Vasculitis

An approach to diagnosis

Vasculitis

- Heterogeneous disorders that are linked by the common finding of destructive inflammation within the walls of blood vessels.

- Current nomenclature and classification schemes recognize nearly 30 primary forms of vasculitis and several major categories of secondary vasculitis (e.g., other rheumatologic diseases, malignancy, and infection;

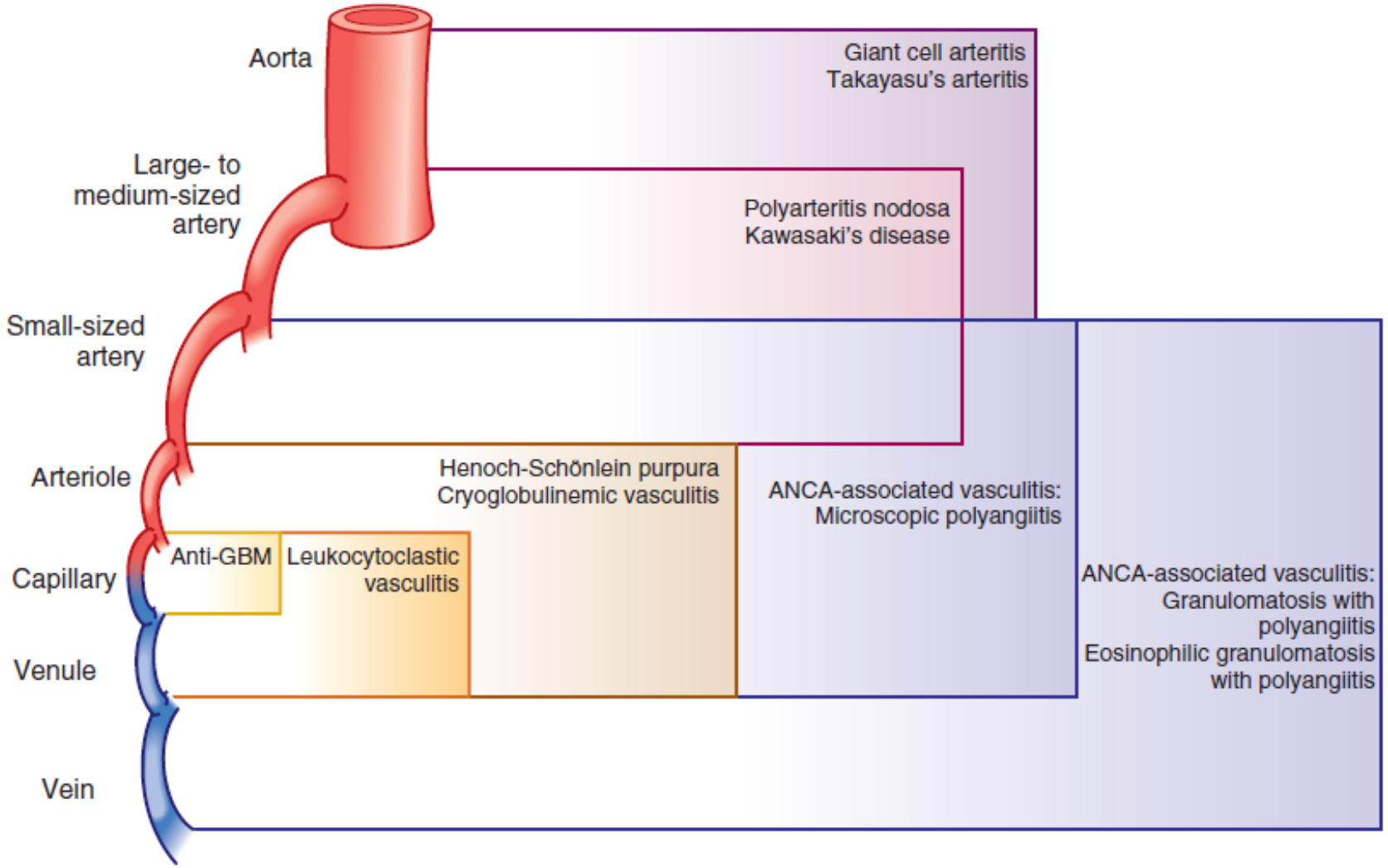


Figure 87-1 Classification by blood vessel size. ANCA, Anti-neutrophil cytoplasmic antibody; GBM, glomerular basement membrane.

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

ANCA, Anti-neutrophil cytoplasmic antibody.

Table 1 Secondary Causes for Vasculitis (The List Includes Most of the Disorders; However, It Is Not a Complete List)

- Infectious etiology
  - Virus
    - Hepatitis B and C
    - Human immunodeficiency virus
    - Parvovirus B19
    - Cytomegalovirus
    - Herpes simplex virus
    - Varicella zoster
  - Bacteria
    - Salmonella
    - Streptococcus
    - Staphylococcus
    - Clostridium septicum
    - Chlamydia pneumoniae
    - Mycobacterium tuberculosis
    - Treponema pallidum
    - Borrelia burgdorferi
    - Mycoplasma
    - Cryptococcus
    - Neisseria
    - Coccidioides
- Connective tissue disorders
  - Relapsing Polychondritis
  - Cogan Syndrome
  - Rheumatoid arthritis
  - Sjögren syndrome
  - Systemic lupus erythematosus
  - Scleroderma
- Drugs
  - D-Penicillamine
  - Penicillin
  - Propylthiouracil
  - Hydralazine
  - Minocycline
  - Cocaine
  - Leukotriene inhibitors (association with Churg-Strauss remains controversial)
  - Sulfasalazine
  - Ciprofloxacin
  - Pantoprazole
  - Phenytoin
  - Allopurinol
  - Sulfonamides
  - Thiazides
- Neoplasia
  - Hematologic malignancies (myeloproliferative and lymphoproliferative disorders)
  - Solid organ tumors including lung, colon, and GI carcinomas

Table 4 Conditions Mimicking Vasculitis (The List Includes Most of the Disorders; However, It Is Not a Complete List)

Conditions mimicking large vessel vasculitis
Inherited genetic disorders: Marfan syndrome, Ehlers-Danlos syndrome type IV, Loeys-Dietz syndrome, neurofibromatosis, and pseudoxanthoma elasticum
Radiation-induced arteritis
Inflammatory aortic aneurysm
Atherosclerosis
Conditions mimicking medium and small vessel vasculitis
Anti–phospholipid antibody syndrome
Thrombotic thrombocytopenic purpura
Inherited genetic disorders similar to large vessel vasculitis
Fibromuscular dysplasia
Segmental arterial mediolysis
Atherosclerosis
Cholesterol embolization syndrome
Vasospastic disease
Atrial myxoma
Infective endocarditis
Vasoconstrictive drugs, for example, ergot poisoning and methysergide
Calciphylaxis
Sickle cell disease
Amyloidosis
Moyamoya

Classification of vasculitis by size

- *Large arteries:* the aorta and its major branches
- *Medium* refers to vessels that are smaller than the major aortic branches yet still large enough to contain four elements: (1) an intima, (2) a continuous internal elastic lamina, (3) a muscular media, and (4) an adventitia.
- A large artery becomes a medium-sized artery when it penetrates a viscus. Thus, the renal artery is considered a large artery, but once it enters the kidney and separates into the smaller arcuate and interlobular arteries, these vessels are regarded as medium-sized arteries.
- *Small-vessel* vasculitis, which incorporates all vessels below macroscopic disease, includes capillaries, postcapillary venules, and arterioles.
- Because glomeruli may be viewed simply as differentiated capillaries, forms of vasculitis that cause glomerulonephritis are considered to be small vessel vasculitides.

- All three major categories of vasculitides (large, medium, and small) can affect arteries of any size. Example: giant cell arteritis, the prototypical “large-vessel” vasculitis: the clinical manifestation of this disease most feared by patients—anterior ischemic optic neuropathy—is caused by small branches of the posterior ciliary and retinal arteries.
- Some vasculitides are not easily classified as primary large, medium, or small-vessel diseases. :variable-vessel vasculitides.” Classic variable vessel vasculitides are Behçet’s disease and Cogan’s syndrome.
- However, categorizing a patient’s vasculitis as primarily large, medium or small vessel remains enormously helpful in focusing the differential diagnosis and initiating treatment plans.

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 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 87-5 Epidemiology of Select Forms of Vasculitis

Disease	INCIDENCE		Age/Sex/Ethnic Predispositions
	United States	Elsewhere	
Giant cell arteritis	240/1 million	240/1 million (Scandinavia)	Age >50 yr, mean age 72 yr; females 3:1/Northern European ancestry
Takayasu's arteritis	3/1 million	200-300/1 million (India)	Age <40 yr; females 9:1/Asian
Behçet's disease	3/1 million	3000/1 million (Turkey)	Silk Route countries
Polyarteritis nodosa	7/1 million	7/1 million (Spain)	Slight male predominance
Kawasaki's disease	100/1 million*	900/1 million (Japan)	Children of Asian ancestry
Granulomatosis with polyangiitis	4/1 million	8.5/1 million (United Kingdom)	Whites ≫ blacks
Henoch-Schönlein purpura	In children: 135-180/1 million; in adults: 13/1 million		Only 10% of cases occur in adults

*Among children younger than 5 years.

From Gonzalez-Gay MA, Garcia-Porrua C: Epidemiology of the vasculitides. *Rheum Dis Clin North Am* 27:729–750, 2001.

Large vessel vasculitis:

Giant Cell Arteritis(GCA)

TABLE 88-1 American College of Rheumatology Classification Criteria for Giant Cell Arteritis

Criterion	Definition
Age at disease onset ≥50 yr	Development of symptoms or findings beginning at age 50 yr or older
New headache	New onset or new type of localized pain in the head
Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
Elevated ESR	ESR ≥50 mm/hr by the Westergren method
Abnormal artery biopsy	Biopsy specimen with artery showing vasculitis, characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

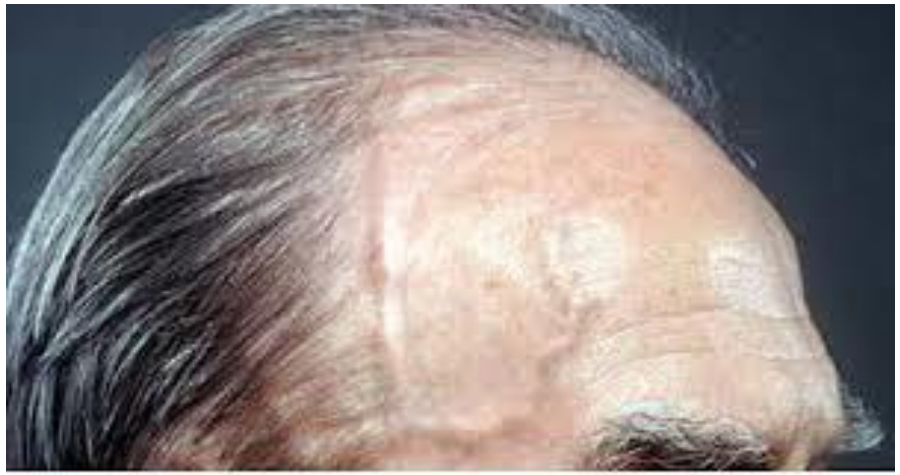
*For purposes of classification, a patient with vasculitis is said to have giant cell (temporal) arteritis if at least three of these five criteria are present. The presence of any three or more criteria yields a sensitivity of 93.5% and a specificity of 91.2%.

ESR, Erythrocyte sedimentation rate.

Case

- A 75-year-old male presented with headache of six weeks' duration. Pain was predominantly over the right hemicranium, with the maximum being over the right temple.
- Pain was excruciating in intensity. There was severe allodynia over the area. There was jaw claudication.
- Constitutional symptoms were present.
- About two weeks after the onset of headache, he developed blurred vision in the right eye.

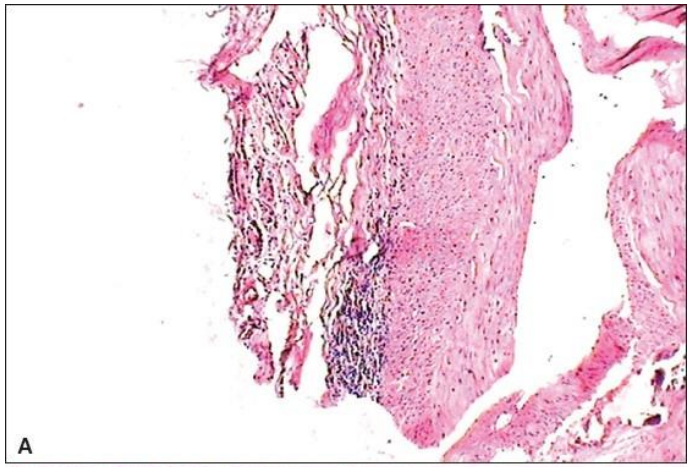
- Examination: tender TA with weak pulses

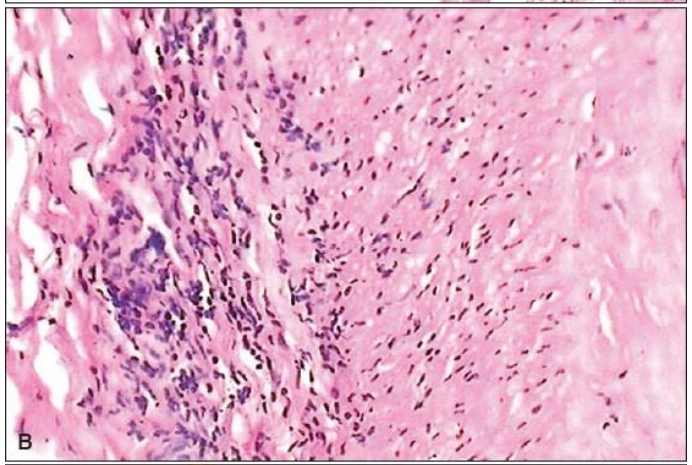


Case 5: questions

- 1- What is the likely diagnosis?
- 2- What additional testing you need to do?

- Labs: Hb 11, ESR 85. CRP 10
- Ophthalmological examination :anterior ischemic optic neuropathy (AION).
- Temporal artery biopsy: classic GCA





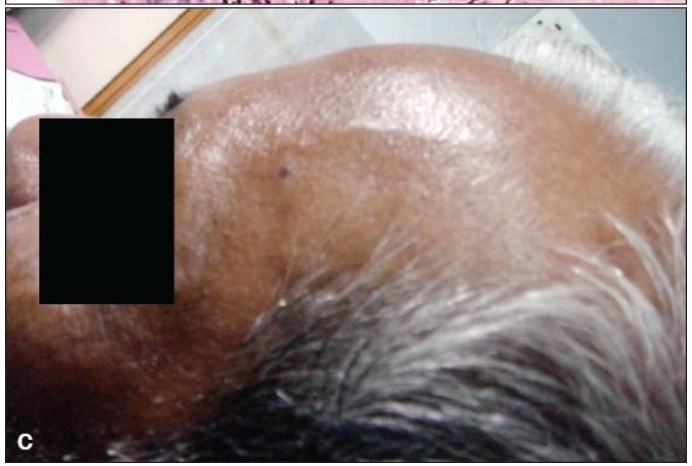


TABLE 88-3 Symptoms of Giant Cell Arteritis

Symptom	Frequency (%)
Headache	76
Weight loss	43
Fever	42
Fatigue	39
Any visual symptom	37
Anorexia	35
Jaw claudication	34
Polymyalgia rheumatica	34
Arthralgia	30
Unilateral visual loss	24
Bilateral visual loss	15
Vertigo	11
Diplopia	9

TABLE 88-5 Physical Findings and Laboratory Abnormalities in Giant Cell Arteritis

Feature	Frequency (%)
Any temporal artery abnormality	65
Prominent or enlarged temporal artery	47
Absent temporal artery pulse	45
Scalp tenderness	31
Any funduscopic abnormality	31
Abnormal ESR ESR >50 mm/hr ESR >100 mm/hr	96 83 39
Anemia	44

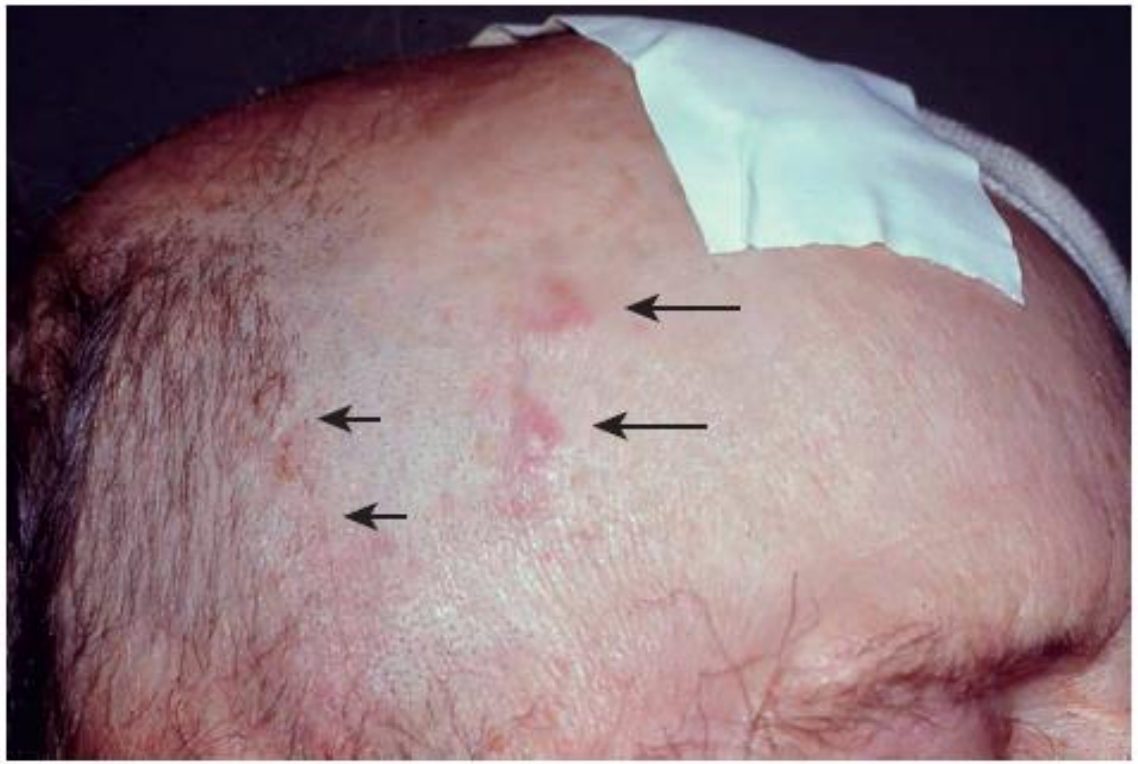


Figure 88-4 Giant cell arteritis (GCA) involving the temporal artery. Short segments of curved artery were erythematous and tender *(long arrows)*. The bandage on the scalp covers a similar artery that was biopsied and showed GCA. A previous biopsy specimen of a proximal segment of the right temporal artery, which was normal on physical examination, was normal histologically. The faint scar from that biopsy can be seen above and anterior to the right ear *(short arrows)*.

TABLE 88-2 Diagnostic* and Classification Criteria for Polymyalgia Rheumatica

Diagnostic Criteria of Chuang and Colleagues (1982)		
Age 50 yr or older		
Bilateral aching and stiffness for 1 month or more and involving two of the following areas: neck or torso, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs		
ESR >40 mm/hr		
Exclusion of all other diagnoses except giant cell arteritis		
Diagnostic Criteria of Healey (1984)		
Pain persisting for at least 1 mo and involving two of the following areas: neck, shoulders, and pelvic girdle		
Morning stiffness lasting >1 hr		
Rapid response to prednisone (≤20 mg/day)		
Absence of other diseases capable of causing the musculoskeletal symptoms		
Age older than 50 yr		
ESR >40 mm/hr		
Classification Criteria of Dasgupta and Colleagues (2012)		
Age 50 years or older, bilateral shoulder aching, and abnormal C-reactive protein and/or ESR†		
	Points Without US (0-6)	**Points With US‡ (0-8)**
Morning stiffness duration >45 min	2	2
Hip pain or limited range of motion	1	1
Absence of rheumatoid factor or anti-citrullinated protein antibody	2	2
Absence of other joint involvement	1	1
At least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis	Not applicable	1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis	Not applicable	1

*For each set of criteria, all the findings must be present for polymyalgia rheumatica to be diagnosed.
†A score of 4 or more is categorized as polymyalgia rheumatica in the algorithm without ultrasound (US), and a score of 5 or more is categorized as polymyalgia rheumatica in the algorithm with US.
‡Optional ultrasound criteria.
ESR, Erythrocyte sedimentation rate.

TABLE 88-4 Atypical Manifestations of Giant Cell Arteritis

Fever of unknown origin
Respiratory symptoms (especially cough)
Otolaryngeal manifestations
Glossitis
Lingual infarction
Throat pain
Hearing loss
Large artery disease
Aortic aneurysm
Aortic dissection
Limb claudication
Raynaud's phenomenon
Neurologic manifestations
Peripheral neuropathy
Transient ischemic attack, stroke
Dementia
Delirium
Myocardial infarction
Tumor-like lesions
Breast mass
Ovarian and uterine mass
Syndrome of inappropriate anti-diuretic hormone secretion
Microangiopathic hemolytic anemia

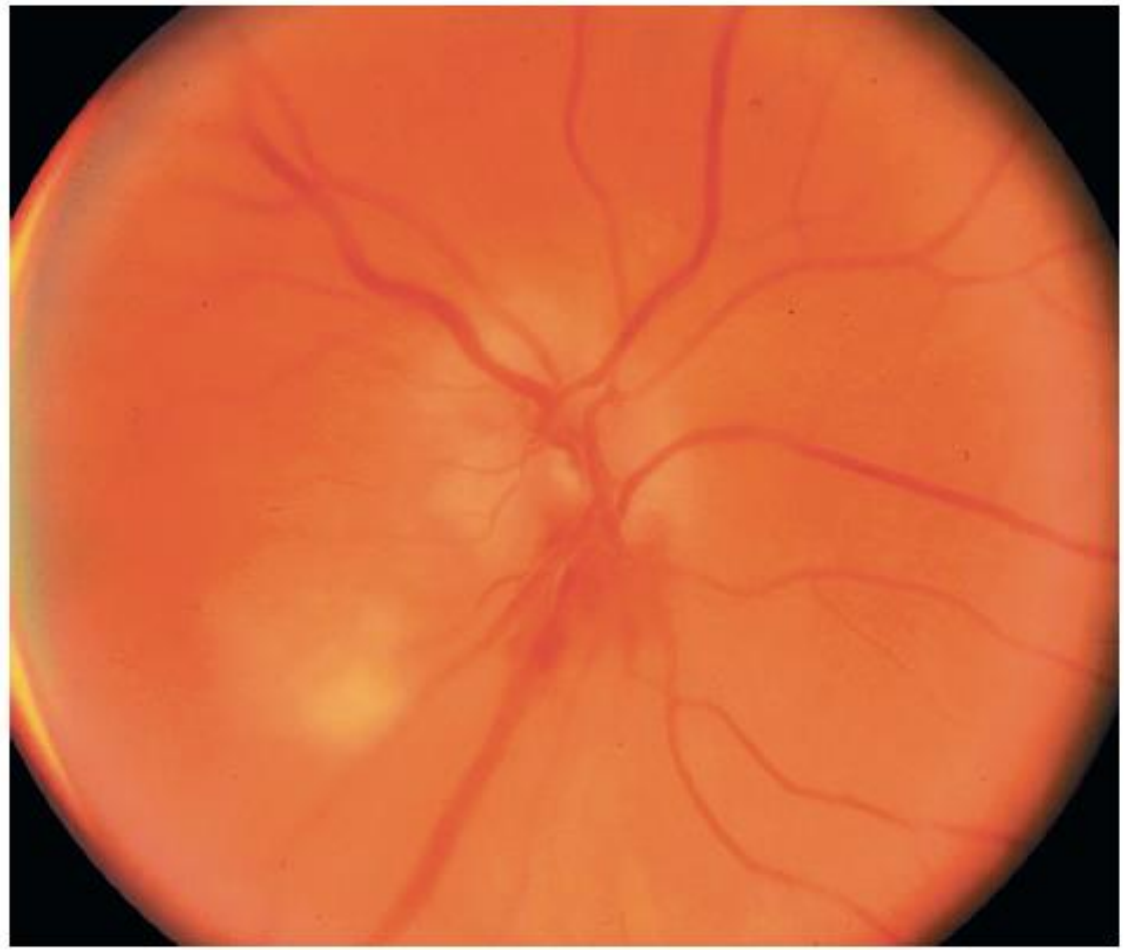


Figure 88-5 Ophthalmoscopic appearance of the acute phase of anterior ischemic optic neuropathy seen in patients with giant cell arteritis and loss of vision. The optic disc is pale and swollen, the retinal veins are dilated, and several flame-shaped hemorrhages and a cotton-wool spot (retinal infarct) are visible. *(Courtesy Dr. Neil R. Miller.)*

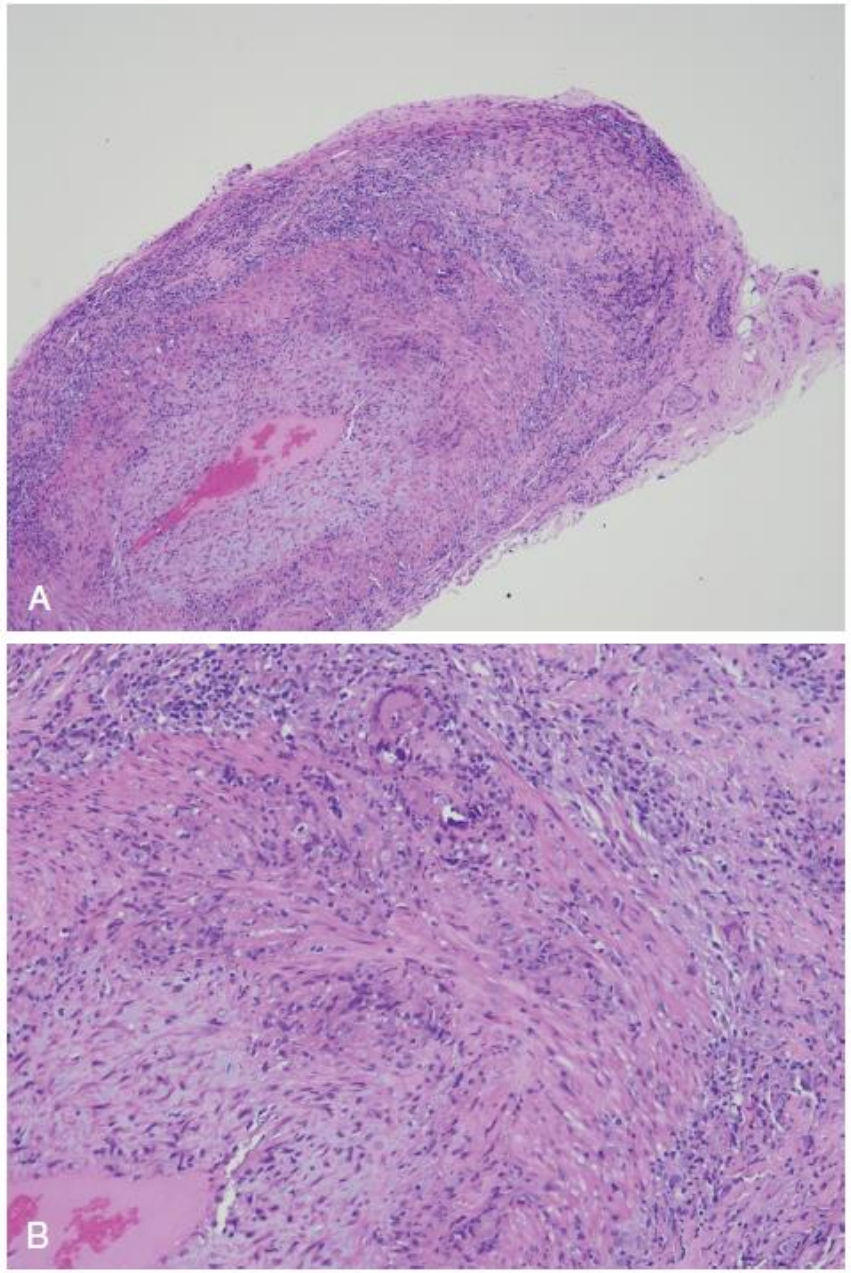


Figure 88-1 Giant cell arteritis. **A,** Cross-section of a temporal artery showing transmural inflammation with mononuclear cells and giant cells (hematoxylin and eosin, ×10). **B,** Higher-power (×100) view demonstrating giant cells infiltrating the media. *(Courtesy Dr. Frederic Askin.)*

TABLE 88-8 American College of Rheumatology Classification Criteria for Takayasu's Arteritis*

Onset before age 40 yr
Limb claudication
Decreased brachial artery pulse
Unequal arm blood pressure (>10 mm Hg)
Subclavian or aortic bruit
Angiographic evidence of narrowing or occlusion of aorta or its primary branches, or large limb arteritis

*The presence of three or more of the six criteria is sensitive (91%) and specific (98%) for the diagnosis of Takayasu's arteritis.

TABLE 88-9 Clinical Features of Takayasu's Arteritis

Feature	At Presentation (%)	Ever Present (%)
Vascular	50	100
Bruit		80
Claudication (upper extremity)	30	62
Claudication (lower extremity)	15	32
Hypertension	20	33
Unequal arm blood pressures	15	50
Carotidynia	15	32
Aortic regurgitation		20
Central nervous system	30	57
Lightheadedness	20	35
Visual abnormality	10	30
Stroke	5	10
Musculoskeletal	20	53
Chest wall pain	10	30
Joint pain	10	30
Myalgia	5	15
Constitutional	33	43
Malaise	20	30
Fever	20	25
Weight loss	15	20
Cardiac	15	38
Aortic regurgitation	8	20
Angina	2	12
Congestive heart failure	2	10

TABLE 88-11 Frequency of Blood Vessel Involvement in Takayasu's Arteritis

Blood Vessel	% Abnormal
Aorta	65
Aortic arch or root	35
Abdominal aorta	47
Thoracic aorta	17
Subclavian artery	93
Common carotid artery	58
Renal artery	38
Vertebral artery	35
Celiac axes	18
Common iliac artery	17
Pulmonary artery	5

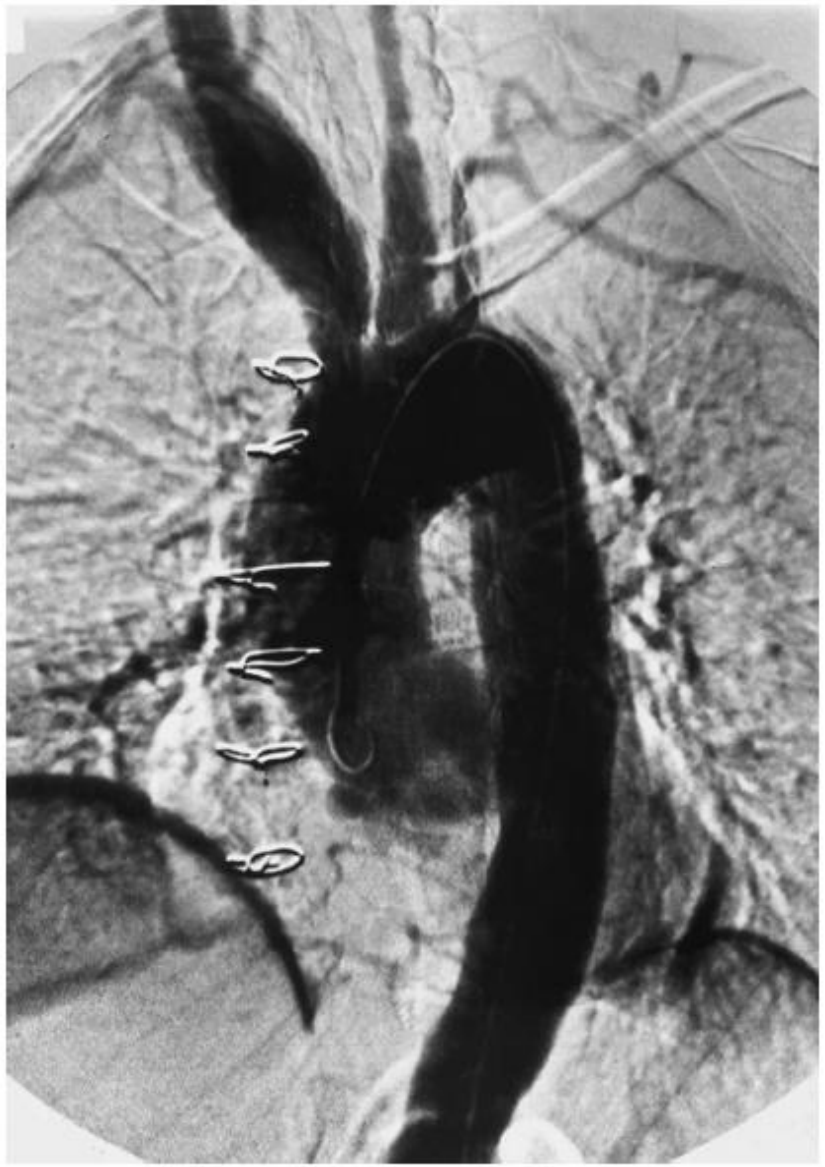


Figure 88-10 Angiogram showing multiple changes of Takayasu's arteritis including dilation of the aortic root (with surgical wires from previous aortic valve replacement), aneurysmal dilation of the innominate and right carotid arteries, and occlusion of the distal left common carotid artery. *(From Hellmann DB, Flynn JA: Clinical presentation and natural history of Takayasu's arteritis and other inflammatory arteritides. In Perler BA, Becker GJ, editors:* Vascular intervention: a clinical approach,

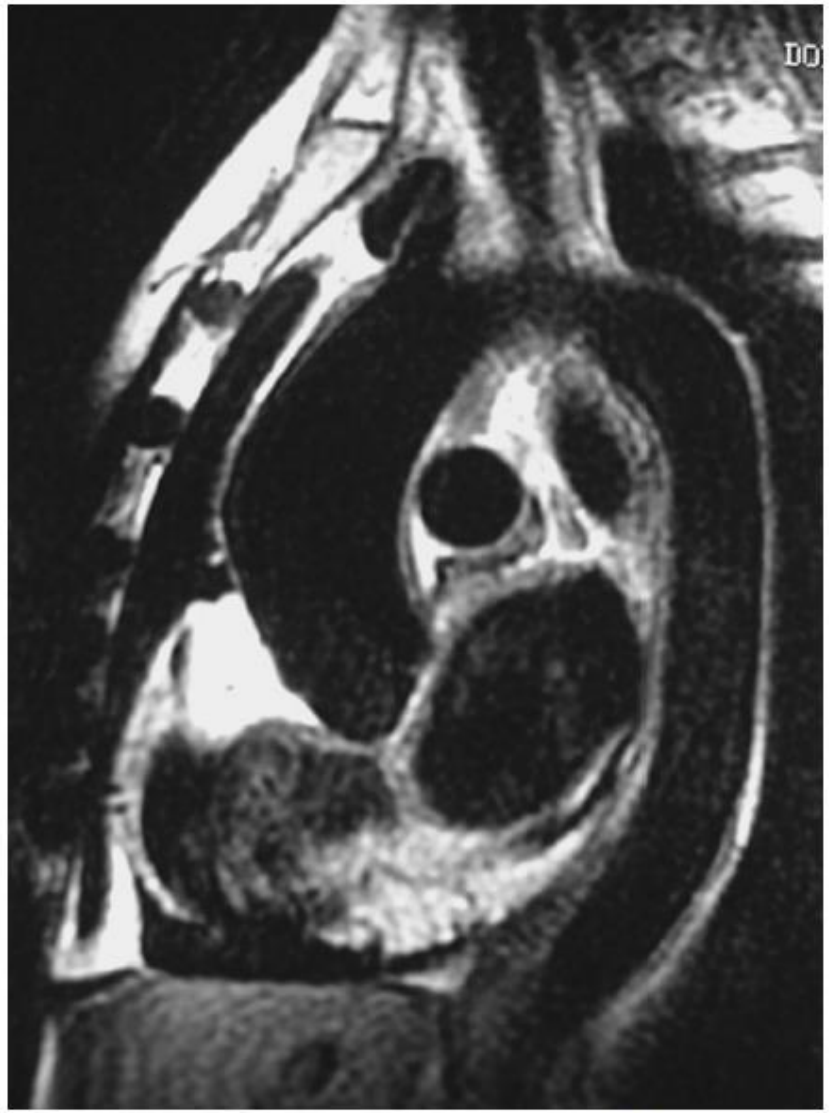


Figure 88-11 Magnetic resonance image (sagittal section) through the chest showing thickening of the ascending and descending thoracic aorta in a 26-year-old woman with Takayasu's arteritis. *(From Hellmann DB: Takayasu arteritis. In Imboden J, Hellmann DB, Stone JH, editors:* Current rheumatology: diagnosis & treatment, *New York, 2004, McGraw-Hill, p 244.)*

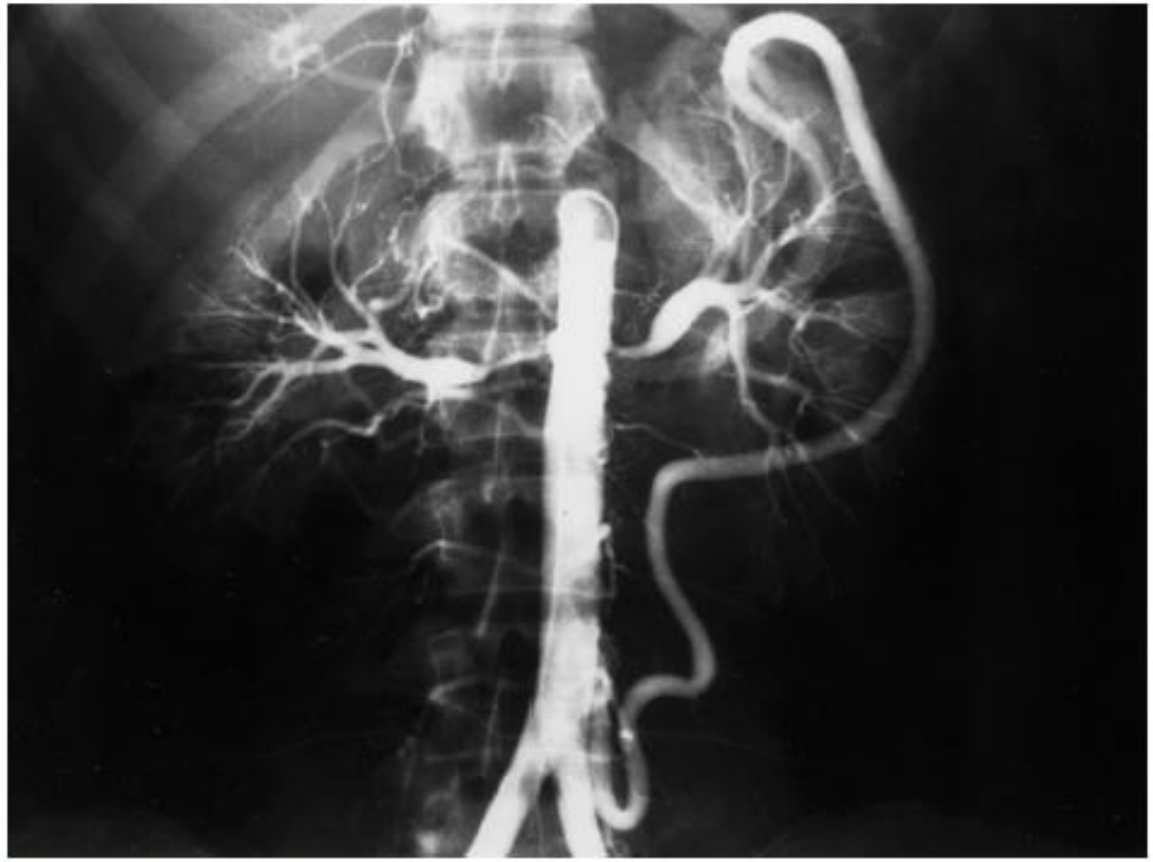


Figure 88-12 Angiogram showing bilateral renal artery stenosis. A large left colic branch of the inferior mesenteric artery provides collateral circulation to the gut. *(From Hellmann DB, Flynn JA: Clinical presentation and natural history of Takayasu's arteritis and other inflammatory arteritides. In Perler BA, Becker GJ, editors:* Vascular intervention: a clinical approach, *New York, 1998, Thieme Medical and Scientific Publisher, pp 249–256.)*

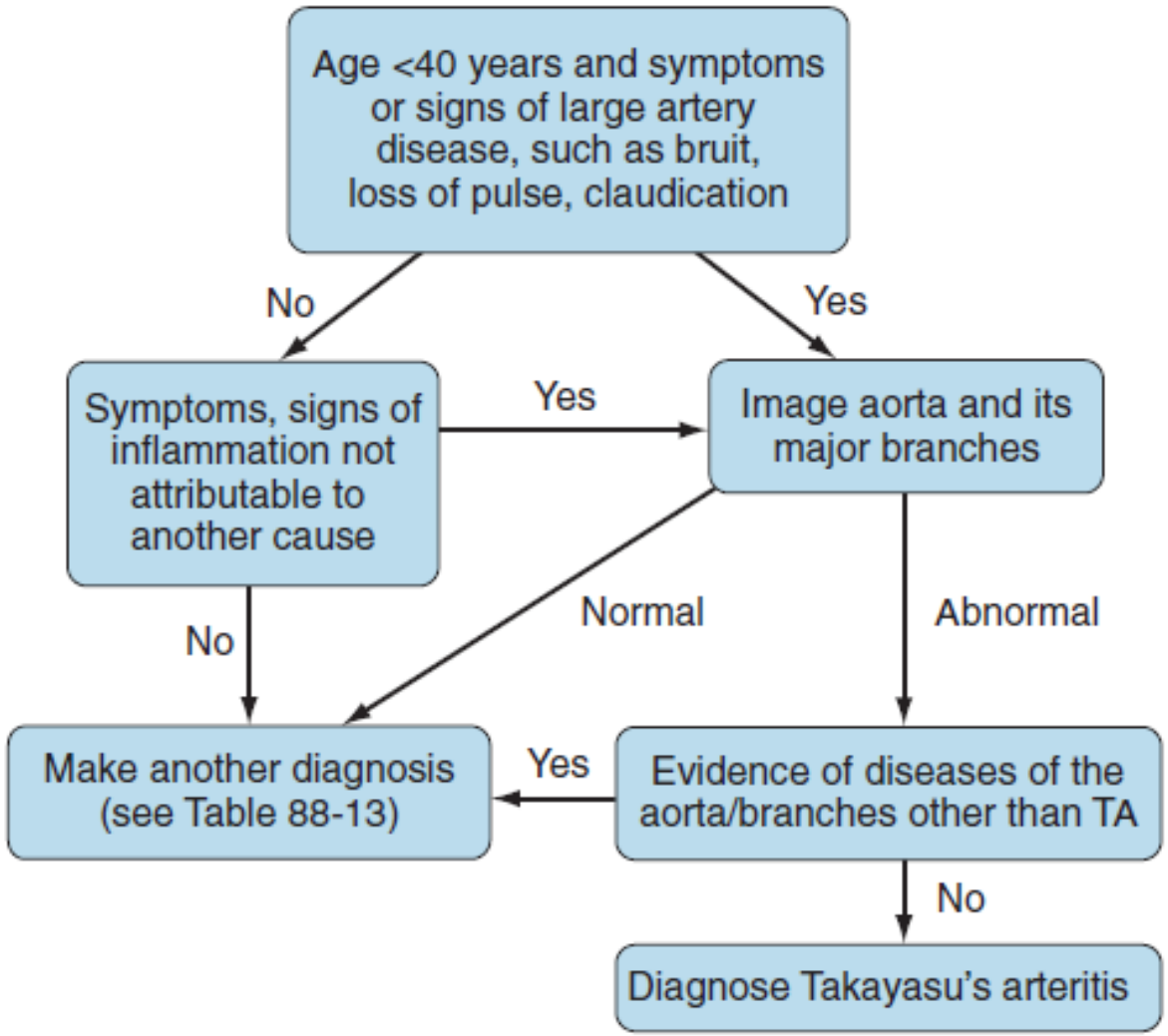


Figure 88-13 Algorithm for the diagnosis of Takayasu's arteritis (TA).

TABLE 88-13 Comparison of Giant Cell Arteritis and Takayasu's Arteritis

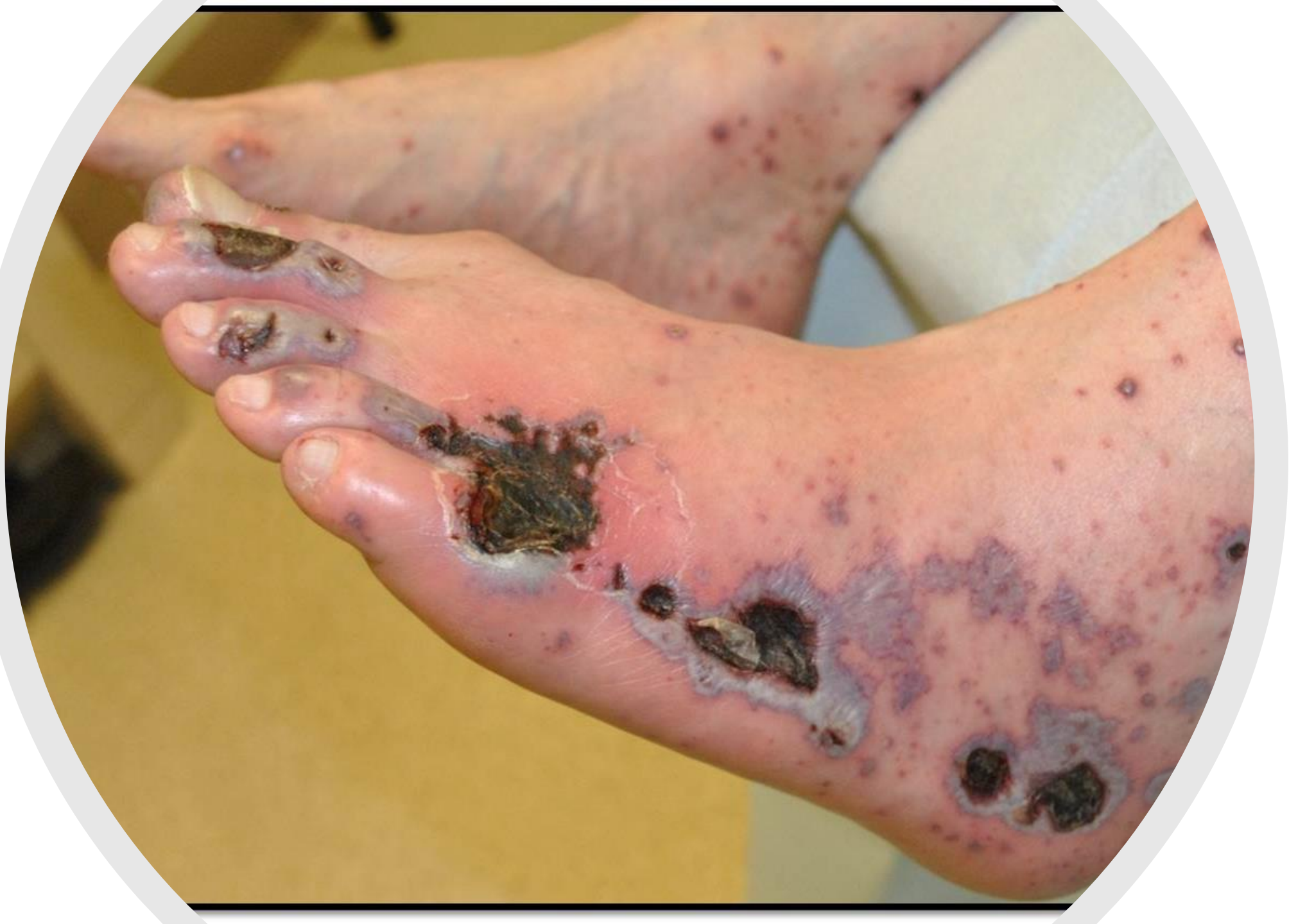
Feature	Giant Cell Arteritis	Takayasu's Arteritis
Female-male ratio	2:1	8:1
Age range	≥50 yr	<40 yr
Average age of onset	72 yr	25 yr
Visual loss	10%-30%	Rare
Involvement of aorta or its major branches	25%	100%
Histopathology	Granulomatous arteritis	Granulomatous arteritis
Pulmonary artery involvement	No	Occasionally
Renal hypertension	Rare	Common
Claudication	Uncommon	Common
Ethnic groups with highest incidence	Scandinavian	Asian
Corticosteroid responsive	Yes	Yes
Bruits present	Minority	Majority
Surgical intervention needed	Rare	Common

TABLE 90-3 Organ Involvement in Polyarteritis Nodosa

System	Comment	Frequency	Reference(s)
Constitutional	Fever and weight loss (current and previous)	>90%	39
Musculoskeletal	Arthritis, arthralgia, myalgia, or weakness; when muscle is involved, it provides a useful site for biopsy	24%-80%	19, 27
Skin	Purpura, nodules, livedo reticularis, ulcers, bullous or vesicular eruptions, and segmental skin edema	44%-50%	19, 39, 112, 113
Cardiovascular	Cardiac ischemia, cardiomyopathy, hypertension	35%	27, 34, 39
Ear, nose, and throat	No involvement; nasal crusting, sinusitis, and hearing loss suggest an alternative diagnosis such as granulomatosis with polyangiitis	None	
Respiratory	Lung involvement not seen in PAN; abnormal respiratory findings suggest an alternative diagnosis	None	
Abdominal	Pain is an early feature of mesenteric artery involvement; progressive involvement may cause bowel, liver, or splenic infarction, bowel perforation, or bleeding from a ruptured arterial aneurysm; less common presentations include appendicitis, pancreatitis, or cholecystitis as a result of ischemia or infarction; the presence of abdominal tenderness or peritonitis and blood loss on rectal examination should be assessed	33%-36%	19, 39
Renal	Vasculitis involving the renal arteries is present in many cases but does not commonly give rise to clinical features; it can present with renal impairment, renal infarcts, or rupture of renal arterial aneurysms; glomerular ischemia may result in mild proteinuria or hematuria, but red cell casts are absent because glomerular inflammation is not a feature; if evidence of glomerular inflammation exists, then an alternative diagnosis such as microscopic polyangiitis or granulomatosis with polyangiitis must be considered; hypertension is a manifestation of renal ischemia causing activation of the renin-angiotensin system	11%-66%	19, 39
Nervous system	Mononeuritis multiplex, with sensory symptoms preceding motor deficits; central nervous system involvement is a less frequent finding and can present with encephalopathy, seizures, and stroke	55%-79%	19, 39
Ocular	Visual impairment, retinal hemorrhage, and optic ischemia	Rare	27, 34
Other	Breast or uterine involvement is rare; testicular pain from ischemic orchitis is a characteristic feature, albeit an uncommon presentation	Rare	114, 115

TABLE 90-1 American College of Rheumatology Criteria for Classification of Polyarteritis Nodosa

Weight loss ≥4 kg
Livedo reticularis
Testicular pain or tenderness
Myalgias, weakness, or leg tenderness
Mononeuropathy or polyneuropathy
Diastolic blood pressure >90 mm Hg
Elevated blood urea nitrogen or creatinine levels
Hepatitis B virus
Arteriographic abnormality
Biopsy of a small- or medium-sized artery containing polymorphonuclear neutrophils



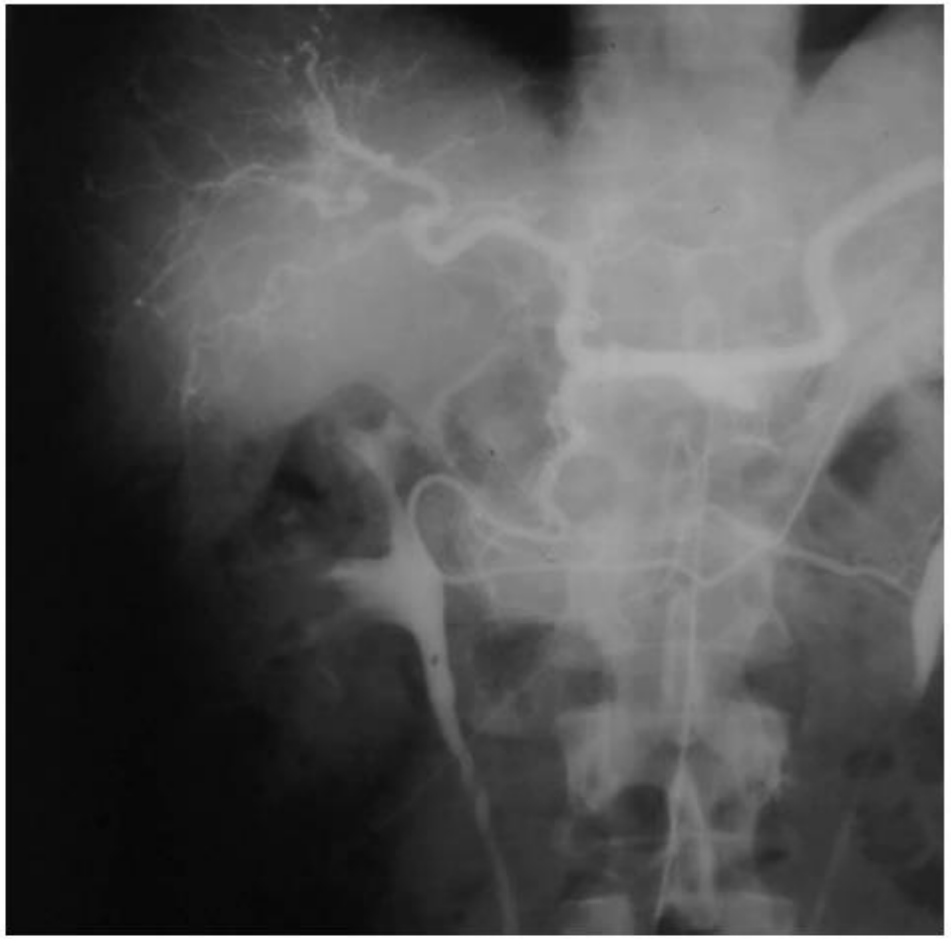


Figure 90-1 This celiac axis angiogram from a patient with polyarteritis nodosa demonstrates an irregular vascular pattern with small aneurysms in the hepatic vessels.

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 vasculitis

Box 1: When to consider ANCA associated vasculitis

Consider a diagnosis of AAV in the following clinical circumstances.[4] Any of these features should prompt consideration of AAV; multiple features are strongly suggestive of AAV.[5] Figures in parentheses are the approximate proportion of incident cases exhibiting each feature.[5 6]

- **Vasculitic rash with systemic features (<20%)**
  - Purpuric ("vasculitic") rash accompanied by features of systemic disease (eg, fever, flu like symptoms, abnormal urinalysis, etc.). Note that an isolated rash in the absence of these features is unlikely to be AAV and a prominent rash at presentation is often more suggestive of immune complex vasculitis such as IgA vasculitis (previously Henoch-Schönlein purpura)
- **Respiratory symptoms (~45%)**
  - Haemoptysis (or other features suggestive of alveolar haemorrhage—eg, shortness of breath and acute drop in haemoglobin)
  - Progressive shortness of breath/cough (particularly if accompanied by systemic symptoms or fine crackles suggestive of pulmonary fibrosis)
  - Refractory/steroid dependent asthma
- **Ear, nose, and throat/upper airways symptoms (~45%)**
  - Long standing/persistent sinusitis or otitis
  - Hearing loss/earache
  - Nasal bridge collapse (a late sign of very advanced disease; see fig 1)
  - Subglottic tracheal stenosis (which may be discovered through investigation of dyspnoea, stridor, or incidentally at the time of elective intubation for general anaesthetic)
- **Eye symptoms (<20%)**
  - Painful, red eye (scleritis)
  - Diplopia with proptosis (caused by retro-orbital granulomatous mass)
- **Nerve symptoms (~30%)**
  - Paraesthesia/weakness in keeping with mononeuritis multiplex or other peripheral neuropathy; consider AAV in the absence of an alternative explanation (eg, diabetes, B12 deficiency) and particularly in wrist drop or foot drop
- **Renal disease (~65%)**
  - Rising serum creatine (or falling eGFR) with more than a trace of blood and protein on urinalysis (ie, suspected glomerulonephritis); in the early phases of disease there may be no symptoms and eGFR may be near normal

ANCA vasculitis

- GPA

✓necrotizing granulomatous inflammation and vascuitis

✓ destructive sinonasal lesions, pulmonary nodules, and pauci-immune glomerulonephritis.

✓GPA is associated with cytoplasmic ANCA and antibodies to proteinase 3 (PR3)

- MPA

✓vasculitis without granulomatous inflammation.

✓ Common clinical manifestations include rapidly progressive pauci-immune glomerulonephritis and alveolar hemorrhage.

✓MPA is associated with perinuclear ANCA and antibodies to myeloperoxidase.

- Both GPA and MPA commonly cause a pulmonary-renal syndrome, with GPA frequently affecting the upper airway as well.

ANCA vasculitis

- EGPA

✓eosinophilic tissue infiltration in addition to vasculitis.

✓Common clinical manifestations include asthma, peripheral eosinophilia, and peripheral neuropathy.

✓ Only 40% of patients produce detectable ANCA.

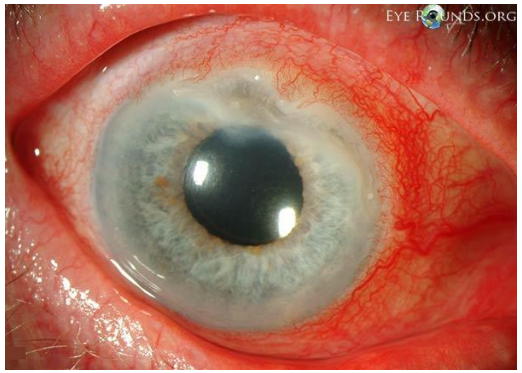
Case

- A 55 year old man presents with a 2-3 week history of fever, cough and migratory arthralgias. This was preceded by persistent nasal stuffiness and a mildly productive cough that on one occasion included bright red blood.
- Additionally, he reports recent malaise and fatigue, with mild dyspnea on exertion.
- For the past 4-5 days, he has had a painful, red left eye.
- He is a non-smoker, with no recent travel or exposures, and he denies cocaine or other drug use.
- He reports a 5-10 year history of recurrent sinus and ear infections that seem unresponsive to antibiotics and decongestants.

- Physical examination reveals an ill-appearing male, with a blood pressure of 140/90 and a pulse of 102, temperature is 101 degrees F.
- There is no skin rash or adenopathy. He is tender over the maxillary sinuses, and the left eye is injected and slightly swollen.
- Chest exam reveals decreased

breath sounds with rales in the

upper lung fields.



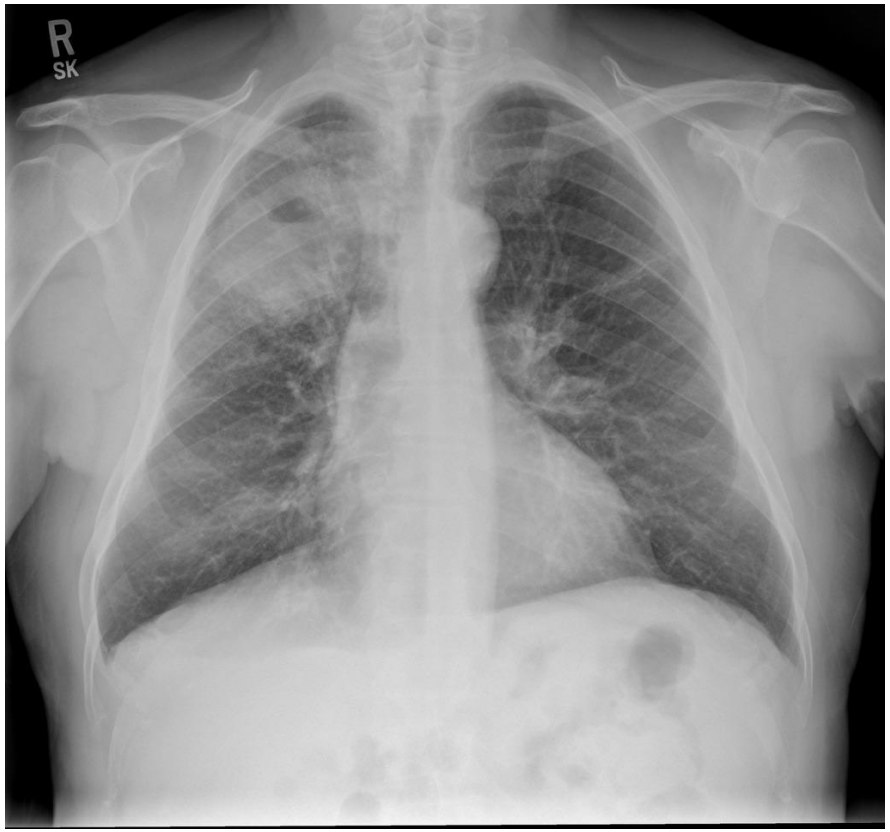
Case 6: questions

- 1- What is your differential diagnosis?
- 2- What investigations you want to request?

- R/O Systemic vasculitis, as well as infection, malignancy, and vasculitis mimics

- CBC with differential, UA, C3 and C4 complement levels, ESR, CRP
- Hepatitis Serologies and HIV
- PPD skin testing and sputum for AFB and fungal cultures
- Urine drug screen if drug use is suspected
- Serum antibody testing for ANA, RF, anti-GBM (Goodpasture's disease),ANCA (with antigen-specific anti-PR3 and anti-MPO if ANCA is positive)
- Biopsy of tissue to look for granulomatous inflammation with necrotizing vasculitis- the highest yield is found with lung biopsy (open or video-assisted thoracoscopic surgery)

- A chest X-ray reveals multiple, large pulmonary nodules in both upper lobes with cavitations in several areas.
- Sinus films show opacification of the left maxillary sinus.



- Laboratory studies include a mild anemia and WBC of 12,200 with a slight left shift and no significant eosinophilia.
- A urinalysis reveals 2+ protein and 20-30 RBCs. Serum creatinine is 1.5.
- ANCA was positive at a titer of 1:1280 with cytoplasmic staining (c-ANCA), and anti-proteinase 3 (PR3) antibodies by ELISA were also positive
- Bronchoscopy revealed no obstructing lesions or bloody secretions. An open lung biopsy was performed, and tissue sections revealed granulomatous inflammation, necrotizing vasculitis, and multi-nucleated giant cells.

The classification criteria for GPA were developed by comparing 85 patients who had GPA with 722 patients who had other forms of vasculitis. Four criteria were selected:

1. Abnormal urinary sediment (red blood cell casts or >5 red blood cells/high-power field)
2. Abnormal findings on a chest radiograph (e.g., nodules, cavities, or fixed infiltrates)
3. Oral ulcers or nasal discharge
4. Biopsy findings of granulomatous inflammation

The presence of two or more of these four criteria was associated with a sensitivity of 88.2% and a specificity of 92.0%.[2] ANCAs were not included in these criteria, given their relatively recent identification and the need to further determine their usefulness at the time of the publication of the criteria.

The classification criteria for EGPA were developed by comparing 20 patients with EGPA with 787 patients who had other forms of vasculitis. Six criteria were selected:

1. Asthma
2. Eosinophilia greater than 10% on white blood cell count differential
3. Mononeuropathy (including multiplex) or polyneuropathy
4. Nonfixed pulmonary infiltrates on a chest radiograph
5. Paranasal sinus abnormality
6. A biopsy specimen containing a blood vessel with extravascular eosinophils

The presence of four or more of these six criteria was associated with a sensitivity of 85% and a specificity of 99.7%.[3]

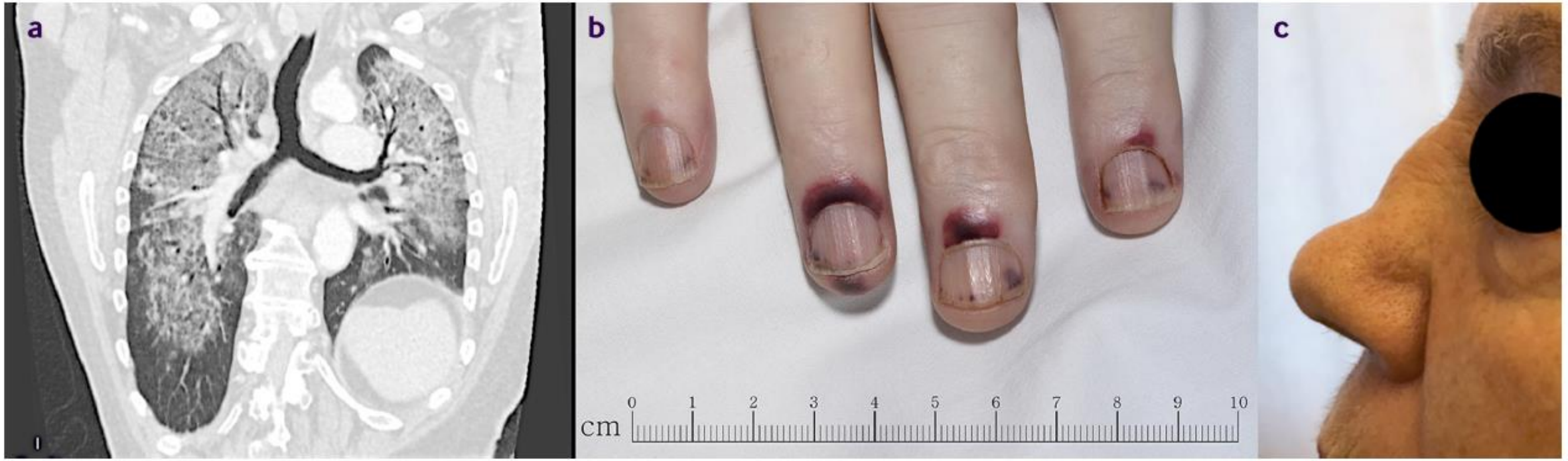
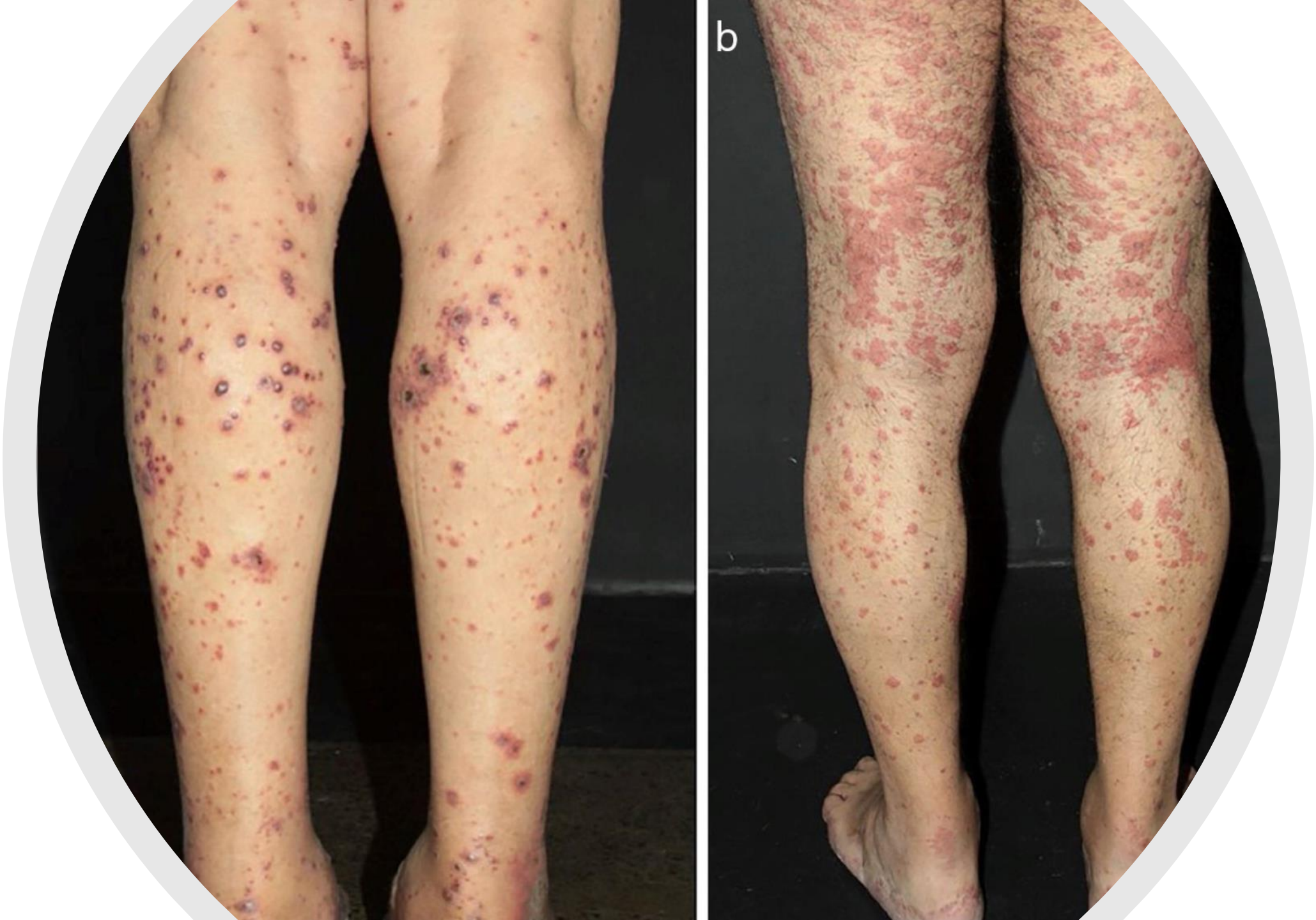


Fig 1 Clinical consequences of AAV. (a) Diffuse alveolar haemorrhage. (b) Nail fold infarction and splinter haemorrhages. (c) Nasal bridge collapse resulting from chronic, erosive inflammation in the upper airways. Delayed diagnosis can result in permanent disability/deformity and early mortality. Manifestations of advanced disease such as a "saddle nose" deformity are relatively rare but can still occur if a diagnosis of AAV is missed (these images are not directly related to the case study in this article)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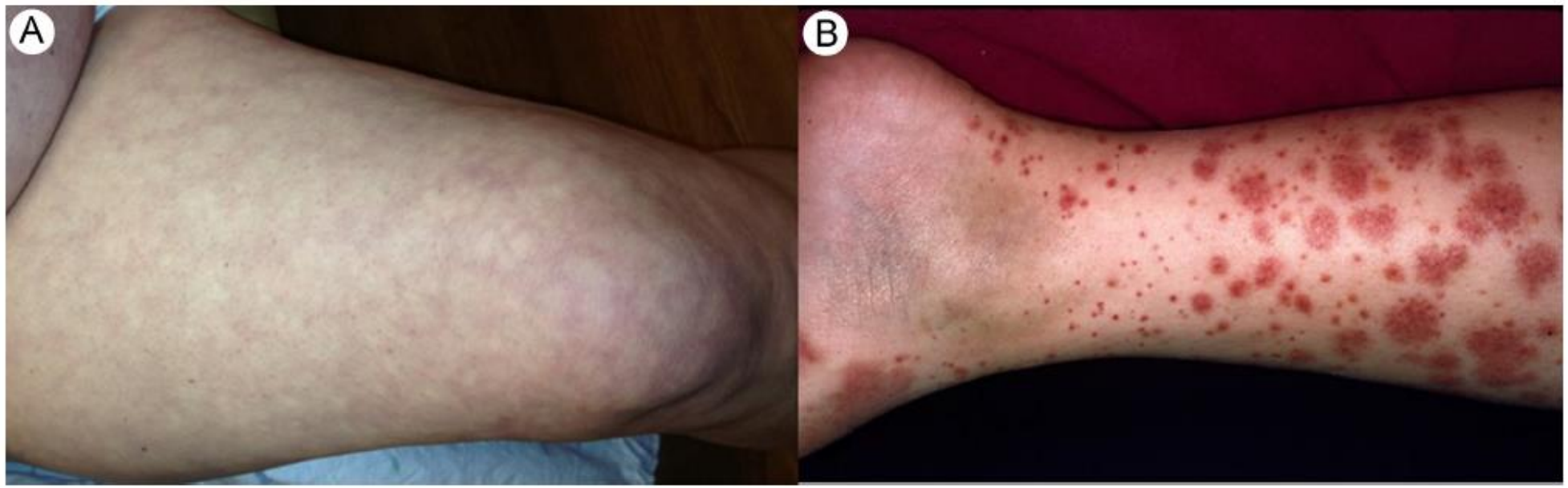

Figure 3 (A) Livedo reticularis (mottled reticulated pattern of lacelike purplish discoloration of the skin) throughout the entire thigh and (B) palpable purpura on the calf. (Color version of figure is available online.)

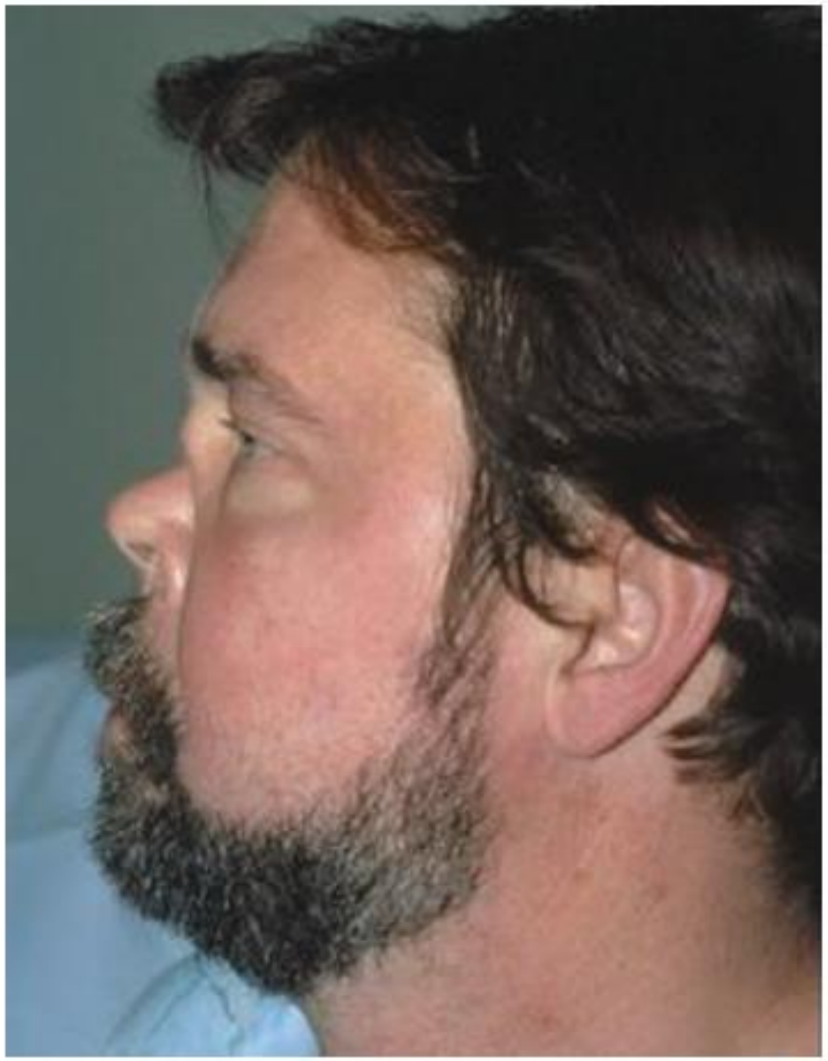

Figure 89-2 Saddle nose deformity in a patient with granulomatosis with polyangiitis. *(Courtesy Dr. G. Hoffman.)*

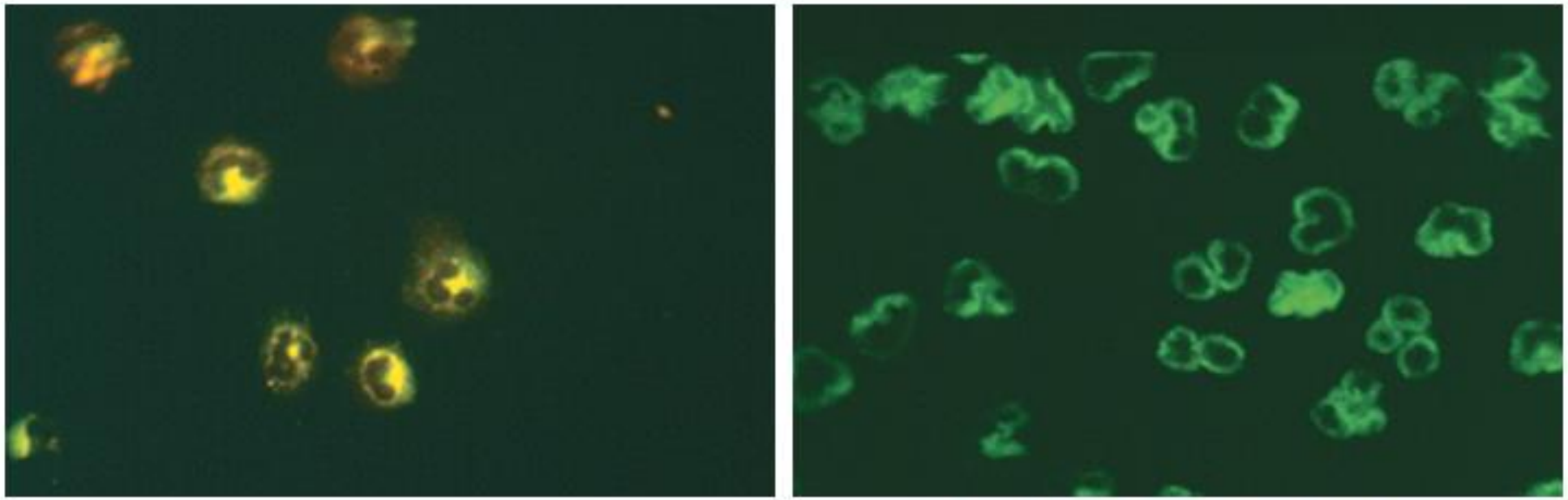

Figure 89-7 Immunofluorescence of cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA, *left*), which is highly correlated with anti-proteinase 3 antibodies, and perinuclear staining (p-ANCA, *right*), which is indicative of anti-myeloperoxidase antibodies. Positive immunofluorescence staining should be confirmed with antigen-specific testing to proteinase 3 and myeloperoxidase. *(Courtesy Dr. C.G.M. Kallenberg.)*

Work up

Box 2: First line investigations

First line investigations support a diagnosis of AAV by evaluating for a chronic inflammatory response or renal failure or by testing for differential diagnoses such as infection and cancer. Given the multi-system nature of AAV, and the broad differential diagnosis, it is usually appropriate to request all of these investigations in cases of suspected AAV. The only exception is the ANCA test which would usually be requested by a specialist service.

- Urinalysis (consider AAV causing glomerulonephritis if more than a trace of either blood or protein is detected; if abnormal then consider quantifying proteinuria with a urine protein:creatine or albumin:creatine ratio)
- Full blood count (normocytic anaemia/thrombocytosis/eosinophilia due to chronic inflammation; microcytic anaemia in chronic covert blood loss in low grade alveolar haemorrhage or gut involvement; rapidly falling haemoglobin in acute alveolar haemorrhage)
- Urea and electrolytes (rising serum creatine/falling eGFR)
- Serum albumin (may be low due to inflammation or nephrotic range proteinuria)
- C reactive protein or erythrocyte sedimentation rate (both measurements are high in inflammation)
- Liver function tests, calcium (typically normal or near-normal in AAV, so abnormalities might suggest an alternative diagnosis such as infection or cancer)
- Chest radiography (may have nodular, fibrotic, or infiltrative lesions in AAV; exclude lung cancer or infection)
- ANCA testing in liaison with specialty service