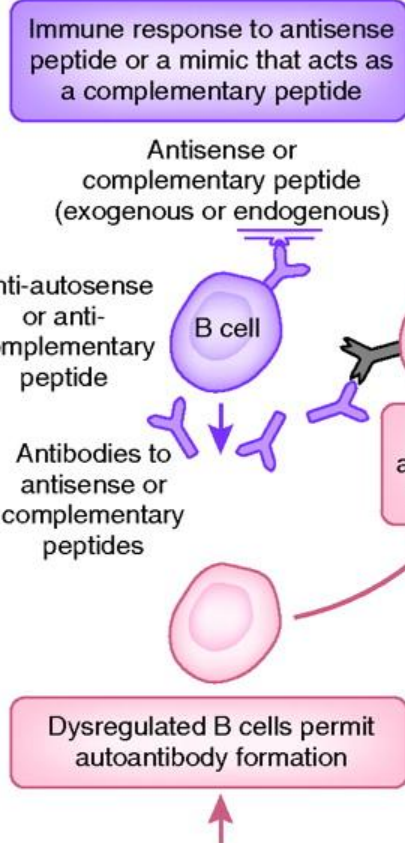
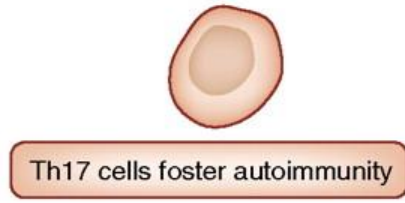
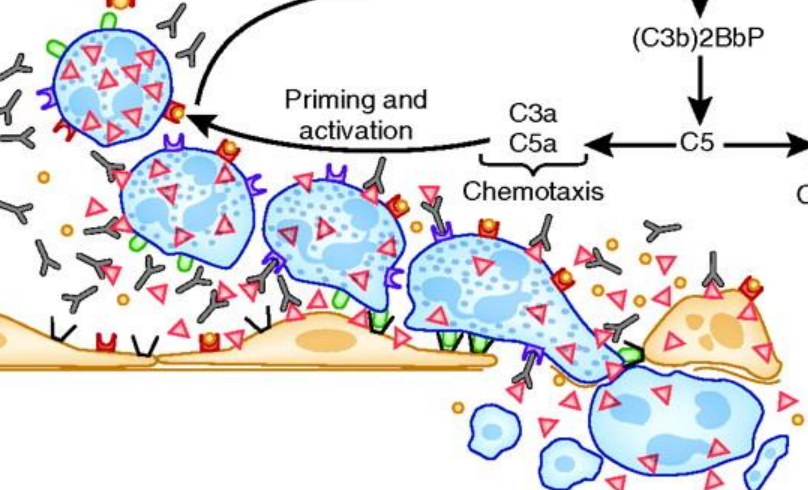
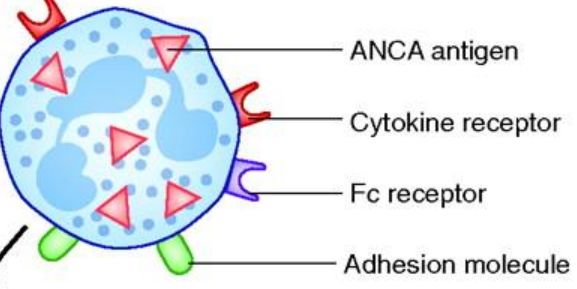
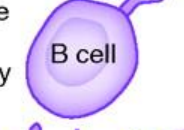
Sense (self) peptide (autoantigen)

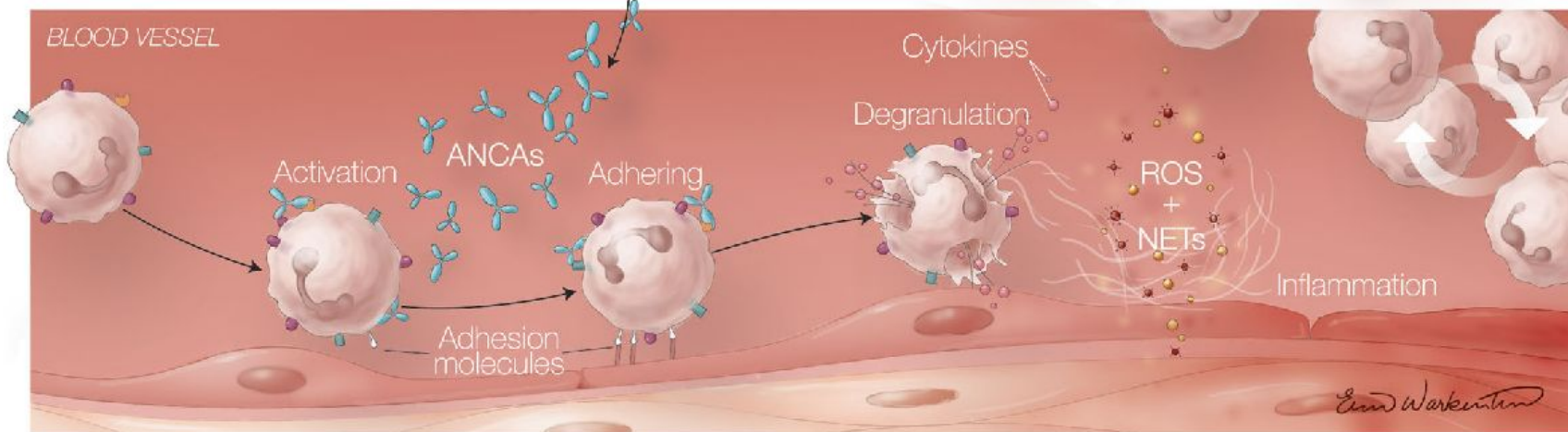
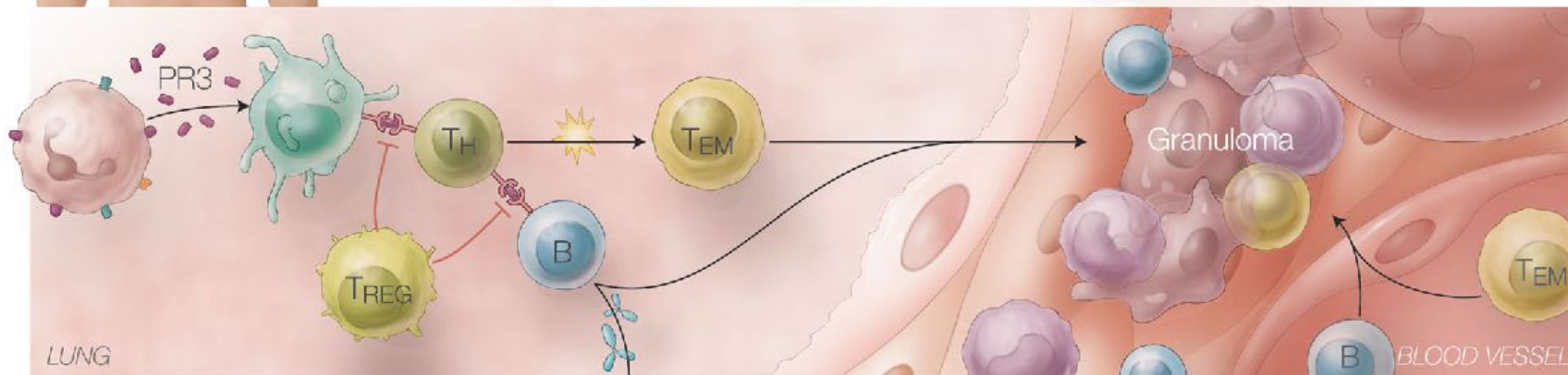
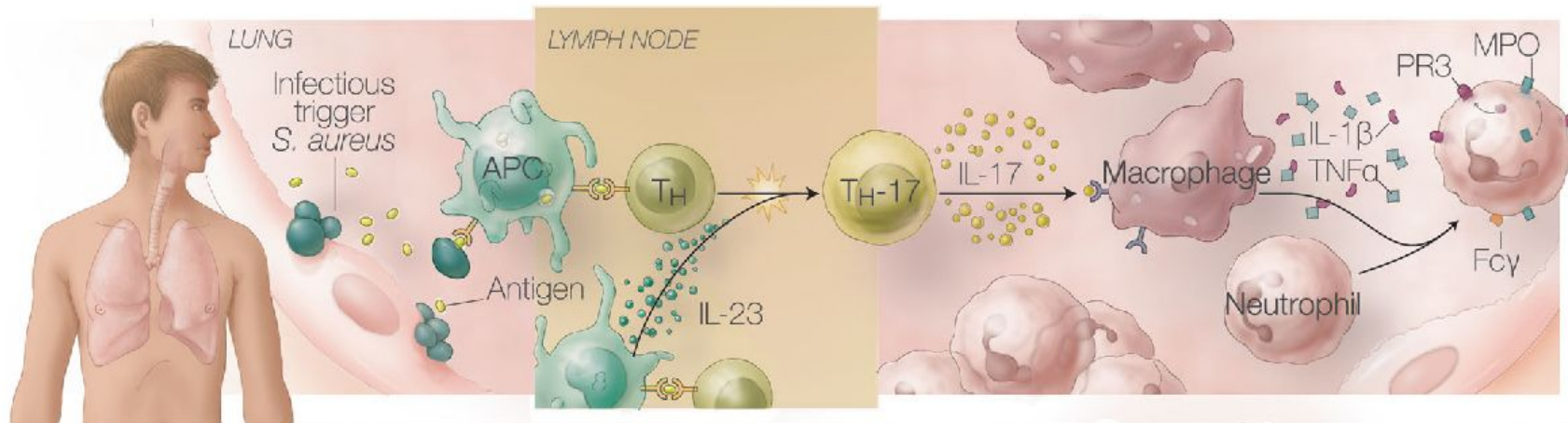
Autoantibodies (anti-idiotypic antibodies)

Autoimmune B cell (anti-idiotypic B cell)

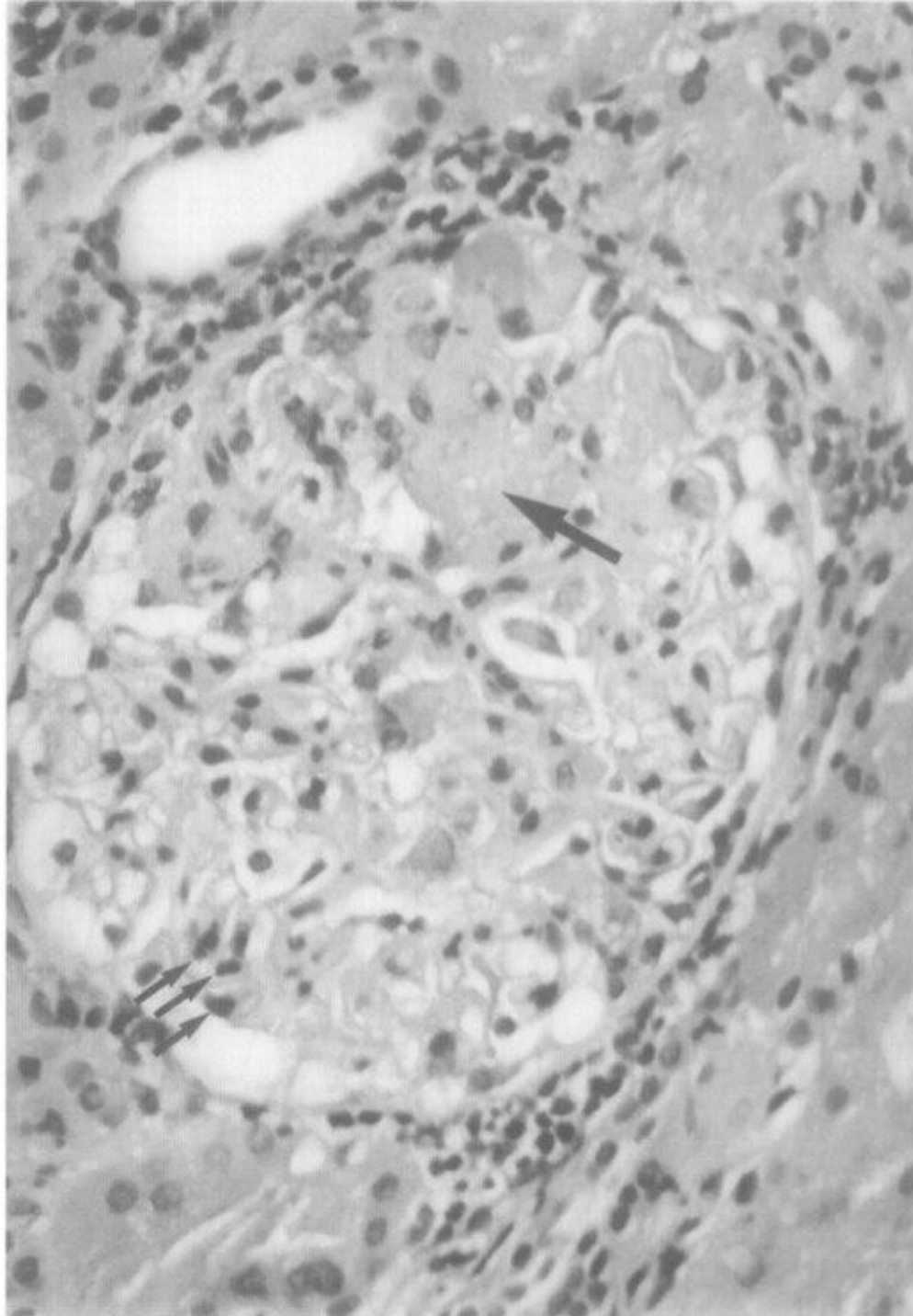
Anti-autosense or anti-complementary peptide

Antibodies to antisense or complementary peptides

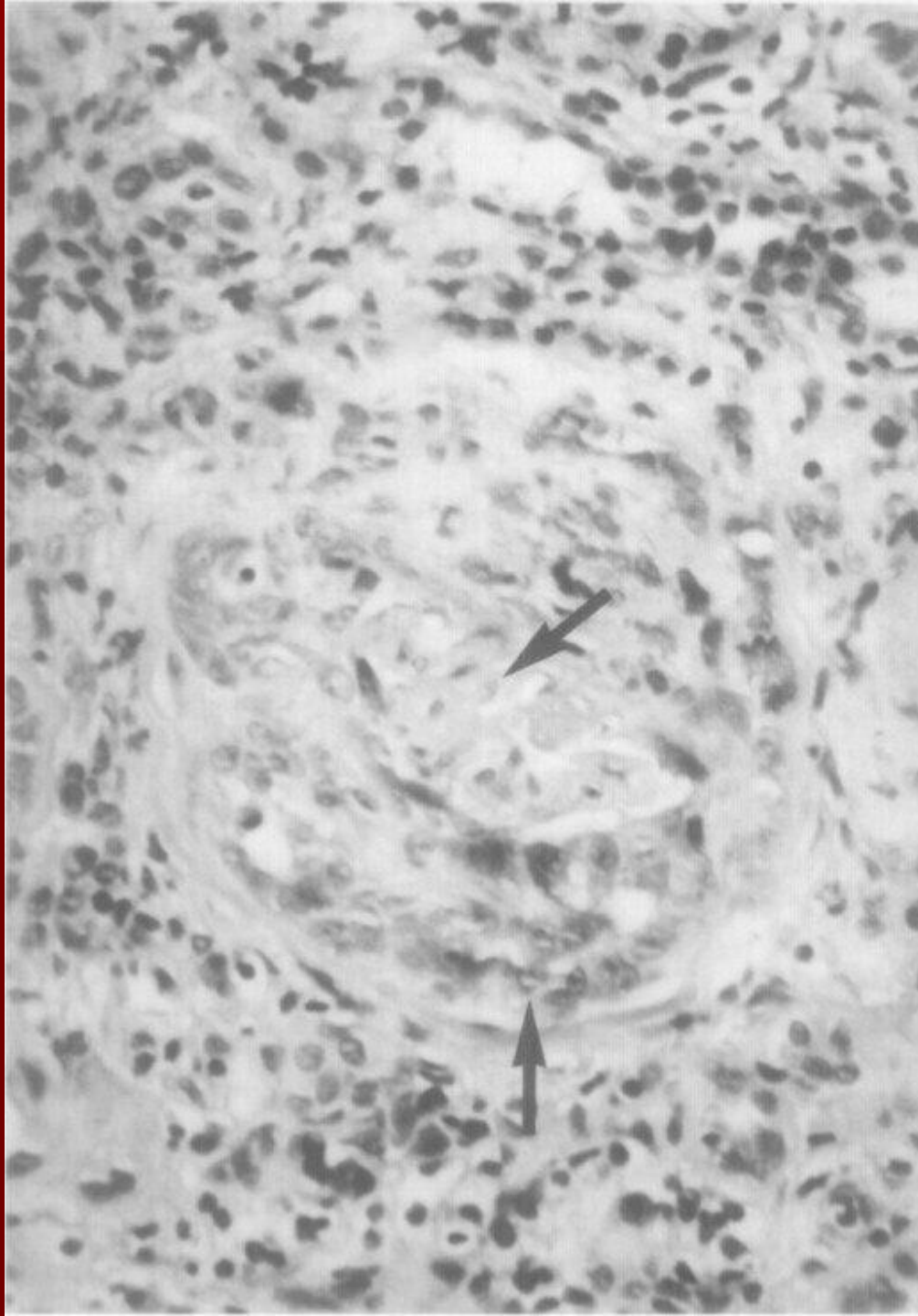




Pathogenesis of anti neutrophil cytoplasm antibody (ANCA) as effector memory T cells (T<sub>EM</sub>), which then form granuloma T



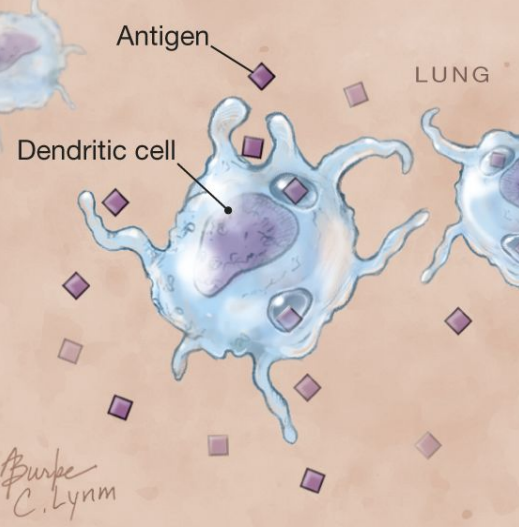
**Fig 2. Glomerulus showing segmental necrosis (top arrow) and a few cells undergoing apoptosis (bottom arrows) (H&E, original magnification  $\times 400$ ).**



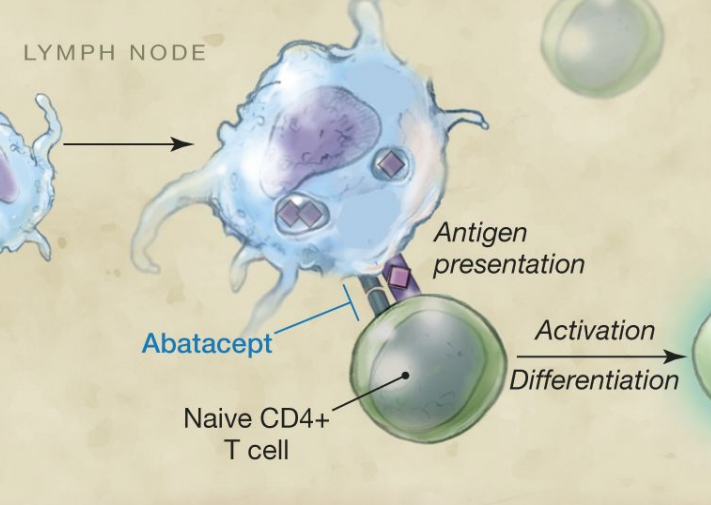
**Fig 3.** Circumferential crescent (bottom arrow) involving a glomerulus and central area of necrosis (top arrow) (Trichrome, original magnification  $\times 400$ ).



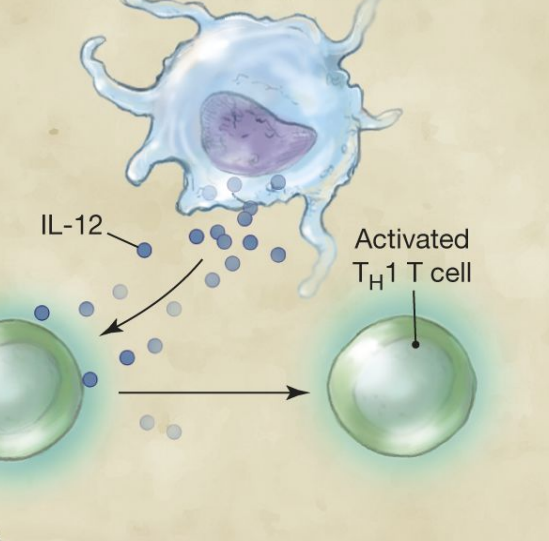
In Wegener granulomatosis, an inciting antigen (perhaps proteinase 3 [PR3]) activates dendritic cells.<sup>a</sup>



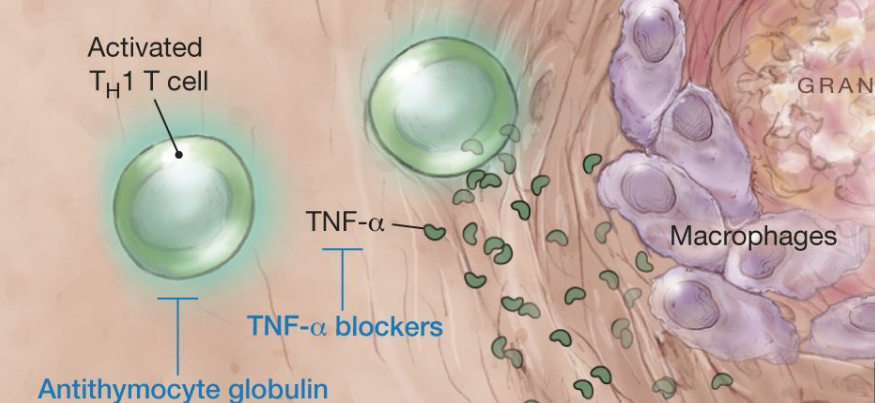
Antigen-loaded activated dendritic cells travel from the lungs to peripheral lymph nodes and present antigen to naive CD4+ T cells, which differentiate into activated antigen-specific T cells.



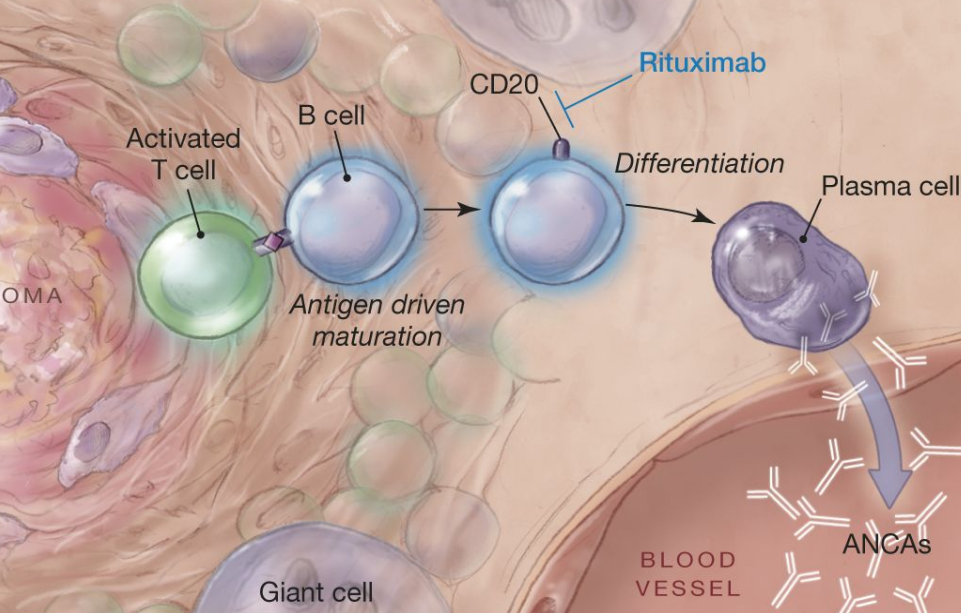
Interleukin 12 (IL-12) produced by activated dendritic cells skew the T cells to a type 1 helper (T<sub>H</sub>1) phenotype.



Proliferating activated T<sub>H</sub>1 cells return to the lungs where antigen persists. Interferon  $\gamma$  (INF- $\gamma$ ) and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) secreted by T<sub>H</sub>1 cells (predominantly CD4+ CD28-) induce macrophage migration and maturation and eventual granuloma formation and tissue destruction.



Chronic T cell activation may promote affinity maturation of autoreactive B cells that results in secretion of PR3-antineutrophil cytoplasmic antibodies (ANCA) in the granulomas.<sup>b</sup>



Normal  
glomerulus

ANCA  
glomerulonephritis

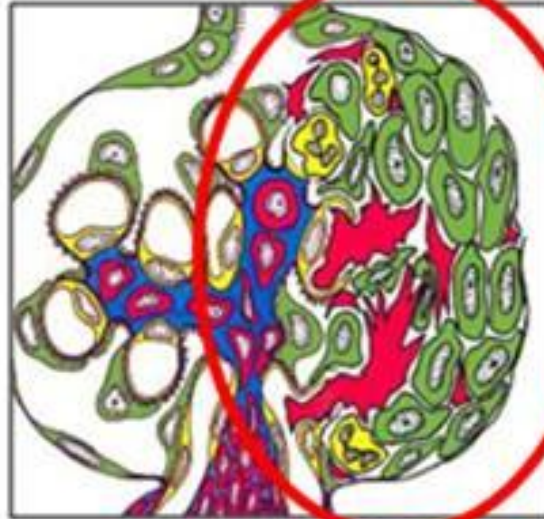
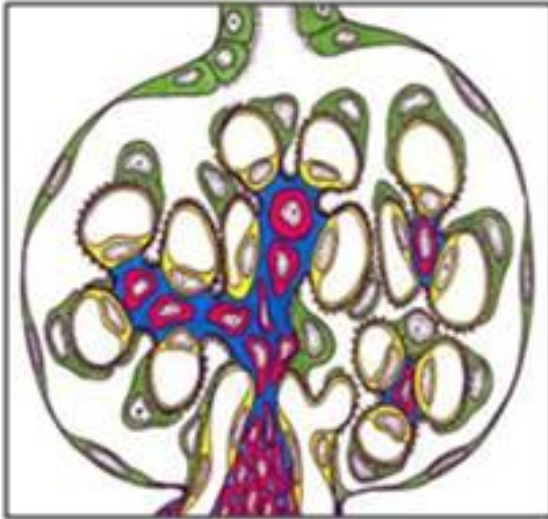
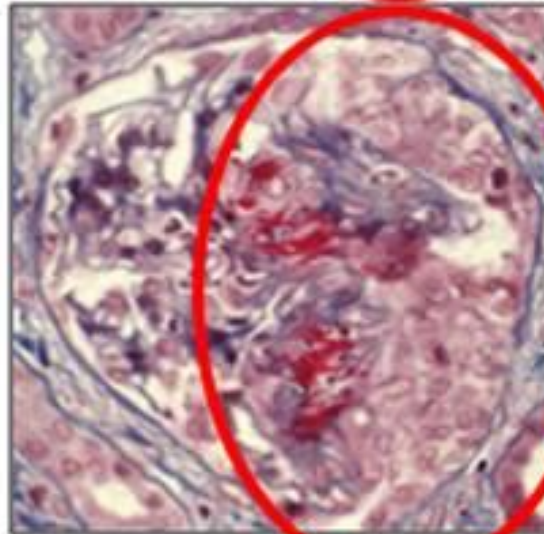
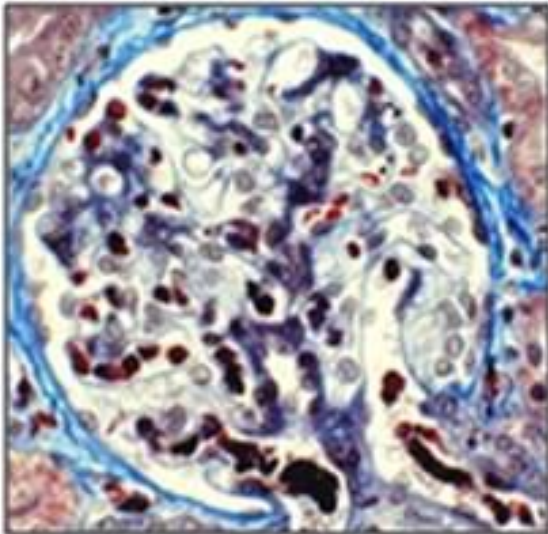
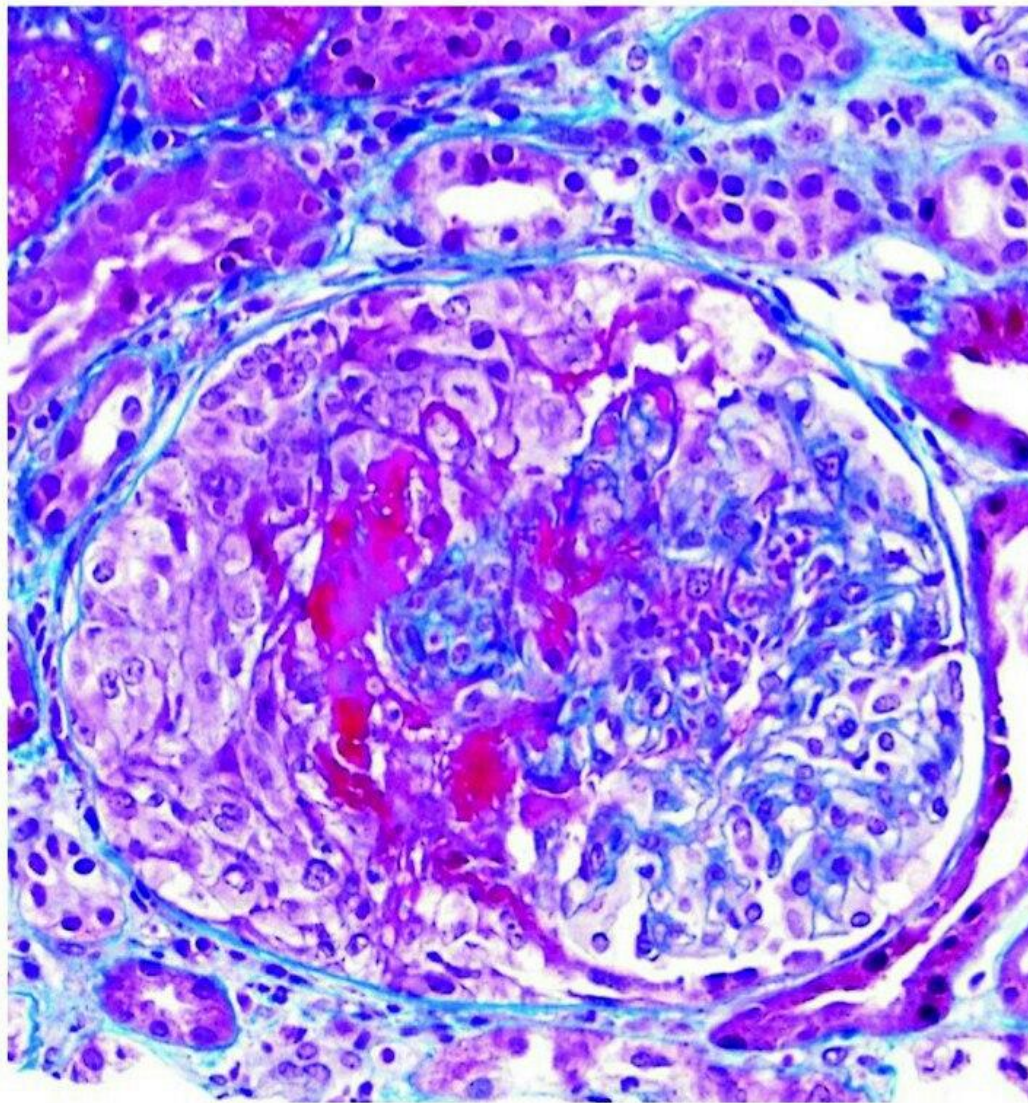


Diagram of  
glomerular  
inflammation  
(glomerulonephritis)



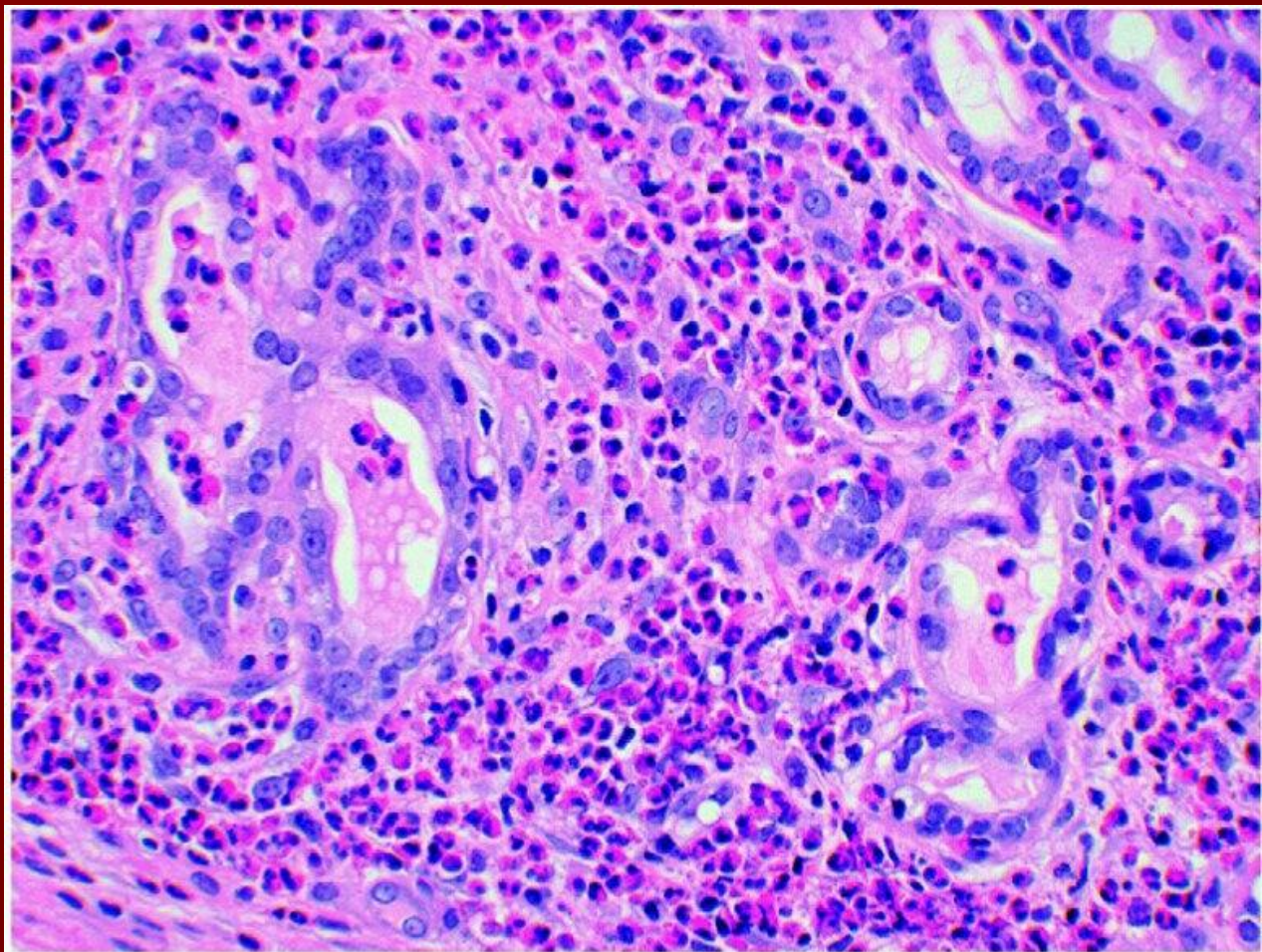
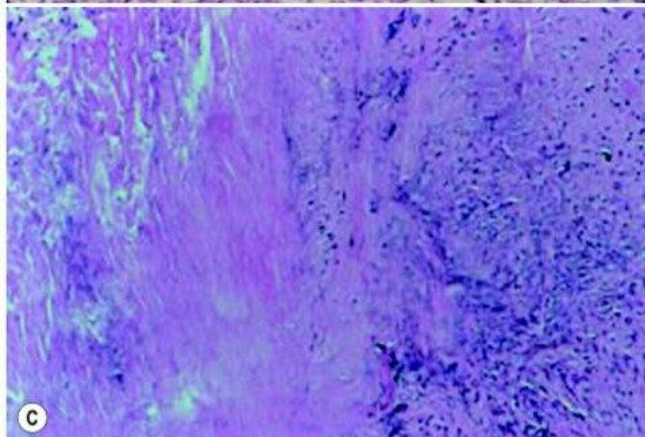
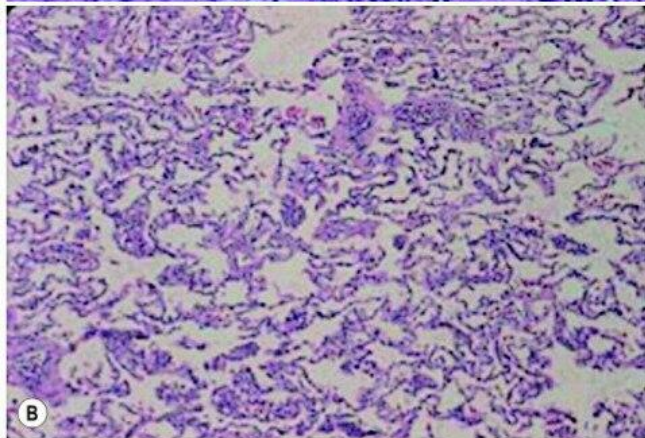
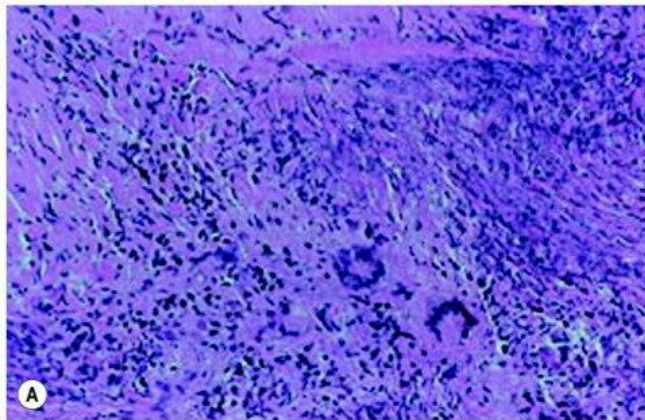
Glomerular  
inflammation  
(glomerulonephritis)  
in a kidney biopsy  
from a patient with  
ANCA vasculitis



**Figure 89-6** Anti-neutrophil cytoplasmic antibody-associated crescentic glomerulonephritis. This Periodic acid-Schiff-stained section demonstrates a glomerulus with a cellular crescent partially obliterating Bowman's space. Because all types of crescentic glomerulonephritis appear similar by light microscopy, immunofluorescence is needed to distinguish among pauci-immune, immune complex, and anti-glomerular basement membrane antibody-mediated etiologies. (Courtesy Dr. S. Bagnasco.)

### **Three phases of eosinophilic granulomatosis with polyangiitis/Churg–Strauss syndrome**

- Prodromal phase, characterized by the presence of allergic disease (typically asthma or allergic rhinitis), which may last from months to many years.
- Eosinophilia/tissue infiltration phase, in which remarkably high peripheral eosinophilia may occur and tissue infiltration by eosinophils is observed in the lung, gastrointestinal tract, and other tissues.
- Vasculitic phase, in which systemic necrotizing vasculitis afflicts a wide range of organs, ranging from the heart and lungs to peripheral nerves and skin.

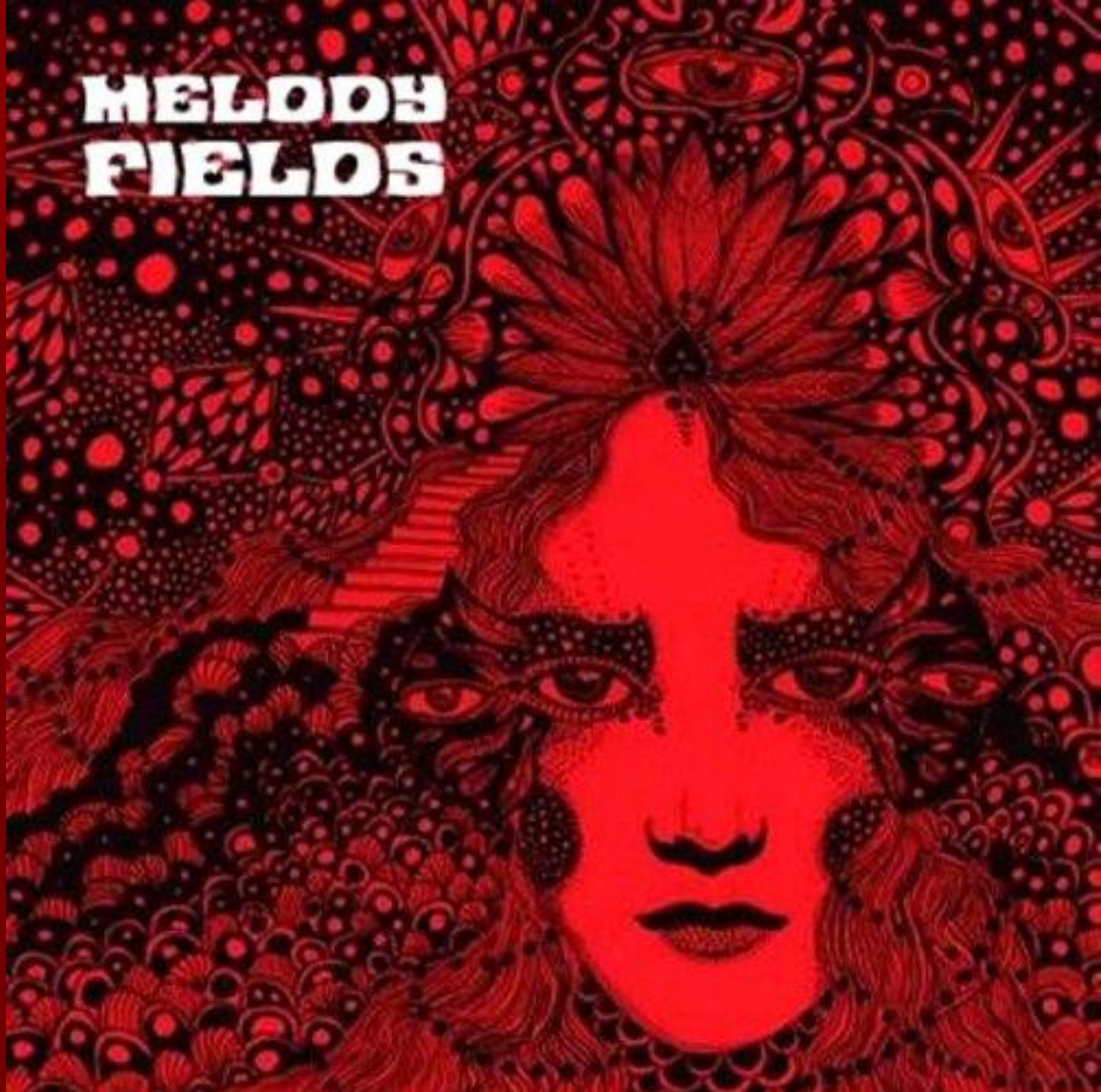


**Fig. 57.8 Eosinophilic infiltration of a salivary gland.**

**Fig. 57.4 Histopathology of granulomatosis with polyangiitis (formerly Wegener's granulomatosis).** The pathologic features of granulomatosis with polyangiitis (formerly Wegener's): (A) Langerhans giant cells and palisading granulomatous inflammation; (B) small-vessel vasculitis and fibrinoid necrosis of the lung; (C) "geographic" necrosis.

**MELODY  
FIELDS**

Клиника



**TABLE 89-2** Manifestations Over Time in the Subtypes of ANCA-Associated Vasculitis in the Largest Published Series\*

| Organ System            | GPA   | MPA    | EGPA   |
|-------------------------|-------|--------|--------|
| ENT                     | 83-99 | 1-20   | 48-77  |
| Joint/muscle            | 59-77 | 14-54+ | 30-39+ |
| Kidney                  | 66-77 | 69-100 | 22-27  |
| Lung                    | 66-85 | 25-55  | 51-58  |
| Eye                     | 34-61 | 1-15   | 7      |
| Heart                   | 8-25  | 3-24   | 16-27  |
| Skin                    | 33-46 | 11-62  | 40-57  |
| Peripheral nerve        | 15-40 | 13-60  | 51-76  |
| CNS                     | 8-11  | 5-12   | 5-14   |
| GI tract                | 6-13  | 3-31   | 22-31  |
| Constitutional symptoms | 58+   | 67-84  | 49-68  |

\*Numbers indicate percentages. Not all manifestations were reported in all studies. Some studies reported separate individual manifestations that were pooled into groups for this table; in such cases, the highest percentage among those separate manifestations was used, and "+" indicates that the percentage for the groups of pooled manifestations is likely to be higher.

EGPA, Eosinophilic granulomatosis with polyangiitis; ENT, ear, nose, and throat; GI, gastrointestinal; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis.

## **Table 1: Clinical Manifestations of Wegener's Granulomatosis**

Upper airway: nasal mucosal ulceration, epistaxis, nasal septal perforation, nasal collapse and deformity, sinusitis

Lower airway: subglottic stenosis, tracheal inflammation, cough, hemoptysis, pleurisy, pulmonary infiltrates or nodules

Renal: glomerulonephritis, renal failure

Ophthalmologic: conjunctivitis, dacryocystitis, scleritis, proptosis, eye pain, visual loss, retinal or corneal disease

Musculoskeletal: arthralgias, arthritis, myalgias

Dermatologic: subcutaneous nodules, palpable purpura, ulcers, vesicles and papules

Neurological: mononeuritis multiplex, stroke, cranial nerve disease, diabetes insipidus

Cardiac: pericarditis, myocardial or coronary artery involvement

Nonspecific: fever, weight loss, anemia



TABLE 385-5

**GRANULOMATOSIS WITH WEGENER'S):  
FREQUENCY OF CLINICAL MANIFESTATIONS IN 158 PATIENTS  
STUDIED AT THE NATIONAL INSTITUTES OF HEALTH**

| Manifestation                  | Percentage at Disease Onset | Percentage Throughout Course of Disease |
|--------------------------------|-----------------------------|---|
| <b>Kidney</b>                  |                             |   |
| Glomerulonephritis             | 18                          | 77                                      |
| <b>Ear/Nose/Throat</b>         |                             |   |
| Sinusitis                      | 51                          | 85                                      |
| Nasal disease                  | 36                          | 68                                      |
| Otitis media                   | 25                          | 44                                      |
| Hearing loss                   | 14                          | 42                                      |
| Subglottic stenosis            | 1                           | 16                                      |
| Ear pain                       | 9                           | 14                                      |
| Oral lesions                   | 3                           | 10                                      |
| <b>Lung</b>                    |                             |   |
| Pulmonary infiltrates          | 25                          | 66                                      |
| Pulmonary nodules              | 24                          | 58                                      |
| Hemoptysis                     | 12                          | 30                                      |
| Pleuritis                      | 10                          | 28                                      |
| <b>Eyes</b>                    |                             |   |
| Conjunctivitis                 | 5                           | 18                                      |
| Dacryocystitis                 | 1                           | 18                                      |
| Scleritis                      | 6                           | 16                                      |
| Proptosis                      | 2                           | 15                                      |
| Eye pain                       | 3                           | 11                                      |
| Visual loss                    | 0                           | 8                                       |
| Retinal lesions                | 0                           | 4                                       |
| Corneal lesions                | 0                           | 1                                       |
| Iritis                         | 0                           | 2                                       |
| <b>Other<sup>a</sup></b>       |                             |   |
| Arthralgias/arthritides        | 32                          | 67                                      |
| Fever                          | 23                          | 50                                      |
| Cough                          | 19                          | 46                                      |
| Skin abnormalities             | 13                          | 46                                      |
| Weight loss (>10% body weight) | 15                          | 35                                      |
| Peripheral neuropathy          | 1                           | 15                                      |
| Central nervous system disease | 1                           | 8                                       |
| Pericarditis                   | 2                           | 6                                       |
| Hyperthyroidism                | 1                           | 3                                       |

<sup>a</sup>Fewer than 1% had parotid, pulmonary artery, breast, or lower genitourinary (urethra, cervix, vagina, testicular) involvement.

**Table 57.4** American College of Rheumatology classification criteria for Churg–Strauss syndrome

| <b>Criterion</b>                 | <b>Definition</b>  |
|----------------------------------|--|
| Asthma                           | History of wheezing or diffuse high-pitched rales on expiration  |
| Eosinophilia                     | Eosinophilia >10% on white blood cell differential count   |
| Mononeuropathy or polyneuropathy | Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy (i.e., stocking/glove distribution)        |
| Pulmonary infiltrates, nonfixed  | Migratory or transitory pulmonary infiltrates on radiographs   |
| Paranasal sinus abnormality      | History of acute or chronic paranasal sinus pain or tenderness, or radiographic opacification of the paranasal sinuses |
| Extravascular eosinophils        | Biopsy including artery, arteriole, or venule, showing accumulations of eosinophils in extravascular areas             |

From Masi A, Hunder G, Lie J, et al. The American College of Rheumatology 1990 criteria for the classification of Churg–Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum* 1990; 33: 1094.

## **Table 1**

Clinical indication for ANCA testing.

(Reproduced with permission from Xavier Bossuyt et al., Nature Review Rheumatology, 2017)

---

Clinical indications for ANCA testing

Glomerulonephritis, especially rapidly progressive glomerulonephritis

Pulmonary hemorrhage, especially pulmonary renal syndrome

Cutaneous vasculitis with systemic features

Multiple lung nodules

Chronic destructive disease of the upper airways

Long-standing sinusitis or otitis

Subglottic tracheal stenosis

Mononeuritis multiplex or other peripheral neuropathy

Retro-orbital mass

Scleritis

|                          | WEGENNER'S GRANULOMATOSIS                          | CHURG SRAUSS SYNDROME                   | MICROSCOPIC POLYANGITIS                        | PAN                                       |
|--------------------------|--|---|--|---|
| M:F                      | 1:1<br>1:14(INDIA)                                 | 1.2:1<br>NO MUCH DIFF. FROM WESTRN DATA | OVER ALL UNKNOWN                               | OVER ALL UNKNOWN<br>4.5:1(INDIA)          |
| TYPE OF VESSELS INVOLVED | SMALL ARTERIES AND VEINS                           | SMALL AND MEDIUM SIZED VESSELS          | SMALL VESSELS (ARTERIES, CAPILLARIES, VENULES) | SMALL AND MEDIUM SIZED ARTERIES ONLY      |
| SPECIFIC FEATURE         | TRIAD: UPPER AND LOWER AIRWAYS WITH KIDNEY LESIONS | EXTRA VASCULAR GRANULOMA                | PULMONARY CAPILLARIES INVOLVED, GNs +NT        | PULMONARY ARTERY NOT INVOLVED, ANEURYSMS  |
| LABORATORY FINDINGS      | C-ANCA(>90%)<br>FALSE +VE REPORTED                 | p-ANCA (>48%)                           | p-ANCA (75%)                                   | HEP B ANTIGENEMIA,<br>HAIRY CELL LEUKEMIA |

**Table 57.2** Hallmarks of granulomatosis with polyangiitis (GPA), Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA)

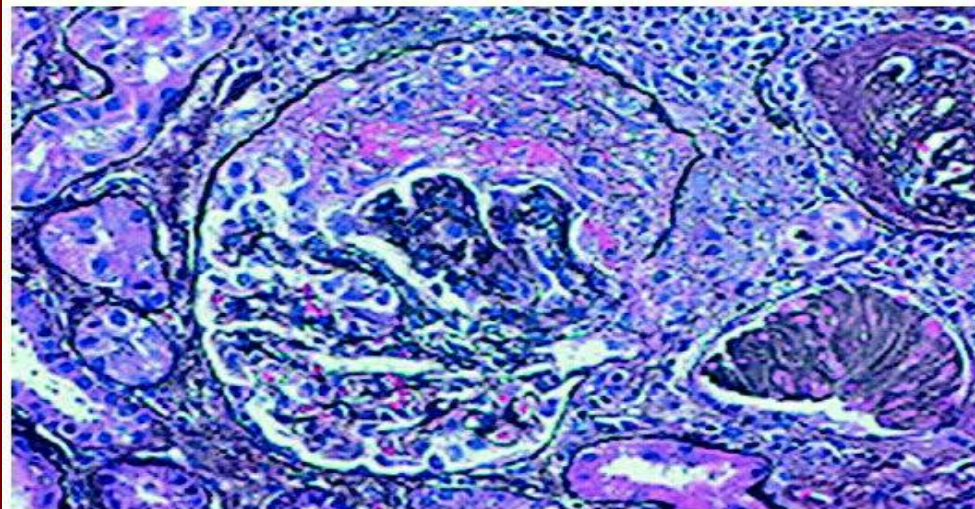
|   | <b>GPA</b>   | <b>MPA</b>                    | <b>EGPA</b>                         |
|---|--|-------------------------------|-------------------------------------|
| ANCA positive   | 80–90%   | 75%                           | 50%                                 |
| Typical immunofluorescence/Enzyme immunoassay results | C-ANCA/PR-3  | P-ANCA/MPO                    | P-ANCA/MPO                          |
| Upper respiratory tract                               | Nasal septal perforation<br>Saddle-nose deformity<br>Subglottic stenosis | Mild                          | Nasal polyps<br>Allergic rhinitis   |
| Lung  | Nodules<br>Cavitary lesions  | Alveolar haemorrhage          | Asthma<br>Fleeting infiltrates      |
| Kidney  | NCGN, occasional granulomatous features                                  | NCGN                          | NCGN (severe renal disease unusual) |
| Distinguishing feature                                | Destructive upper airway disease   | No granulomatous inflammation | Allergy<br>Eosinophilia             |

ANCA, anti-neutrophil cytoplasmic antibody; C-ANCA, cytoplasmic ANCA; MPO, myeloperoxidase; NCGN, necrotizing crescentic glomerulonephritis; P-ANCA, perinuclear ANCA; PR-3, proteinase 3.

Adapted from Rao JY, Weinberger M, Oddone EZ, et al. The role of antineutrophil cytoplasmic antibody (C-ANCA) testing in the diagnosis of Wegener's granulomatosis. *Ann Intern Med* 1995; 123: 425.

**Table 57.3** Features of microscopic polyangiitis versus classic polyarteritis nodosa

| <b>Feature</b>                                       | <b>Microscopic polyangiitis</b> | <b>Classic polyarteritis nodosa</b> |
|--|---------------------------------|-------------------------------------|
| Granulomas   | No                              | No                                  |
| Vessel size  | Small (and medium)              | Medium                              |
| Renovascular hypertension                            | No                              | Yes                                 |
| Rapidly progressive glomerulonephritis               | Yes                             | No                                  |
| Lung involvement                                     | Alveolar haemorrhage            | No                                  |
| Mononeuritis multiplex                               | Yes                             | Yes                                 |
| Anti-neutrophil cytoplasmic antibody (ANCA)-positive | P-ANCA (anti-myeloperoxidase)   | Rare                                |
| Hepatitis B association                              | No                              | Sometimes (10%)                     |
| Vascular aneurysms                                   | Occasionally                    | Commonly                            |



**Fig. 57.6 Crescentic glomerulonephritis in microscopic polyangiitis.** Glomerular crescent in a patient with rapidly progressive glomerulonephritis secondary to microscopic polyangiitis.

Диагностика





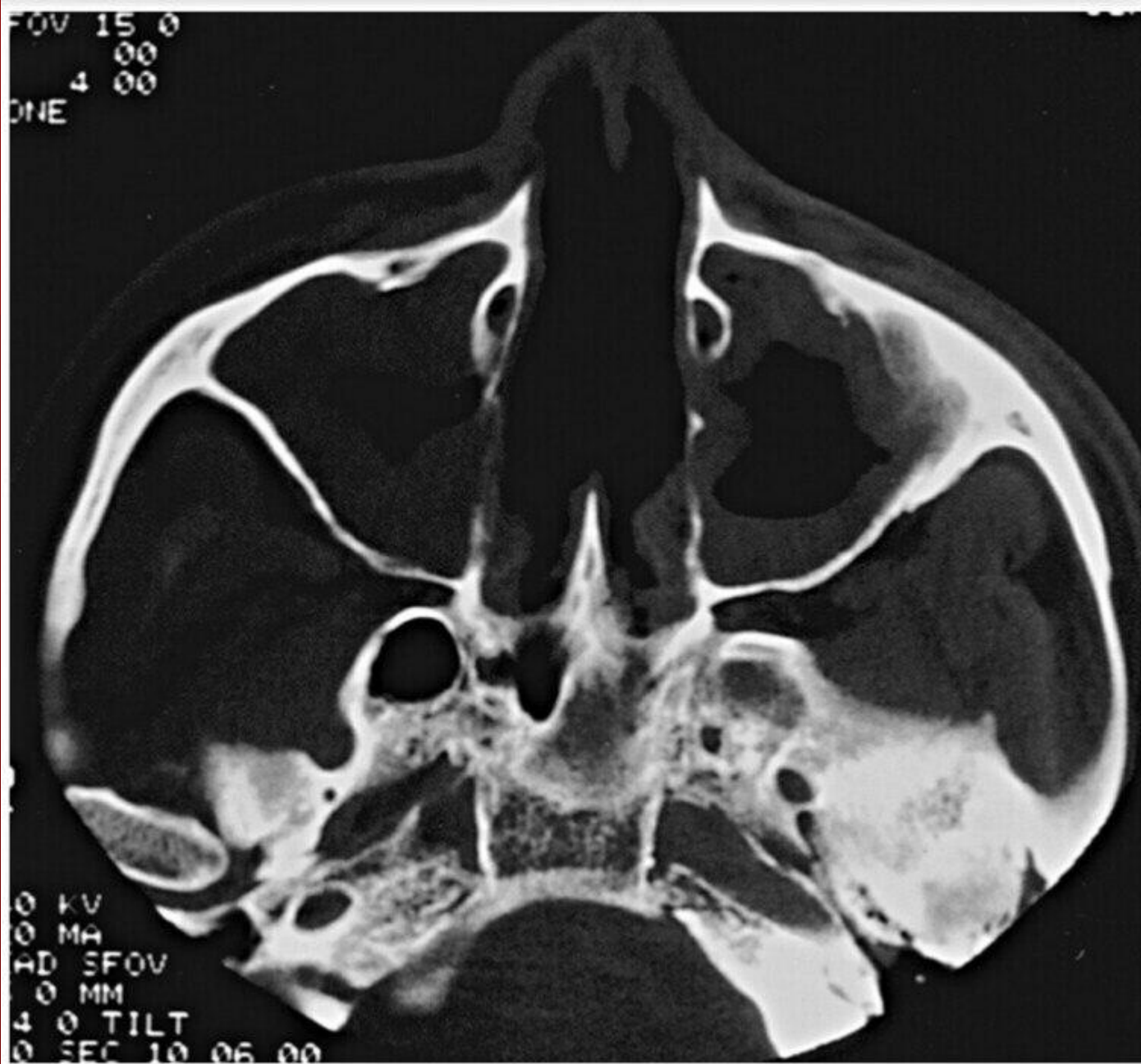
**Fig. 57.2 Saddle-nose deformity in granulomatosis with polyangiitis (formerly Wegener's granulomatosis).** Saddle-nose deformity and a left sixth cranial nerve lesion (the latter caused by meningeal inflammation) in a patient with granulomatosis with polyangiitis (formerly Wegener's).

(Reproduced with permission from Jinnah H, Dixon A, Brat D, Hellmann D. Chronic meningitis with cranial neuropathies in Wegener's granulomatosis: Case report and review of the literature. *Arthritis Rheum* 1997; 40: 573.)

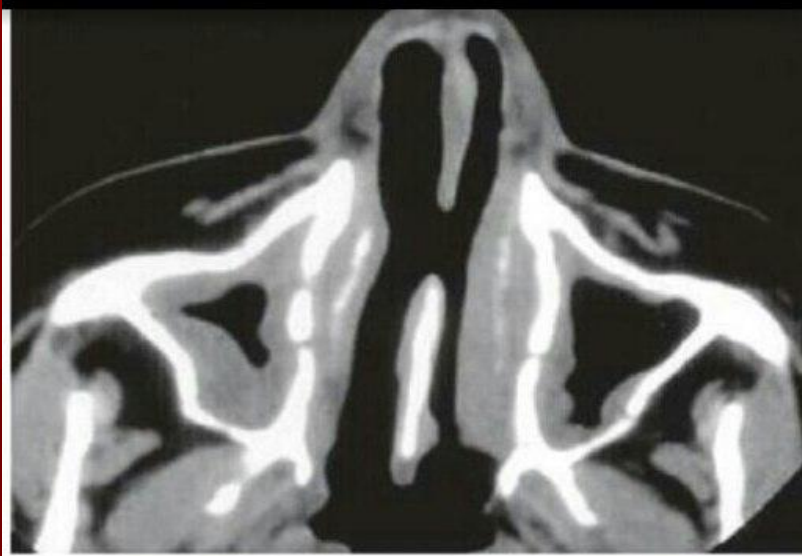




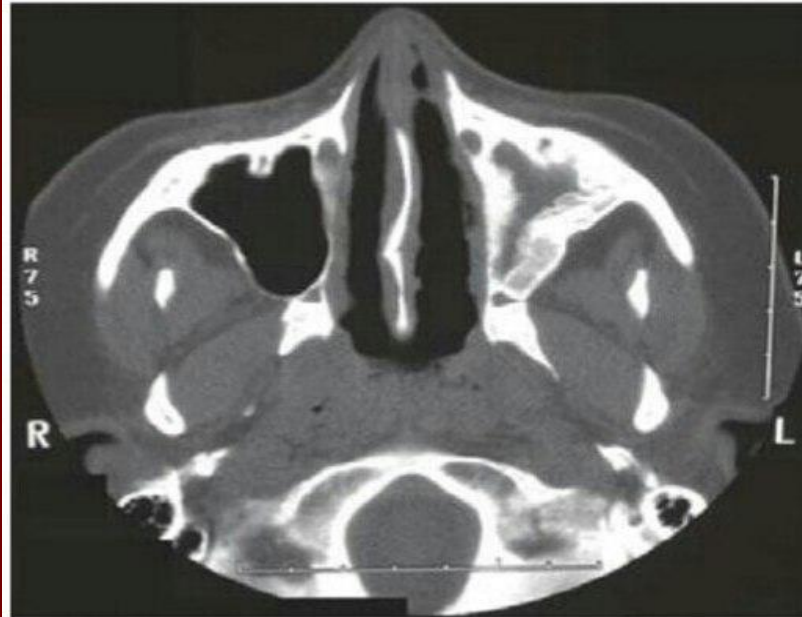
**Figure 89-2** Saddle nose deformity in a patient with granulomatosis with polyangiitis. (Courtesy Dr. G. Hoffman.)



**Figure 89-1** Computed tomography scan of the sinuses, showing sinusitis and destruction of the nasal septum.

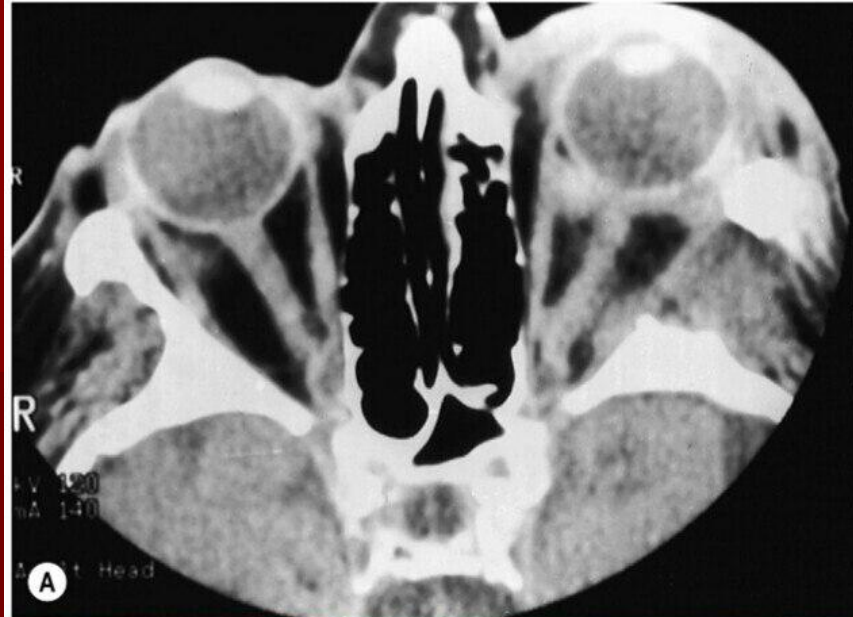


**A**

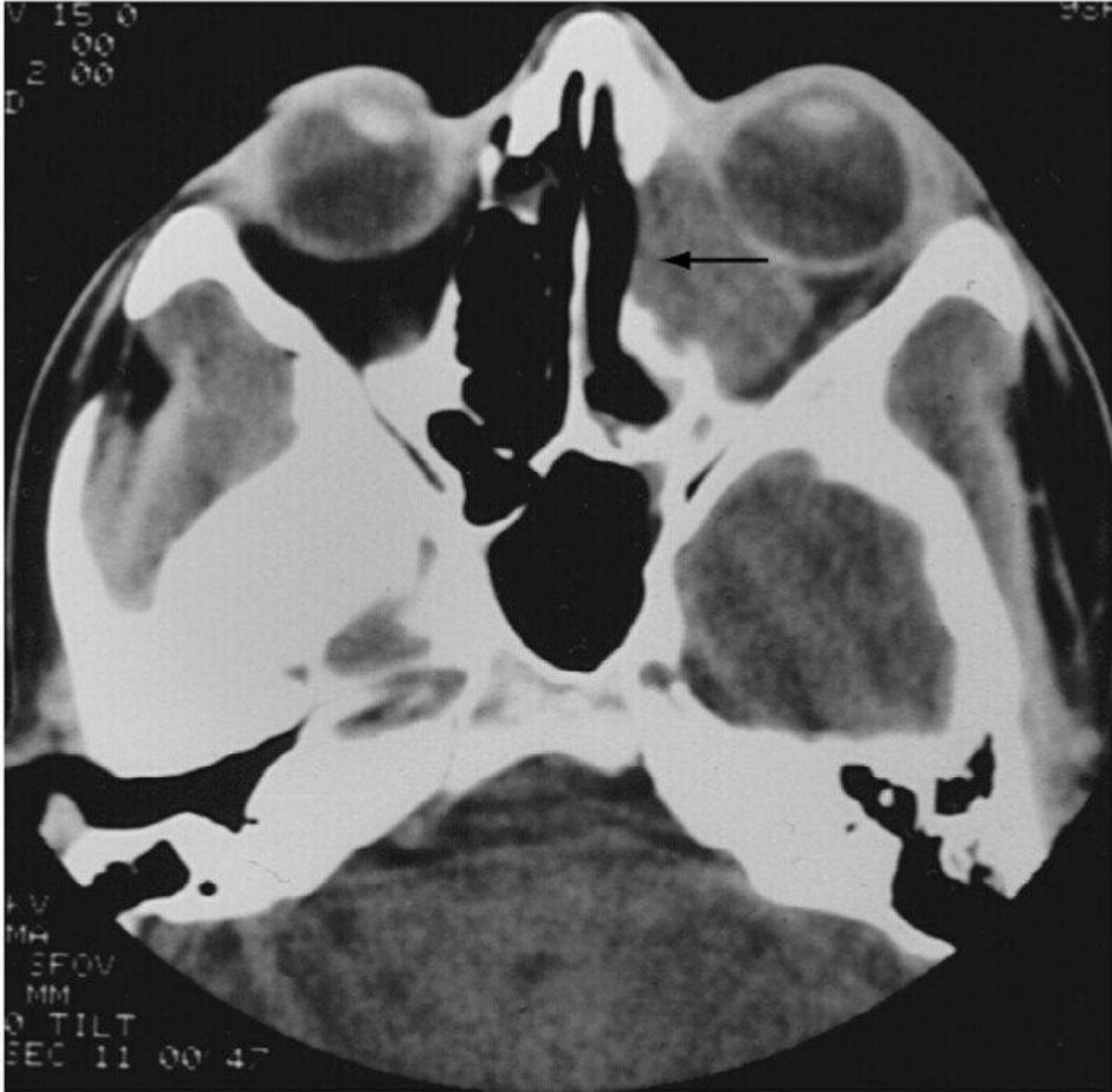


**B**

**FIGURE 386e-6 Computed tomography of the sinuses** in two patients with granulomatosis with polyangiitis (Wegener's). (**A**) Mucosal thickening of the bilateral maxillary sinuses and a perforation of the nasal septum. (**B**) Osteitis with obliteration of the left maxillary sinus in a patient with long-standing sinus disease.



**Fig. 57.3** The cardinal ocular manifestations of granulomatosis with polyangiitis (formerly Wegener's granulomatosis). (A) bilateral retro-orbital masses, causing proptosis of the left eye; (B) necrotizing scleritis.



**Figure 89-4** Computed tomography scan of the orbits, showing a retro-orbital mass (orbital pseudotumor).



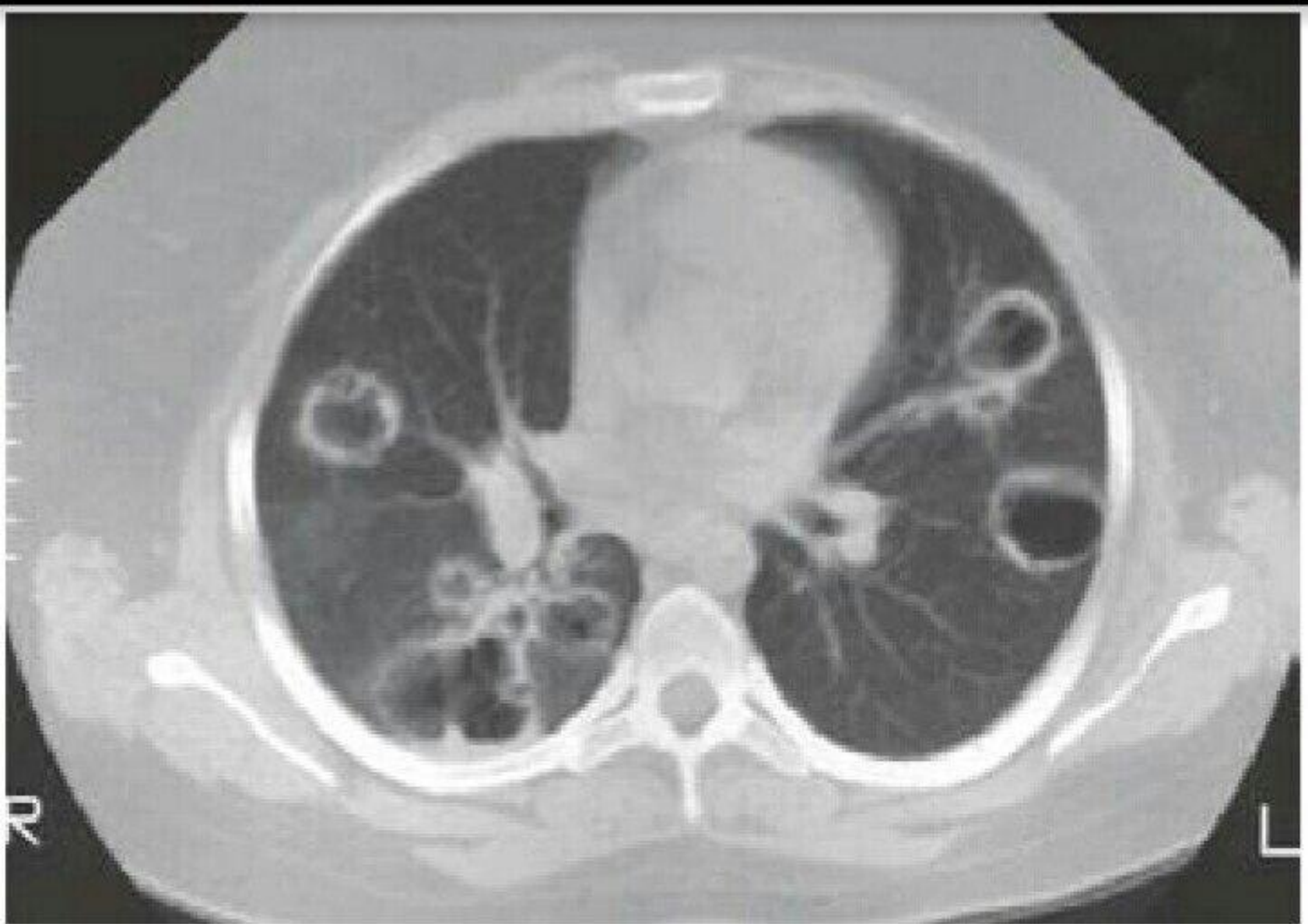
**FIGURE 386e-4** Computed tomography of the chest demonstrating a dense infiltrate with air bronchograms involving a segment of the right upper lobe due to bacterial pneumonia in an immunosuppressed patient with granulomatosis with polyangiitis (Wegener's). Collapse of the left upper lobe secondary to endobronchial stenosis from granulomatosis with polyangiitis (Wegener's) also is seen on this image.



**FIGURE 386e-5** Computed tomography of the orbits in a patient with granulomatosis with polyangiitis (Wegener's) who presented with right-eye proptosis. The image demonstrates inflammatory tissue extending from the ethmoid sinus through the lamina papyracea and filling the orbital space.

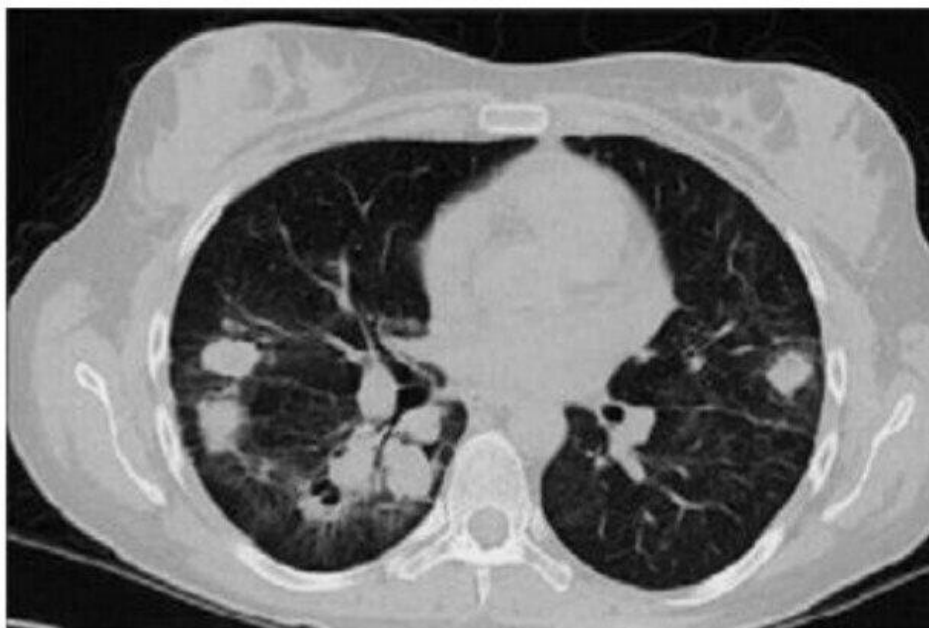


Computed tomography of the lungs, showing pulmonary nodules. The right-sided nodule is cavitary (*arrow*).

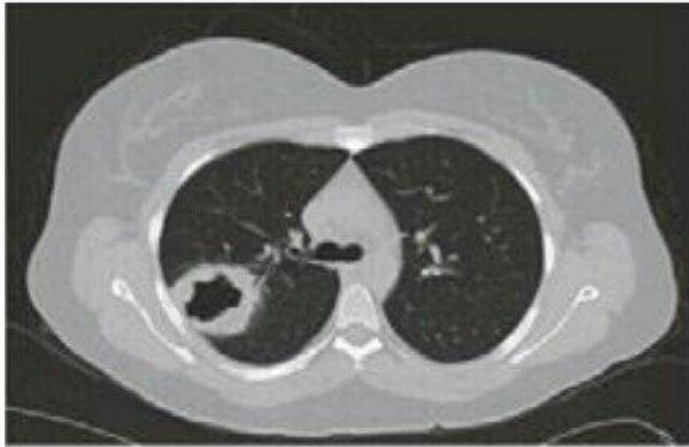


**FIGURE 385-3** Computed tomography scan of a patient with **granulomatosis with polyangiitis (Wegener's)**. The patient developed multiple, bilateral, and cavitary infiltrates.

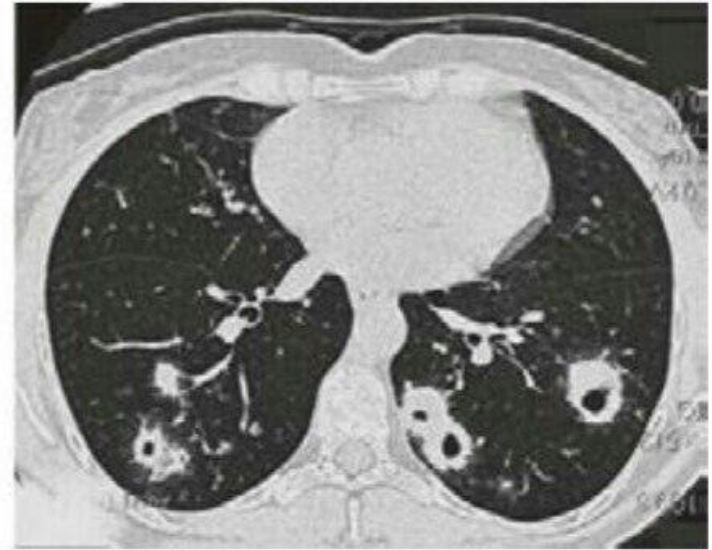




**FIGURE 386e-1** Bilateral nodular infiltrates seen on computed tomography of the chest in a 40-year-old woman with granulomatosis with polyangiitis (Wegener's).

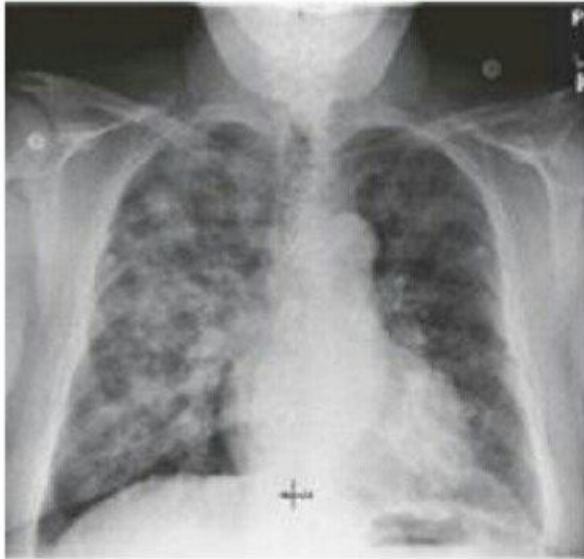


**A**

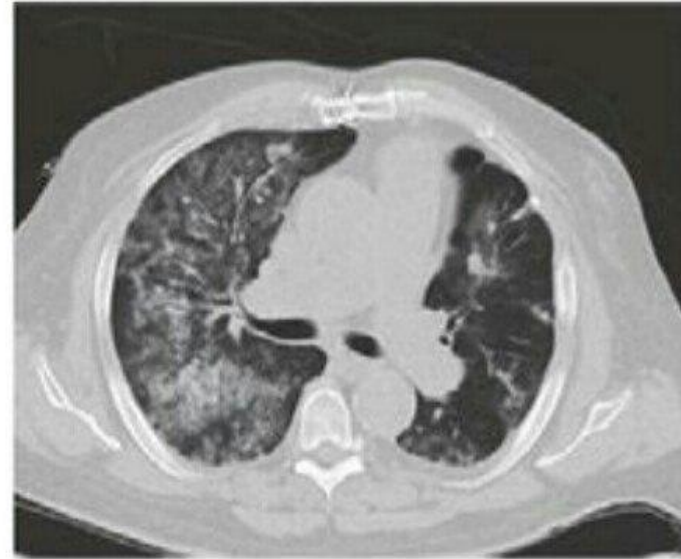


**B**

**FIGURE 386e-2** Computed tomography of the chest in two patients with granulomatosis with polyangiitis (Wegener's) demonstrating (A) single and (B) multiple cavitary lung lesions.

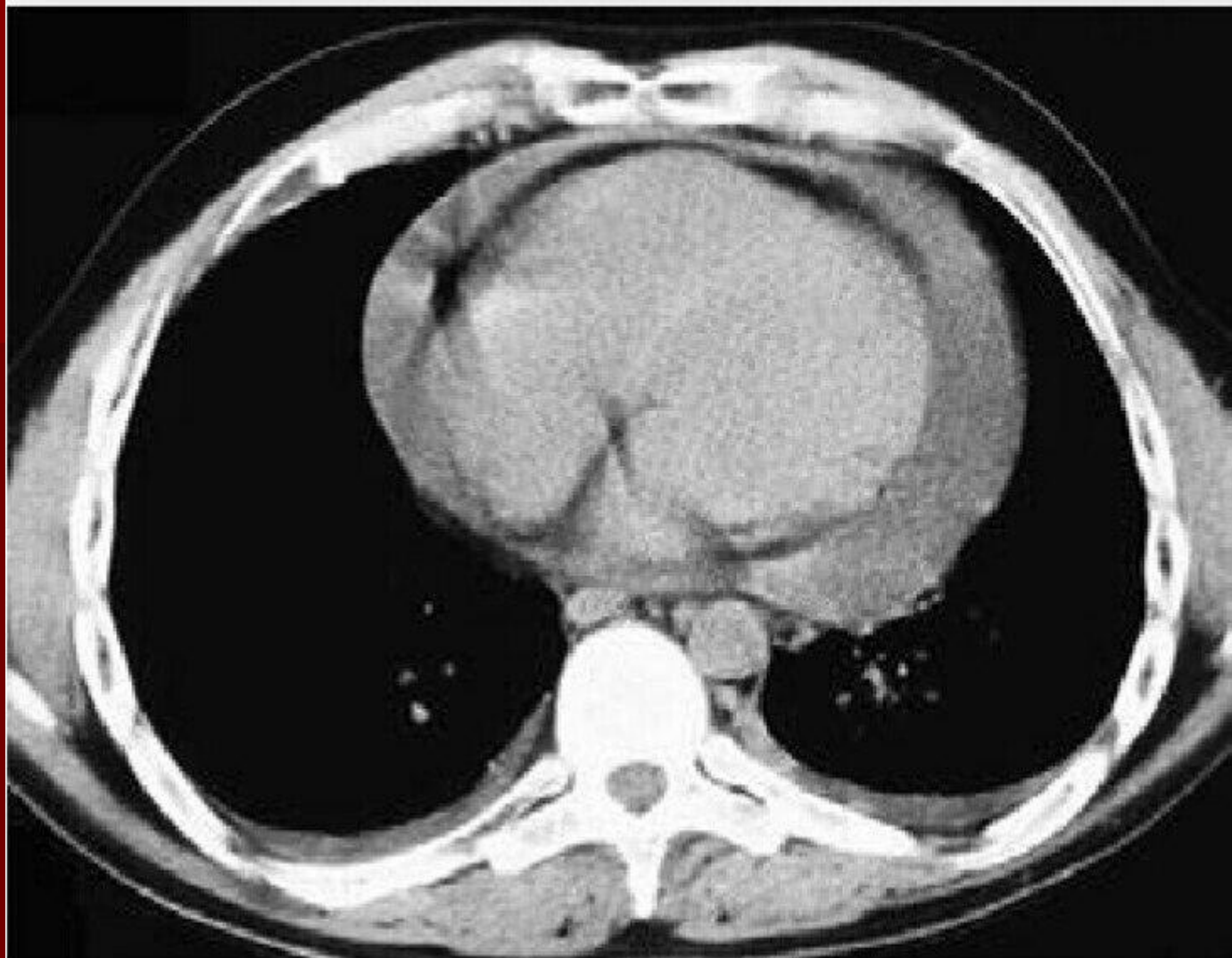


**A**

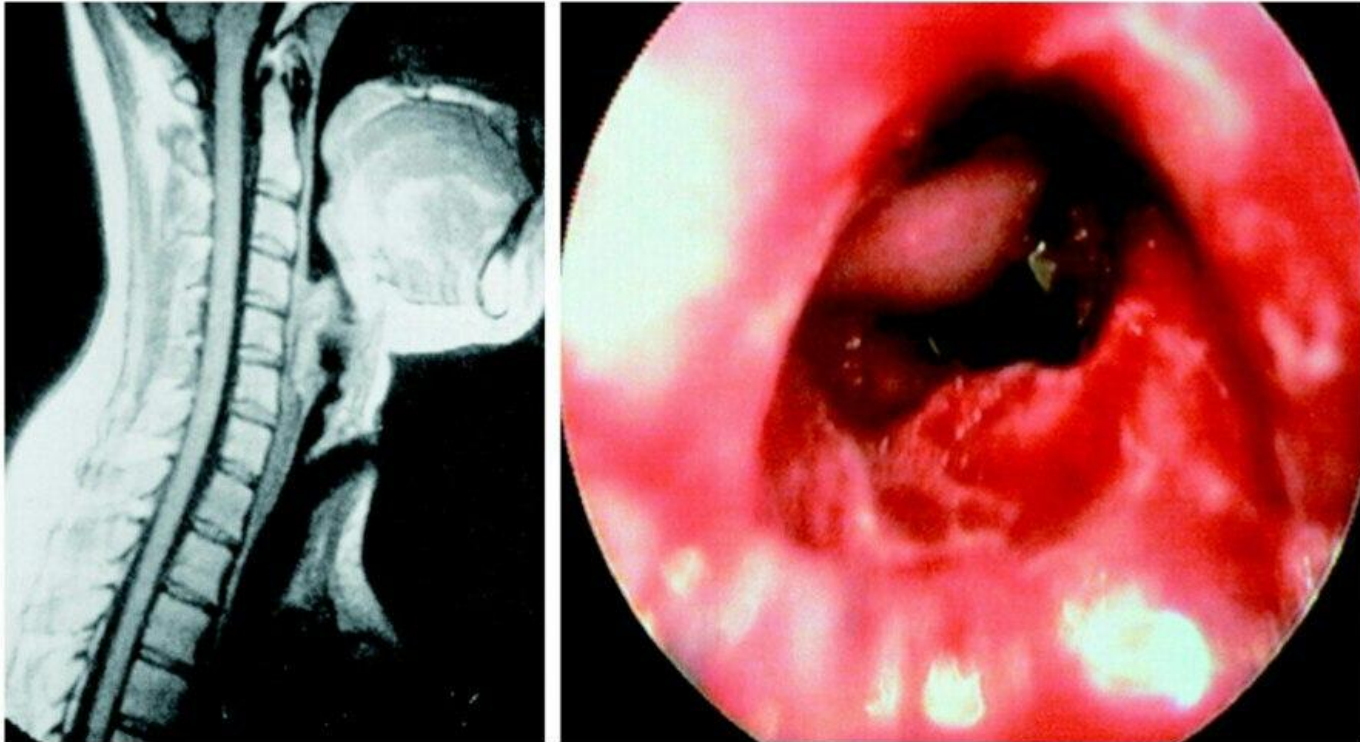


**B**

**FIGURE 386e-3** Bilateral ground-glass infiltrates due to alveolar hemorrhage from pulmonary capillaritis as seen in the same patient by (A) chest radiograph and (B) computed tomography. This manifestation can occur in granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis.

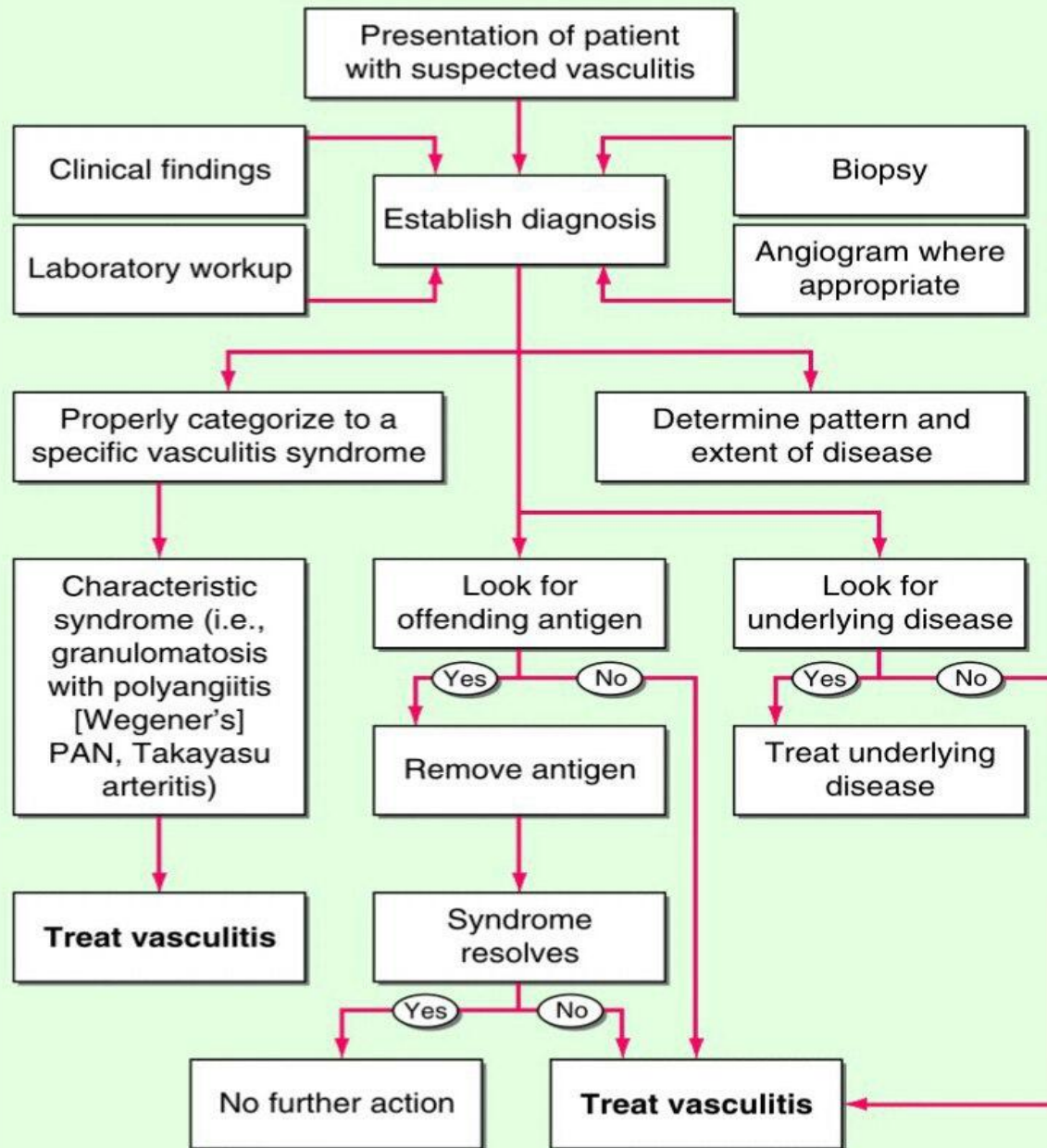


**FIGURE 386e-7** Computed tomography of the chest demonstrating a large pericardial effusion in a patient with eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Cardiac involvement is an important cause of morbidity and mortality in eosinophilic granulomatosis with polyangiitis and can include myocarditis, endocarditis, and pericarditis.



**Figure 89-3** Subglottic stenosis in a patient with granulomatosis with polyangiitis. MRI (*left*) and endoscopic view (*right*). (Courtesy Dr. G. Hoffman. From Hoffman GS, Kerr GS, Leavitt RY, et al: Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 116:488–498, 1992.)

# SUSPECTED VASCULITIS



**FIGURE 385-1** Algorithm for the approach to a patient with suspected diagnosis of vasculitis. PAN, polyarteritis nodosa.

Терапия



## Treatment of ANCA-associated vasculitides

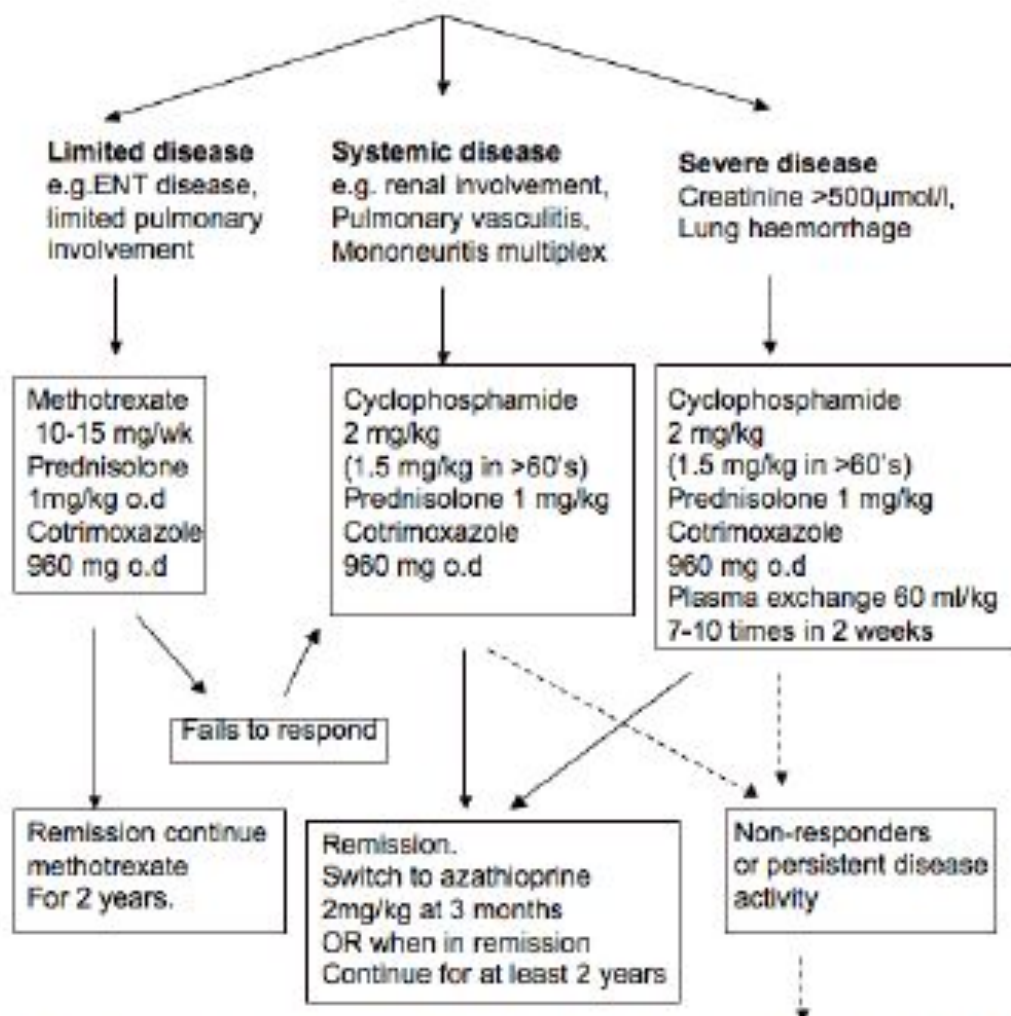
- The presence of symptoms that constitute immediate threats to either function of vital organs or to survival requires urgent treatment with high doses of glucocorticoids and a second immunosuppressant. Alternatives for the second immunosuppressant include rituximab and cyclophosphamide. Data on long-term efficacy, safety, and cost-effectiveness are awaited to further refine the optimal immunosuppressive regimen for each patient.
- Limited forms of granulomatosis with polyangiitis (Wegener's) may respond to a combination of glucocorticoids and methotrexate, but durable remissions with this regimen are rare and rituximab may be a better choice for remission induction in these patients.
- In eosinophilic granulomatosis with polyangiitis/Churg–Strauss syndrome patients without serious organ involvement, treatment with glucocorticoids is a reasonable first approach. However, the presence of glomerulonephritis or mononeuritis multiplex requires immediate treatment with cyclophosphamide and glucocorticoids.



| Study                                   | Subjects  | Therapy   | Endpoint  | Comment   |
|---|---|---|---|---|
| CYCAZAREM <sup>[54]</sup>               | 115 patients with newly diagnosed AAV and renal involvement | AZA vs. oral CYC, both in combination with prednisolone, after achieving remission with oral CYC and steroids | Relapse at 18 months  | AZA and CYC associated with similar rates of relapse. Cumulative exposure to CYC is reduced   |
| IMPROVE <sup>[55]</sup>                 | 156 patients with newly diagnosed AAV                       | AZA vs. MMF after achieving remission with CYC and steroids   | Relapse free survival at 39 months  | AZA superior to MMF at maintaining disease remission with similar rates of adverse events   |
| WEGENT <sup>[56]</sup>                  | 159 patients with newly diagnosed AAV                       | AZA vs. MTX after achieving remission with IV-CYC and steroids  | Adverse event requiring drug discontinuation or causing death. Relapse as secondary end point. Mean follow up 29 months | AZA and MTX associated with similar rates of adverse events and relapse   |
| MAINRITSAN <sup>[58]</sup>              | 115 patients with newly diagnosed or relapsing AAV          | Rituximab vs. AZA after achieving remission with CYC and steroids   | Rate of major relapse at 28 months  | Rituximab superior to AZA at maintaining remission and not associated with increased severe adverse events<br>Currently in recruiting phase |
| RITAZAREM <sup>[62]</sup>               | 160 patients with relapsing AAV                             | Rituximab vs. AZA after achieving remission with Rituximab and steroids                                       | Rate of relapse   |   |
| BREVAS <sup>[66]</sup><br>NCT01663623   | 400 patients with AAV following standard therapy            | Belimumab plus Azathioprine vs Placebo plus Azathioprine  | Time to First Relapse   | Currently in Recruitment phase  |
| ABROGATE <sup>[67]</sup><br>NCT02108860 | 150 patients with AAV following standard therapy            | Abatacept vs placebo  | Treatment failure after 12 months   | Recruitment phase   |
| TAPIR <sup>[64]</sup>                   | 60 patients with GPA who are in remission                   | Low dose (5mg ) Prednisone vs No dose (0mg) Prednisone  | Proportion requiring increased dose relapse   | Recruitment phase   |

ANCA: Anti-neutrophil cytoplasmic antibody, AAV: ANCA associated vasculitis, IV: Intravenous, AZA: Azathioprine, CYC: Cyclophosphamide, MMF: Mycophenolate mofetil, MTX: Methotrexate

## ANCA associated systemic vasculitis



**Grumbling disease activity** i) Infliximab anti-TNF treatment 5mg/kg at weeks 0, 2, 6, 10 and continue with monthly injections if signs of response ii) Switch to methotrexate may be beneficial when creat <150.

**Persistent systemic disease** i) Rituximab 1000mg at weeks 0 and 2 with IV hydrocortisone 200mg. Monitor CD19 B cell count ii) Infliximab as above iii) Campath 1H anti T-cell therapy or ATG.

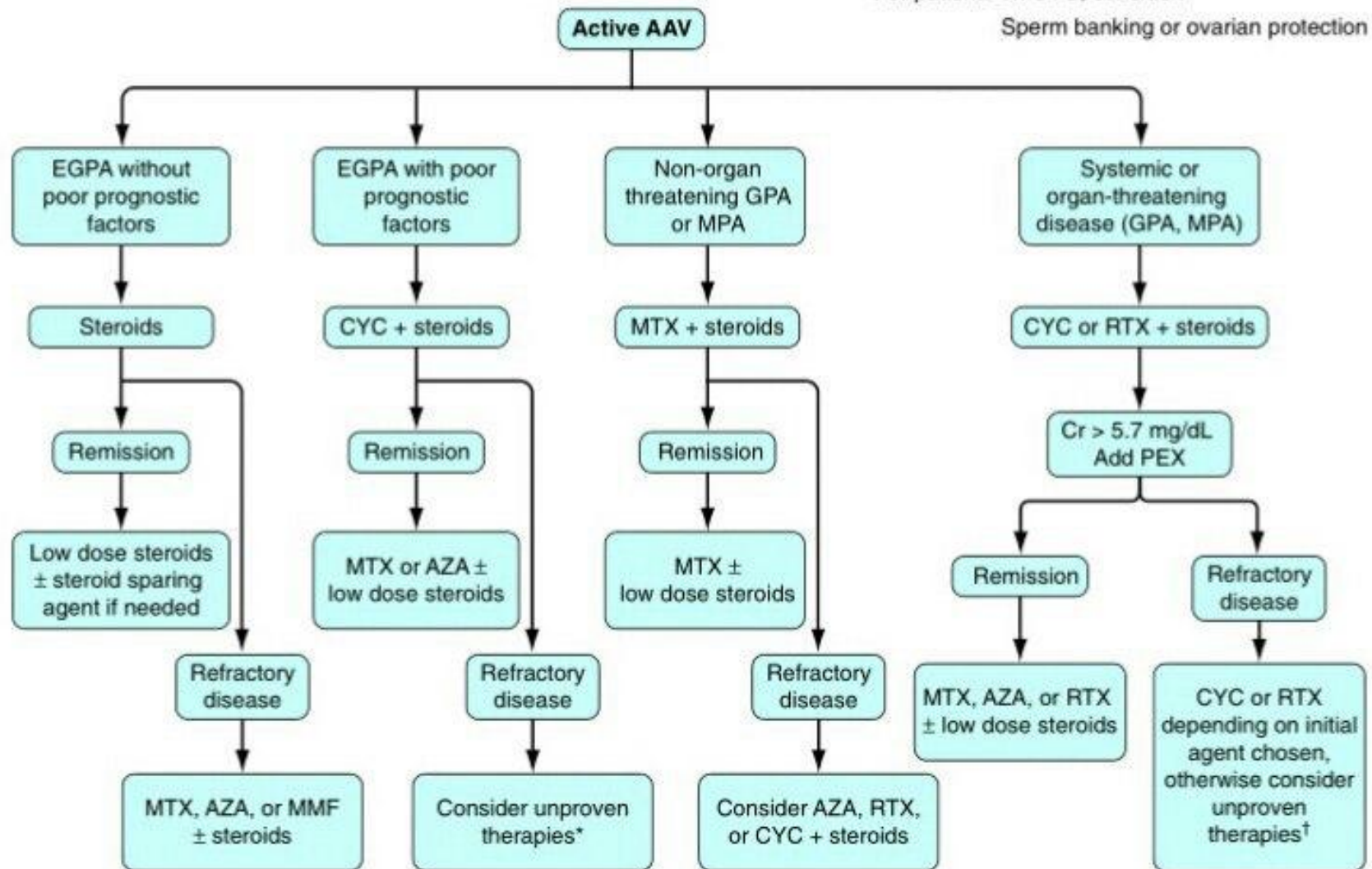
For all patients, consider:

Pneumocystis jirovecii prophylaxis

Bone and GI protection

For patients on CYC, consider:

Sperm banking or ovarian protection



\*Includes RTX, mepolizumab, hydroxurea, MTX, AZA, mycophenolate mofetil.

†Includes infliximab, mycophenolate mofetil, intravenous immunoglobulin, 15-deoxyspergualin.

**Figure 89-8** Treatment algorithm for the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV). AZA, Azathioprine; Cr, serum creatinine; CYC, cyclophosphamide; EGPA, eosinophilic granulomatosis with polyangiitis; GI, gastrointestinal; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MTX, methotrexate; PEX, plasma exchange; RTX, rituximab.

**Glucocorticoids**

|  |                                |
|--|--------------------------------|
| Osteoporosis   | Growth suppression in children |
| Cataracts  | Hypertension                   |
| Glaucoma   | Avascular necrosis of bone     |
| Diabetes mellitus  | Myopathy                       |
| Electrolyte abnormalities  | Alterations in mood            |
| Metabolic abnormalities  | Psychosis                      |
| Suppression of inflammatory and immune responses leading to opportunistic infections | Pseudotumor cerebri            |
| Cushingoid features  | Peptic ulcer diathesis         |
|  | Pancreatitis                   |

**Cyclophosphamide**

|                              |                          |
|------------------------------|--------------------------|
| Bone marrow suppression      | Hypogammaglobulinemia    |
| Cystitis                     | Pulmonary fibrosis       |
| Bladder carcinoma            | Myelodysplasia           |
| Gonadal suppression          | Oncogenesis              |
| Gastrointestinal intolerance | Teratogenicity           |
|                              | Opportunistic infections |

**Methotrexate**

|  |                          |
|--|--------------------------|
| Gastrointestinal intolerance                       | Pneumonitis              |
| Stomatitis   | Teratogenicity           |
| Bone marrow suppression                            | Opportunistic infections |
| Hepatotoxicity (may lead to fibrosis or cirrhosis) |                          |

**Azathioprine**

|                              |                          |
|------------------------------|--------------------------|
| Gastrointestinal intolerance | Opportunistic infections |
| Bone marrow suppression      | Hypersensitivity         |
| Hepatotoxicity               |                          |

**Rituximab**

|  |                          |
|--|--------------------------|
| Infusion reactions                         | Opportunistic infections |
| Progressive multifocal leukoencephalopathy | Hepatitis B reactivation |
| Mucocutaneous reactions                    | Tumor lysis syndrome     |

