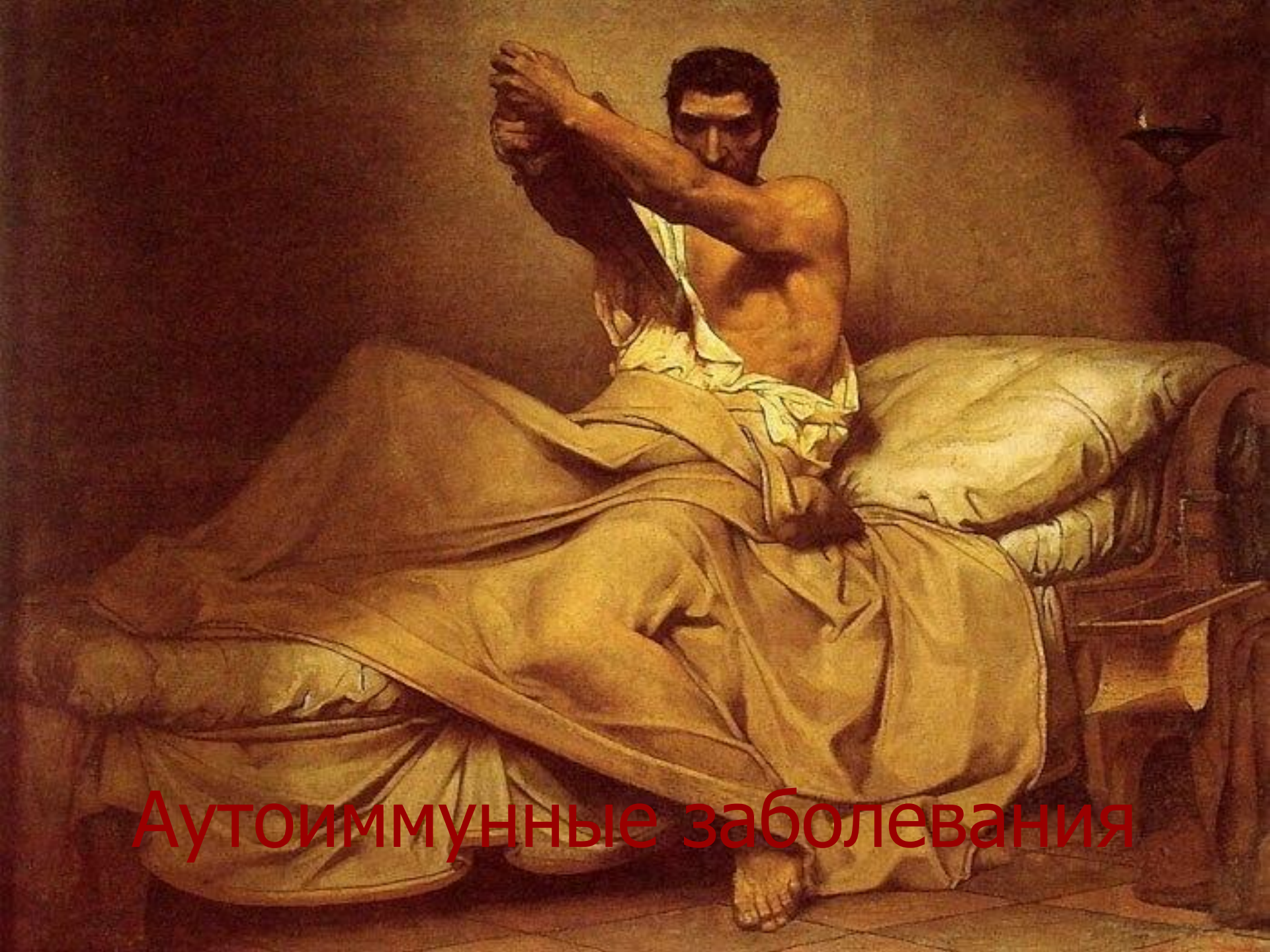


Аутоиммунные заболевания

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

TABLE 377e-2 MECHANISMS OF AUTOIMMUNITY

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

TABLE 385-2 POTENTIAL MECHANISMS OF VESSEL DAMAGE IN VASCULITIS SYNDROMES

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)

Source: Adapted from MC Sneller, AS Fauci: Med Clin North Am 81:221, 1997.

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

Primary Vasculitis Syndromes	Secondary Vasculitis Syndromes
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_4-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

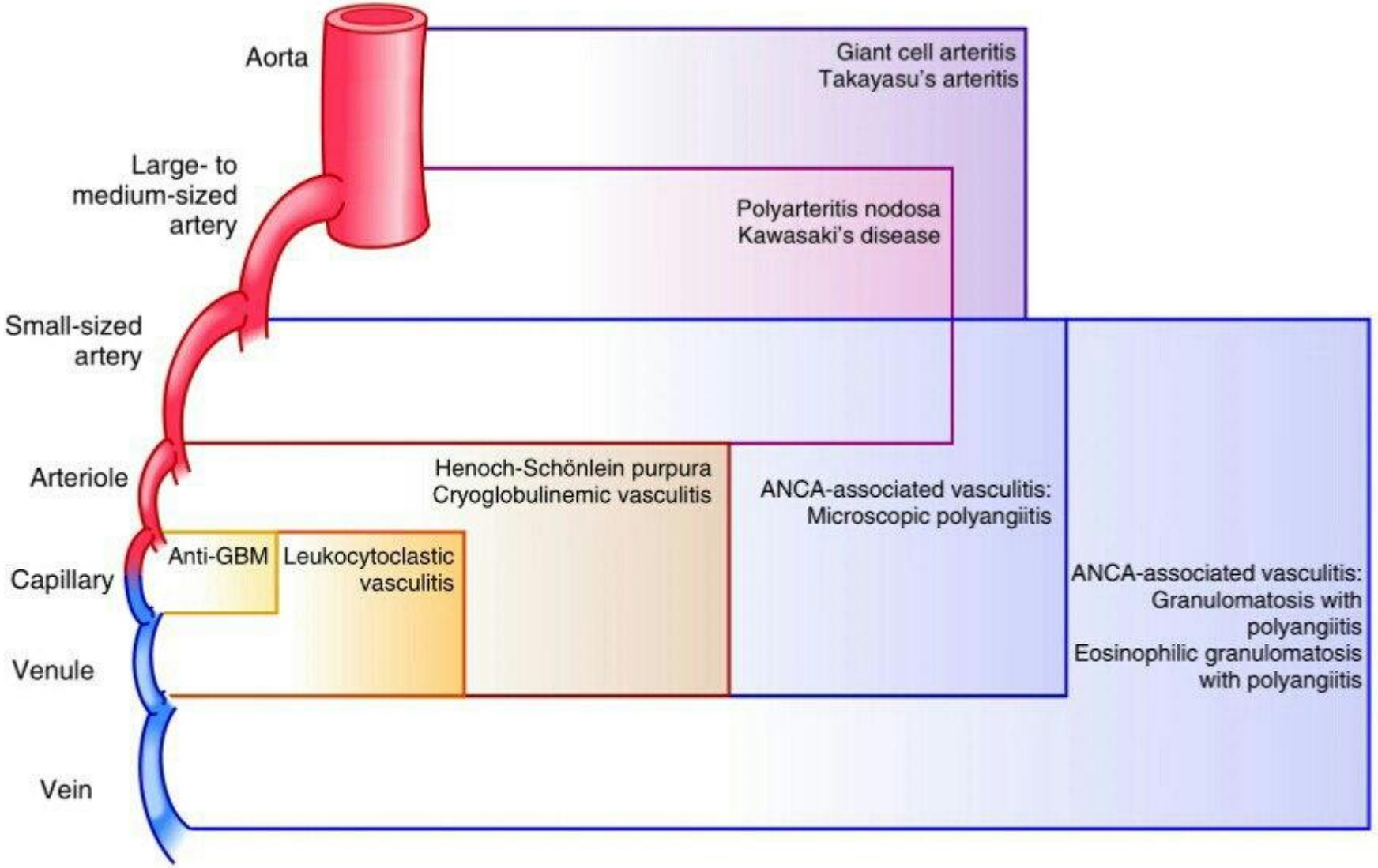


Figure 87-1 Classification by blood vessel size. ANCA, Anti-neutrophil cytoplasmic antibody; GBM, glomerular basement membrane.

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, Anti-neutrophil cytoplasmic antibody; GBM, glomerular basement membrane; MPO, myeloperoxidase; PR3, proteinase 3.

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 immunoflourescence 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)

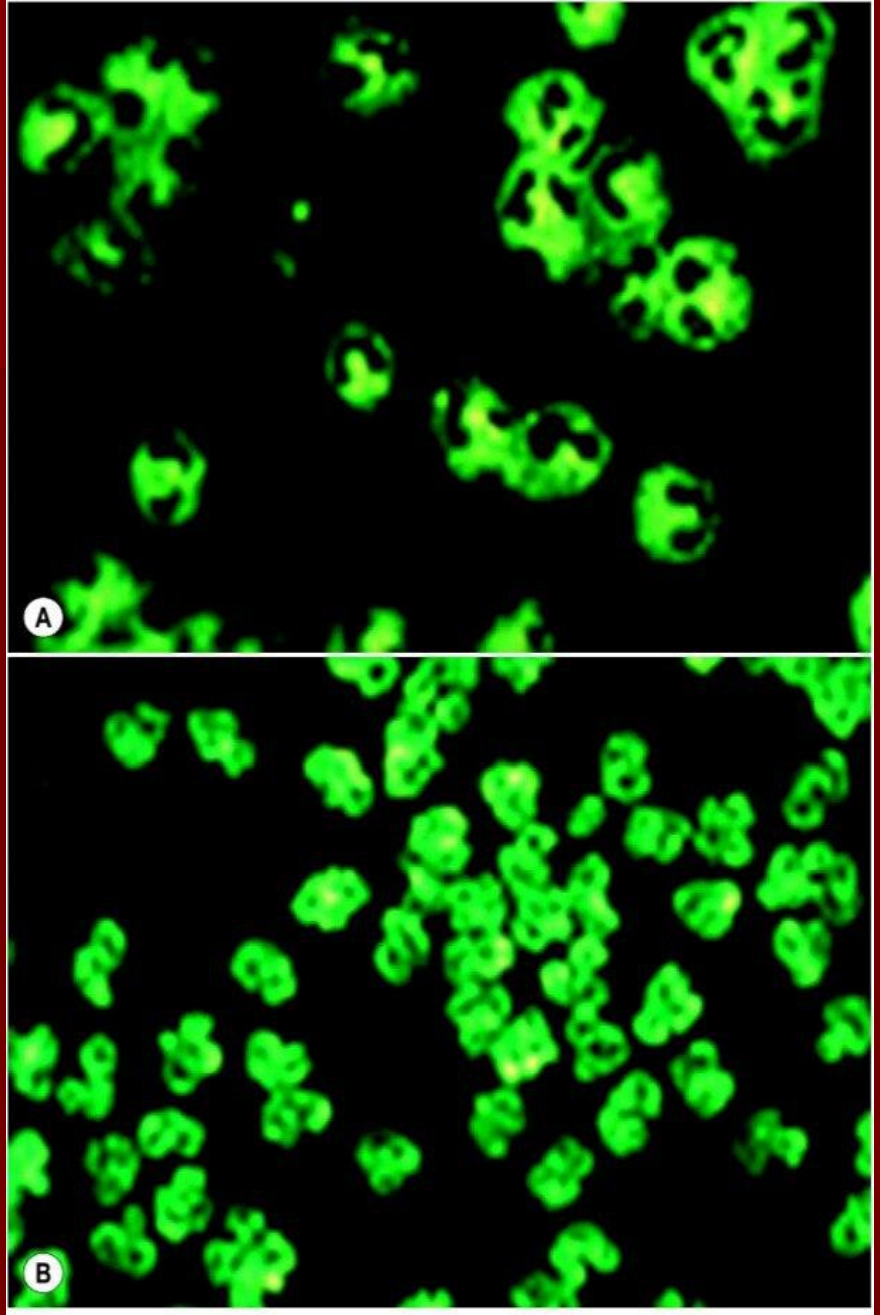


Fig. 57.1 ANCA patterns. (A) Immunofluorescence study of serum on the substrate of human neutrophils, demonstrating cytoplasmic immunofluorescence (a positive ANCA assay, C-ANCA pattern). (B) Perinuclear immunofluorescence (P-ANCA pattern).

Table 3
Spectrum of ANCA positive diseases.

- ANCA-associated vasculitides (GPA, MPA, EGPA)
- Non-ANCA-associated vasculitis (i.e., Takayasu, GCA, polyartheritis 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-α), infections, inflammation → *primed* neutrophils.

2) *Primed* neutrophils → membrane expression of azurophilic granule contents by translocation (*e.g.*, proteinase-3).

3) Proteinase-3 + ANCA (α-proteinase-3) → proteinase-3-IgG complex.

4) Proteinase-3-IgG complex + FcγR bridging → cell signaling events, neutrophil *activation*. Reaction is amplified by 5-lipoxygenase pathway leukotrienes.

5) At surface of endothelial cells: *activated* neutrophils → respiratory burst, degranulation → VASCULITIS.

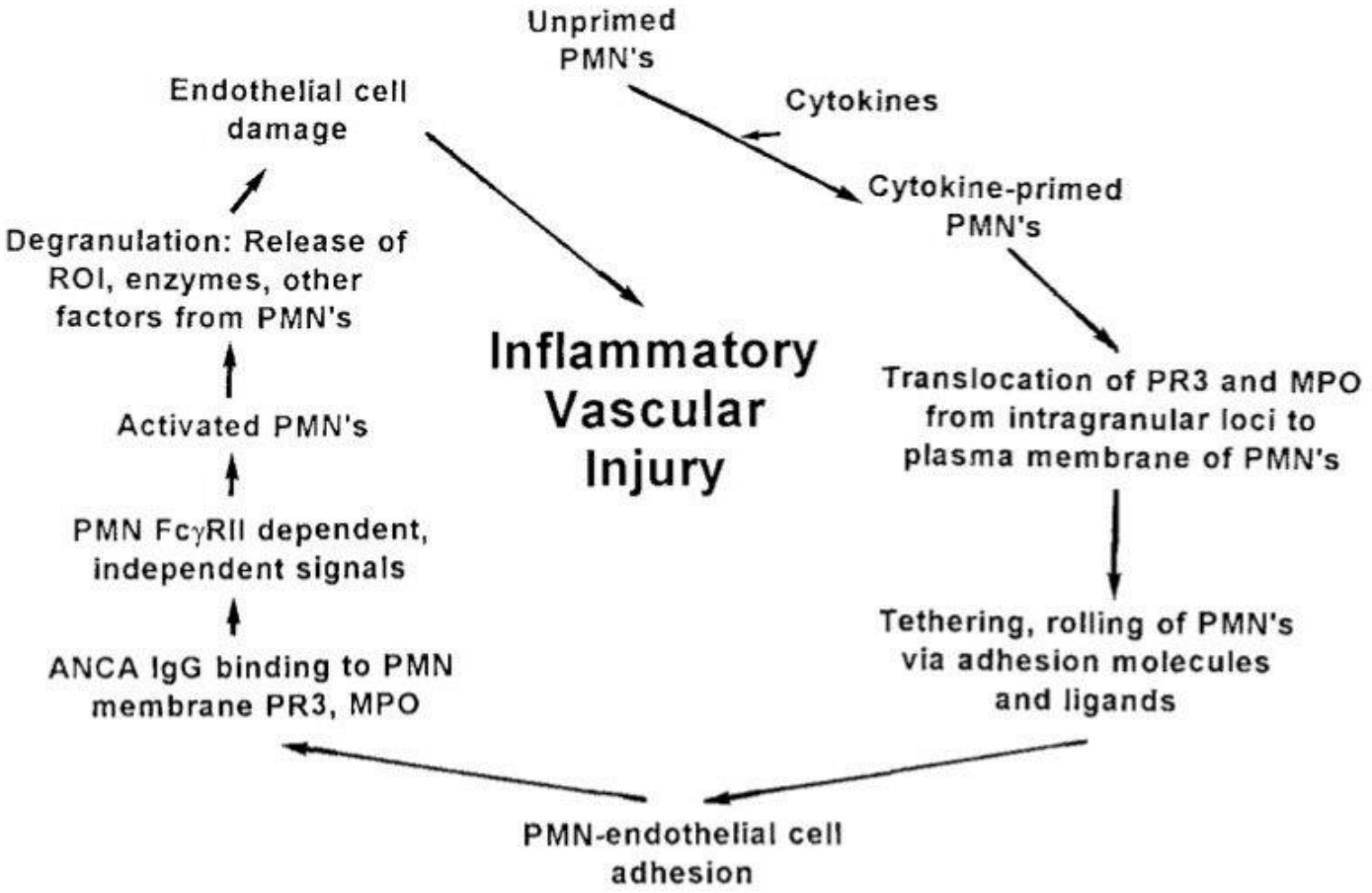
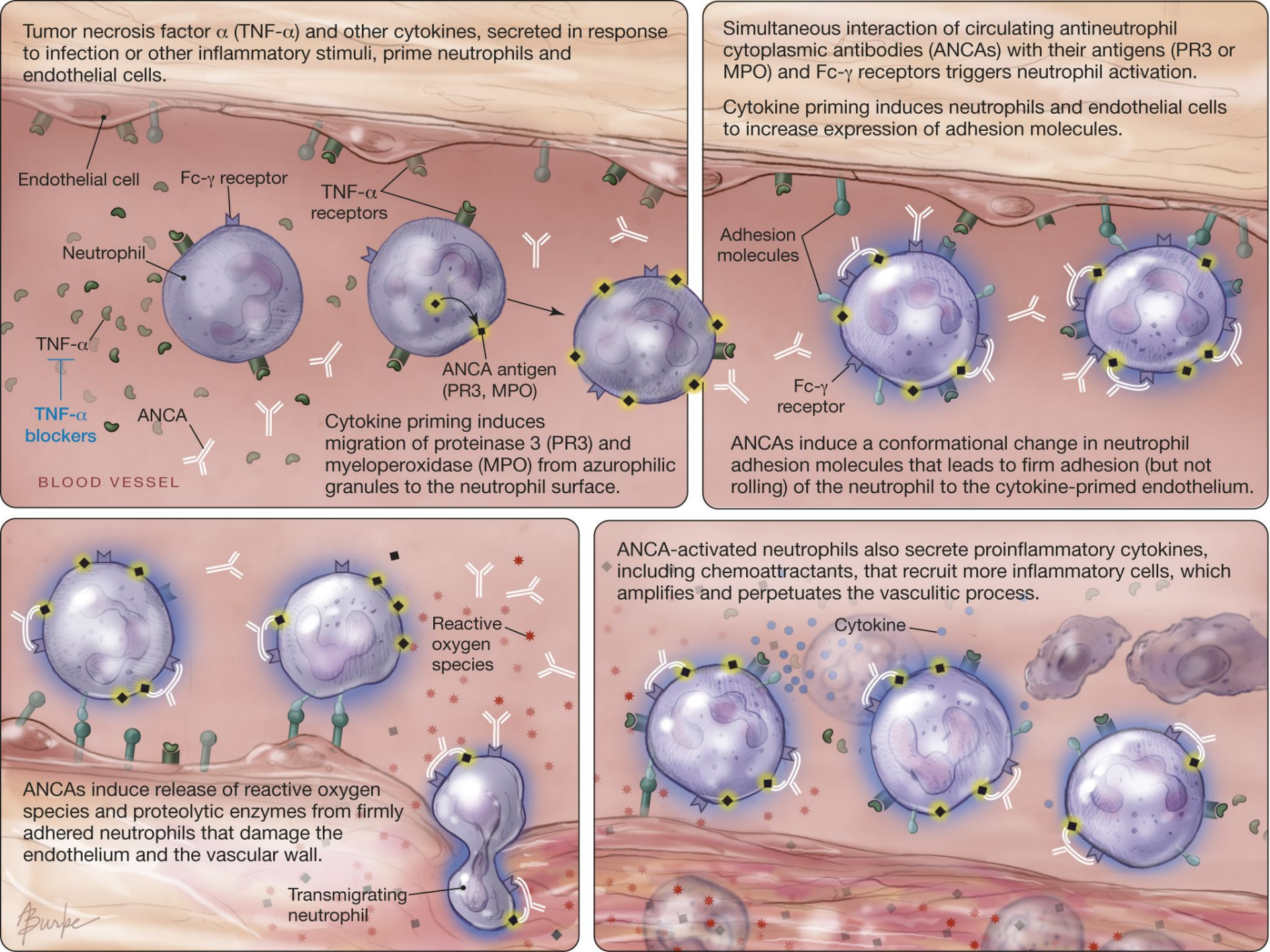
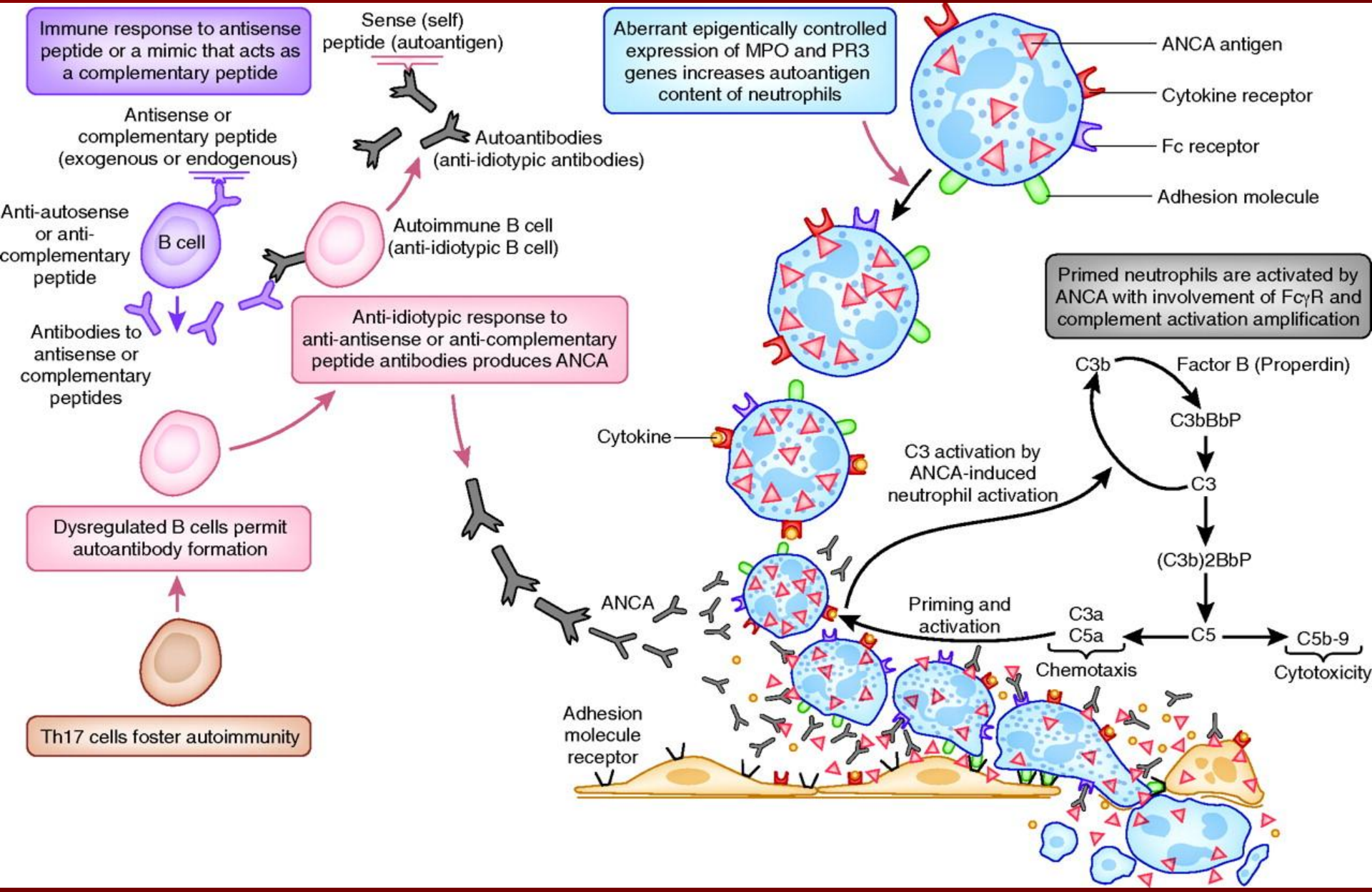
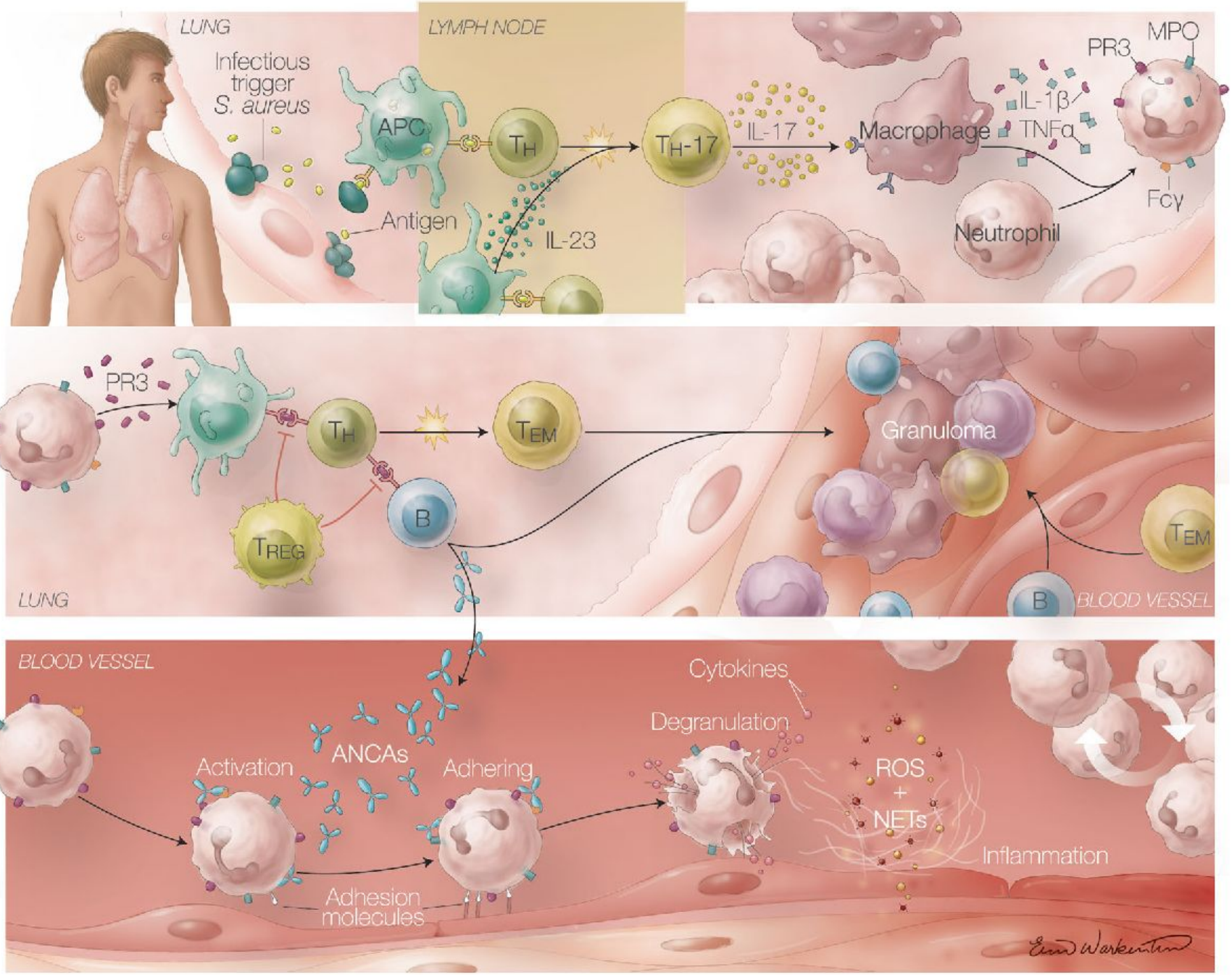


Fig 2: Hypothetical sequence of events of ANCA IgG-activation of PMNs and endothelial cell damage, leading to inflammatory vascular injury. The diagram was compiled from data in references 20, 96, 100, 101, and 103.


Tumor necrosis factor α (TNF-α) and other cytokines, secreted in response to infection or other inflammatory stimuli, prime neutrophils and endothelial cells.
Endothelial cell
Fc-γ receptor
TNF-α receptors
Neutrophil
TNF-α
TNF-α blockers
ANCA
ANCA antigen (PR3, MPO)
BLOOD VESSEL
Cytokine priming induces migration of proteinase 3 (PR3) and myeloperoxidase (MPO) from azurophilic granules to the neutrophil surface.
Simultaneous interaction of circulating antineutrophil cytoplasmic antibodies (ANCAs) with their antigens (PR3 or MPO) and Fc-γ receptors triggers neutrophil activation.
Cytokine priming induces neutrophils and endothelial cells to increase expression of adhesion molecules.
Adhesion molecules
Fc-γ receptor
ANCAs induce a conformational change in neutrophil adhesion molecules that leads to firm adhesion (but not rolling) of the neutrophil to the cytokine-primed endothelium.
Reactive oxygen species
ANCAs induce release of reactive oxygen species and proteolytic enzymes from firmly adhered neutrophils that damage the endothelium and the vascular wall.
Transmigrating neutrophil
ANCA-activated neutrophils also secrete proinflammatory cytokines, including chemoattractants, that recruit more inflammatory cells, which amplifies and perpetuates the vasculitic process.
Cytokine


Immune response to antisense peptide or a mimic that acts as a complementary peptide
Sense (self) peptide (autoantigen)
Antisense or complementary peptide (exogenous or endogenous)
Autoantibodies (anti-idiotypic antibodies)
Anti-autosense or anti-complementary peptide
B cell
Autoimmune B cell (anti-idiotypic B cell)
Antibodies to antisense or complementary peptides
Anti-idiotypic response to anti-antisense or anti-complementary peptide antibodies produces ANCA
Dysregulated B cells permit autoantibody formation
Th17 cells foster autoimmunity
Aberrant epigentically controlled expression of MPO and PR3 genes increases autoantigen content of neutrophils
ANCA antigen
Cytokine receptor
Fc receptor
Adhesion molecule
Primed neutrophils are activated by ANCA with involvement of FcγR and complement activation amplification
C3b
Factor B (Properdin)
C3bBbP
C3
(C3b)2BbP
C5
C5b-9
Cytotoxicity
C3a
C5a
Chemotaxis
Cytokine
C3 activation by ANCA-induced neutrophil activation
ANCA
Priming and activation
Adhesion molecule receptor



Pathogenesis of anti-neutrophil cytoplasm antibody (ANCA) as ... effector memory T cells (T_{EM}), which then form granulomata. T

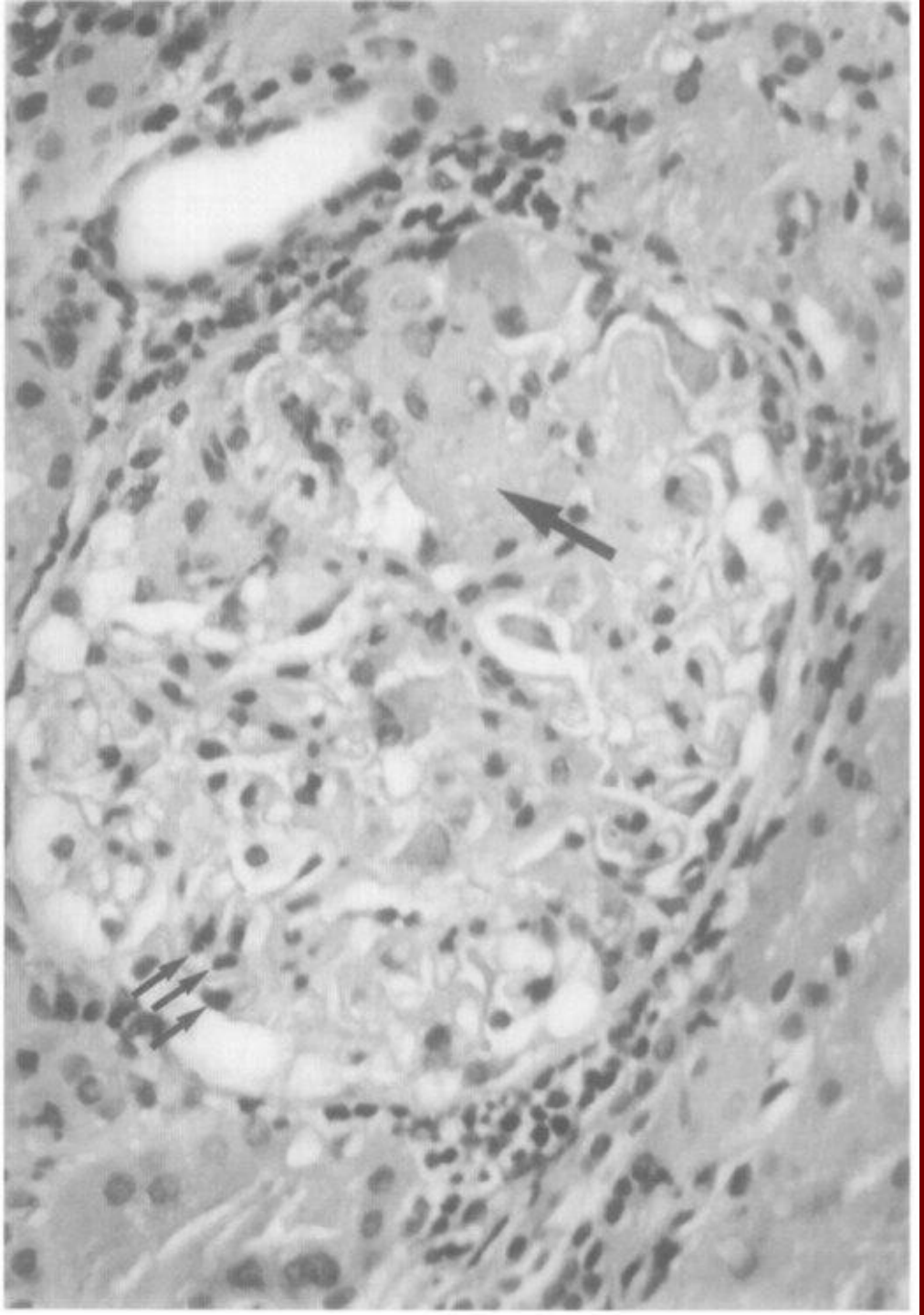


Fig 2. Glomerulus showing segmental necrosis (top arrow) and a few cells undergoing apoptosis (bottom arrows) (H&E, original magnification ×400).

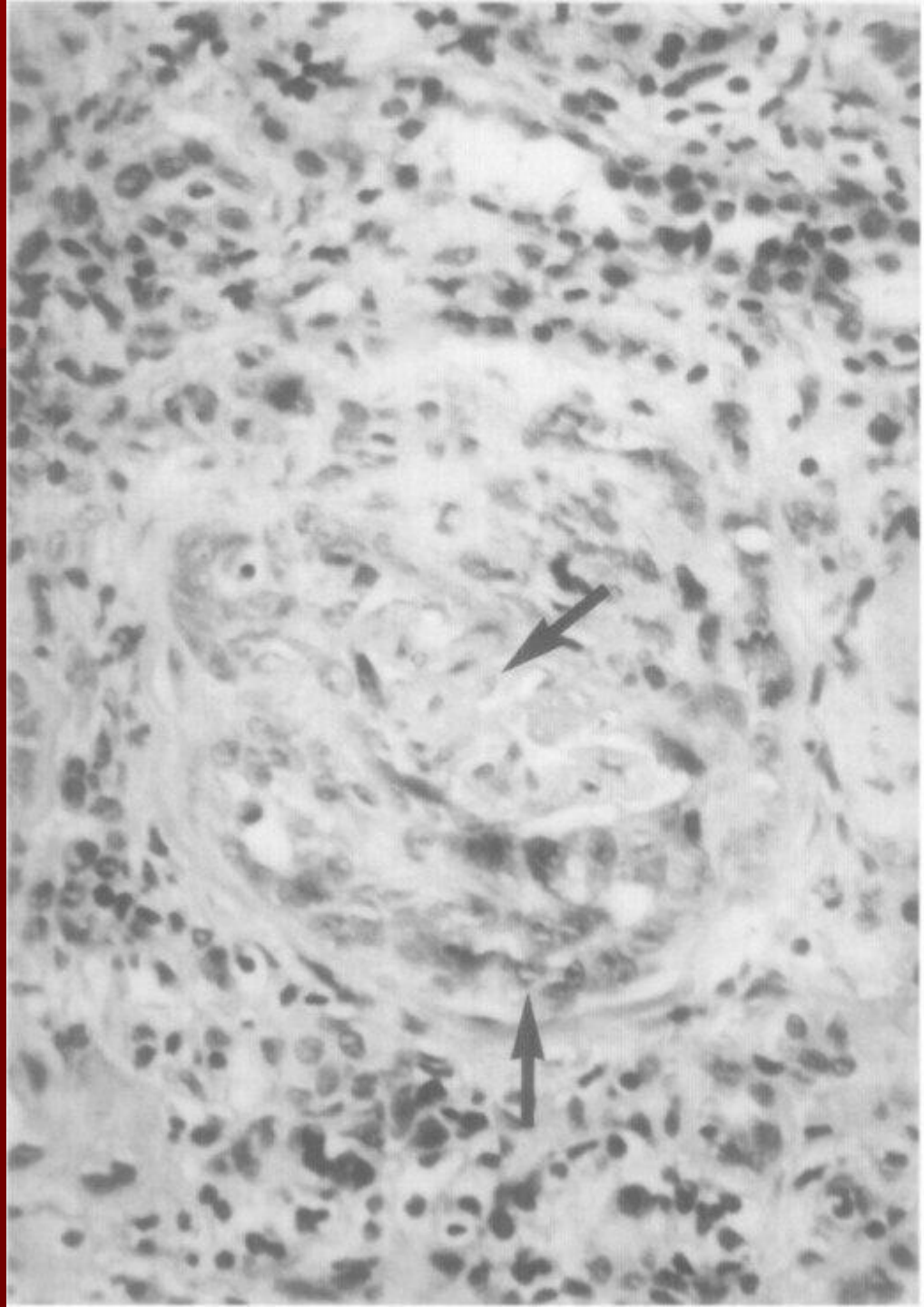
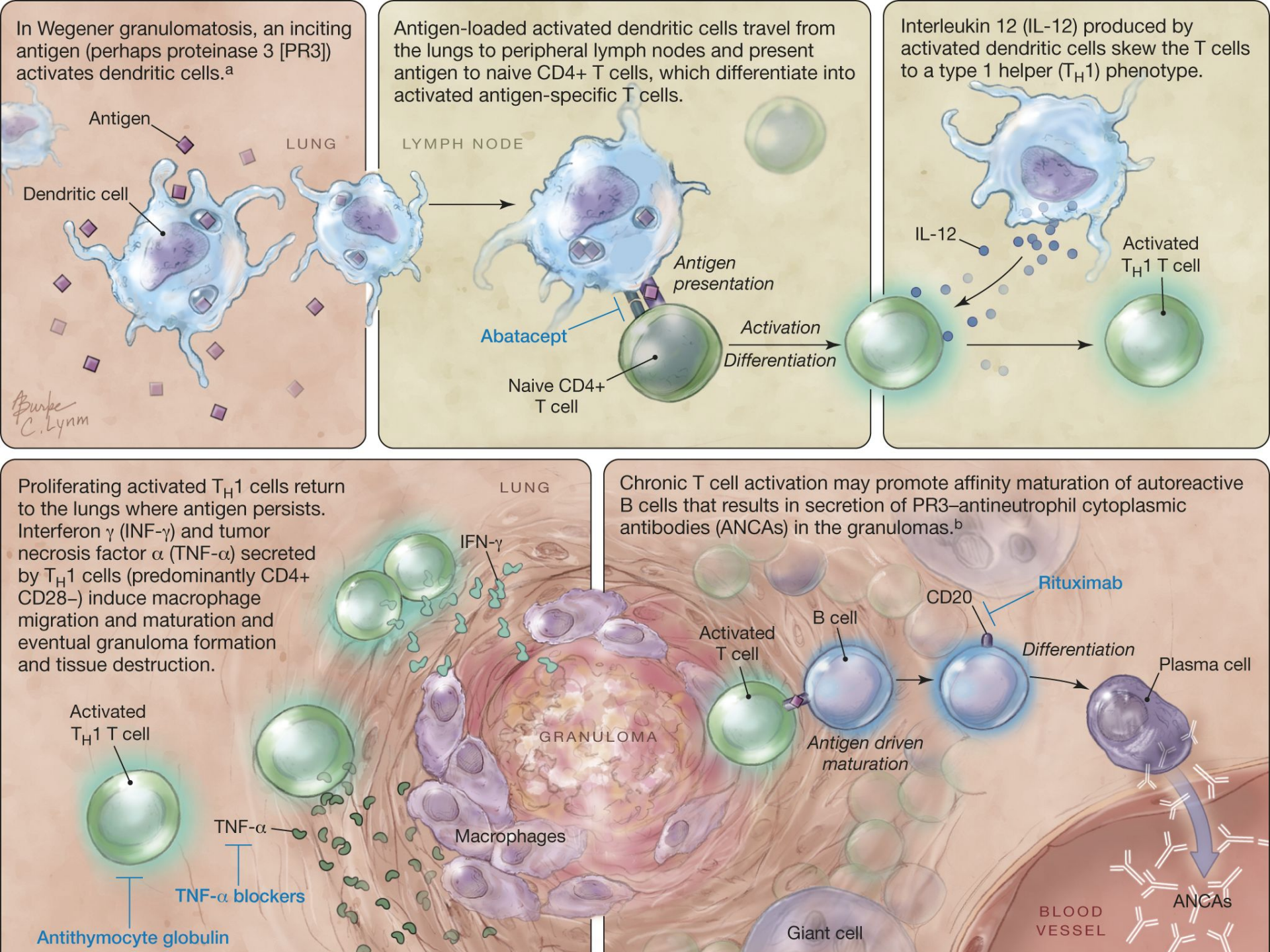
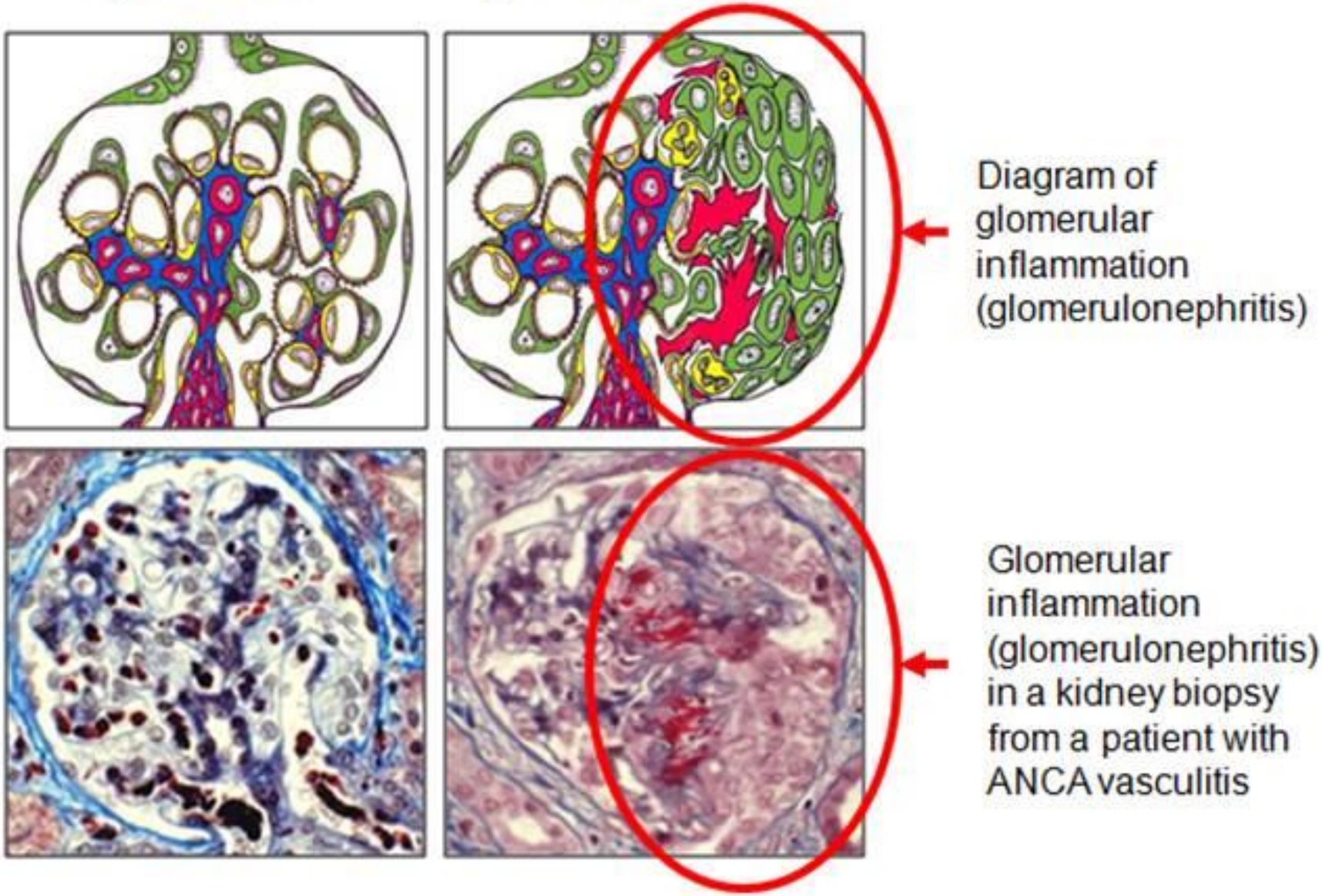


Fig 3. Circumferential crescent (bottom arrow) involving a glomerulus and central area of necrosis (top arrow) (Trichrome, original magnification ×400).


In Wegener granulomatosis, an inciting antigen (perhaps proteinase 3 [PR3]) activates dendritic cells.[a]
Antigen
LUNG
Dendritic cell
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.
LYMPH NODE
Antigen presentation
Abatacept
Activation
Differentiation
Naive CD4+ T cell
Interleukin 12 (IL-12) produced by activated dendritic cells skew the T cells to a type 1 helper (T_H1) phenotype.
IL-12
Activated T_H1 T cell
Proliferating activated T_H1 cells return to the lungs where antigen persists. Interferon γ (INF-γ) and tumor necrosis factor α (TNF-α) secreted by T_H1 cells (predominantly CD4+ CD28–) induce macrophage migration and maturation and eventual granuloma formation and tissue destruction.
LUNG
IFN-γ
Activated T_H1 T cell
GRANULOMA
TNF-α
Macrophages
TNF-α blockers
Antithymocyte globulin
Chronic T cell activation may promote affinity maturation of autoreactive B cells that results in secretion of PR3–antineutrophil cytoplasmic antibodies (ANCAs) in the granulomas.[b]
Rituximab
CD20
B cell
Activated T cell
Differentiation
Plasma cell
Antigen driven maturation
Giant cell
BLOOD VESSEL
ANCAs


Normal glomerulus
ANCA glomerulonephritis
Diagram of glomerular inflammation (glomerulonephritis)
Glomerular inflammation (glomerulonephritis) in a kidney biopsy from a patient with ANCA vasculitis

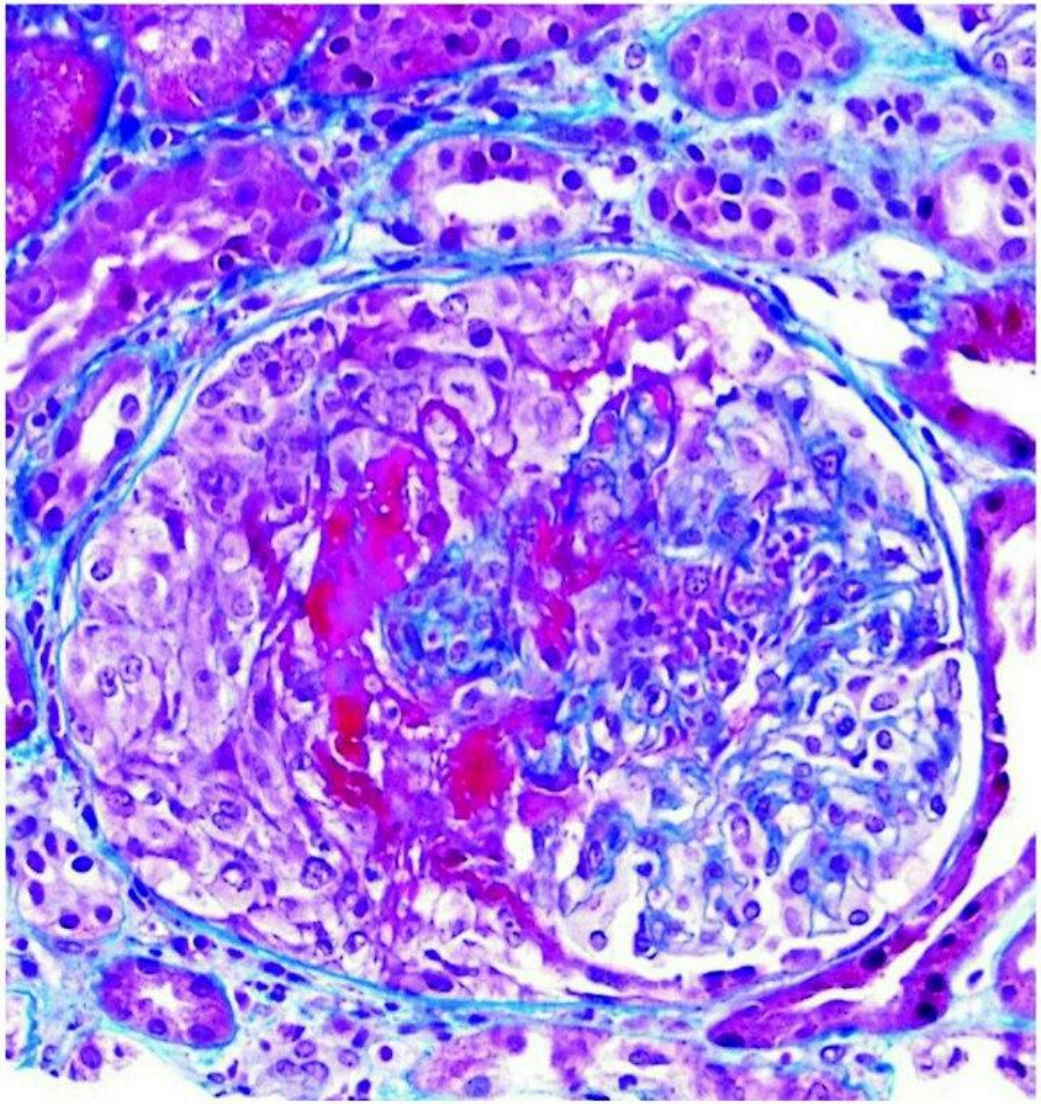


Figure 89-6 Anti-neutrophil cytoplasmic antibody–associated crescentic glomerulonephritis. This Periodic acid–Schiff–stained section demonstrates a glomerulus with a cellular crescent partially obliterating Bowman's space. Because all types of crescentic glomerulonephritis appear similar by light microscopy,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

CLINICAL PEARLS

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.

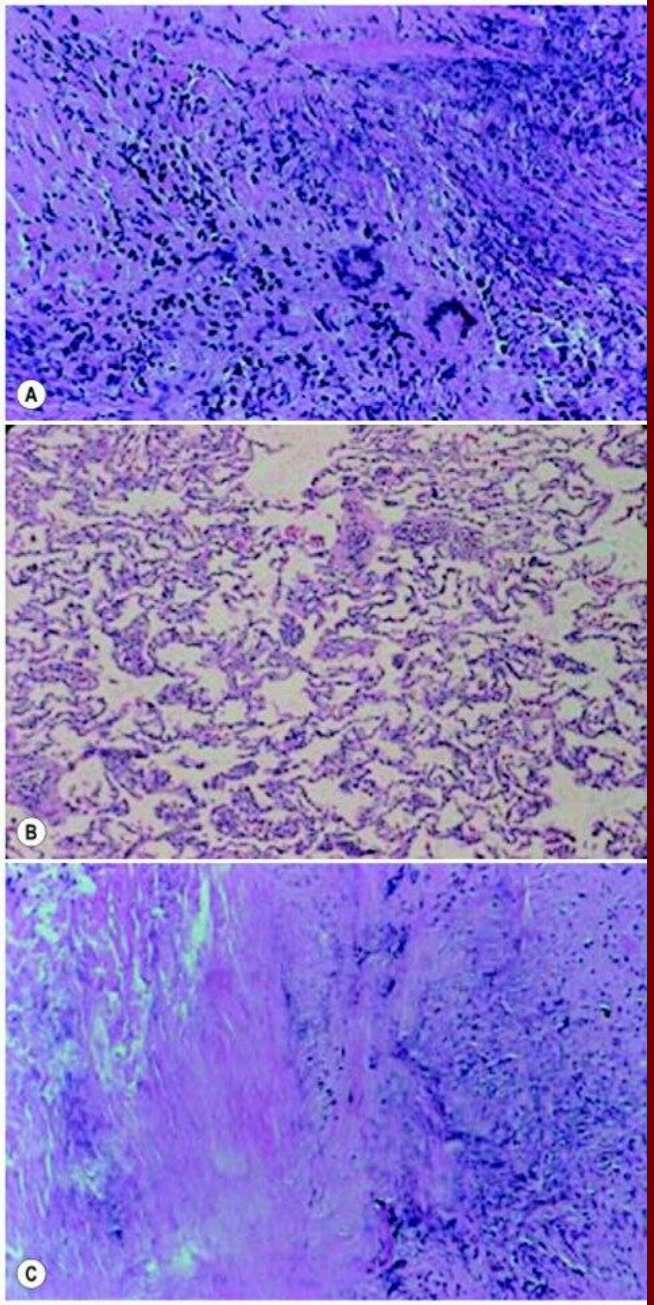


Fig. 57.4 **Histopathology of granulomatosis with polyangiitis (formerly Wegener's granulomatosis).** The pathologic features of granulomatosis with polyangiitis (formerly Wegener's): (A) Langerhans giant cells and palisading granulomatous inflammation; (B) small-vessel vasculitis and fibrinoid necrosis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

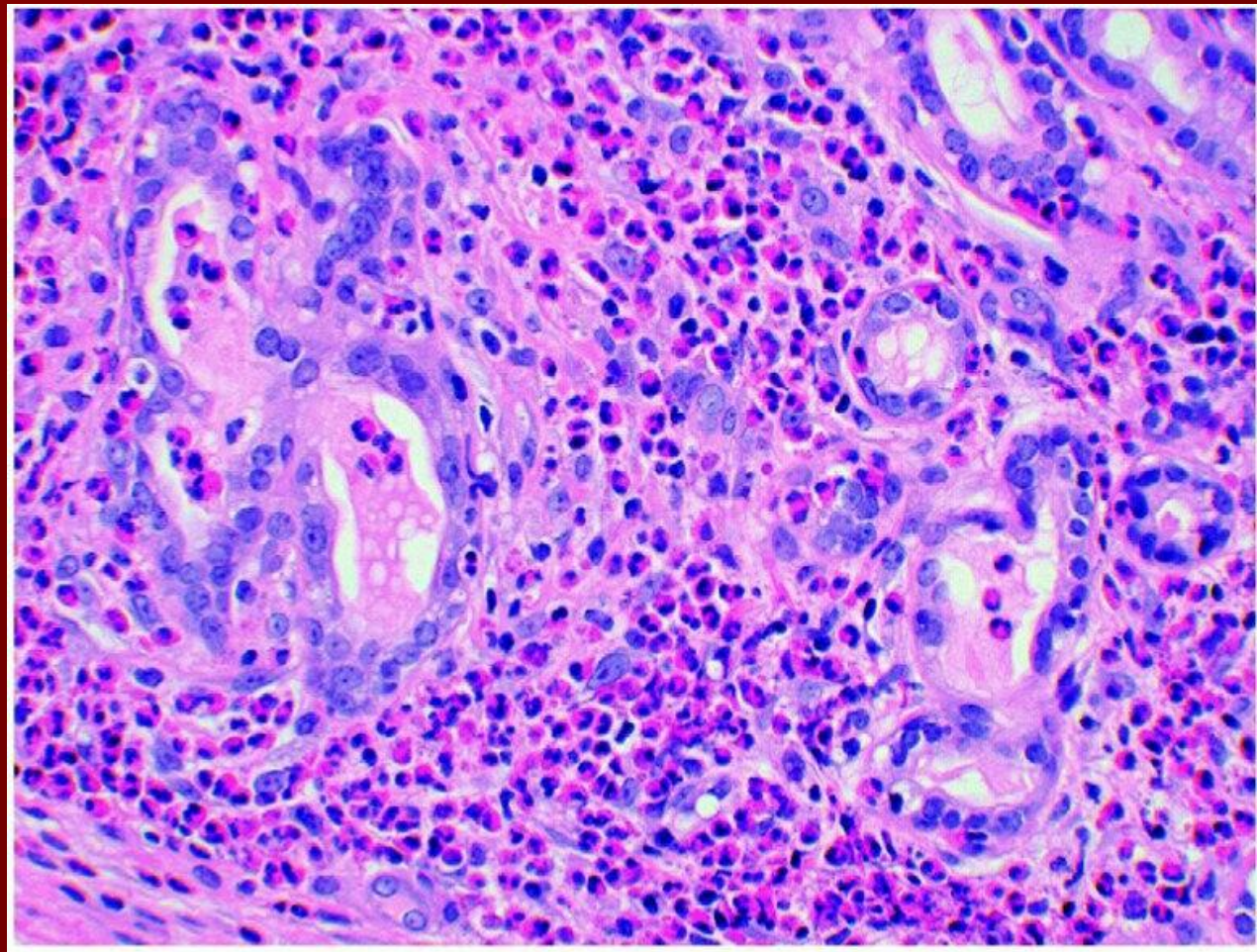


Fig. 57.8 **Eosinophilic infiltration of a salivary gland.**

Клиника

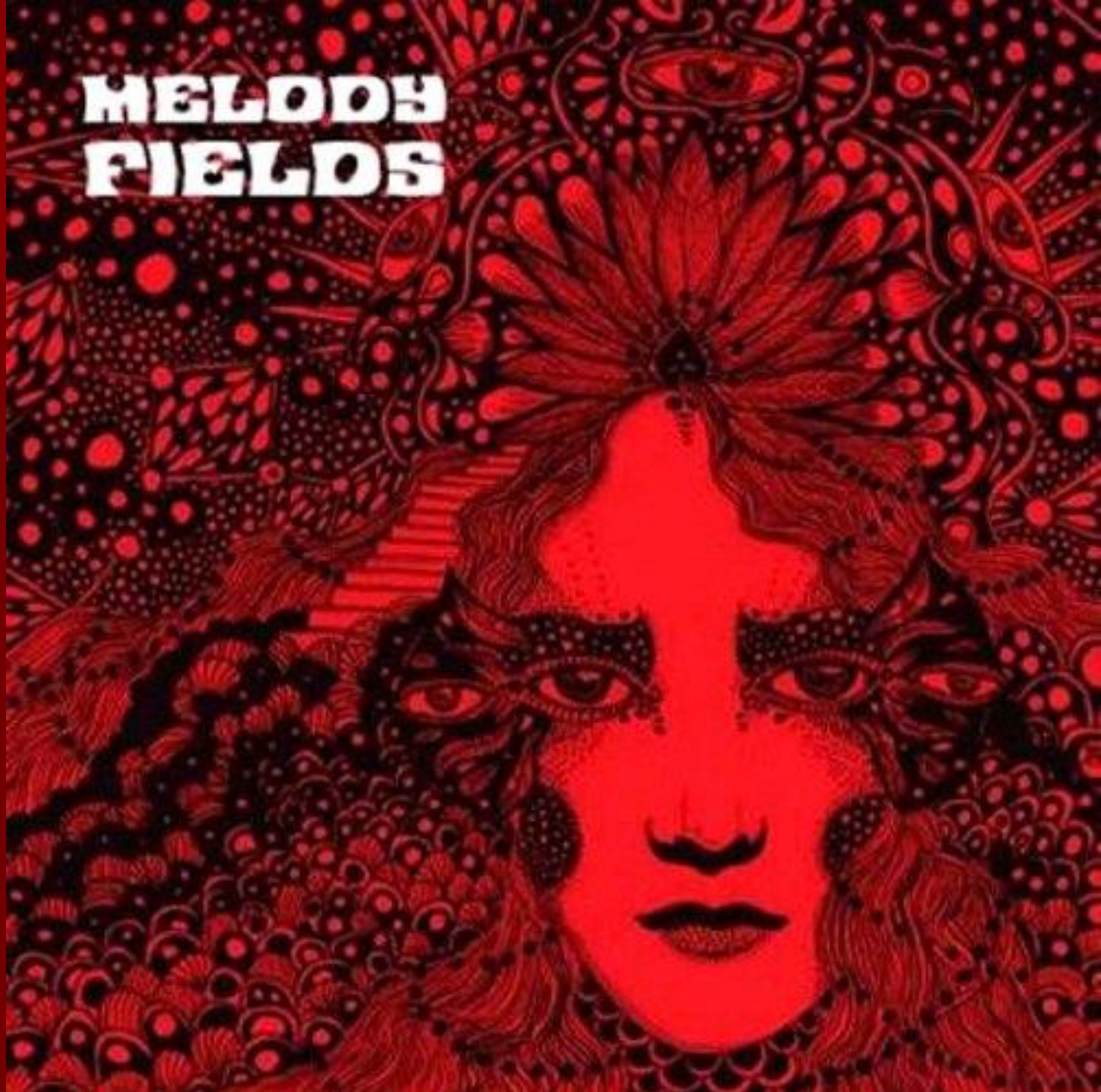


TABLE 89-2 Manifestations Over Time in the Subtypes of ANCA-Associated Vasculitis in the Largest Published Series*

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 POLYANGIITIS (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
Kidney		
Glomerulonephritis	18	77
Ear/Nose/Throat	73	92
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
Lung	45	85
Pulmonary infiltrates	25	66
Pulmonary nodules	24	58
Hemoptysis	12	30
Pleuritis	10	28
Eyes		
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
Other[a]		
Arthralgias/arthritis	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

[a]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

Criterion	Definition
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 1:14(INDIA)	1.2:1 NO MUCH DIFF. FROM WESTRN DATA	OVER ALL UNKNOWN	OVER ALL UNKNOWN 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 AIR WAYS WITH KIDNEY LESIONS	EXTRA VASCULAR GRANULOMA	PULMONARY CAPILLARIES INVOLVED, GNs +NT	PULMONARY ARTERY NOT INVOLVED, ANEURYSMS
LABORATORY FINDINGS	C-ANCA(>90%) FALSE +VE REPORTED	p-ANCA (>48%)	p-ANCA (75%)	HEP B ANTIGENEMIA, 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)

	GPA	MPA	EGPA
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 Saddle-nose deformity Subglottic stenosis	Mild	Nasal polyps Allergic rhinitis
Lung	Nodules Cavitary lesions	Alveolar haemorrhage	Asthma Fleeting infiltrates
Kidney	NCGN, occasional granulomatous features	NCGN	NCGN (severe renal disease unusual)
Distinguishing feature	Destructive upper airway disease	No granulomatous inflammation	Allergy 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

Feature	Microscopic polyangiitis	Classic polyarteritis nodosa
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

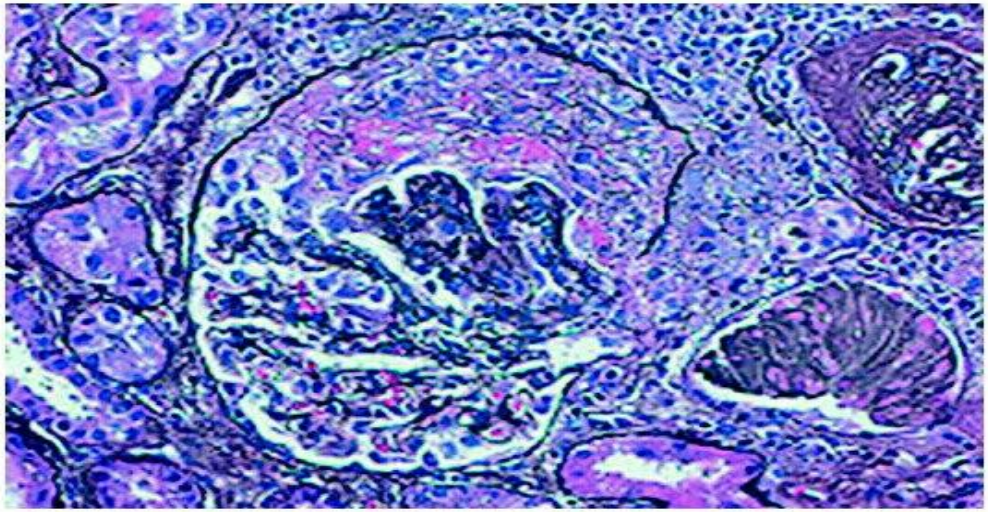


Fig. 57.6 Crescentic glomerulonephritis in microscopic polyangiitis. Glomerular crescent in a patient with rapidly progressive glomerulonephritis secondary to microscopic polyangiitis.

Диагностика

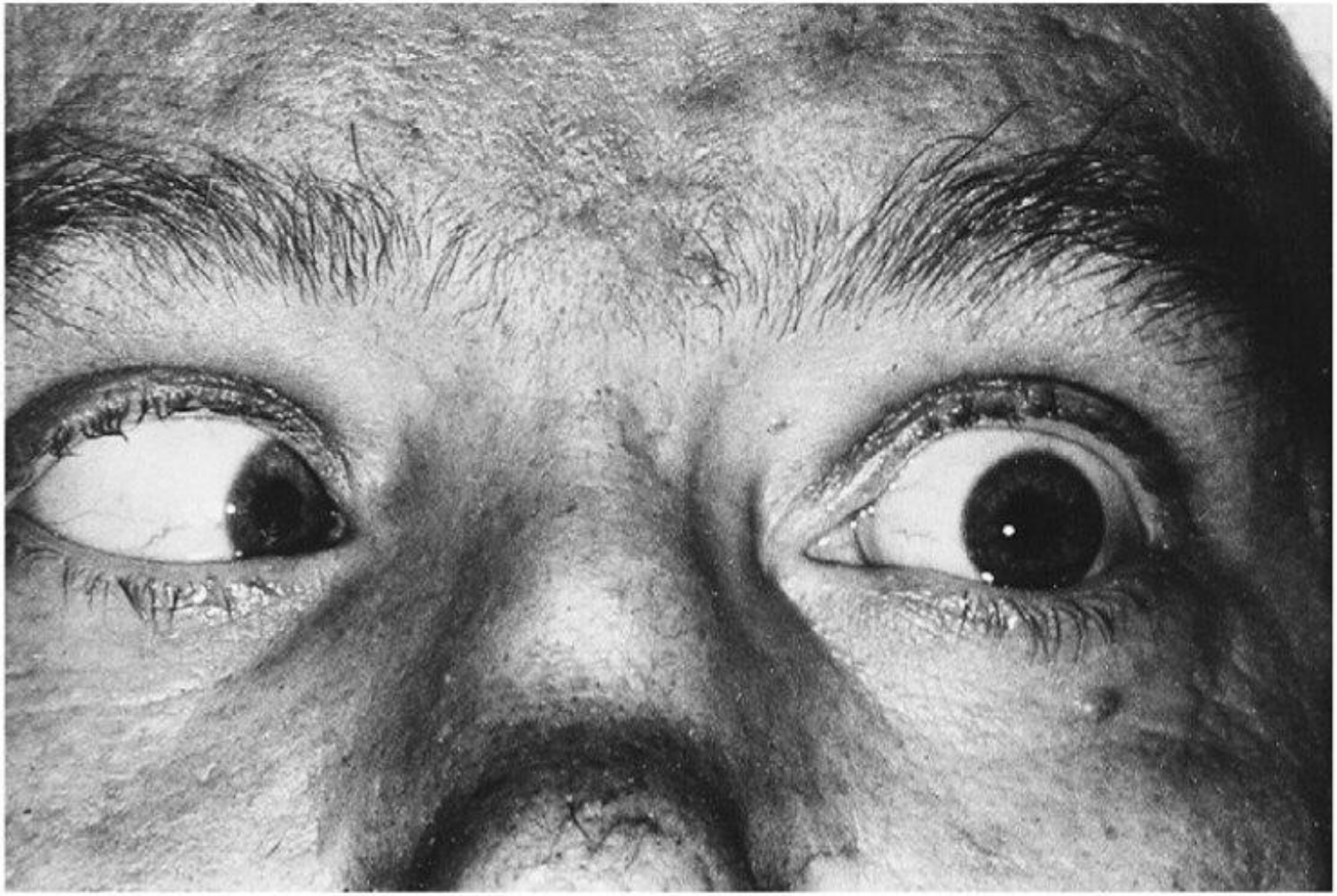


Fig. 57.2 Saddle-nose deformity in granulomatosis with polyangiitis (formerly Wegener's granulomatosis). Saddle-nose deformity and a left sixth cranial nerve lesion (the latter caused by meningeal inflammation) in a patient with granulomatosis with polyangiitis (formerly Wegener's).

(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.)

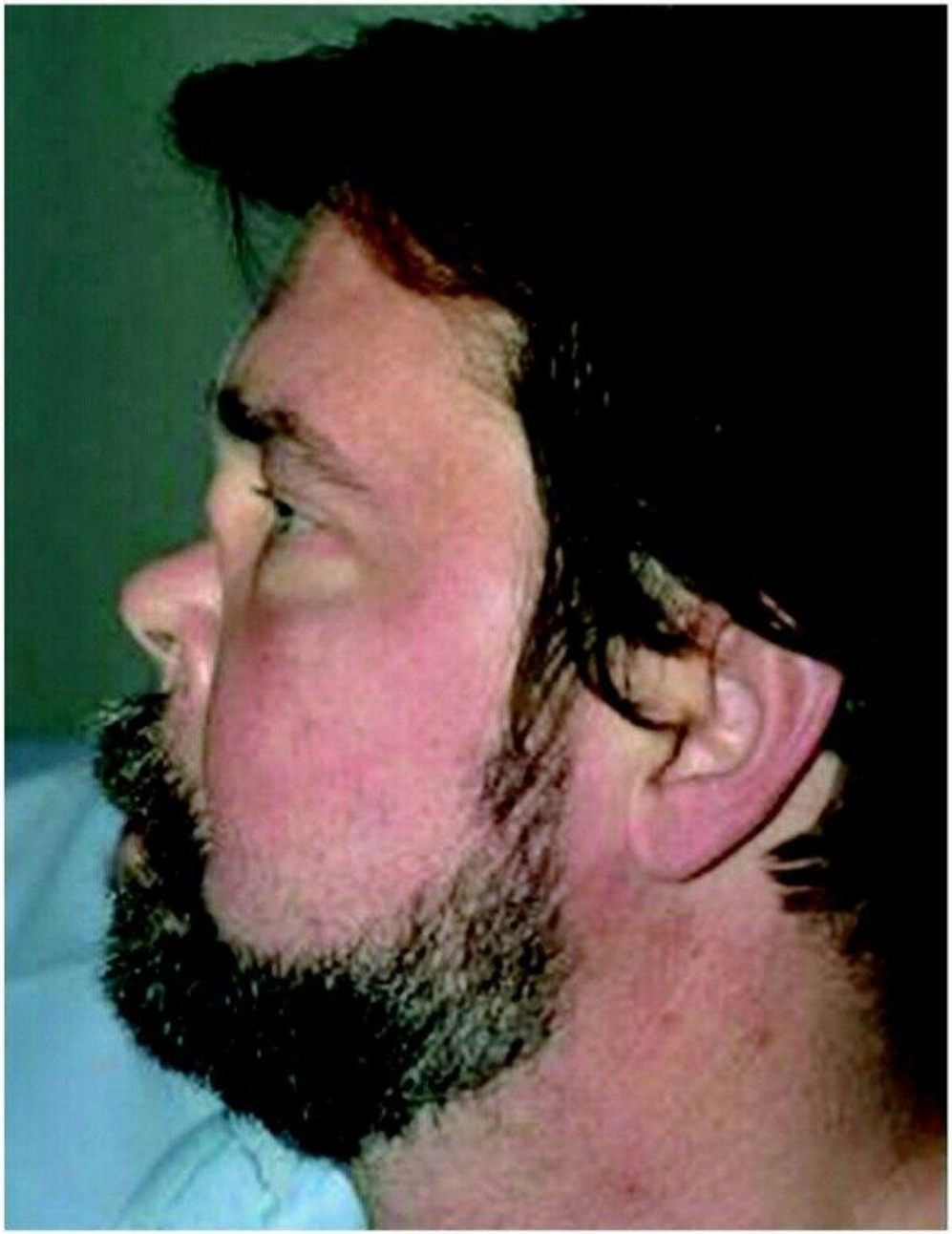


Figure 89-2 Saddle nose deformity in a patient with granulomatosis with polyangiitis. *(Courtesy Dr. G. Hoffman.)*

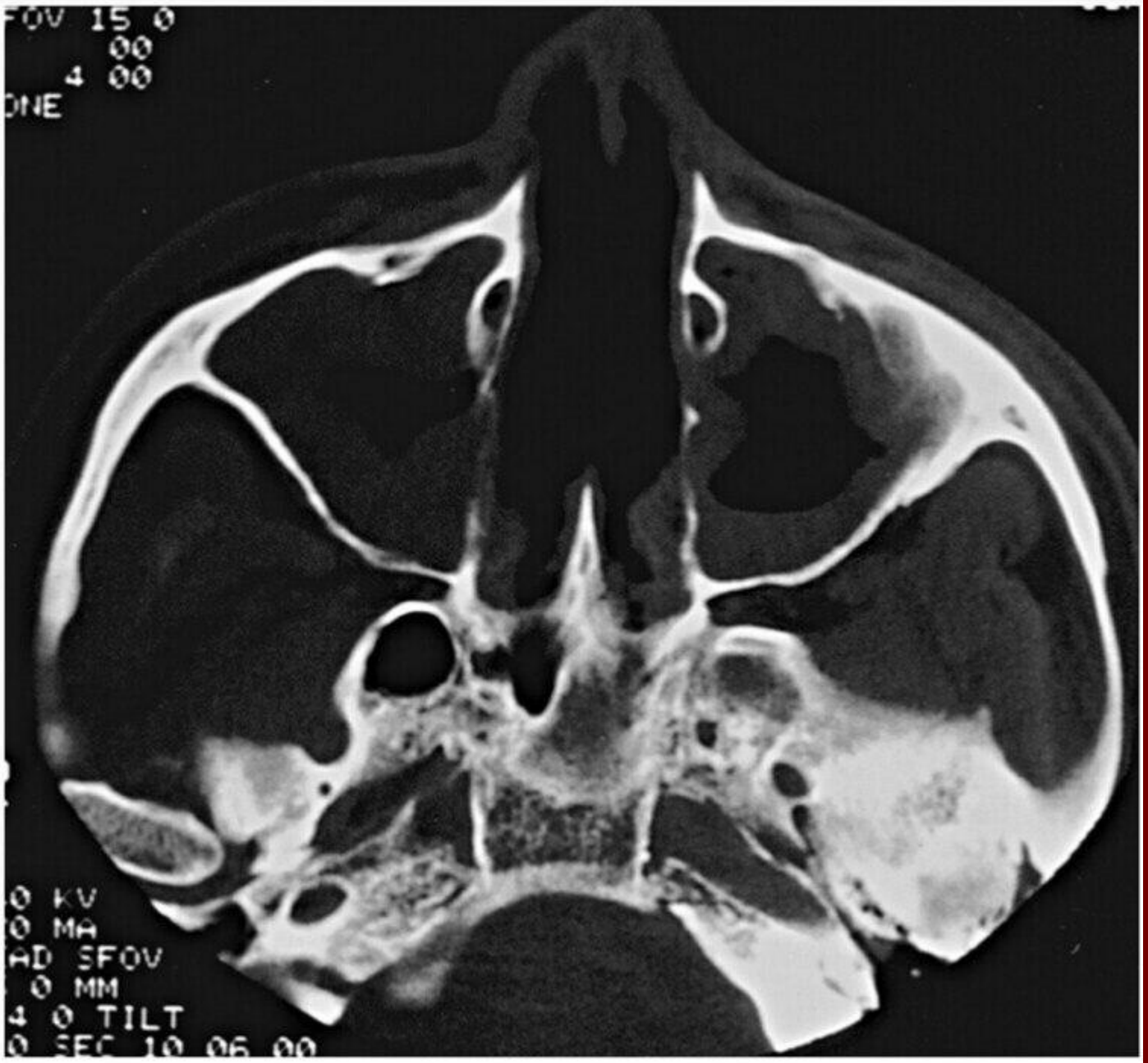
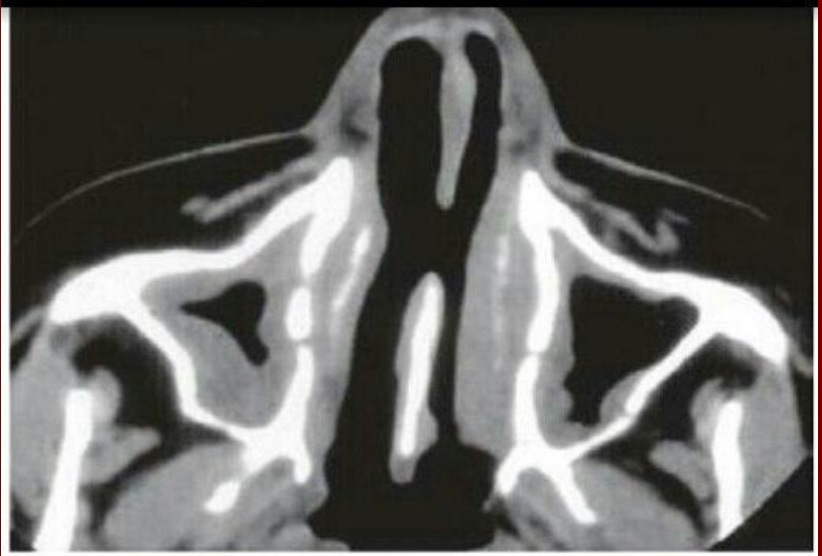
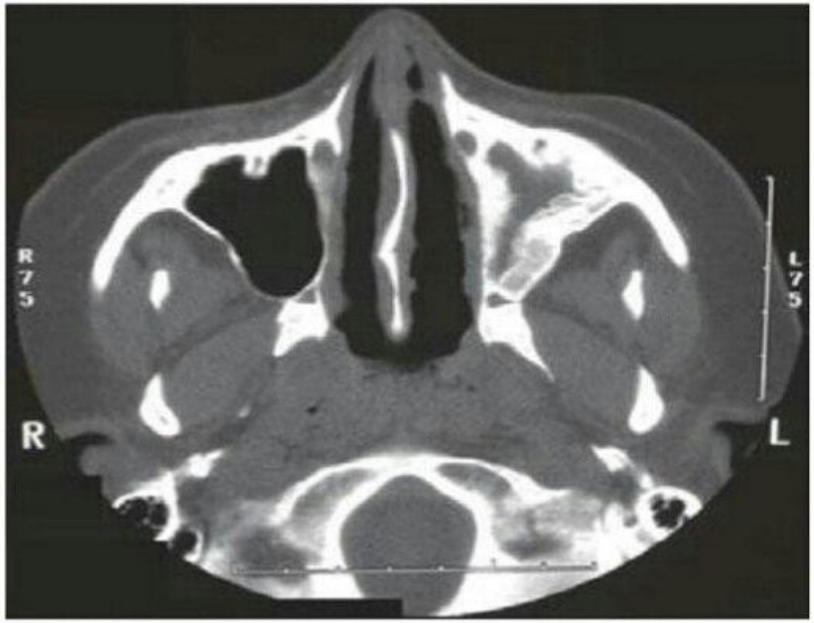


Figure 89-1 Computed tomography scan of the sinuses, showing sinusitis and destruction of the nasal septum.



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.

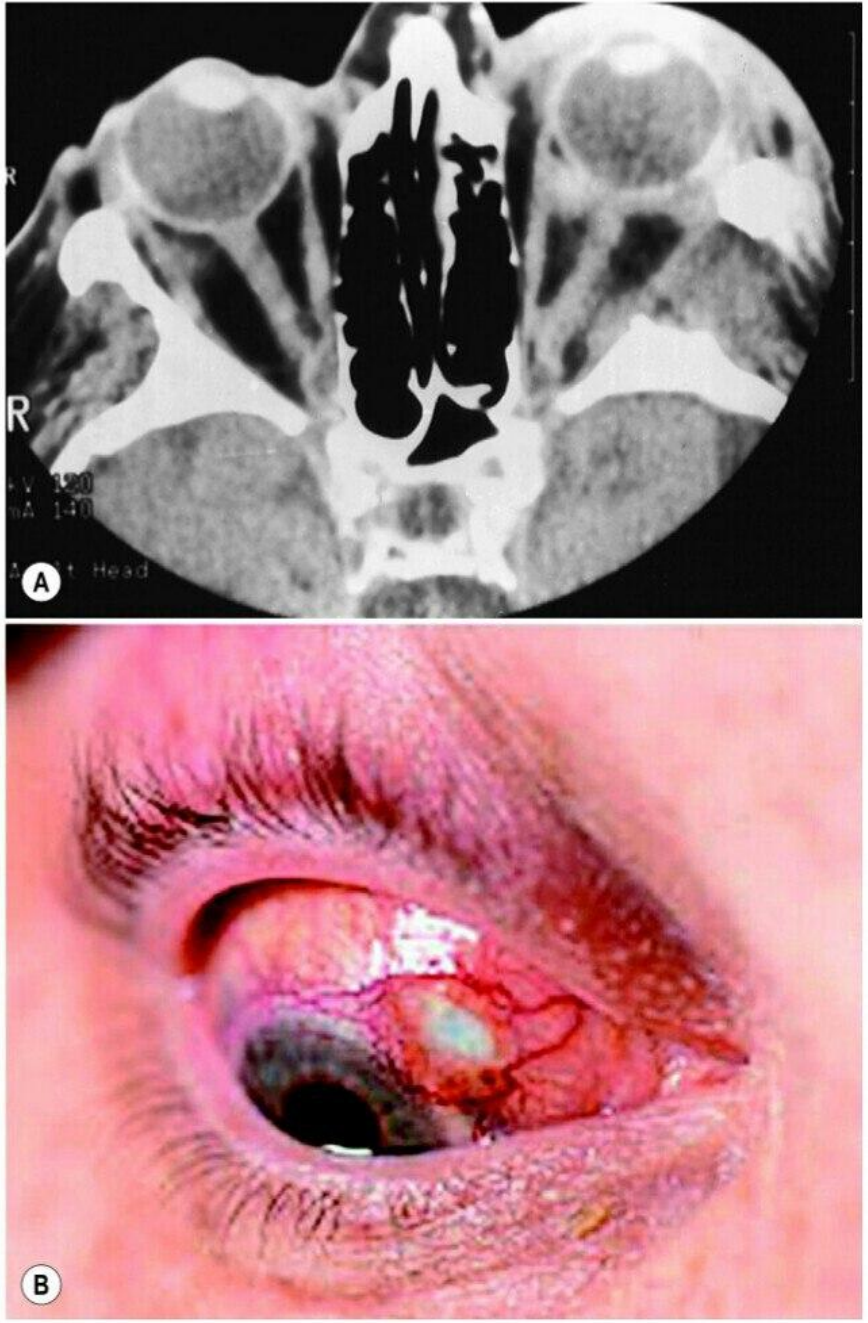


Fig. 57.3 The cardinal ocular manifestations of granulomatosis with polyangiitis (formerly Wegener's granulomatosis). (A) bilateral retro-orbital masses, causing proptosis of the left eye; (B) necrotizing scleritis.

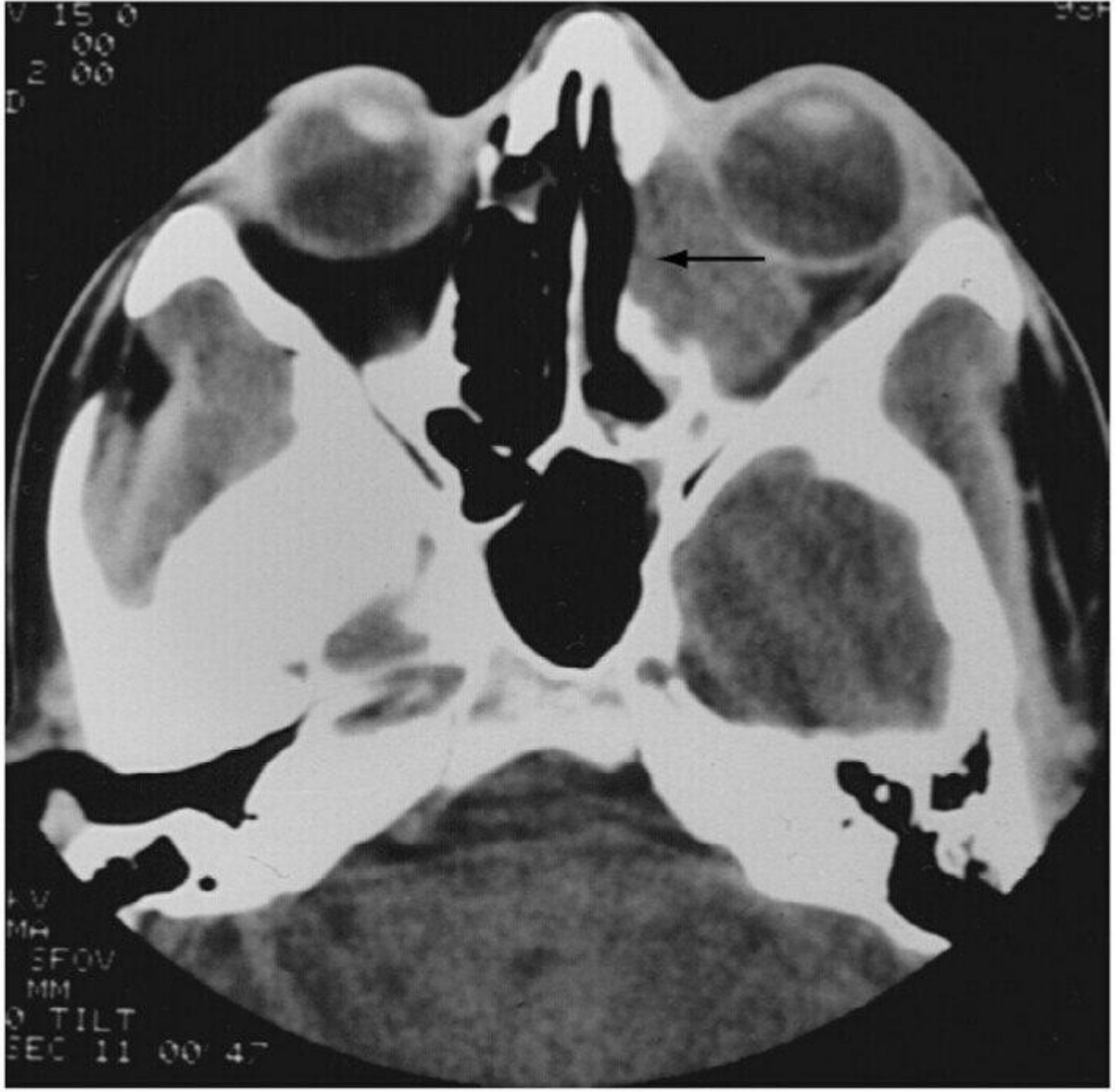


Figure 89-4 Computed tomography scan of the orbits, showing a retro-orbital mass (orbital pseudotumor).

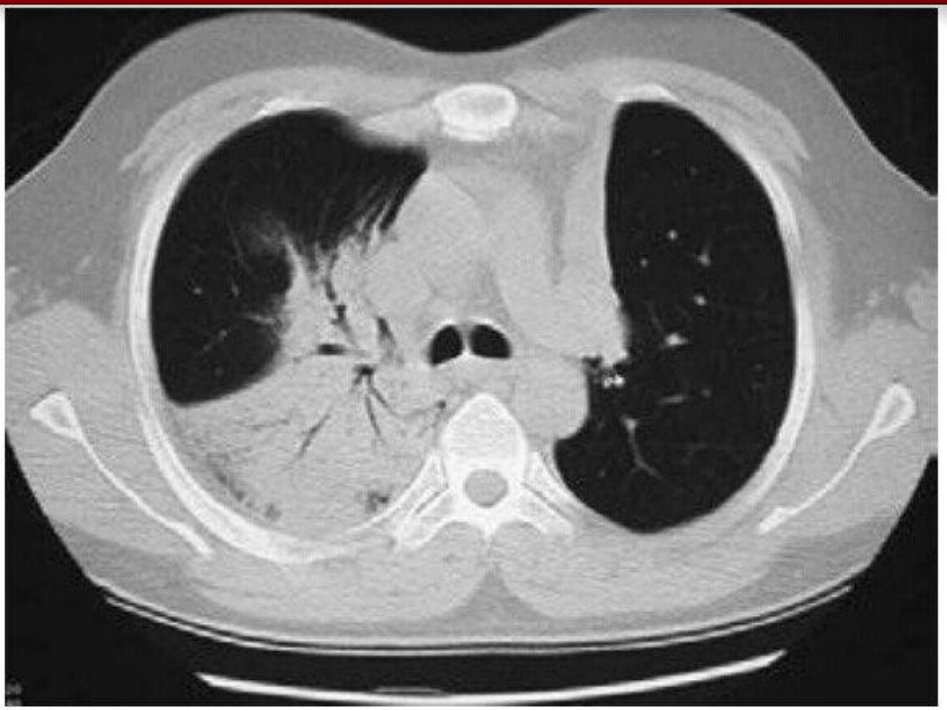


FIGURE 386e-4 **Computed tomography of the chest** demonstrating a dense infiltrate with air bronchograms involving a segment of the right upper lobe due to bacterial pneumonia in an immunosuppressed patient with granulomatosis with polyangiitis (Wegener's). Collapse of the left upper lobe secondary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

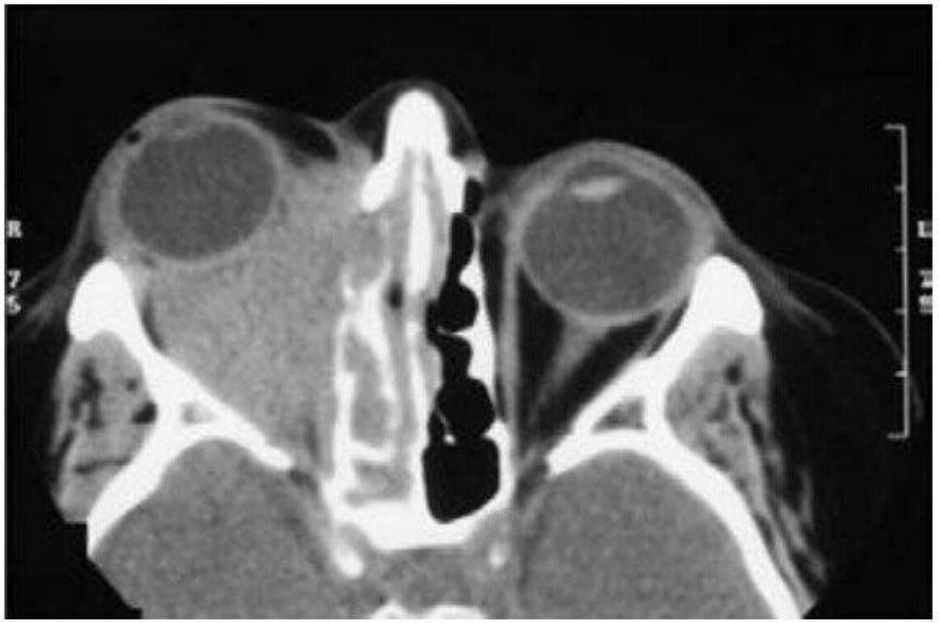
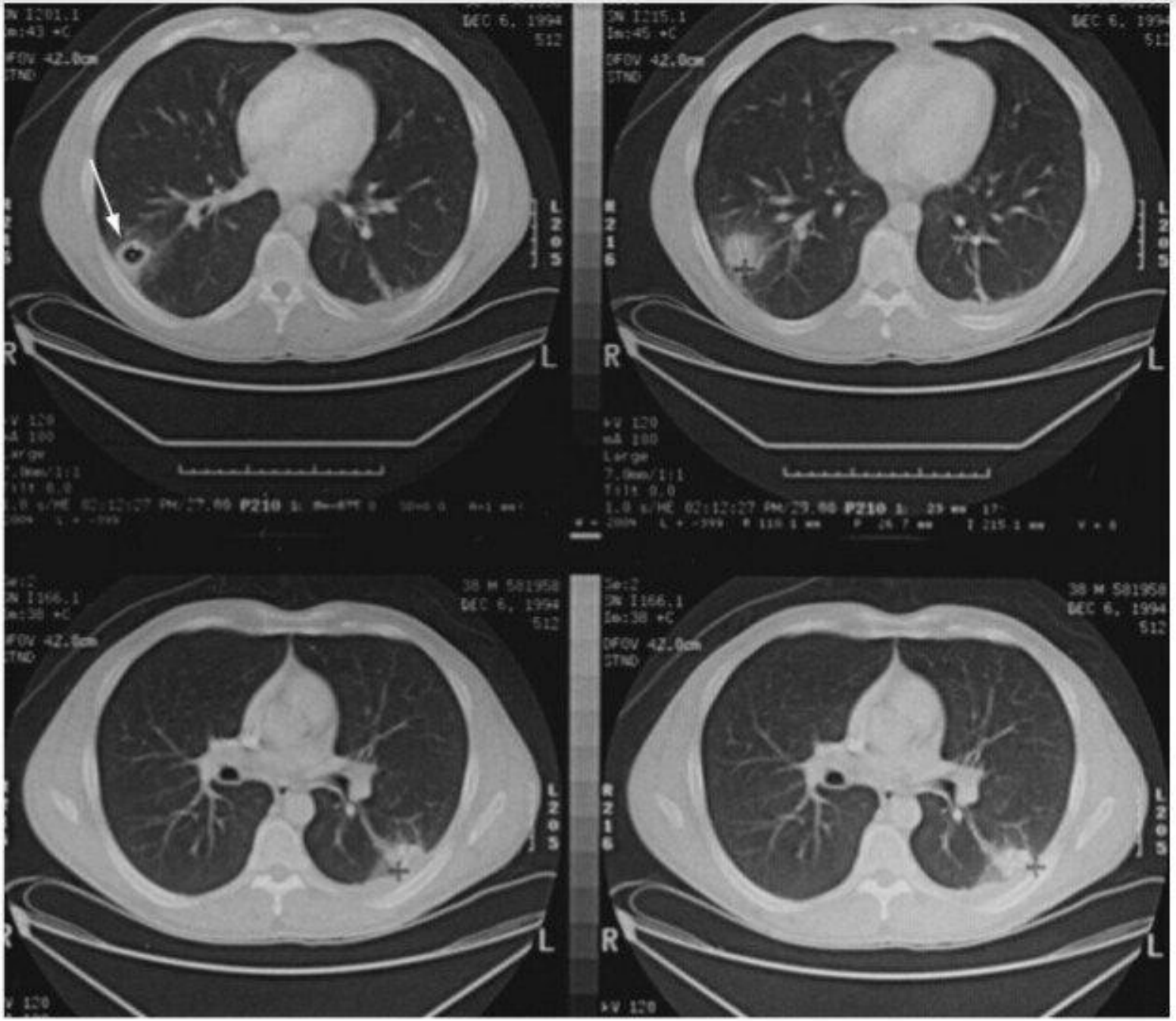


FIGURE 386e-5 **Computed tomography of the orbits** in a patient with granulomatosis with polyangiitis (Wegener's) who presented with right-eye proptosis. The image demonstrates inflammatory tissue extending from the ethmoid sinus through the lamina papyracea and filling the orbital space.



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

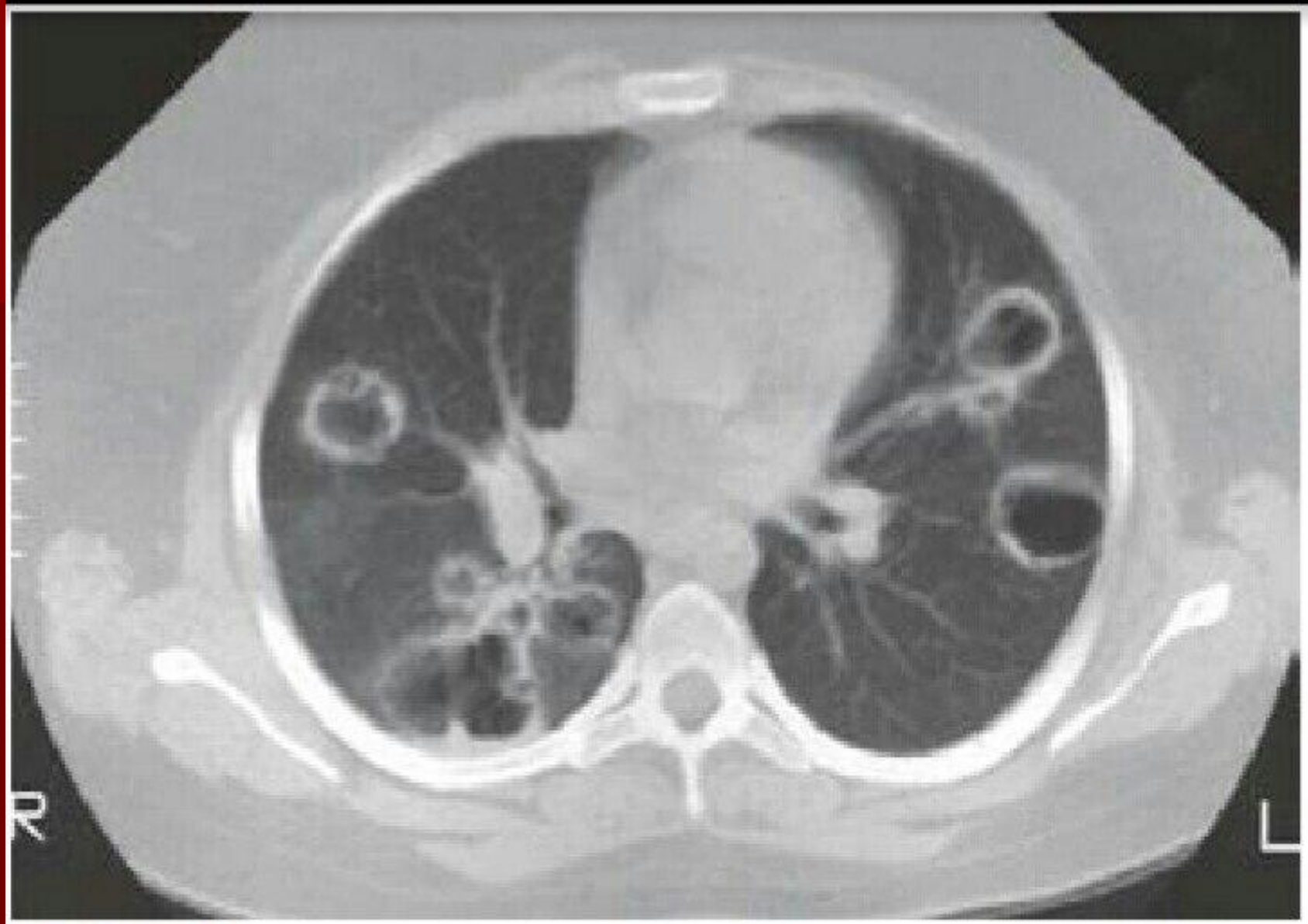


FIGURE 385-3 Computed tomography scan of a patient with granulomatosis with polyangiitis (Wegener's). The patient developed multiple, bilateral, and cavitary infiltrates.

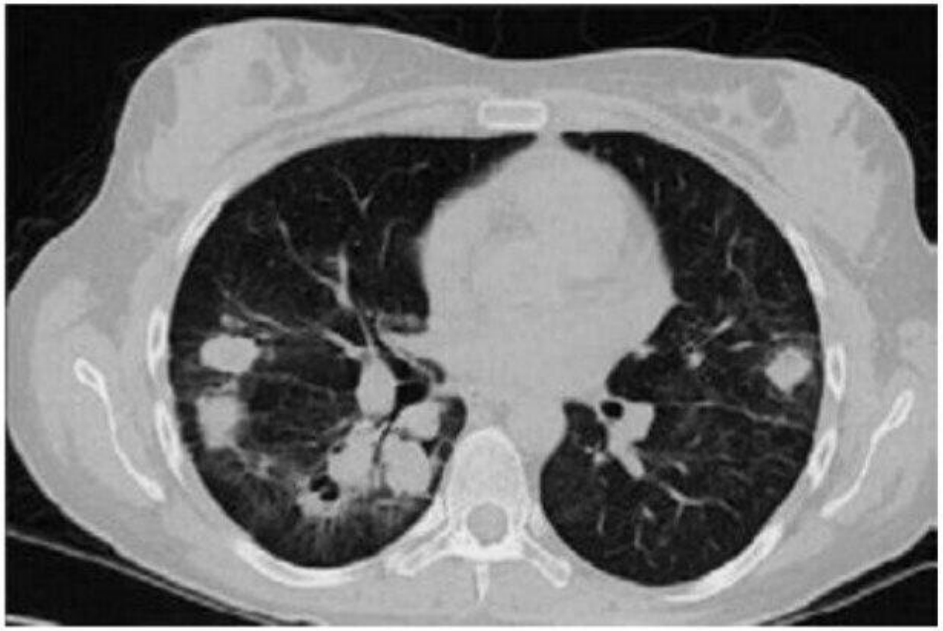
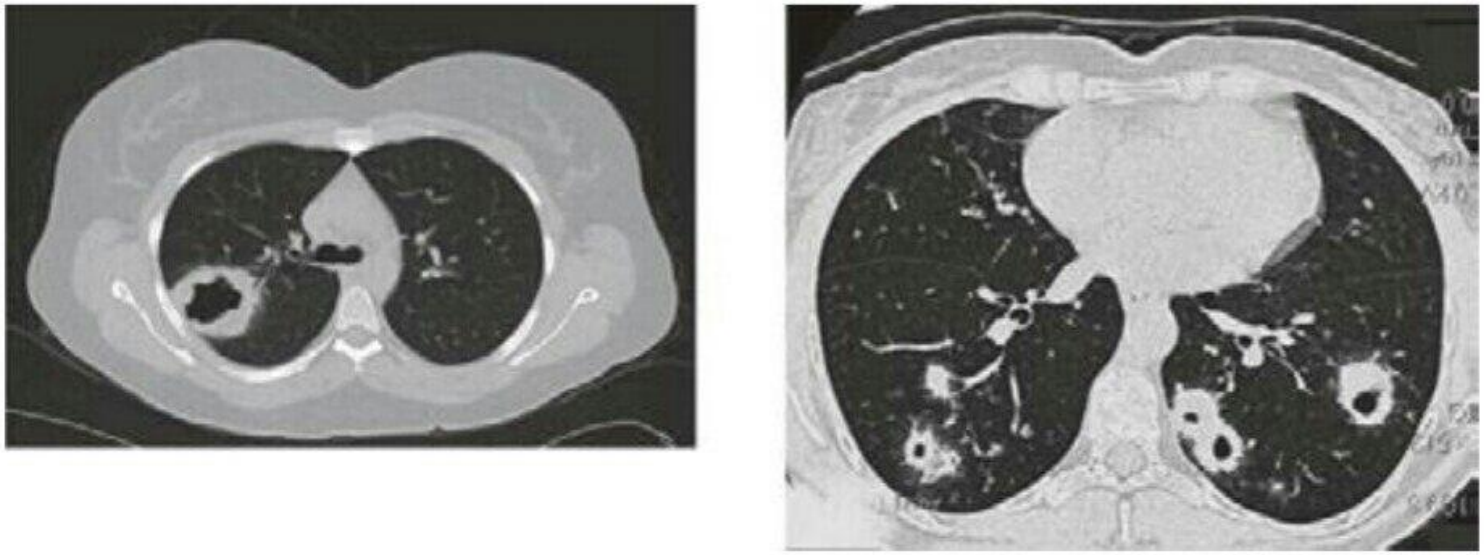
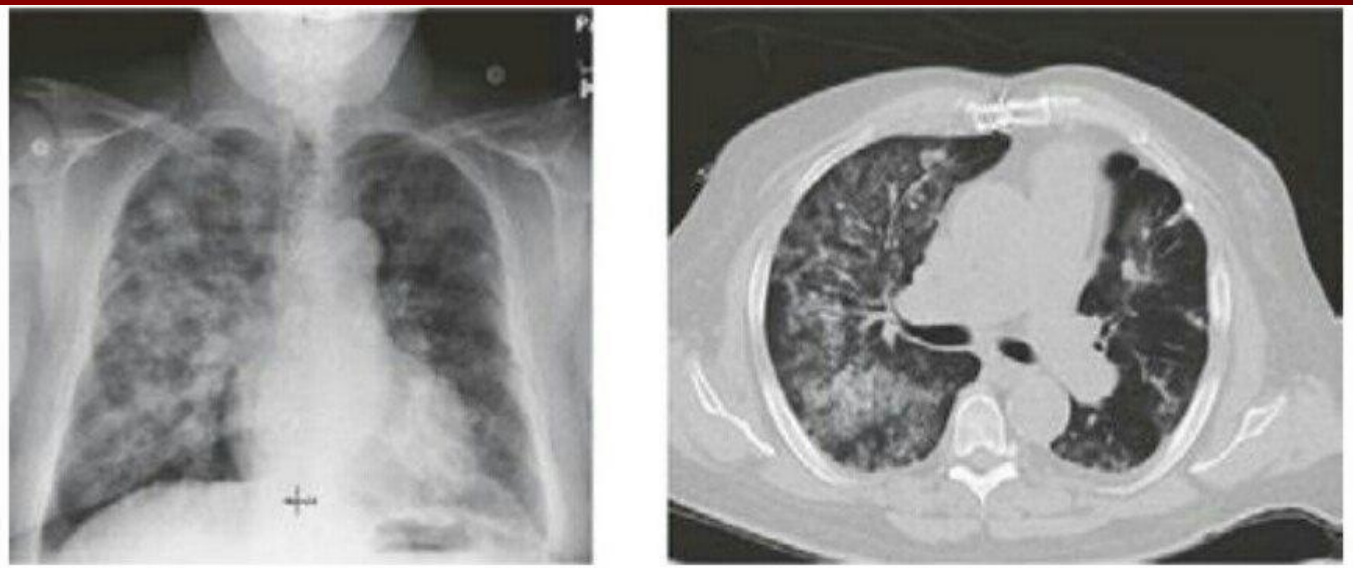


FIGURE 386e-1 Bilateral nodular infiltrates seen on computed tomography of the chest in a 40-year-old woman with granulomatosis with polyangiitis (Wegener's).



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.

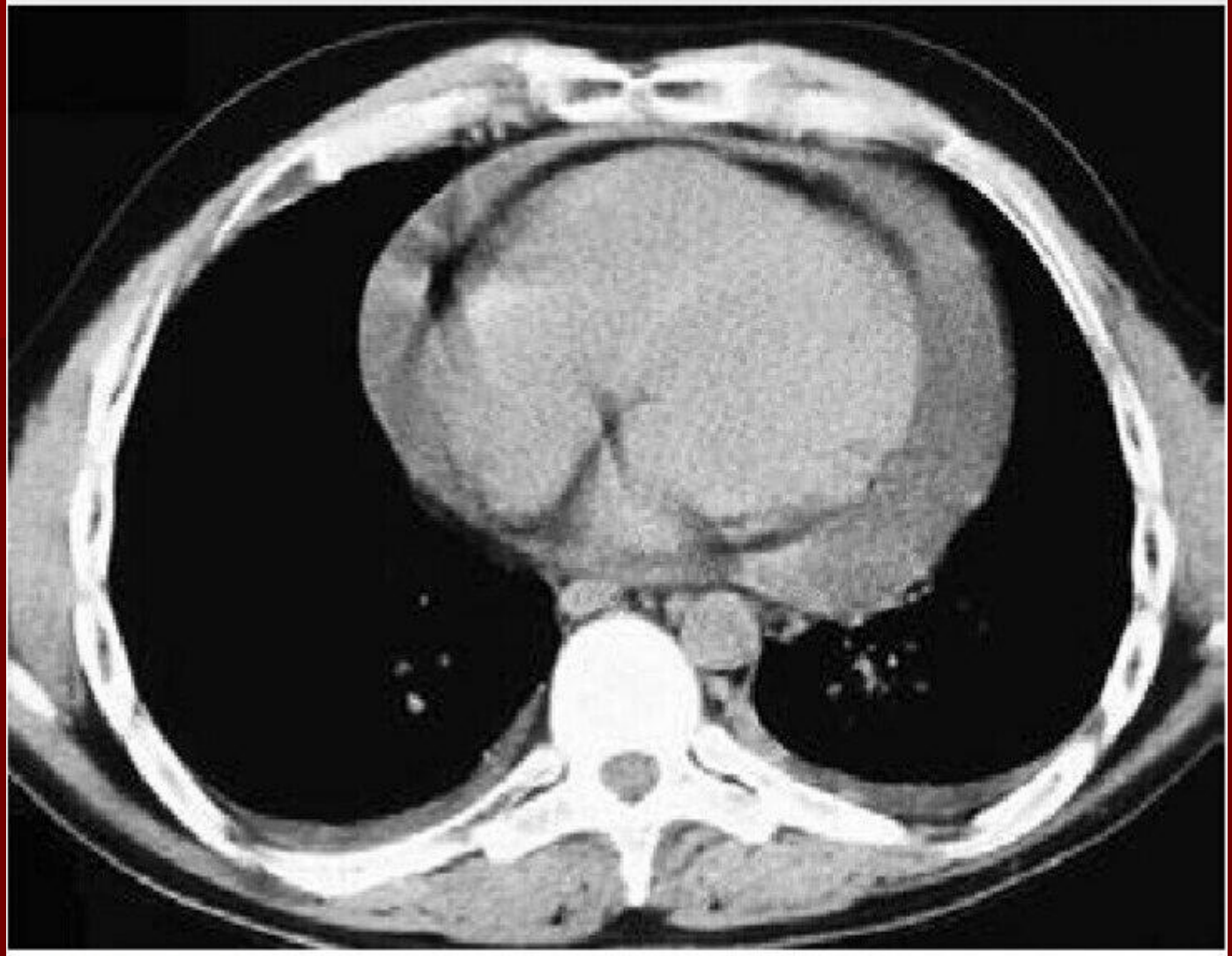


FIGURE 386e-7 Computed tomography of the chest demonstrating a large pericardial effusion in a patient with eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Cardiac involvement is an important cause of morbidity and mortality in eosinophilic granulomatosis with polyangiitis and can include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

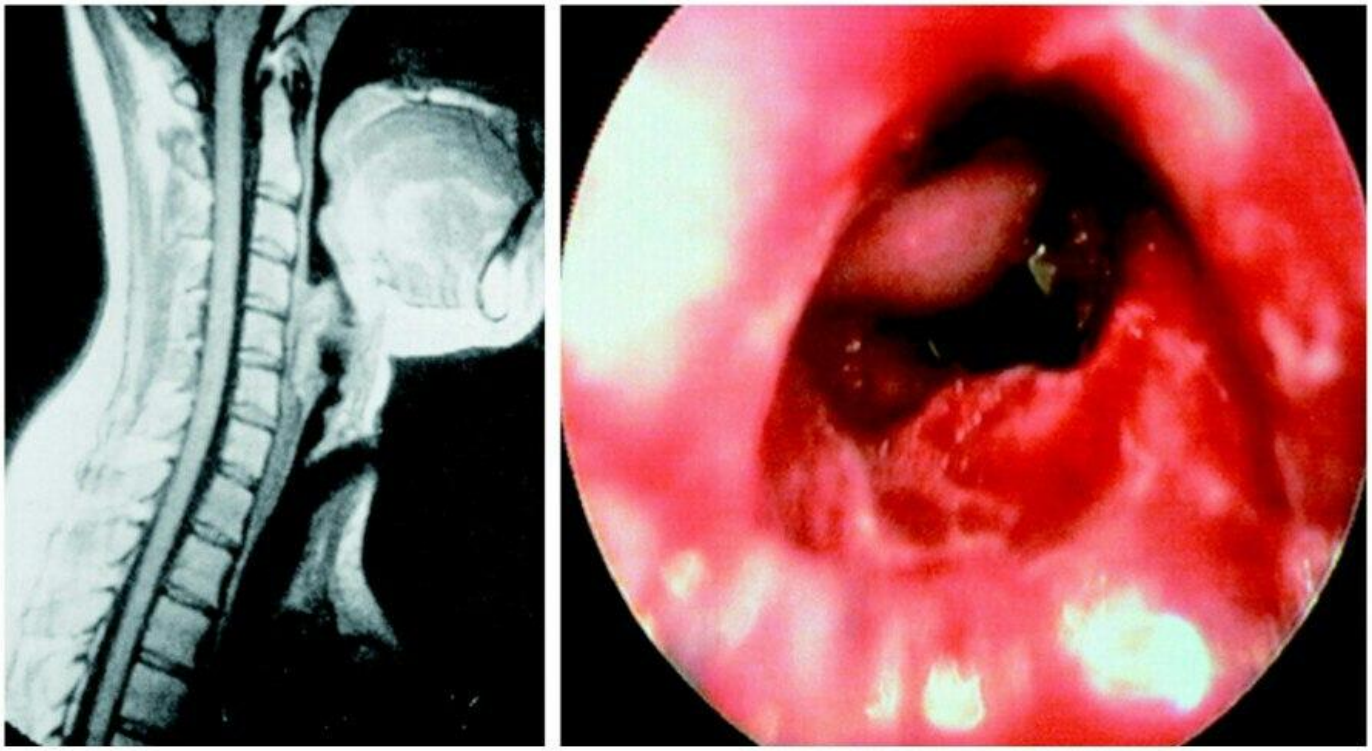


Figure 89-3 Subglottic stenosis in a patient with granulomatosis with polyangiitis. MRI *(left)* and endoscopic view *(right)*. *(Courtesy Dr. G. Hoffman. From Hoffman GS, Kerr GS, Leavitt RY, et al: Wegener granulomatosis: an analysis of 158 patients.* Ann Intern Med *116:488–498, 1992.)*

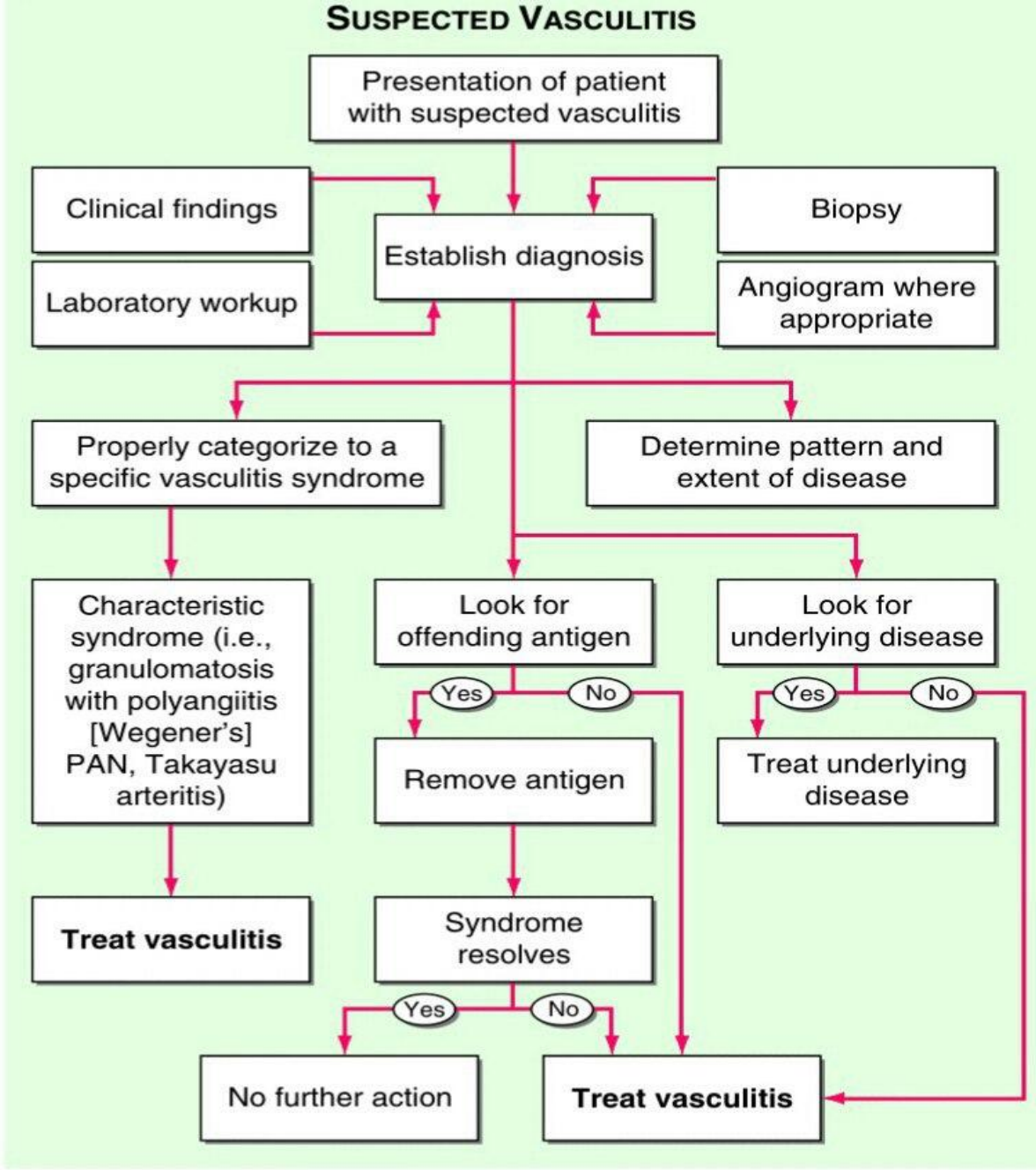


FIGURE 385-1 Algorithm for the approach to a patient with suspected diagnosis of vasculitis. PAN, polyarteritis nodosa.

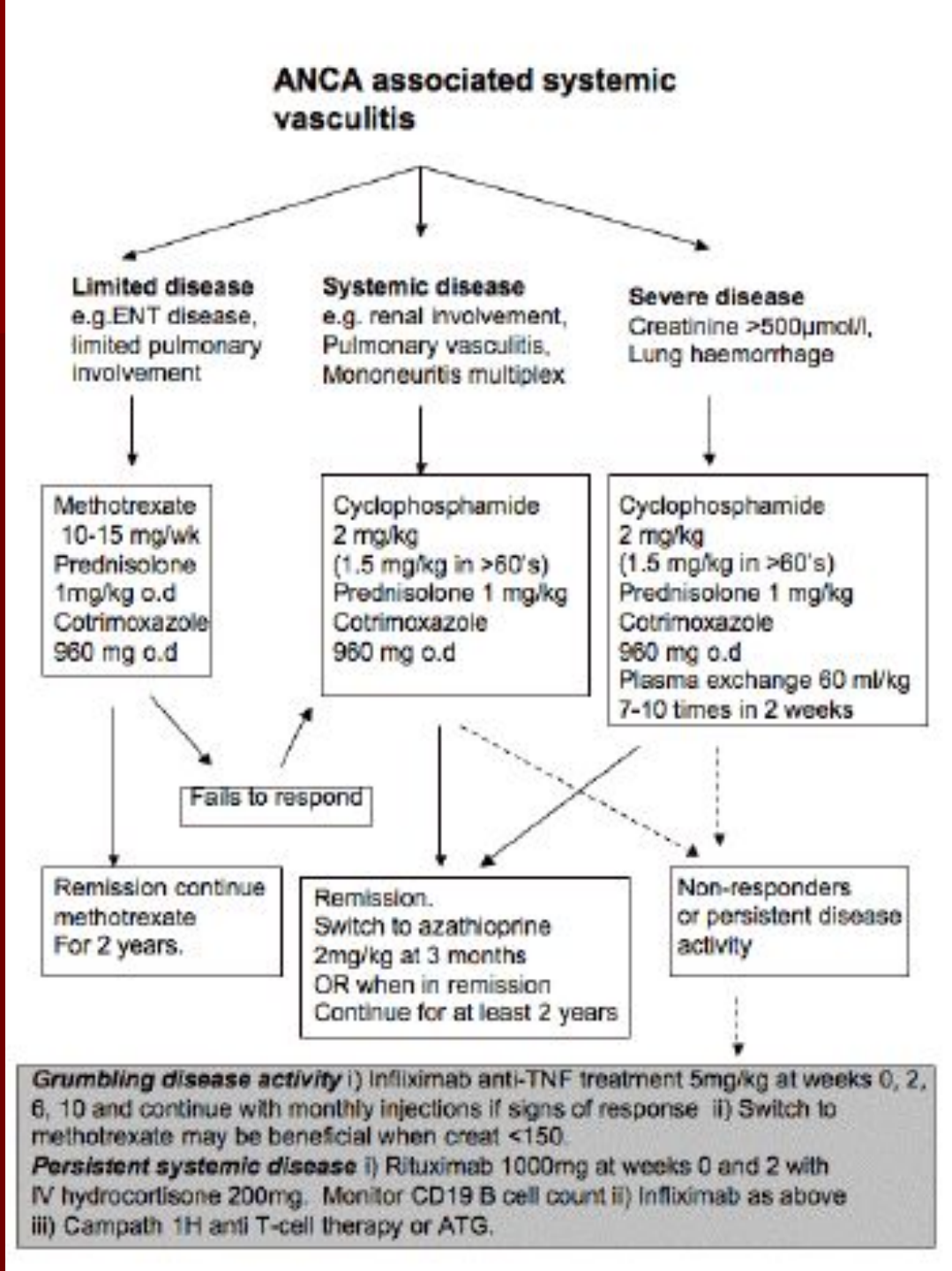
Терапия

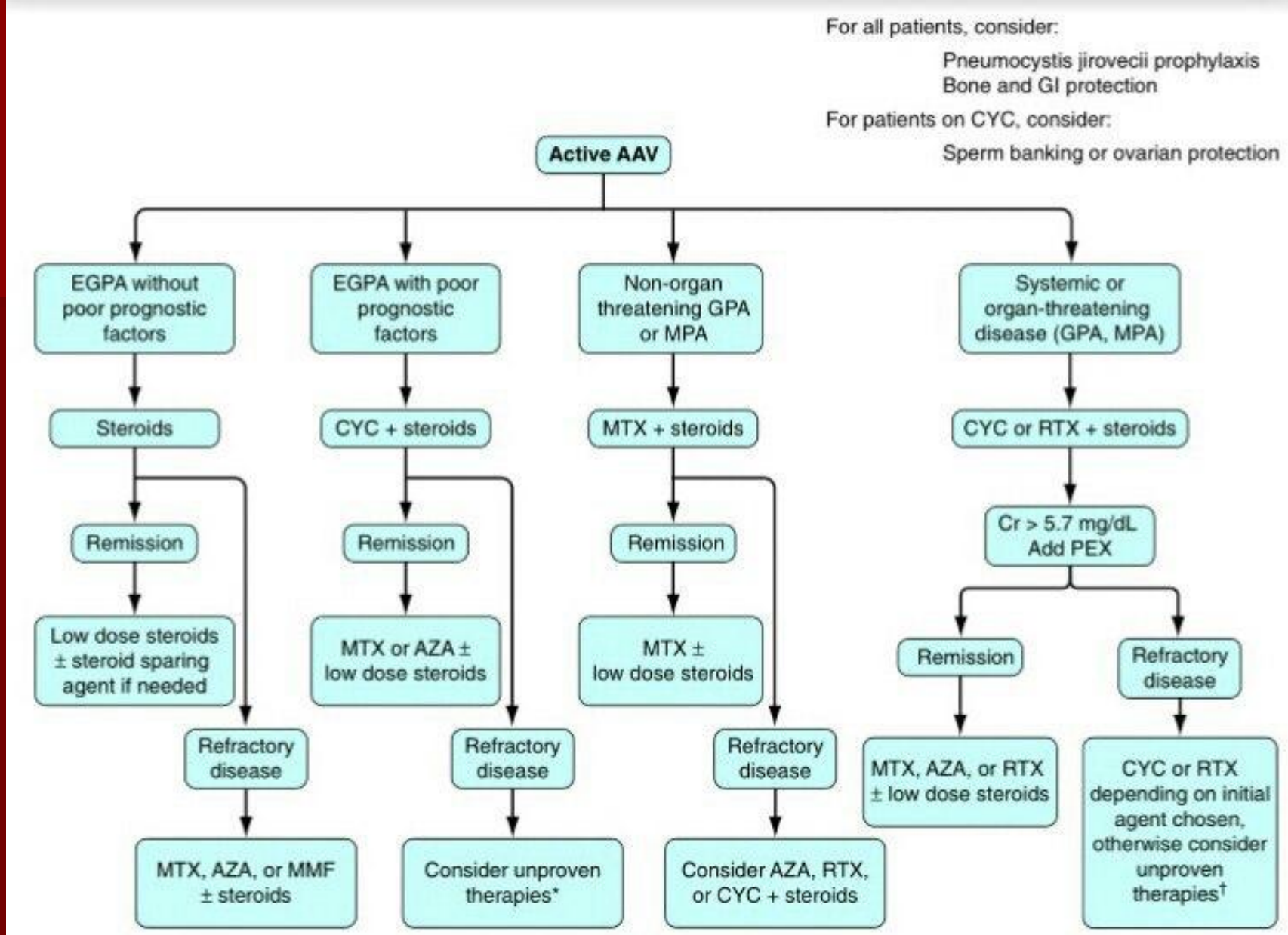
Treatment of ANCA-associated vasculitides

- 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 immunusuppressive 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[54]	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[55]	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[56]	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[58]	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
RITAZAREM[62]	160 patients with relapsing AAV	Rituximab vs. AZA after achieving remission with Rituximab and steroids	Rate of relapse	Currently in recruiting phase
BREVAS[66] NCT01663623	400 patients with AAV following standard therapy	Belimumab plus Azathioprine vs Placebo plus Azathioprine	Time to First Relapse	Currently in Recruitment phase
ABROGATE[67] NCT02108860	150 patients with AAV following standard therapy	Abatacept vs plaacebo	Treatment failure after 12 months	Recruitment phase
TAPIR[64]	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
Limited disease
e.g.ENT disease, limited pulmonary involvement
Systemic disease
e.g. renal involvement, Pulmonary vasculitis, Mononeuritis multiplex
Severe disease
Creatinine >500µmol/l, Lung haemorrhage
Methotrexate 10-15 mg/wk
Prednisolone 1mg/kg o.d
Cotrimoxazole 960 mg o.d
Cyclophosphamide 2 mg/kg
(1.5 mg/kg in >60's)
Prednisolone 1 mg/kg
Cotrimoxazole 960 mg o.d
Cyclophosphamide 2 mg/kg
(1.5 mg/kg in >60's)
Prednisolone 1 mg/kg
Cotrimoxazole 960 mg o.d
Plasma exchange 60 ml/kg 7-10 times in 2 weeks
Fails to respond
Remission continue methotrexate For 2 years.
Remission.
Switch to azathioprine 2mg/kg at 3 months
OR when in remission
Continue for at least 2 years
Non-responders or persistent disease activity
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.



*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.

TABLE 385-4 MAJOR TOXIC SIDE EFFECTS OF DRUGS USED IN THE TREATMENT OF SYSTEMIC VASCULITIS

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
	Peptic ulcer diathesis
	Pancreatitis
Cushingoid features	
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 leuko-encephalopathy	Hepatitis B reactivation
	Tumor lysis syndrome
Mucocutaneous reactions	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