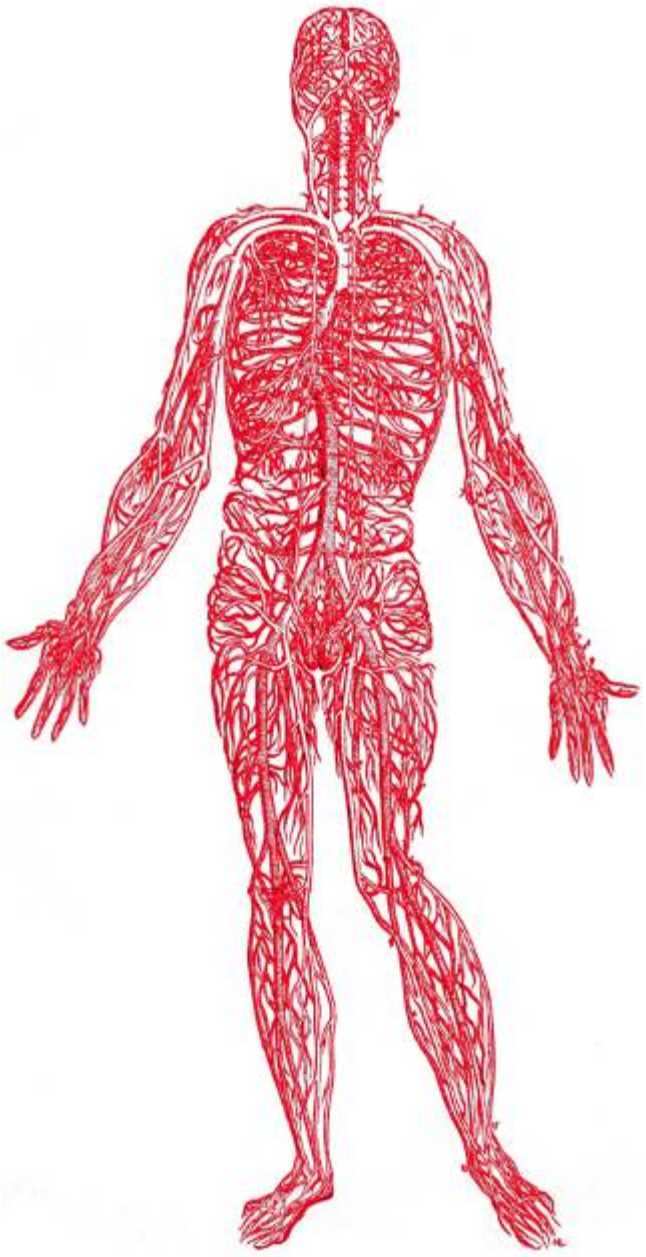


An approach to vasculitis

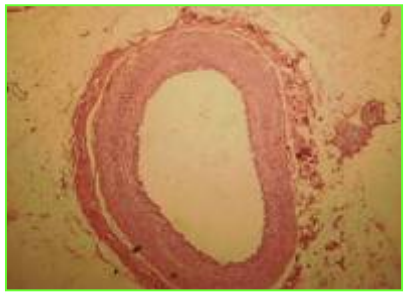
Sept 2018
MSH
C Pagnoux

cpagnoux@mtsinai.on.ca

Objectives

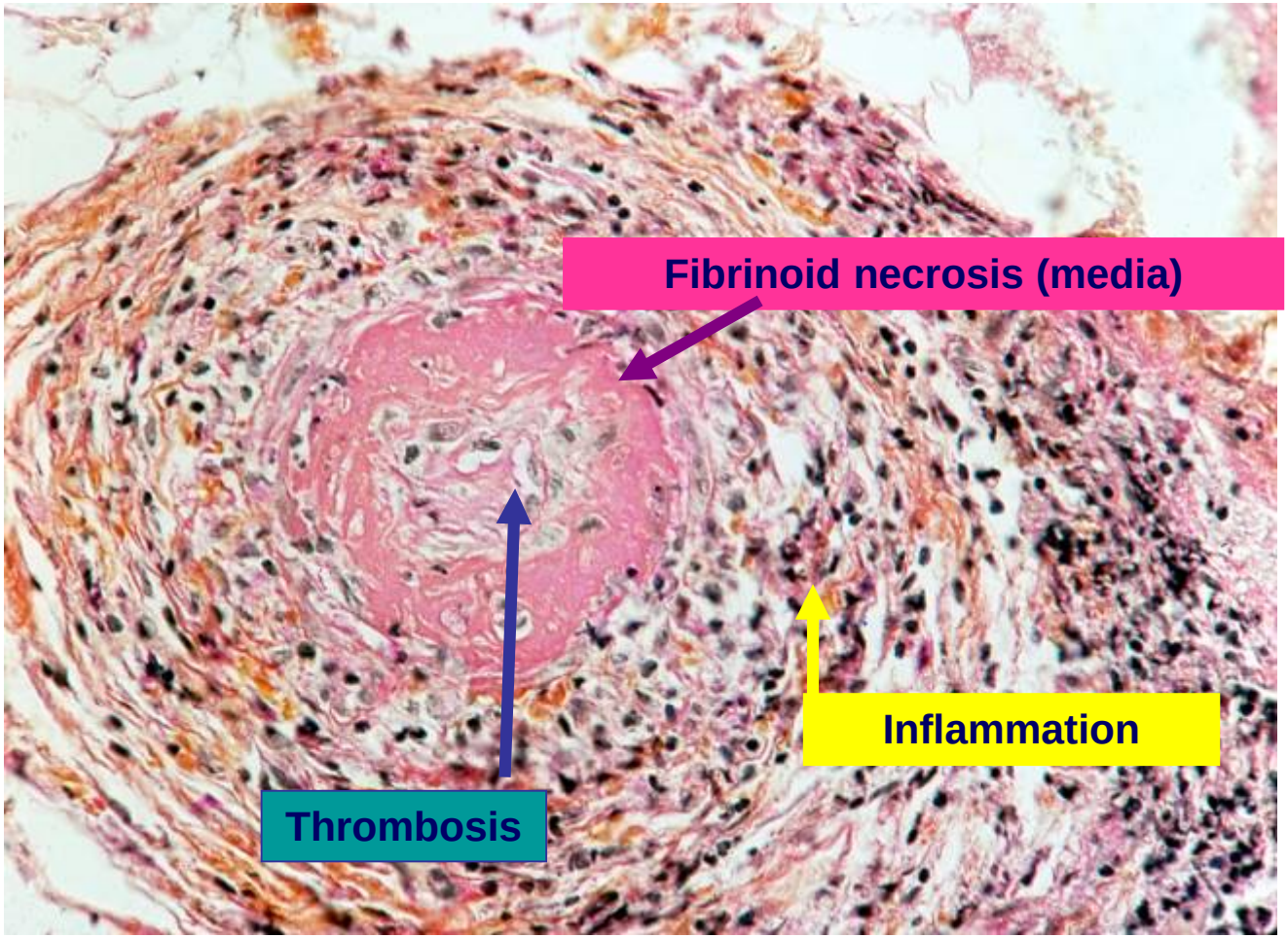
- Describe the clinical features typical for vasculitis involving small, medium or large vessels
- Describe the appropriate investigations to address the possibility of vasculitis
- Describe an approach to the initial management of the patient presenting with a vasculitic problem

What is vasculitis?

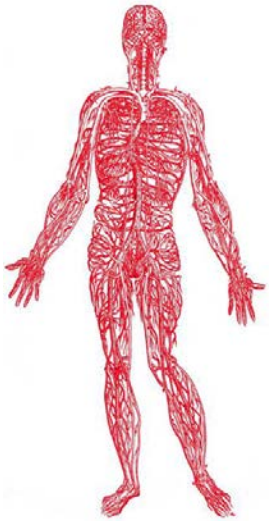


Normal artery

Vasculitis



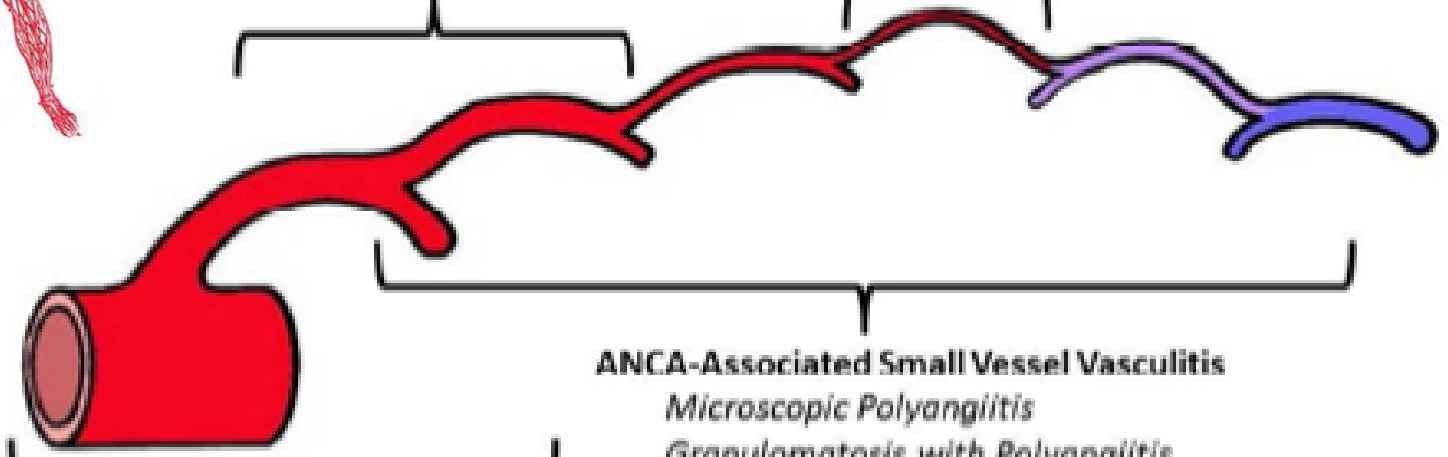
2012 revised Chapel hill nomenclature



Immune Complex Small Vessel Vasculitis
Cryoglobulinemic Vasculitis
IgA Vasculitis (Henoch-Schönlein)
Hypocomplementemic Urticarial Vasculitis
(Anti-C1q Vasculitis)

Medium Vessel Vasculitis
Polyarteritis Nodosa
Kawasaki Disease

Anti-GBM Disease



ANCA-Associated Small Vessel Vasculitis
Microscopic Polyangiitis
Granulomatosis with Polyangiitis
(Wegener's)
Eosinophilic Granulomatosis with Polyangiitis
(Churg-Strauss)

Large Vessel Vasculitis
Takayasu Arteritis
Giant Cell Arteritis

Jennette et al. Arthritis Rheum. 2012 Oct 8.

2012 revised Chapel hill nomenclature

- **Variable Vessel Vasculitis (VVV):** Behçet's Disease (BD) and Cogan's Syndrome (CS).
- **Single Organ Vasculitis (SOV):** Cutaneous Leukocytoclastic Angiitis, Cutaneous Arteritis, Primary CNS Vasculitis and Isolated Aortitis.

- **Vasculitis Associated with Systemic Disease:** Lupus Vasculitis, Rheumatoid Vasculitis and Sarcoid Vasculitis.

- **Vasculitis Associated with Probable Etiology:** Hepatitis C Virus-Associated Cryoglobulinemic Vasculitis, Hepatitis B Virus-Associated Vasculitis, Syphilis-Associated Aortitis, Serum Sickness-Associated Immune Complex Vasculitis, Drug-Associated Immune Complex Vasculitis, Drug-Associated ANCA-Associated Vasculitis and Cancer-Associated Vasculitis.

ARTHRITIS & RHEUMATOLOGY
Vol. 70, No. 2, February 2018, pp 171–184
DOI 10.1002/art.40375

SPECIAL ARTICLE

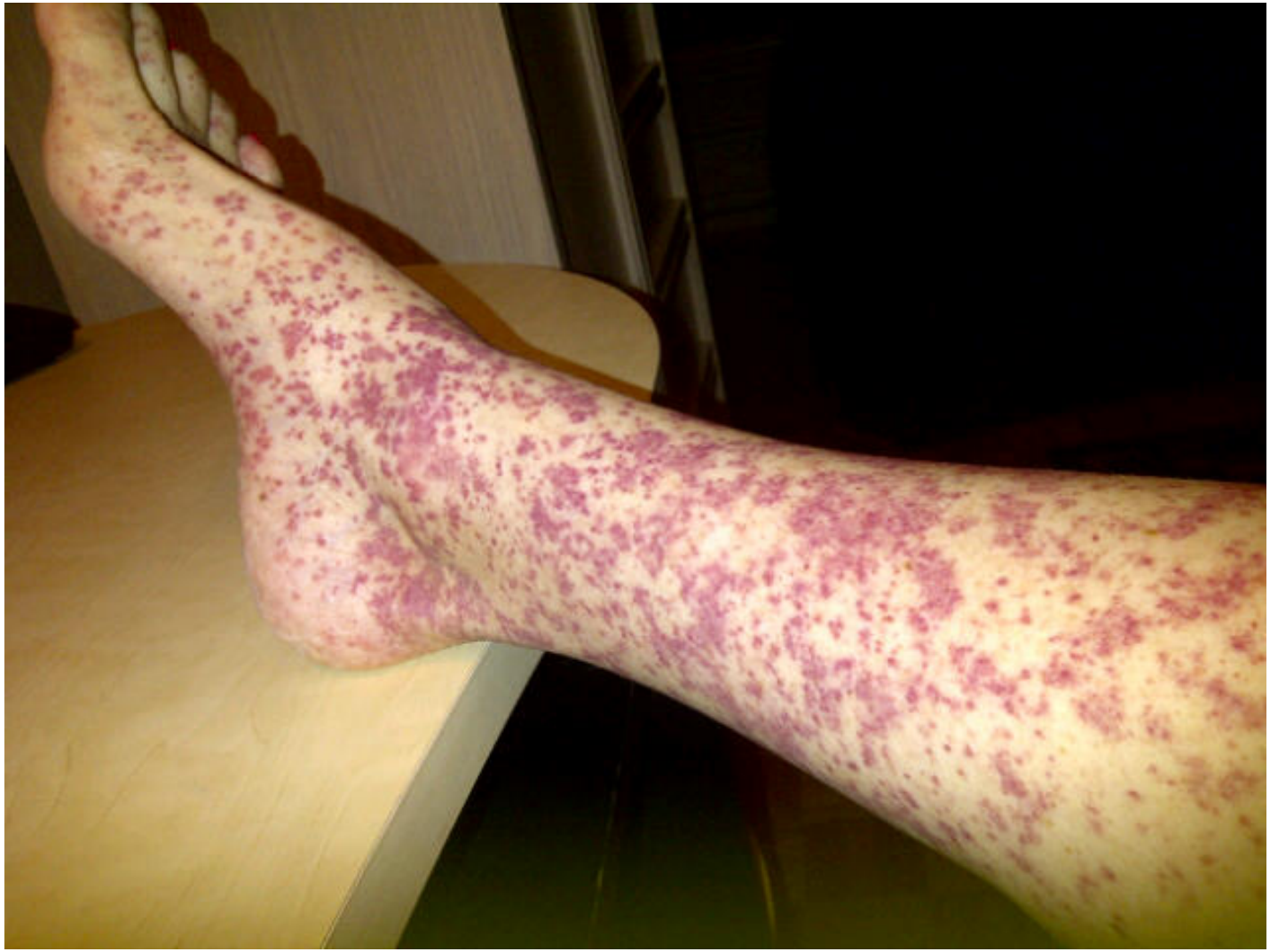
Nomenclature of Cutaneous Vasculitis

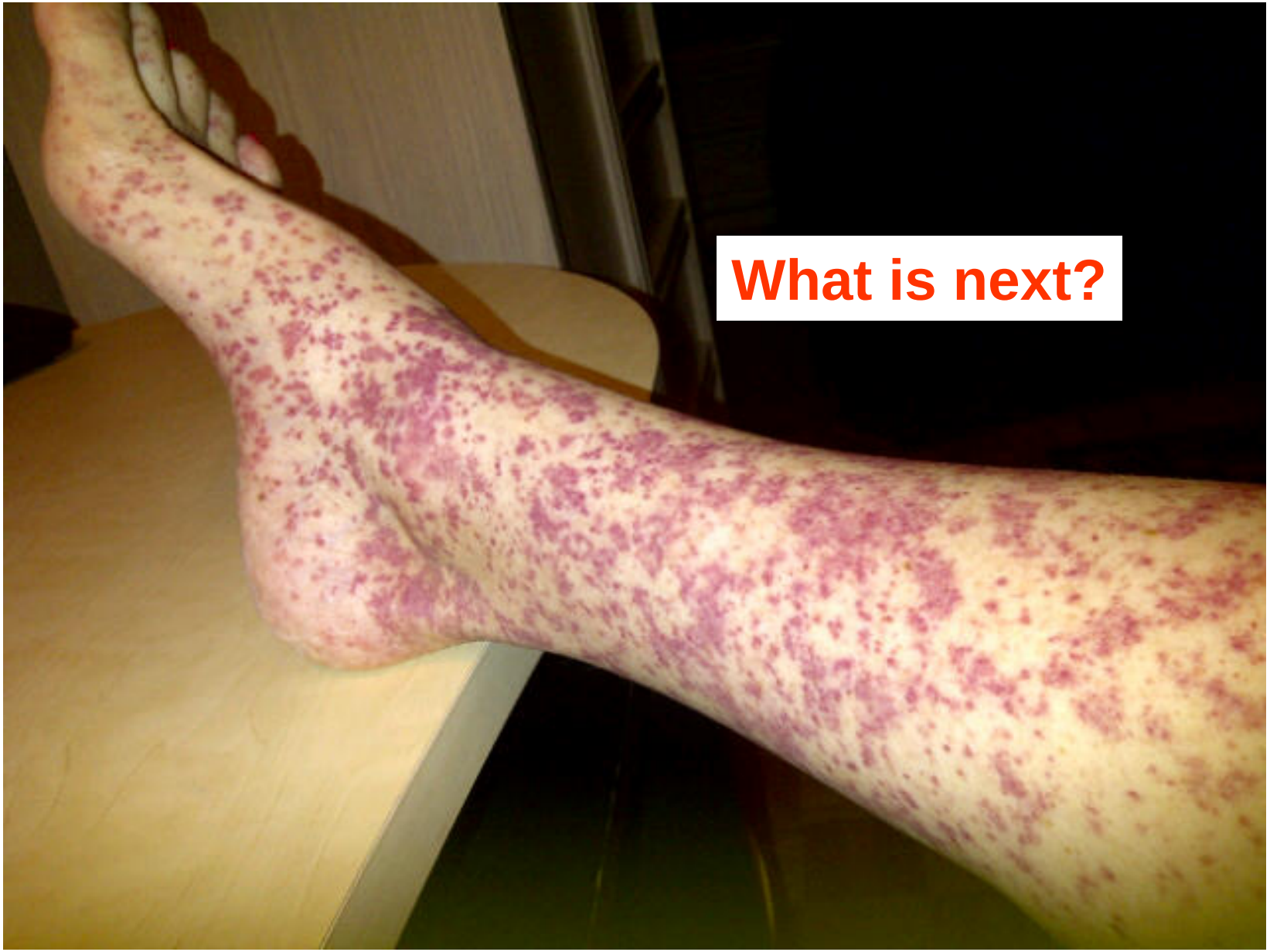
Dermatologic Addendum to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides

ARTHRITIS & RHEUMATOLOGY
Vol. 70, No. 2, February 2018, pp 171–184
DOI 10.1002/art.40375

CHCC2012 vasculitis category, name	Skin involvement status	
	Cutaneous component of systemic vasculitis	Skin-limited or skin-dominant variant
Large vessel vasculitis		
Takayasu arteritis	No	No
Giant cell arteritis	Rare	No
Medium vessel vasculitis		
Polyarteritis nodosa	Yes	Yes
Kawasaki disease	No	No
Small vessel vasculitis		
Microscopic polyangiitis	Yes	Yes
Granulomatosis with polyangiitis	Yes	Yes
Eosinophilic granulomatosis with polyangiitis	Yes	Yes
Anti–glomerular basement membrane disease	No	No
Cryoglobulinemic vasculitis	Yes	Yes
IgA vasculitis (Henoch-Schönlein)	Yes	Yes
Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)	Yes	Yes
Variable vessel vasculitis		
Behçet's disease	Yes	Yes
Cogan's syndrome	Rare	No
Vasculitis associated with systemic disease		
SLE, rheumatoid arthritis, sarcoidosis, etc.	Yes	Yes
Vasculitis associated with probable etiology		
Drugs, infections, sepsis, autoimmune diseases, etc.	Yes	Yes
Cutaneous SOV (not included in CHCC2012)		
IgM/IgG vasculitis	No (not observed yet)	Yes (as SOV)
Nodular vasculitis (erythema induratum of Bazin)	No	Yes (as SOV)
Erythema elevatum et diutinum	No	Yes (as SOV)
Hypergammaglobulinemic macular vasculitis	No	Yes (as SOV)
Normocomplementemic urticarial vasculitis	No	Yes (as SOV)

Referrals for ?vasculitis




What is next?

What's next?
Isolated? Not isolated?

CBC, lytes, LFT, CK

Creat, UA

CRP, ESR

SPEP, TSH

Serologies HBV HCV HIV (syphilis, Lyme)

ANA (ENA), ANCA, RF, C3 C4, cryog/cryof (cold agglu, APL/ACL)

CXR

If Bx → with IF

Primary vasculitis?

→ which one (what else)?

Secondary vasculitis?

→ drugs / allergy

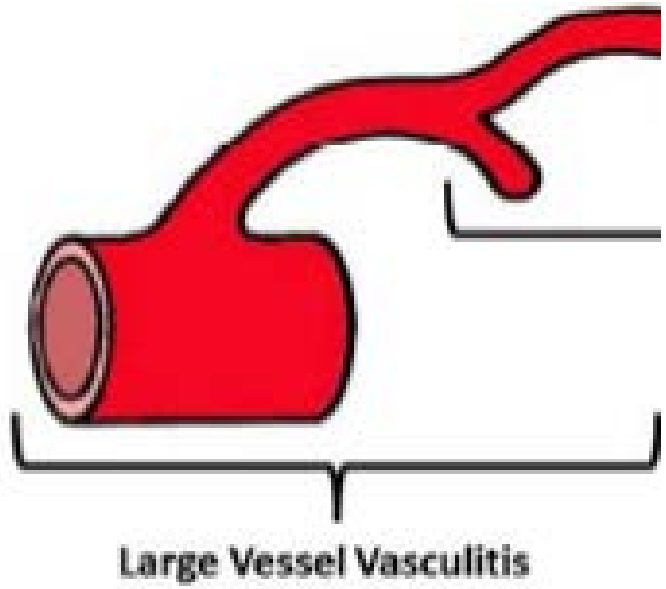
→ neoplasm

→ infection

→ other systemic disease

Rx: colchicine, dapsone, HCQ, danazol, aza, lef, mmf, mtx… prednisone

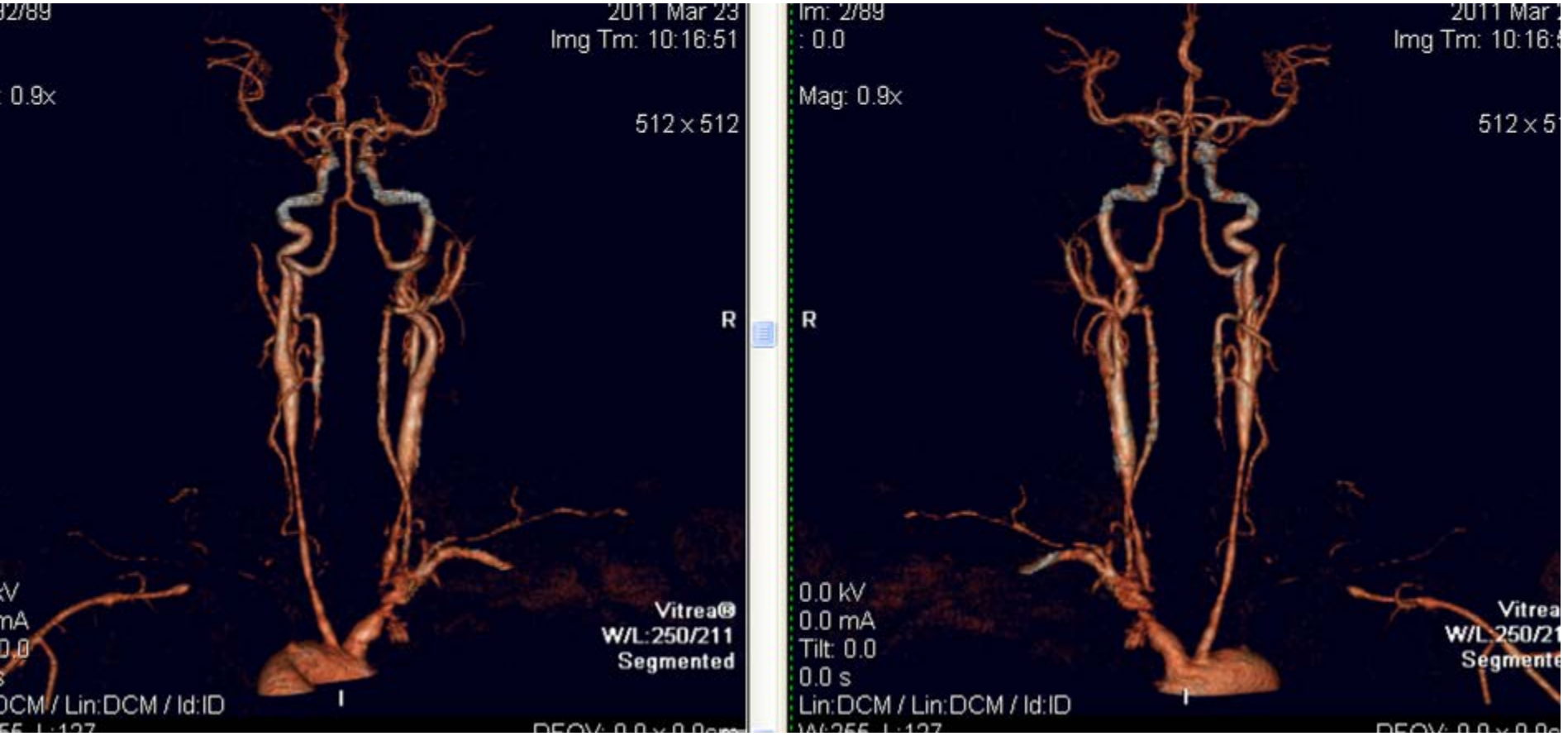
2012 revised Chapel hill nomenclature



Jennette et al. Arthritis Rheum. 2012 Oct 8.

TAKAYASU arteritis

- Pulseless women
- Women 15-25 years-old, Asians/Indians+
- Chronic disease
- Aorta and its first branches (arch++)

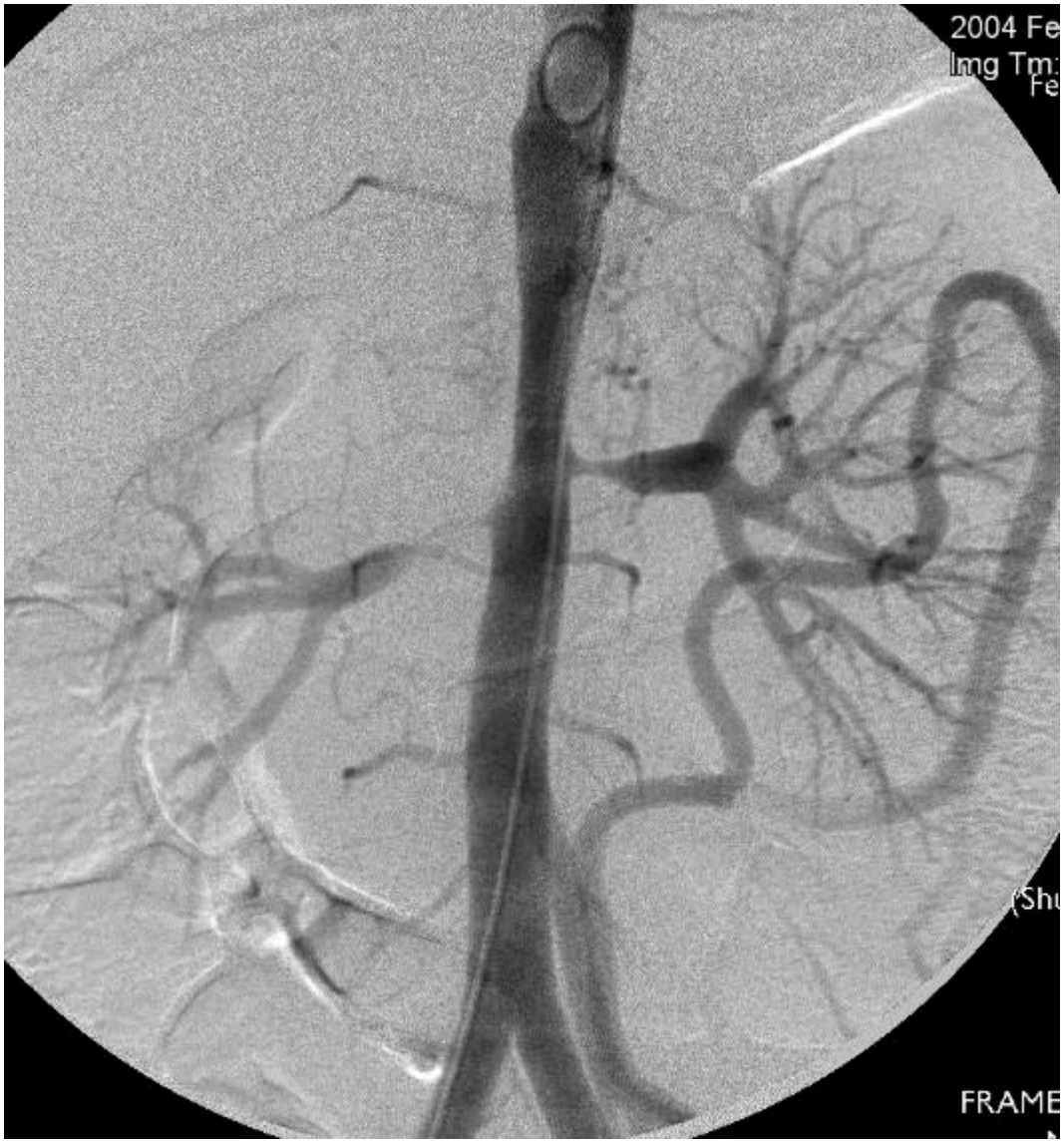


Limb artery stenosis

→<u>Claudication</u>

Cervical-cerebral arteries

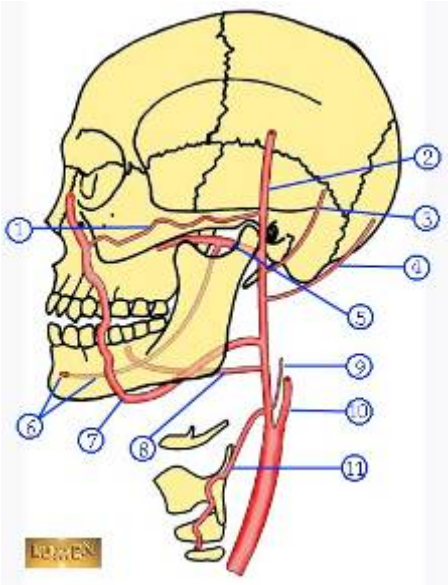
→<u>Strokes</u>



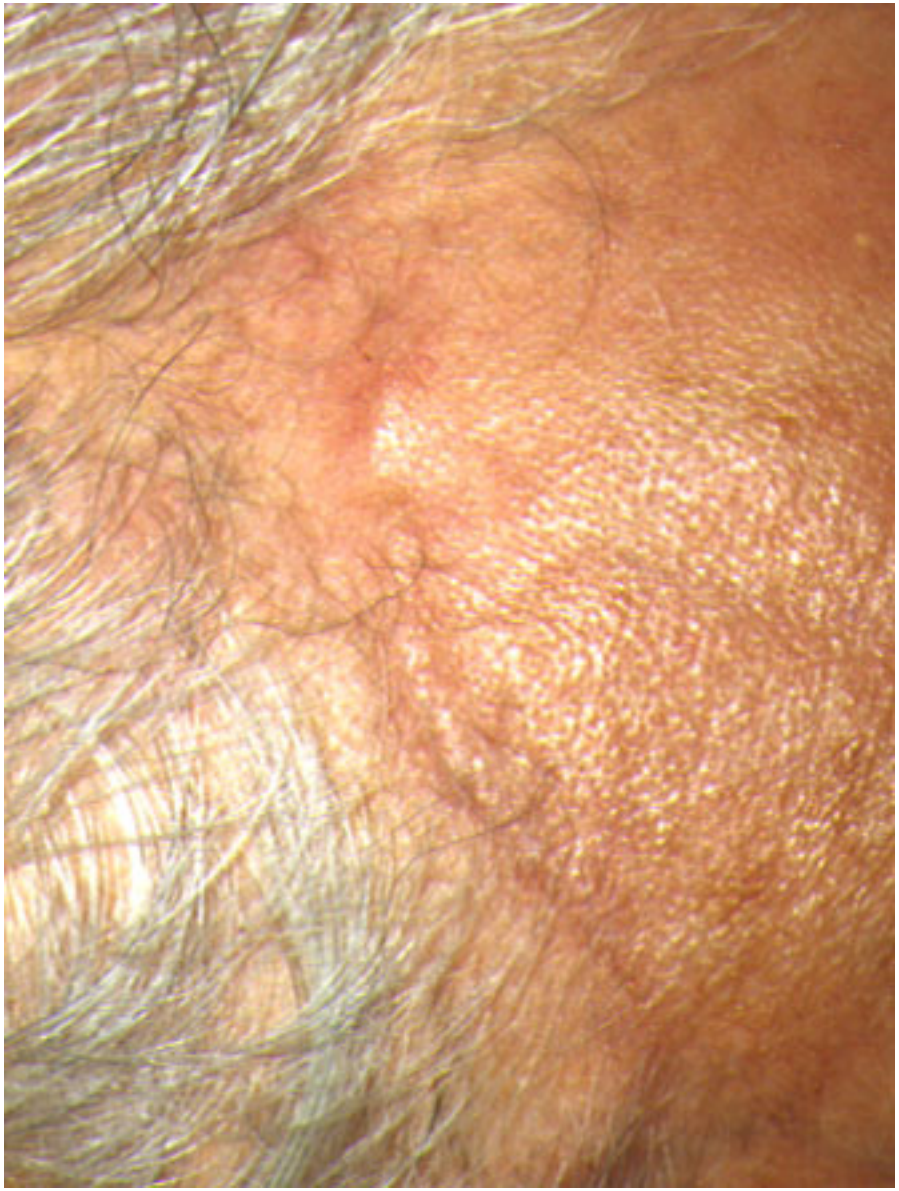
Renal artery stenosis

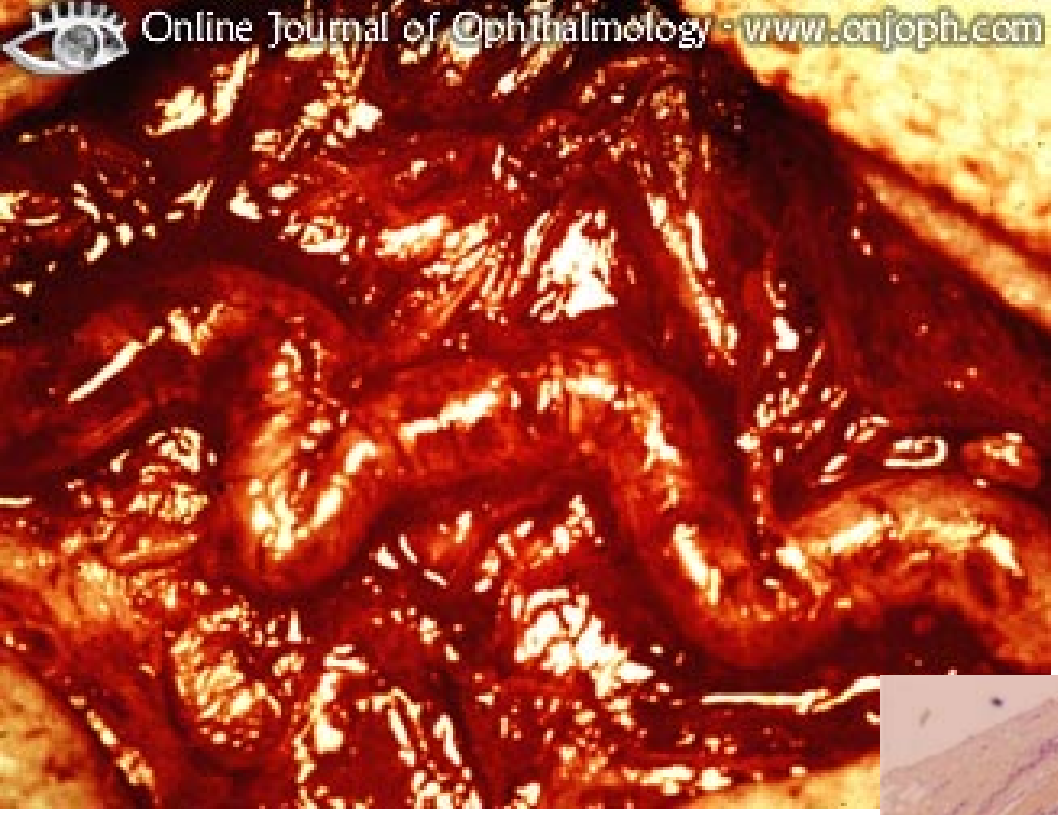
→ <u>High blood pressure</u>

Giant cell arteritis



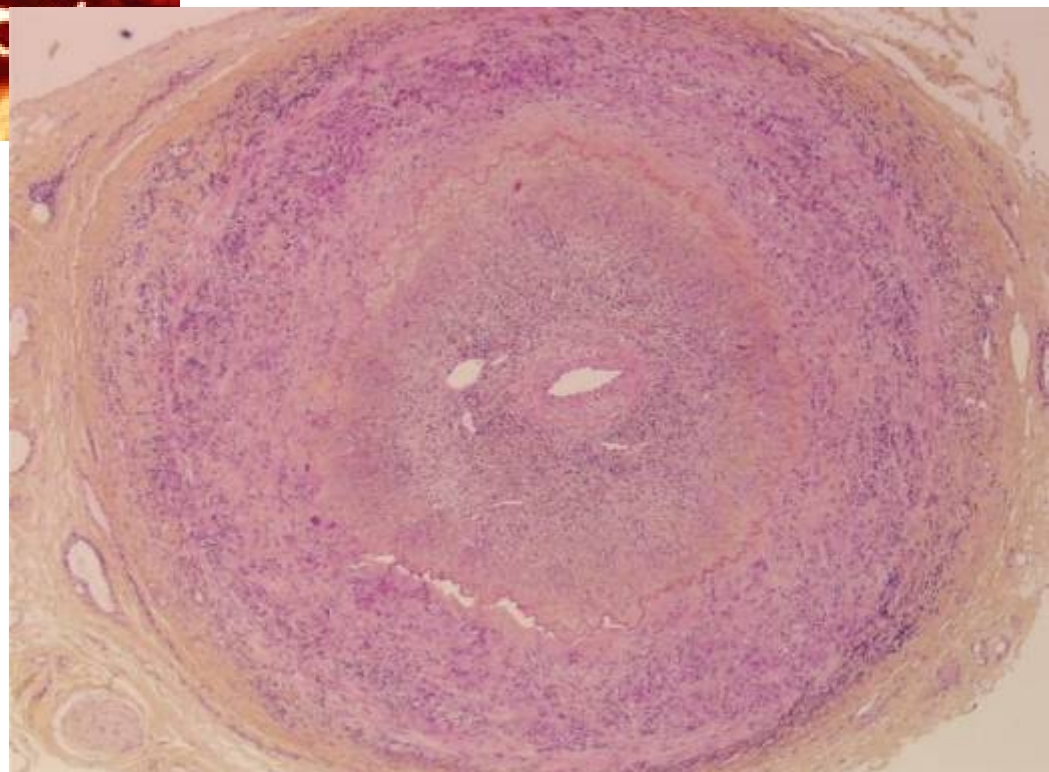
External carotid branches

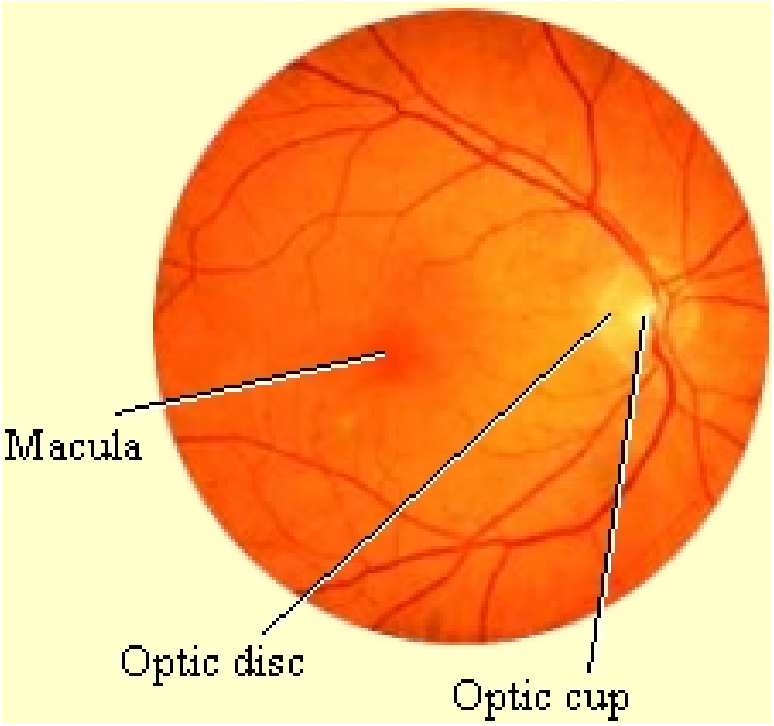


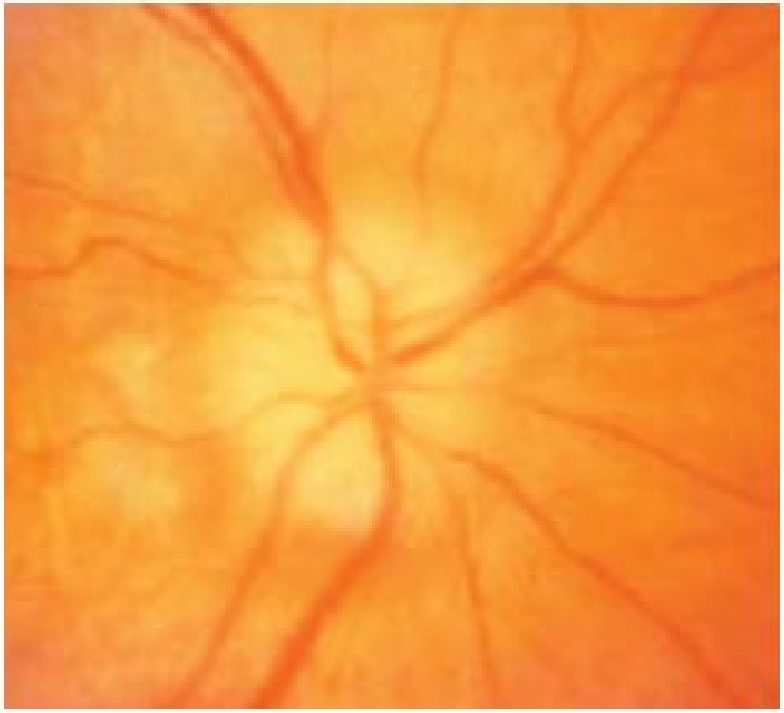


Giant cell arteritis

Risk of occlusion +++

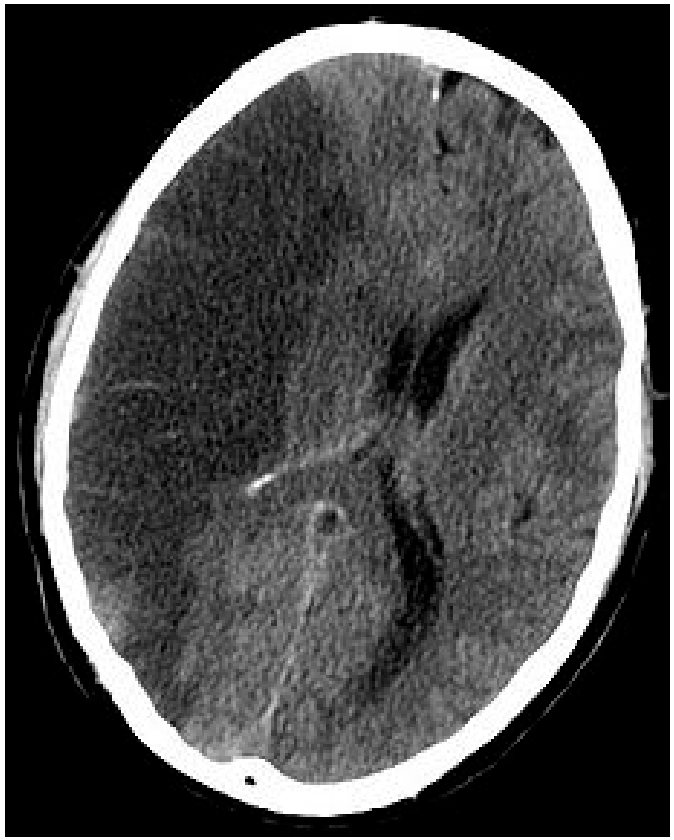






14. Arteritic anterior ischemic optic neuropathy. Note the pallid swelling.

Denise Goodwin, Review of Optometry



Stroke 4%

Aortic involvement

- **Aortitis in 3 to 18% of GCA patients**
- FDG-TEP scanner → **up to 50%**

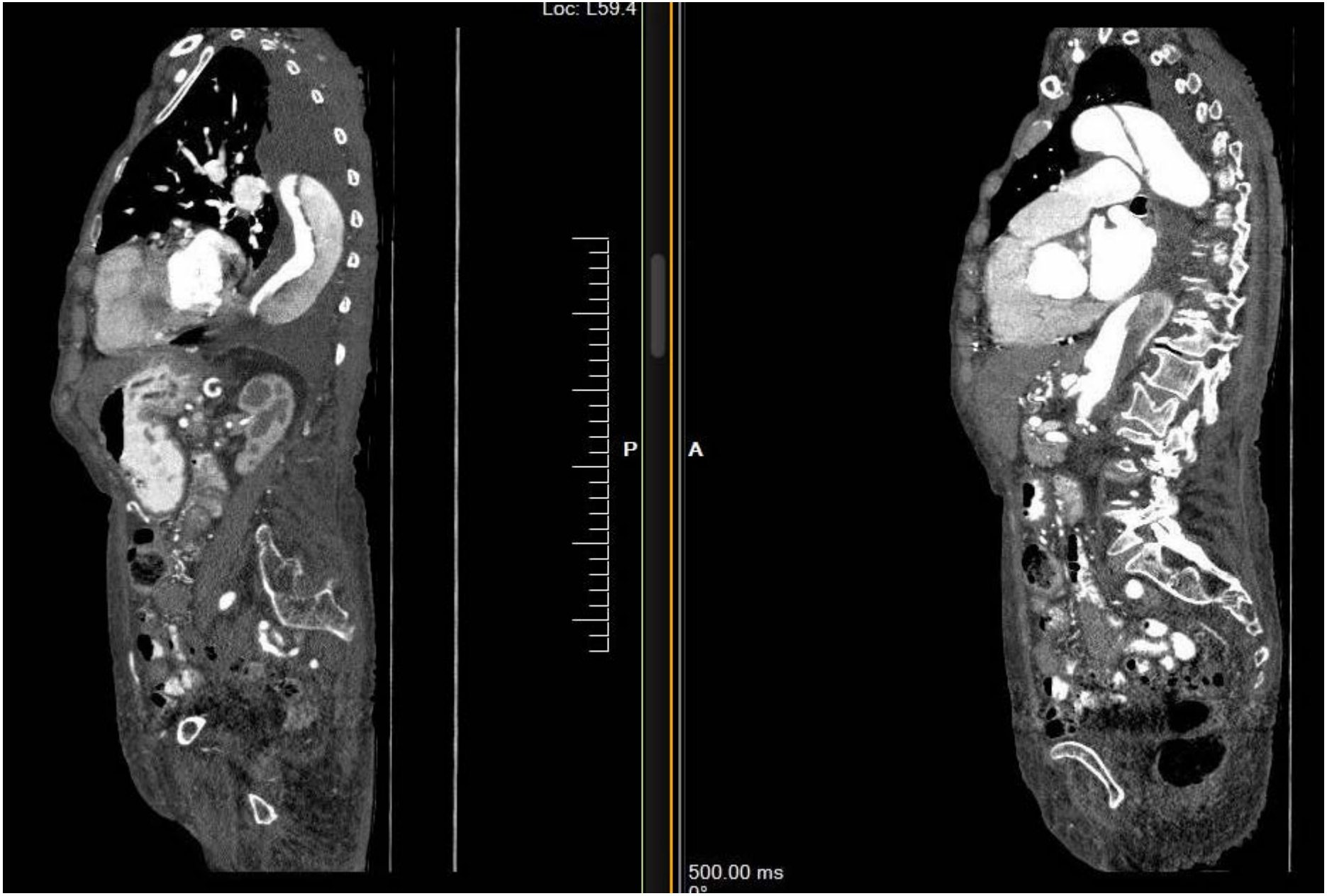
- predominant involvement of the **thoracic aorta**
- at diagnosis 85%, later 15%
- resolution or improvement under Rx 53% (back to normal 9%)
- **increased risk of aneurysm (RR=17, women+, ascending ao+)**, even **(mainly) after treatment** discontinuation (5-11 years later)

→ chest X-ray, echocardiogram, abdomen Doppler-US

or → CT scan of the chest and abdomen

YEARLY??

Marie et al, Medicine (Baltimore) 2009;88:182-92


Loc: L59.4
P
A
500.00 ms

Referrals for ?vasculitis

- M 80 years old
- 2 months history of weakness, mild headaches
- Difficulty to walk

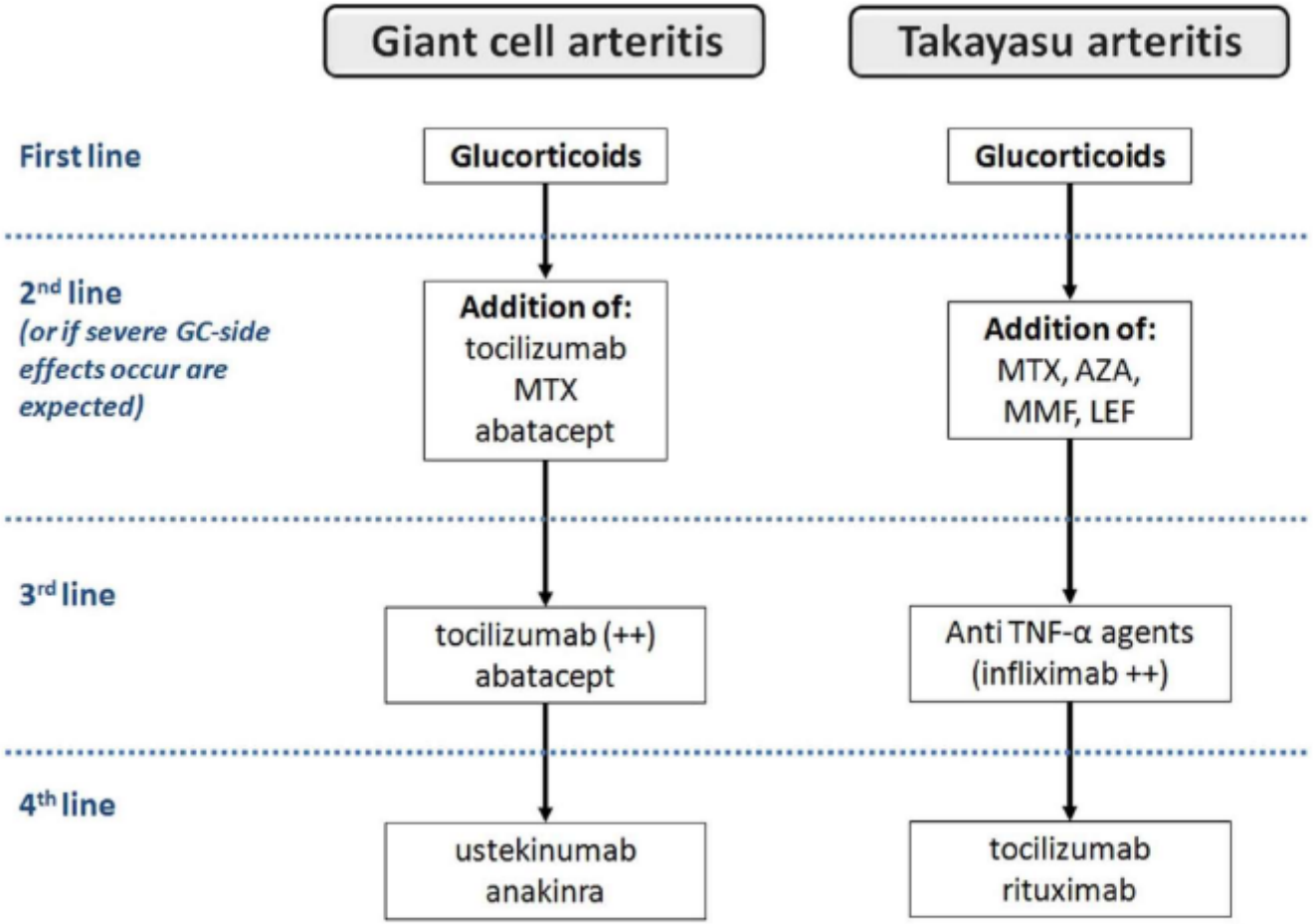
- ESR 65

So, what is next?

Inflammation

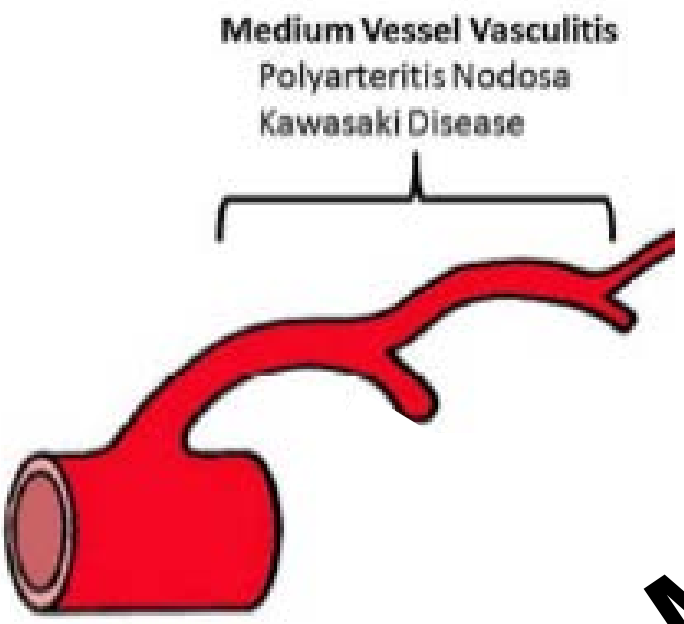
- Increased C-reactive protein
- Increased Sedimentation rate
- Increased WBC (neutrophils)

…. SPEP



Samson et al. European Journal Internal Medicine 2018

2012 revised Chapel hill nomenclature

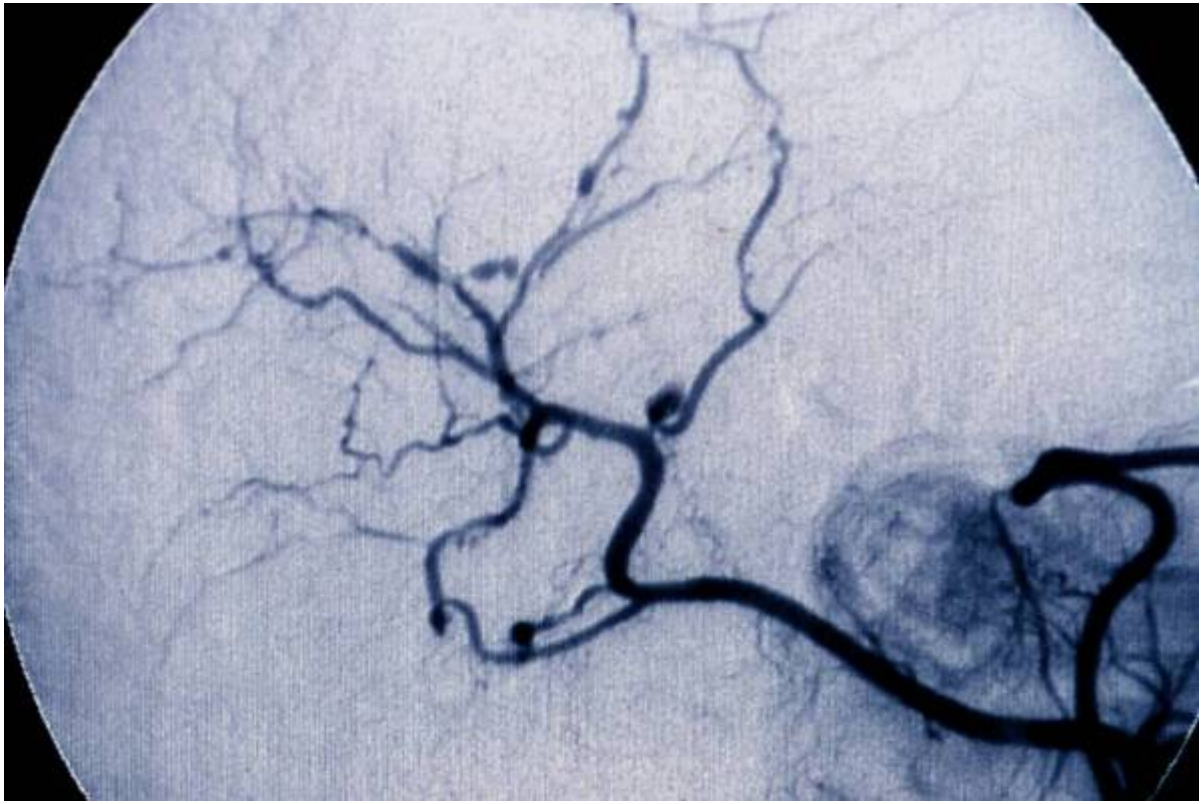


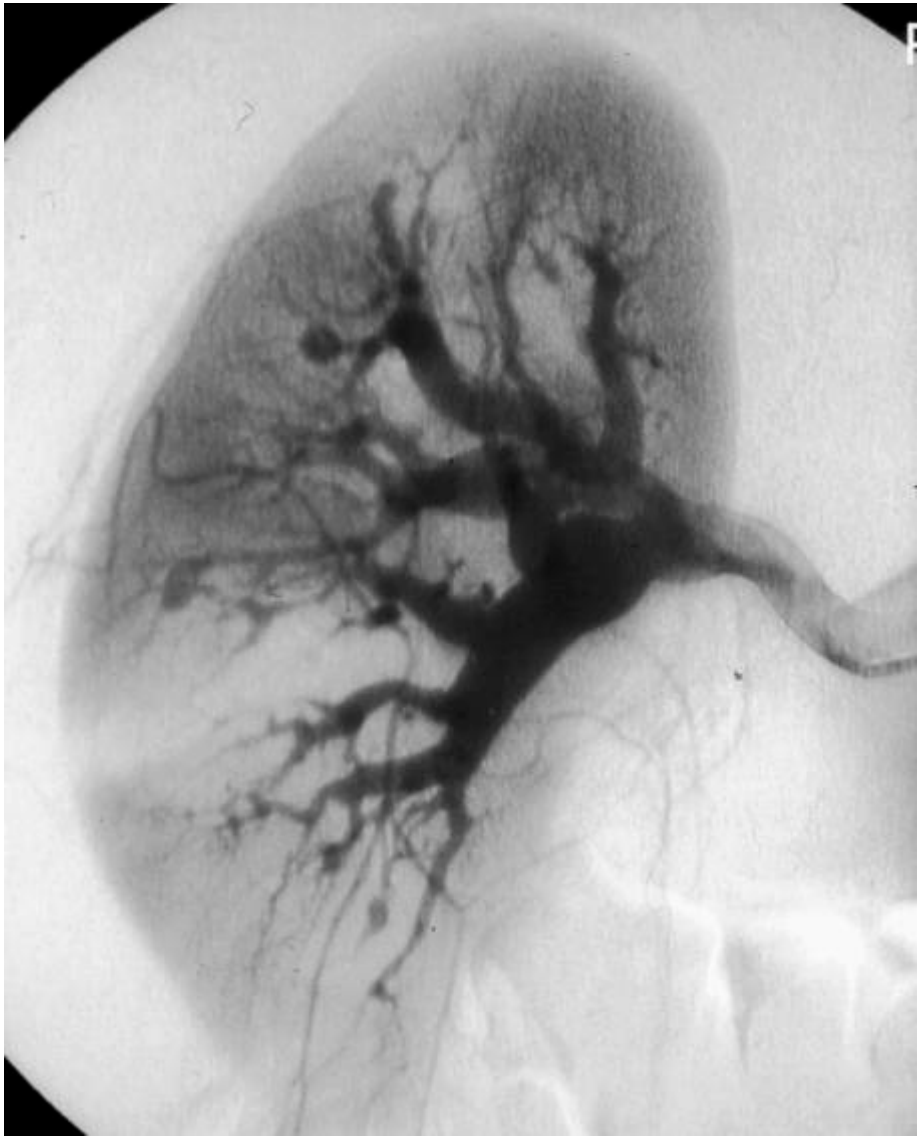
Medium vessel

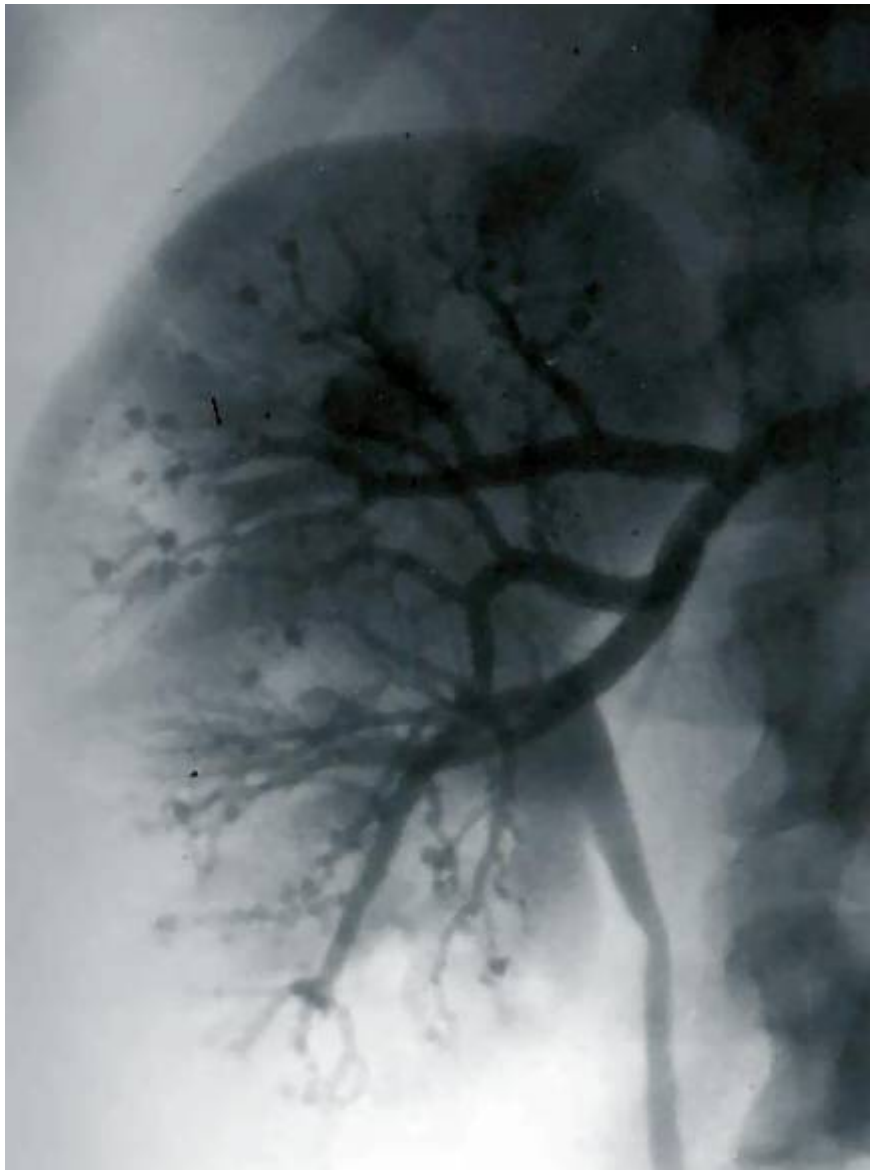
Jennette et al. Arthritis Rheum. 2012 Oct 8.

Polyarteritis nodosa

- Kussmaul 1866
- Necrotizing vasculitis → microaneurisms

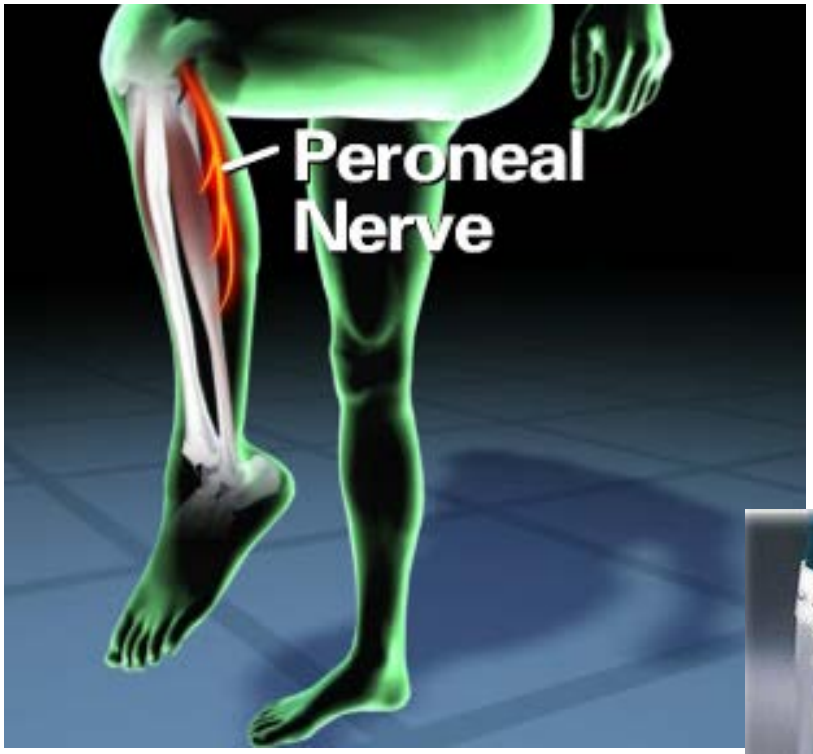


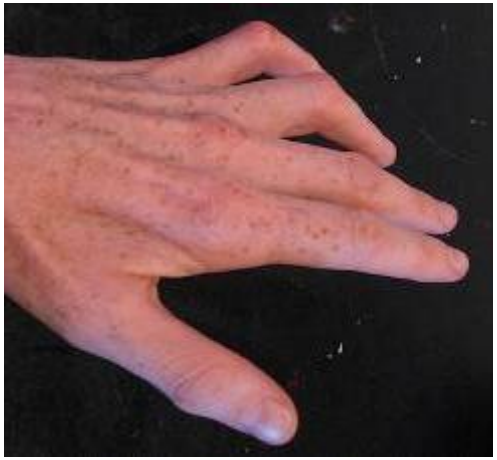


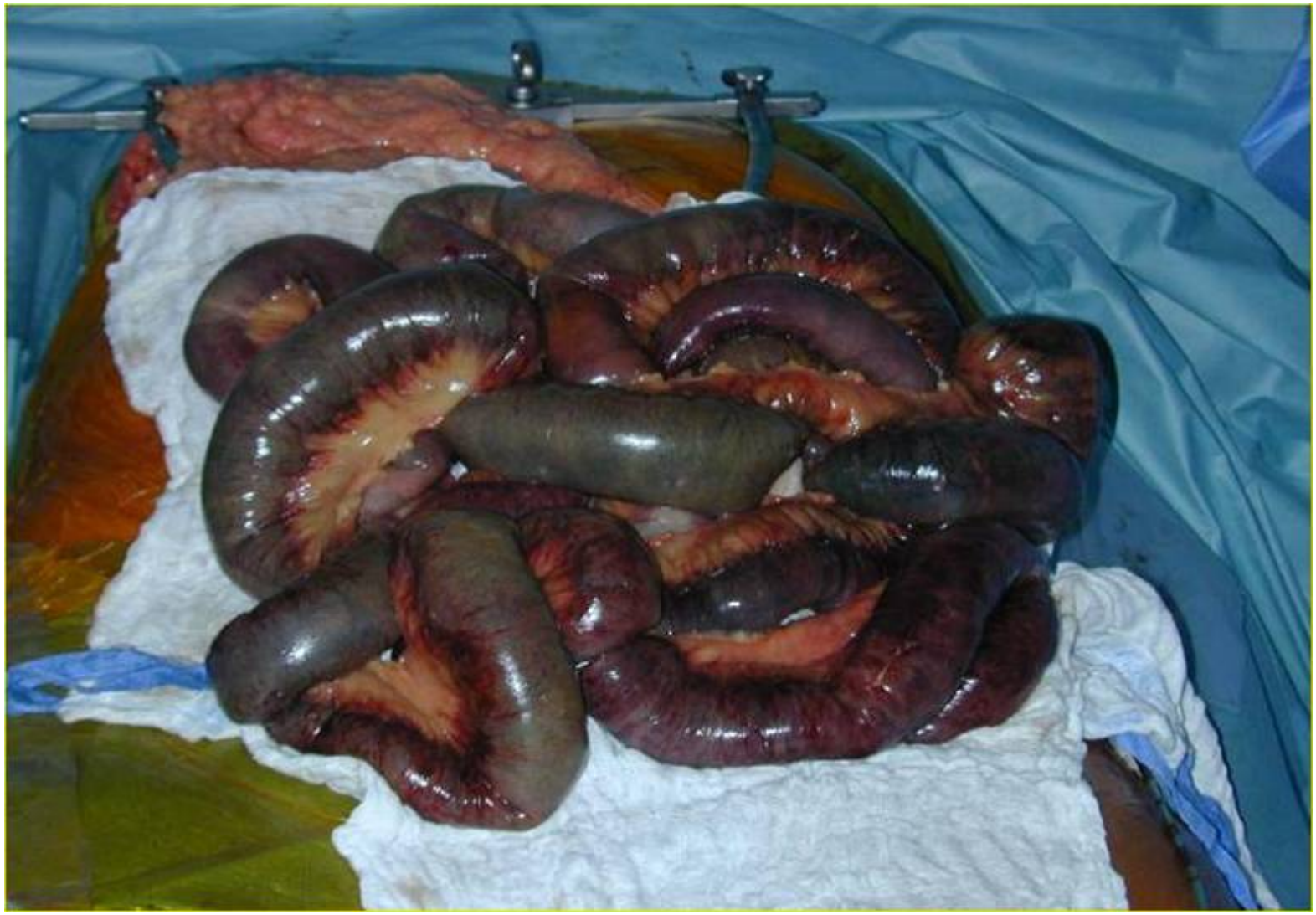


PNS involvement

11-67% of the SNV patients
→ MONONEURITIS MULTIPLEX

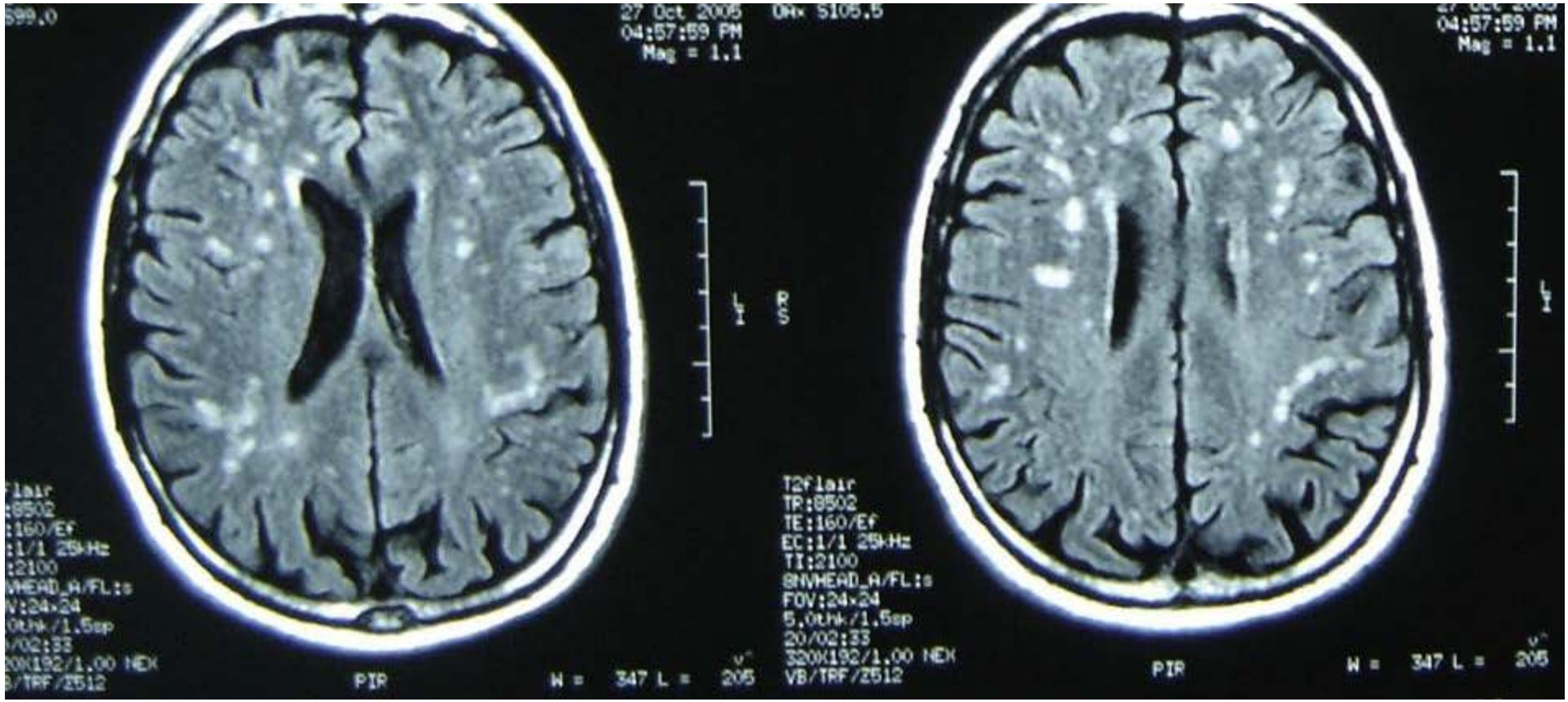


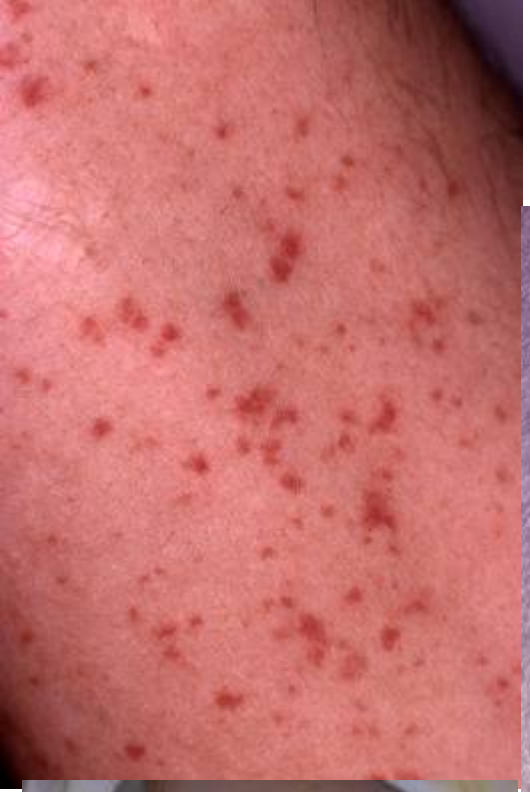


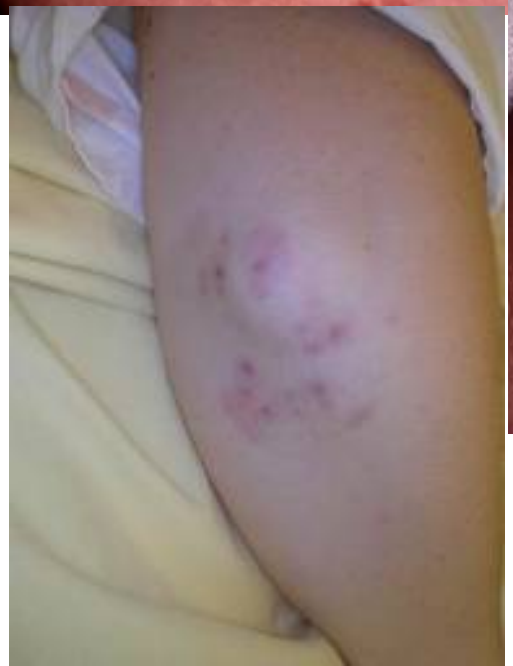


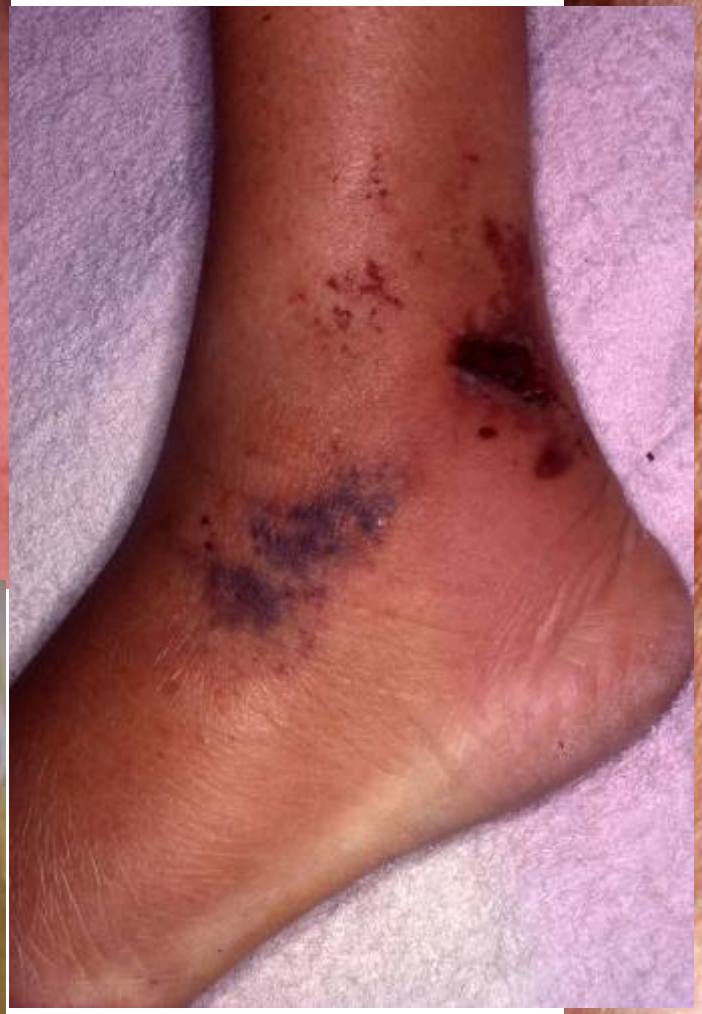
CNS involvement <10% of the GPA patients

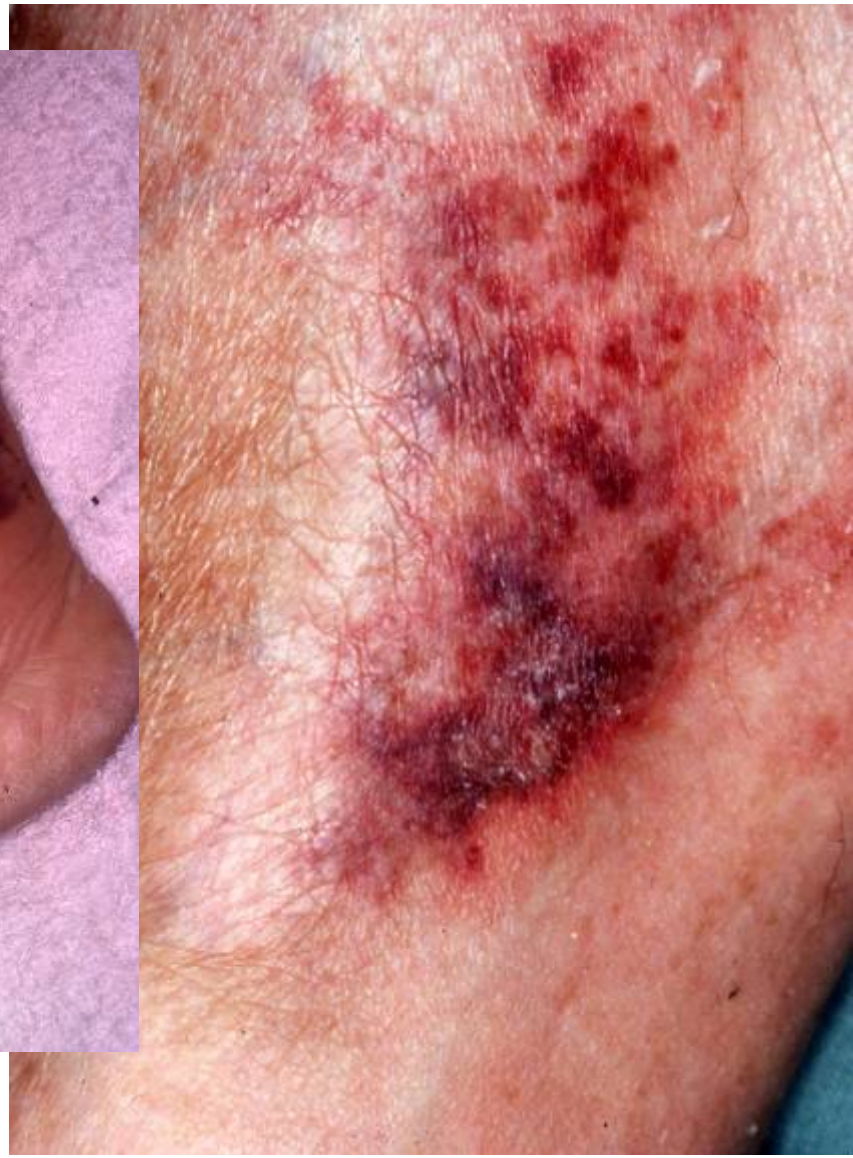
- Stroke
- Hypersignals

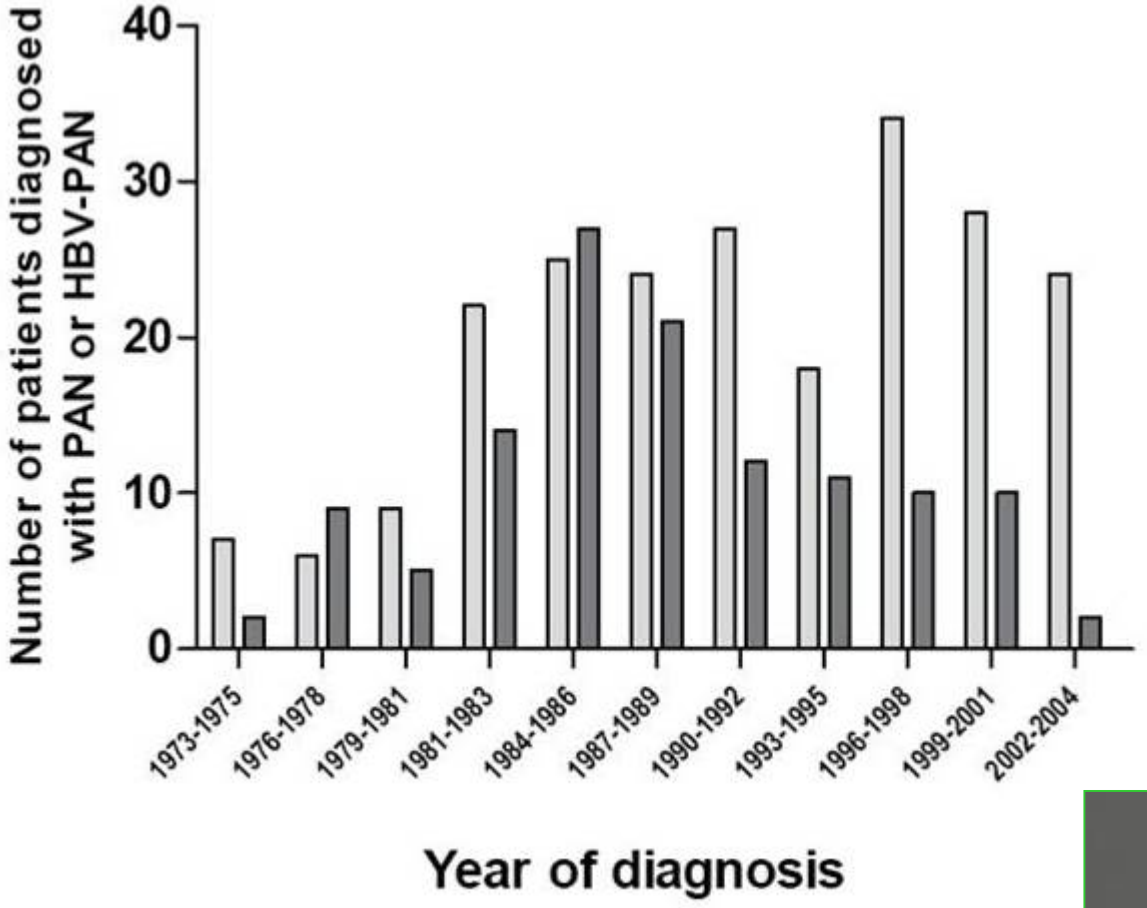


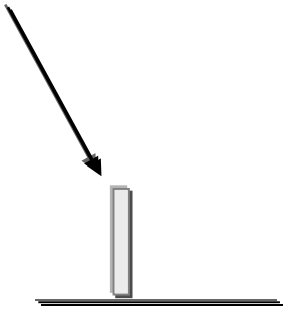


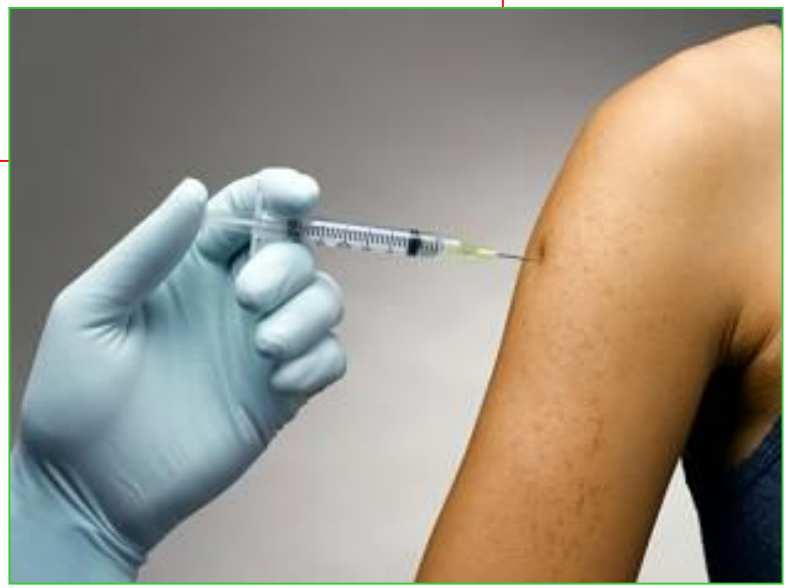












Pagnoux et al. *Arthritis Rheum* 2010;62(2):616-26

ORIGINAL ARTICLE

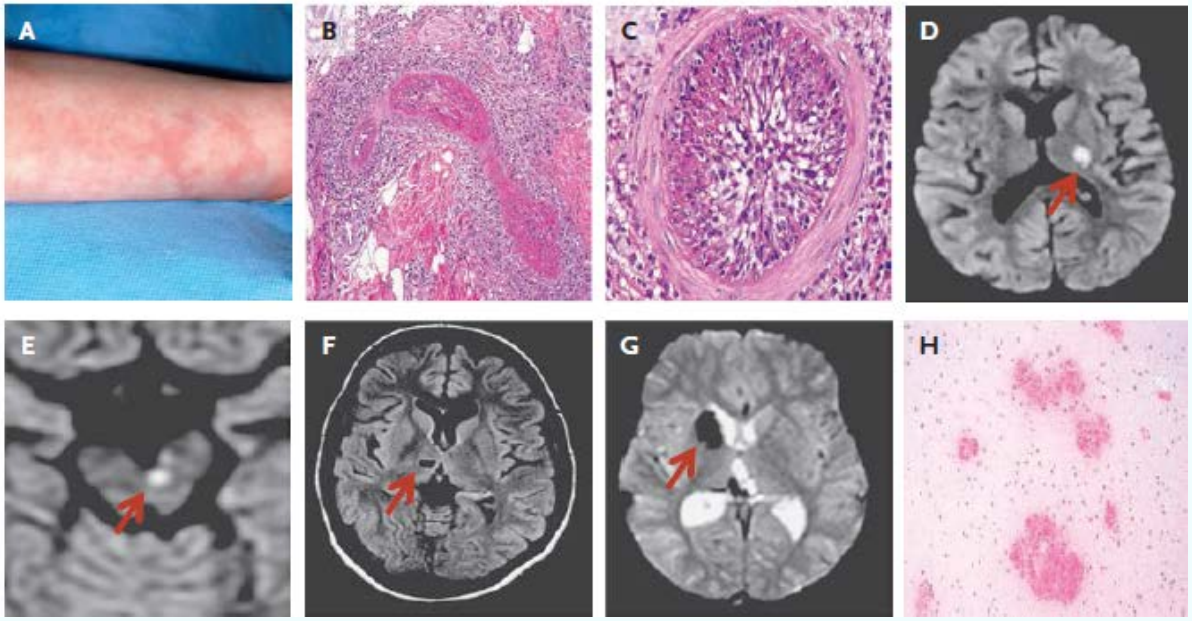
Early-Onset Stroke and Vasculopathy Associated with Mutations in ADA2

Q. Zhou, D. Yang, A.K. Ombrello, Andrey V. Zavialov, C. Toro, Anton V. Zavialov, D.L. Stone, J.J. Chae, S.D. Rosenzweig, K. Bishop, K.S. Barron, H.S. Kuehn, P. Hoffmann, A. Negro, W.L. Tsai, E.W. Cowen, W. Pei, J.D. Milner, C. Silvin, T. Heller, D.T. Chin, N.J. Patronas, J.S. Barber, C.-C.R. Lee, G.M. Wood, A. Ling, S.J. Kelly, D.E. Kleiner, J.C. Mullikin, N.J. Ganson, H.H. Kong, S. Hambleton, F. Candotti, M.M. Quezado, K.R. Calvo, H. Alao, B.K. Barham, A. Jones, J.F. Meschia, B.B. Worrall, S.E. Kasner, S.S. Rich, R. Goldbach-Mansky, M. Abinun, E. Chalom, A.C. Gotte, M. Punaro, V. Pascual, J.W. Verbsky, T.R. Torgerson, N.G. Singer, T.R. Gershon, S. Ozen, O. Karadag, T.A. Fleisher, E.F. Remmers, S.M. Burgess, S.L. Moir, M. Gadina, R. Sood, M.S. Hershfield, M. Boehm, D.L. Kastner, and I. Aksentijevich

ORIGINAL ARTICLE

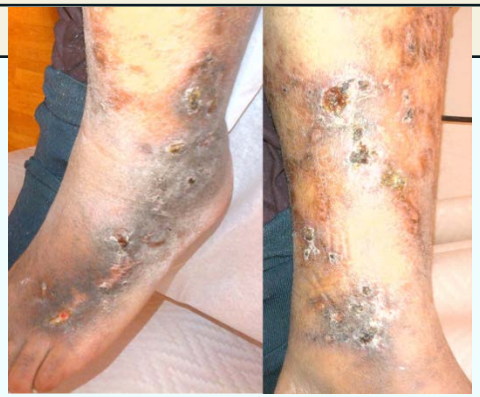
Mutant Adenosine Deaminase 2 in a Polyarteritis Nodosa Vasculopathy

Paulina Navon Elkan, M.D., Sarah B. Pierce, Ph.D., Reeval Segel, M.D., Tom Walsh, Ph.D., Judith Barash, M.D., Shai Padeh, M.D., Abraham Zlotogorski, M.D., Yackov Berkun, M.D., Joseph J. Press, M.D., Masha Mukamel, M.D., Isabel Voth, M.D., Philip Hashkes, M.D., Liora Harel, M.D., Vered Hoffer, M.D., Eduard Ling, M.D., Ph.D., Fatos Yalcinkaya, M.D., Ozgur Kasapcopur, M.D., Ming K. Lee, Ph.D., Rachel E. Klevit, D.Phil., Paul Renbaum, Ph.D., Ariella Weinberg-Shukron, B.Sc.Med., Elif F. Sener, Ph.D., Barbara Schormair, Ph.D., Sharon Zeligson, M.Sc., Dina Marek-Yagel, Ph.D., Tim M. Strom, M.D., Mordechai Shohat, M.D., Amihood Singer, M.D., Alan Rubinow, M.D., Elon Pras, M.D., Juliane Winkelmann, M.D., Mustafa Tekin, M.D., Yair Anikster, M.D., Ph.D., Mary-Claire King, Ph.D., and Ephrat Levy-Lahad, M.D.



N Engl J Med 2014; 370:911-31

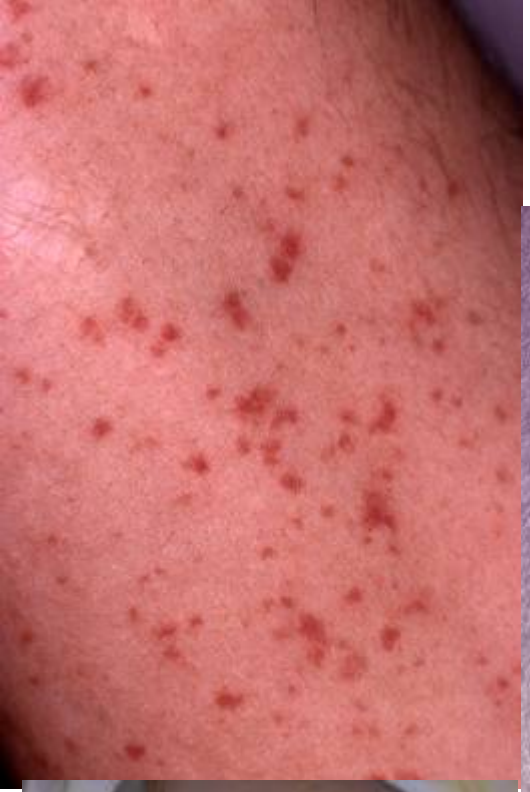
Classification criteria of Adult PAN	Clinical features of DADA2
Documented vasculitis	Necrotizing vasculitis in medium arteries seen on biopsy Brain imaging showing stroke or aneurysm
Characteristic arteriographic abnormalities	
A biopsy of small- or medium-sized artery	
Weight loss >4 kg	
Livedo reticularis	Skin involvement: Livedo reticularis/racemosa, nodules, infarcts, purpura, Raynaud's, erythema nodosum
Testicular pain or tenderness	Testicular pain
Myalgias, weakness of muscles	Myalgias, arthralgias, arthritis
Mononeuropathy or polyneuropathy	Peripheral neuropathy
New-onset diastolic blood pressure >90 mmHg	Hypertension
Elevated levels of serum blood urea nitrogen or creatinine	Renal involvement Proteinuria, Hematuria
Evidence of hepatitis B virus infection	
Central Nervous System involvement	CNS involvement: Stroke – ischemic or hemorrhagic
Gastrointestinal involvement	Gastrointestinal involvement
Fever	Fever
Eye involvement	Eye involvement
	Immune dysfunction • B cell abnormalities • Common variable immunodeficiency • Castleman-like disease • Lymphoproliferative disease
	Bone marrow dysfunction • Pure red cell aplasia • Hemolytic anemia • Thrombocytopenia

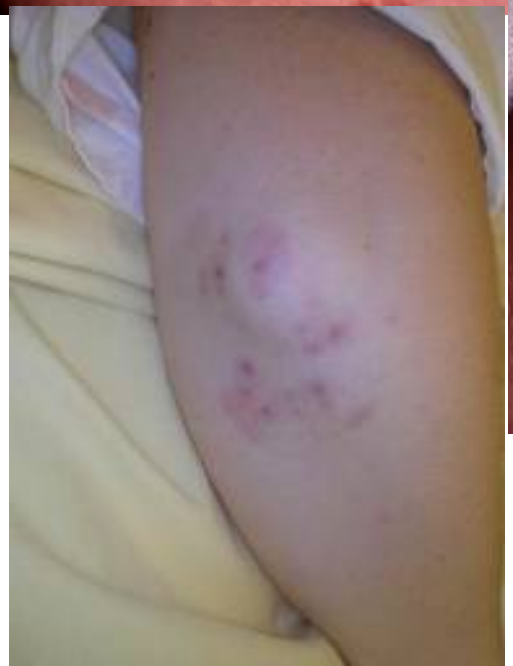


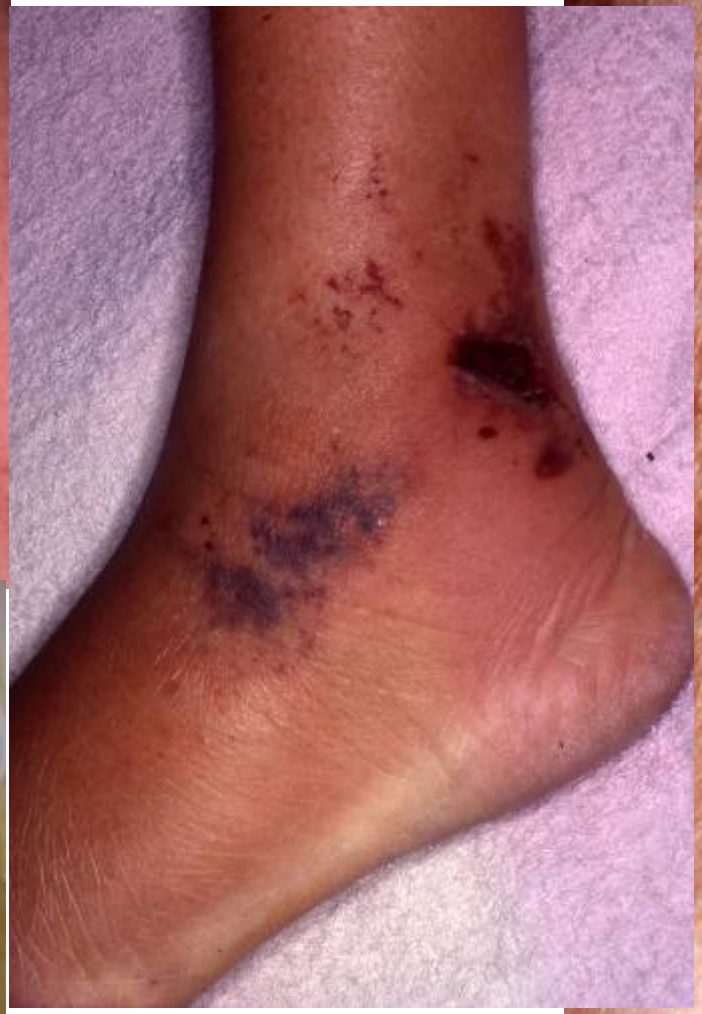
Human et al. Int J Rheum Dis 2018 Apr [Epub]

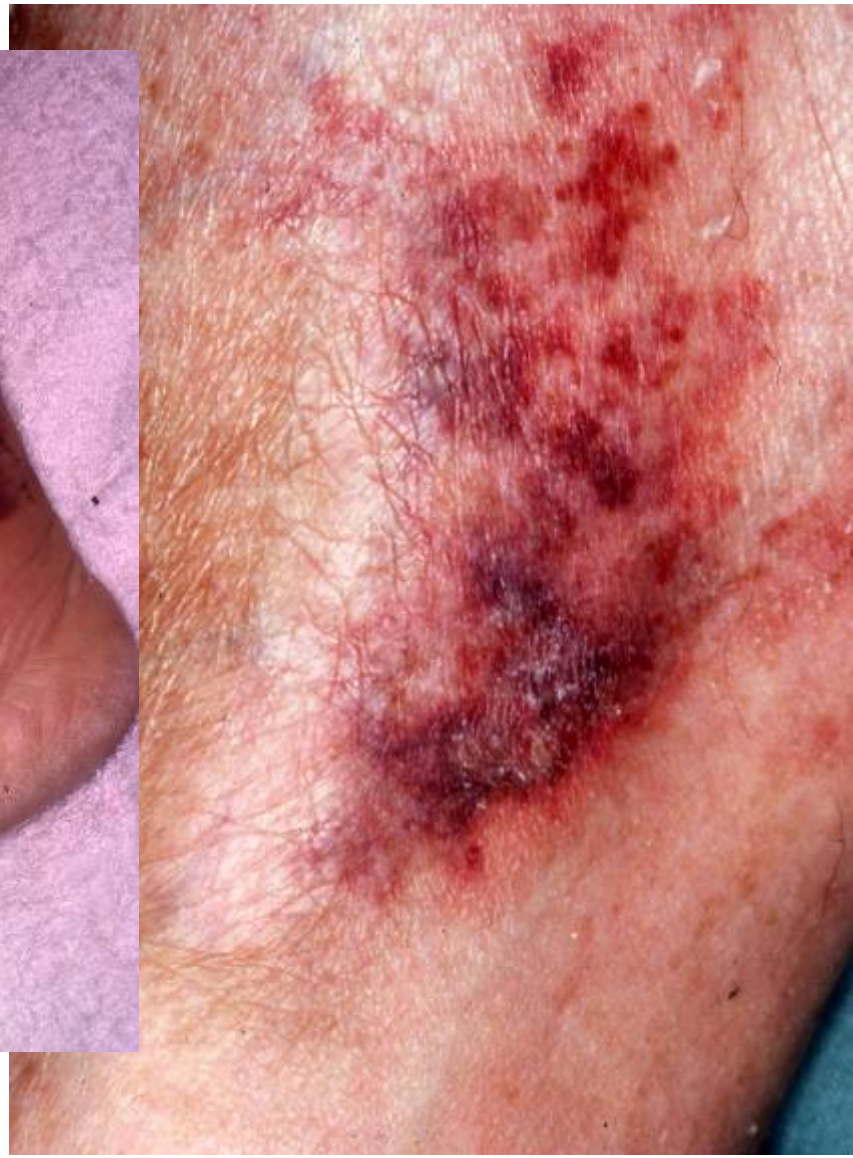
Medium Vessel

Small Vessel

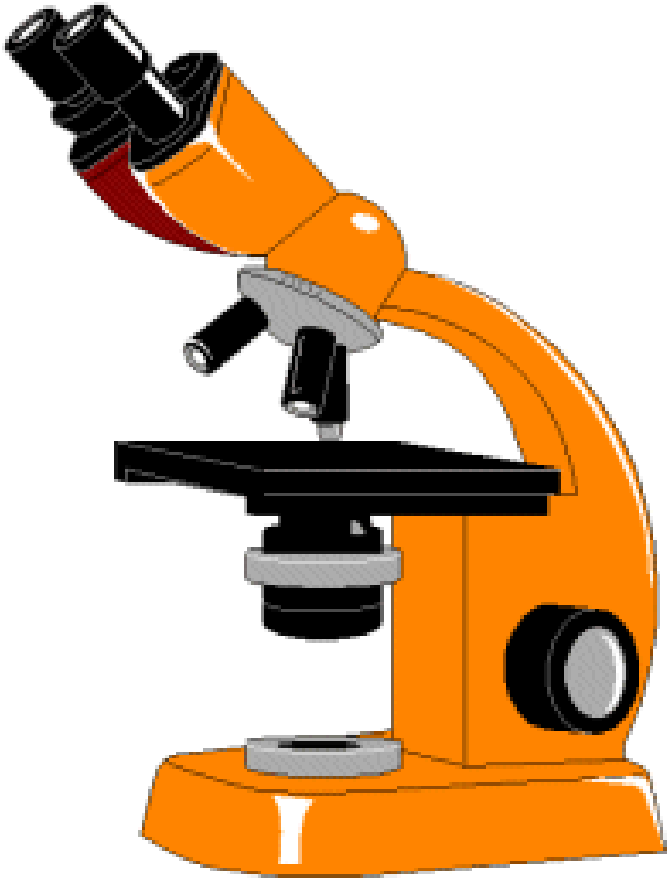






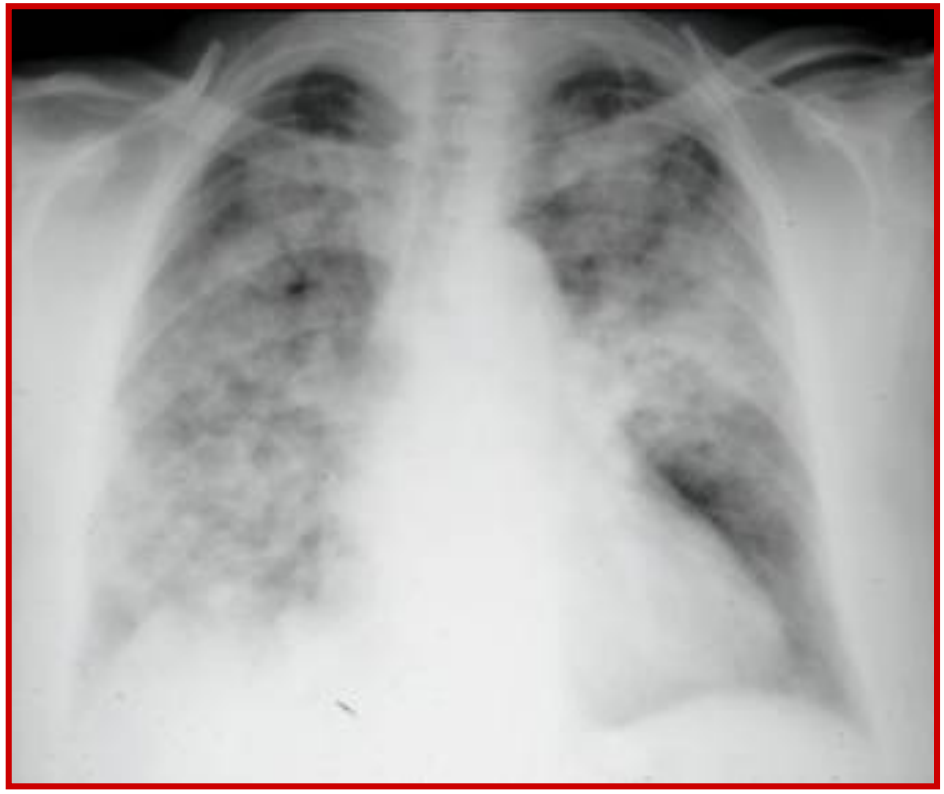


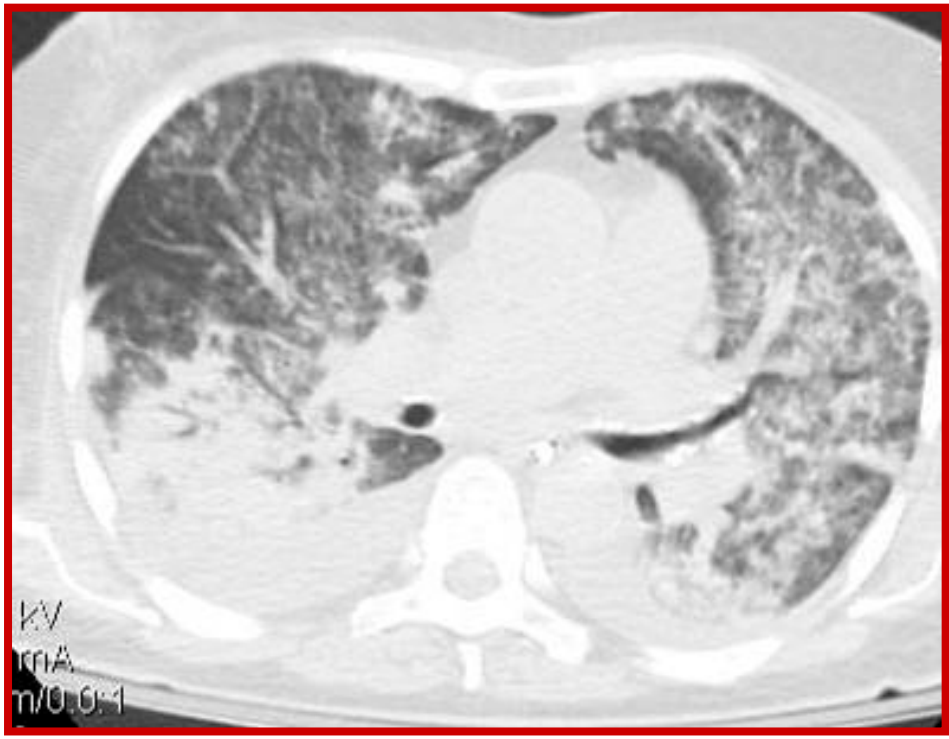
Medium vessel

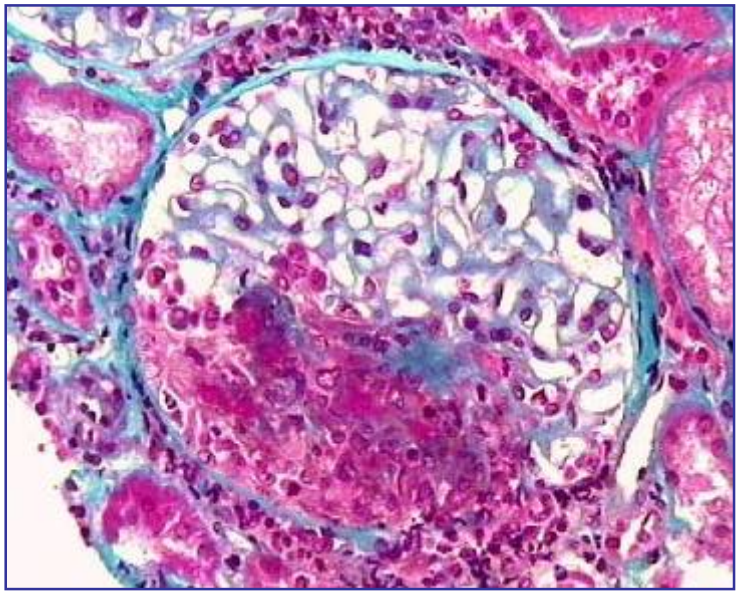


Small vessel

Alveolar hemorrhage



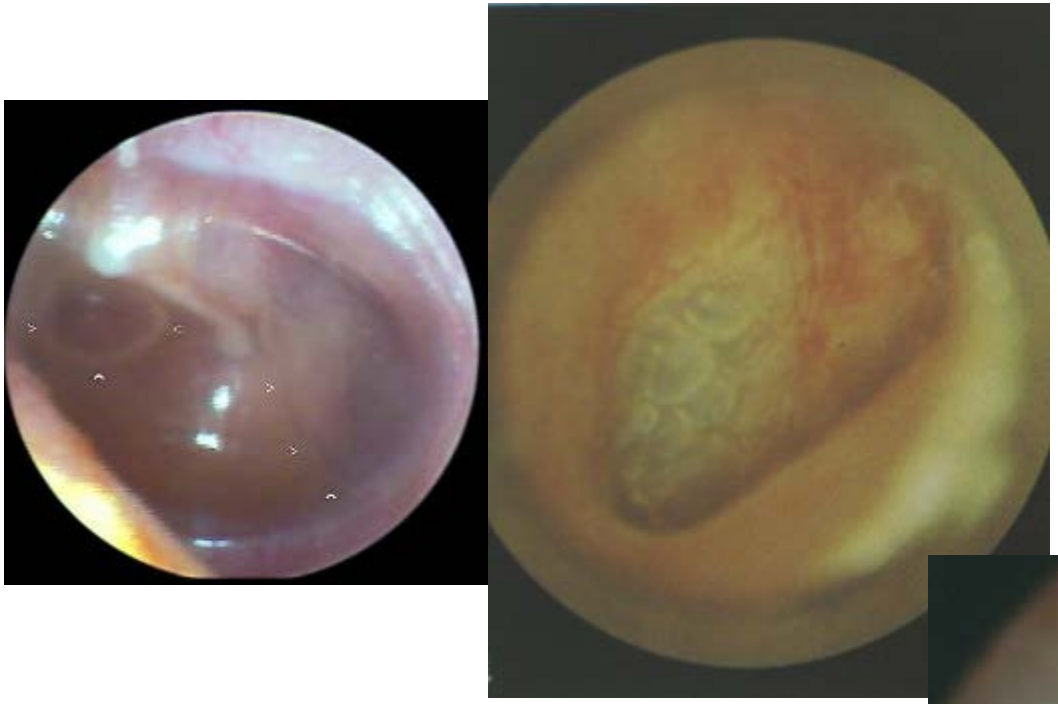




Necrotizing extracapillary GN

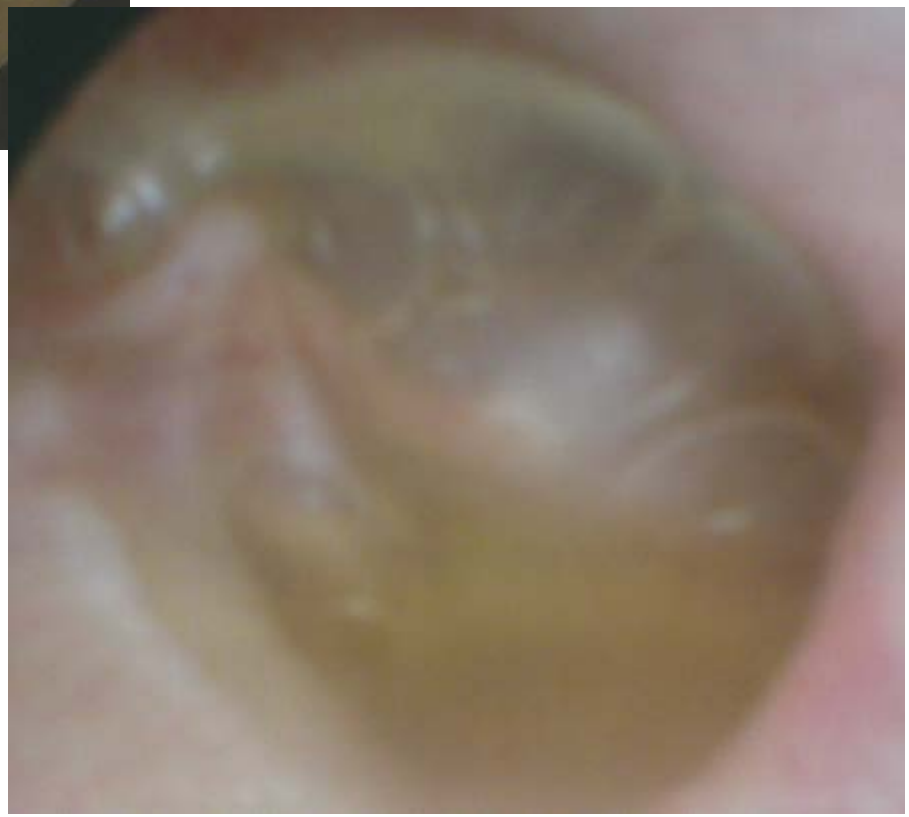
Rapidly progressive GN

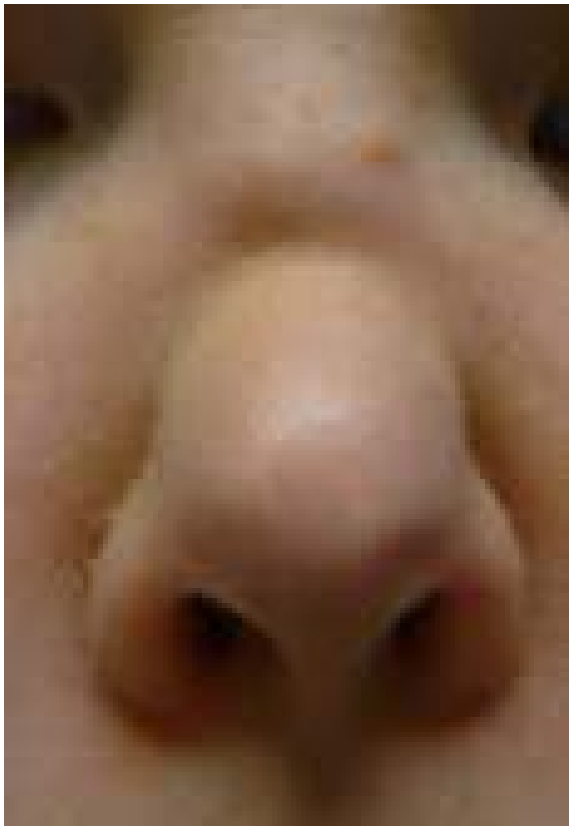
Pauci-immune GN

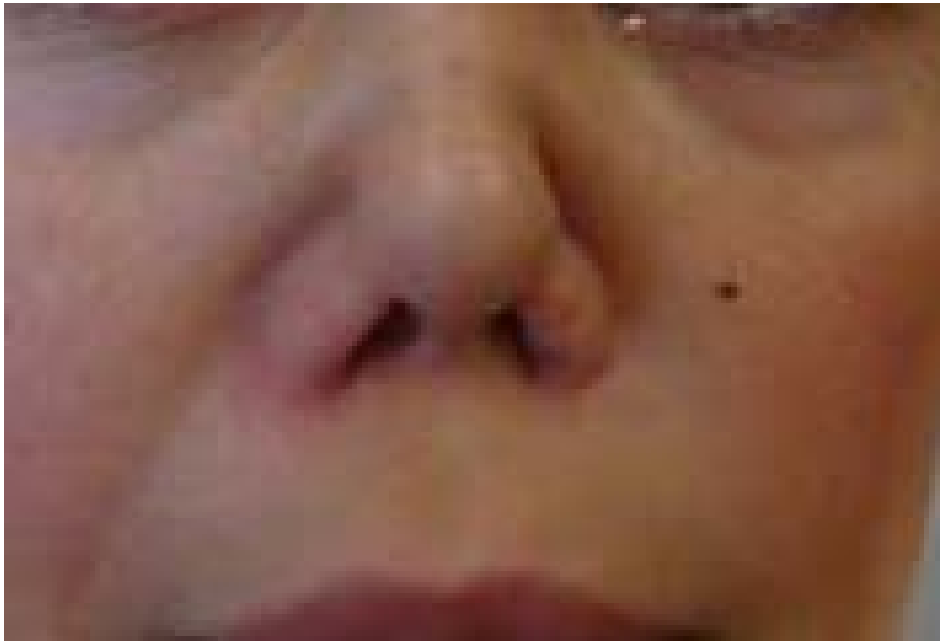


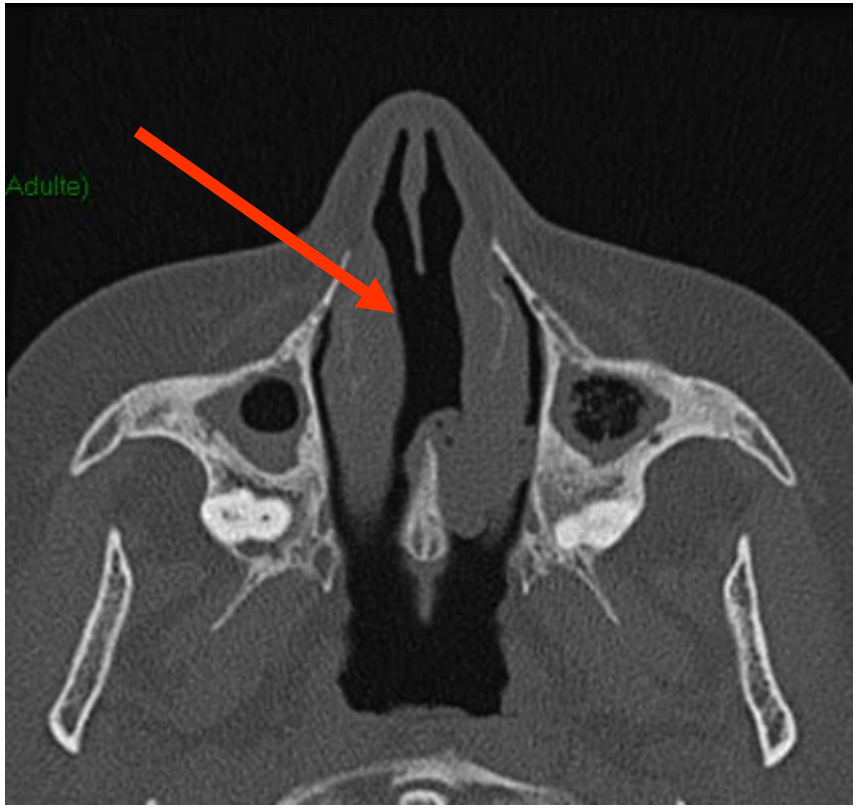
Serous otitis media
(bullaes)

Granulomatosis with polyangiitis (Wegener)

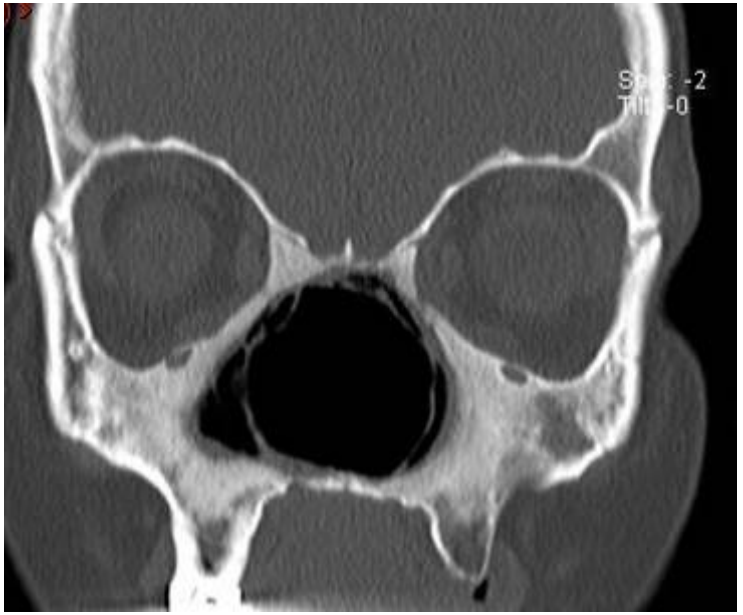


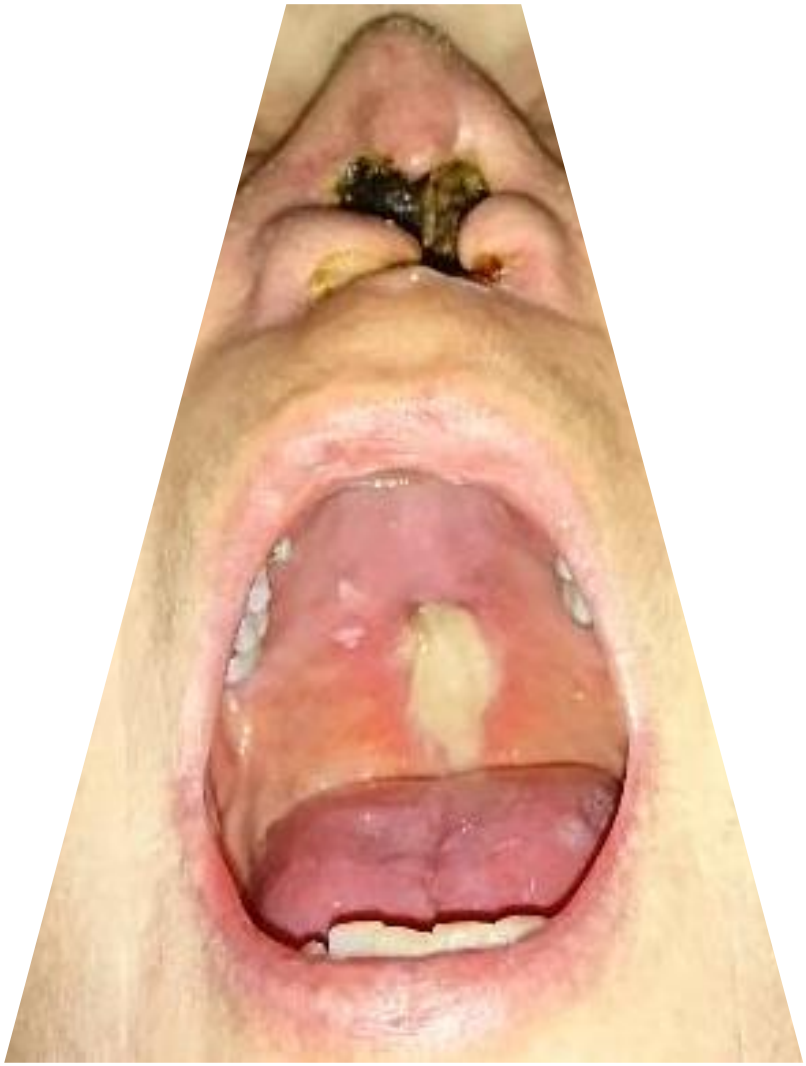


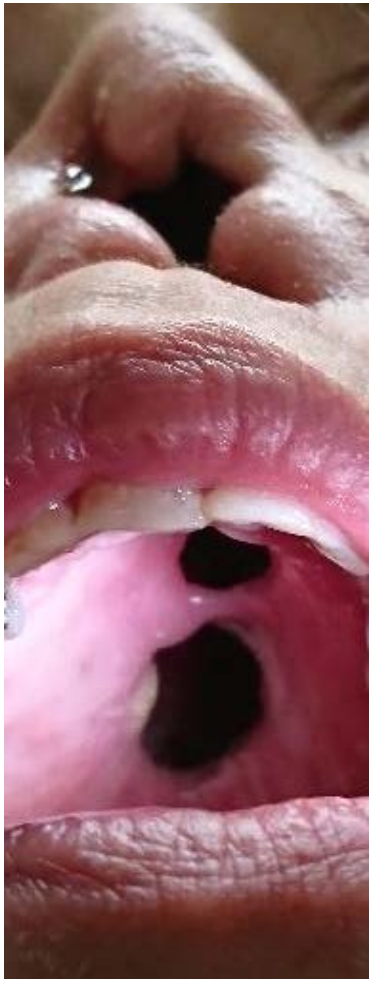


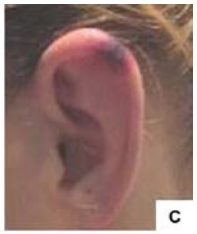


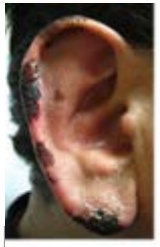
Septal perforation

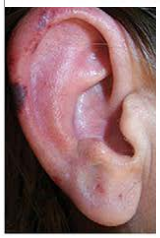


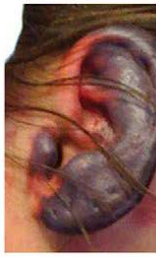


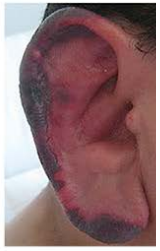


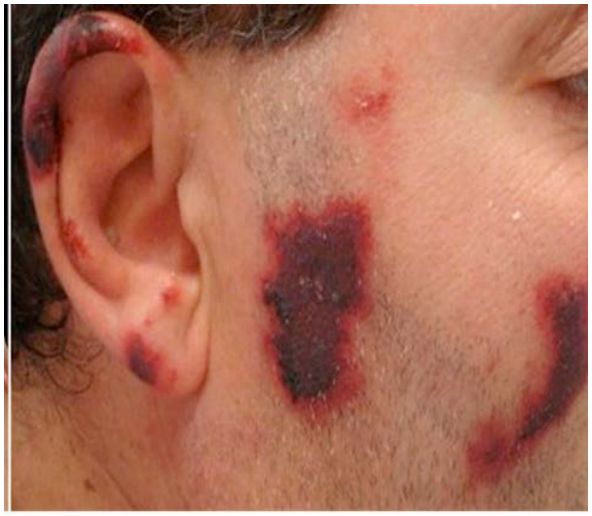


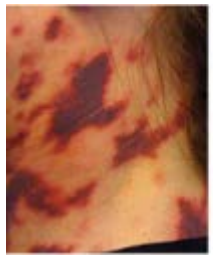


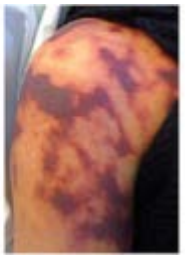


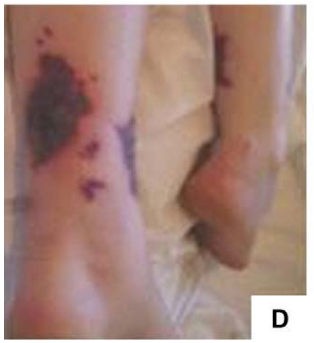


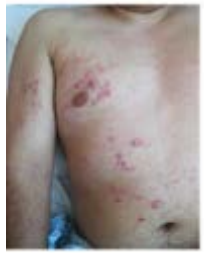


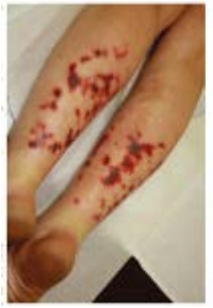


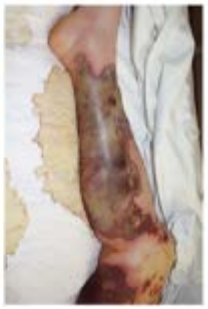


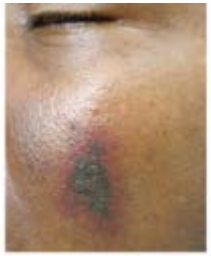


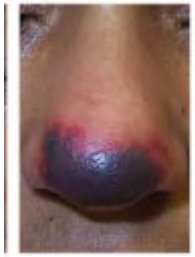


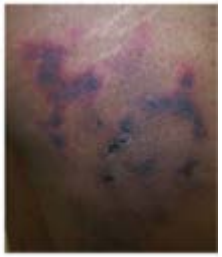


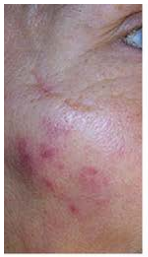


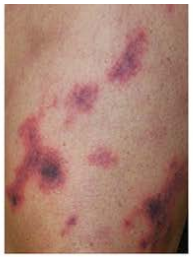








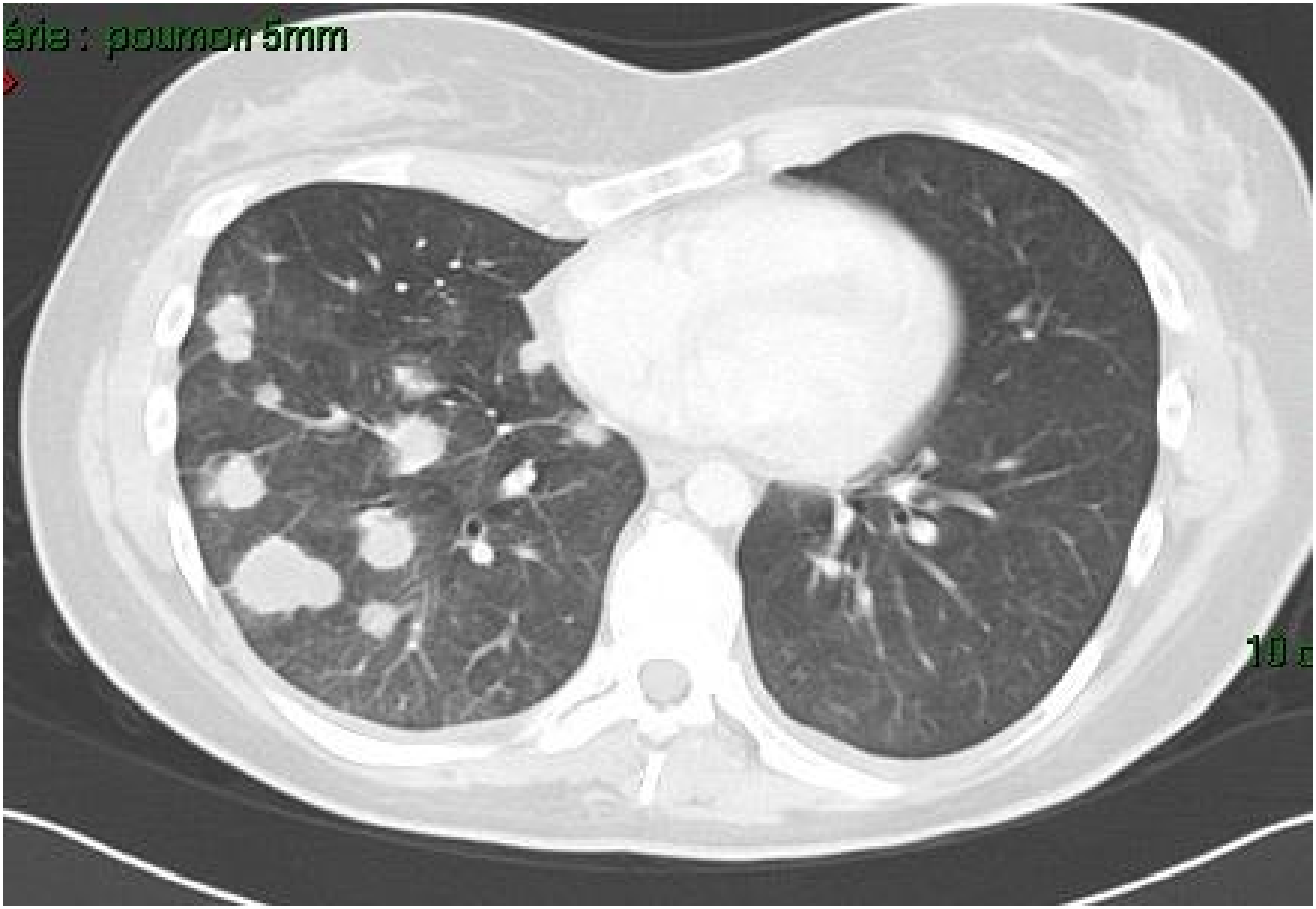




retiform purpura

Dual IIF and/or ELISA ANCA
Discordant antiPR3 P-ANCA
(anti-elastase)

Jenkins et al, J Am Acad Dermatol, July 2011
Chung C et al. J Am Acad Dermatol. Jun 2011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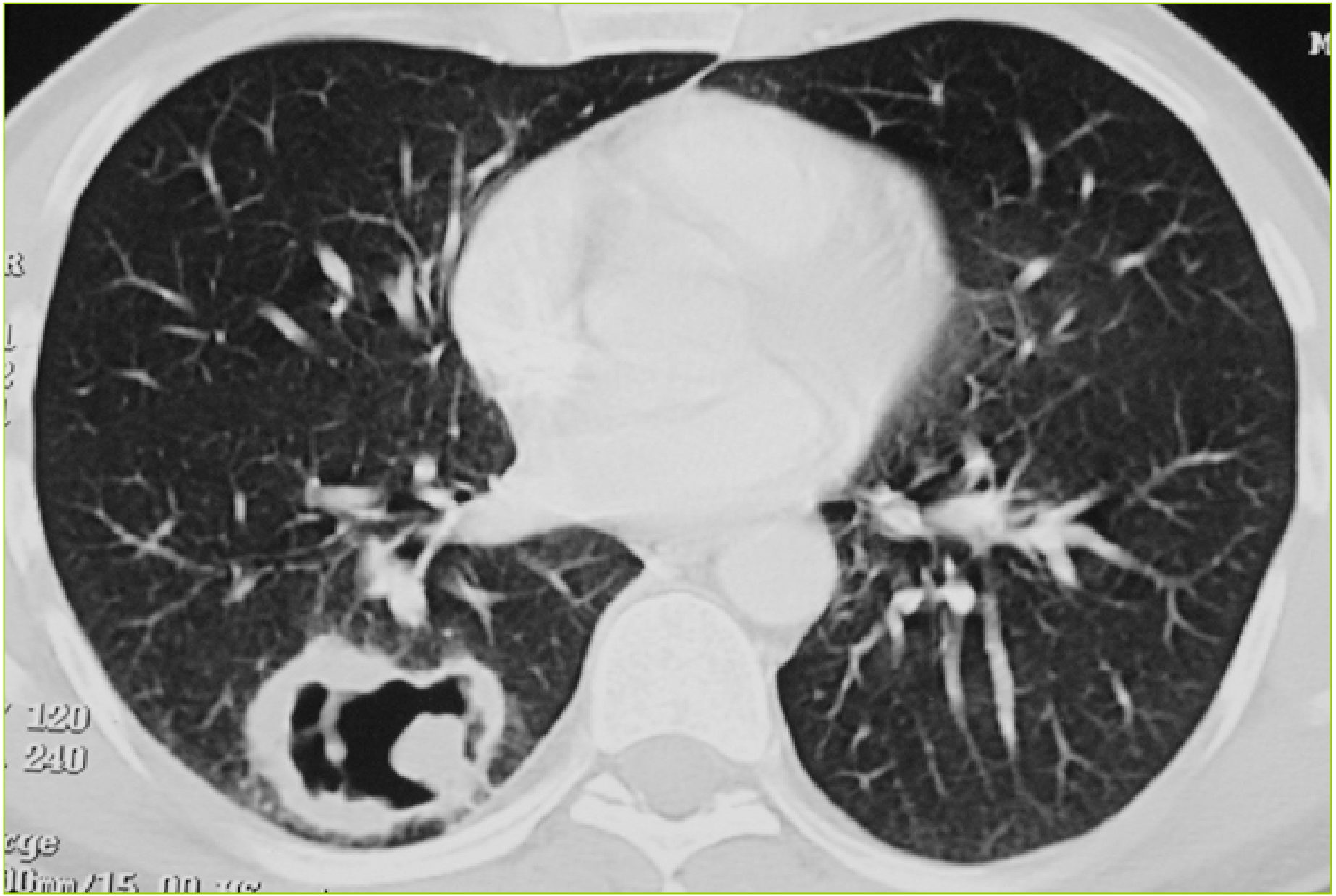
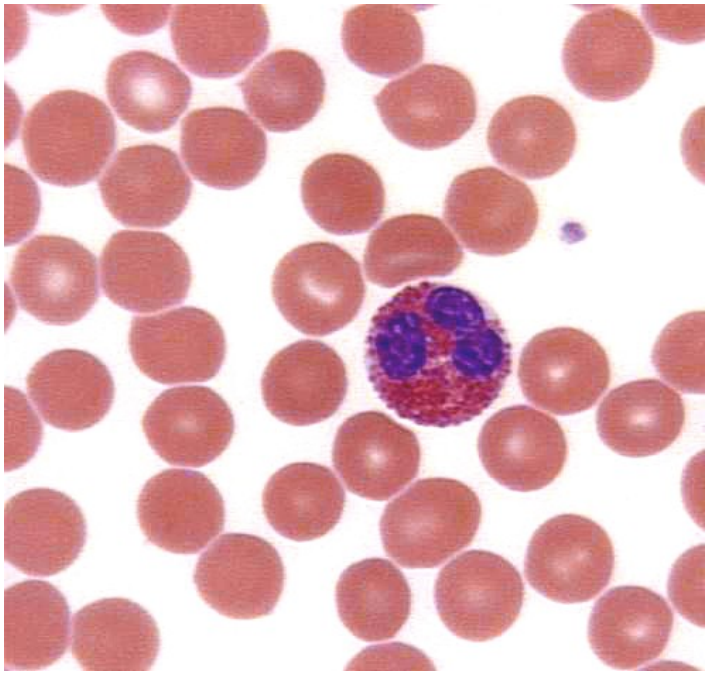




→ **EGPA (or HES…???)**

Referrals for ?vasculitis

- W 60 years old
- 2 months history of fatigue, anemia and weakness
- Rapid-onset SDRA with alveolar hemorrhage and AKI

- CRP 125, Creatinine 353

Referrals for ?vasculitis

- W 60 years old
- 2 months history of fatigue, anemia and weakness
- Rapid-onset SDRA with alveolar hemorrhage and AKI

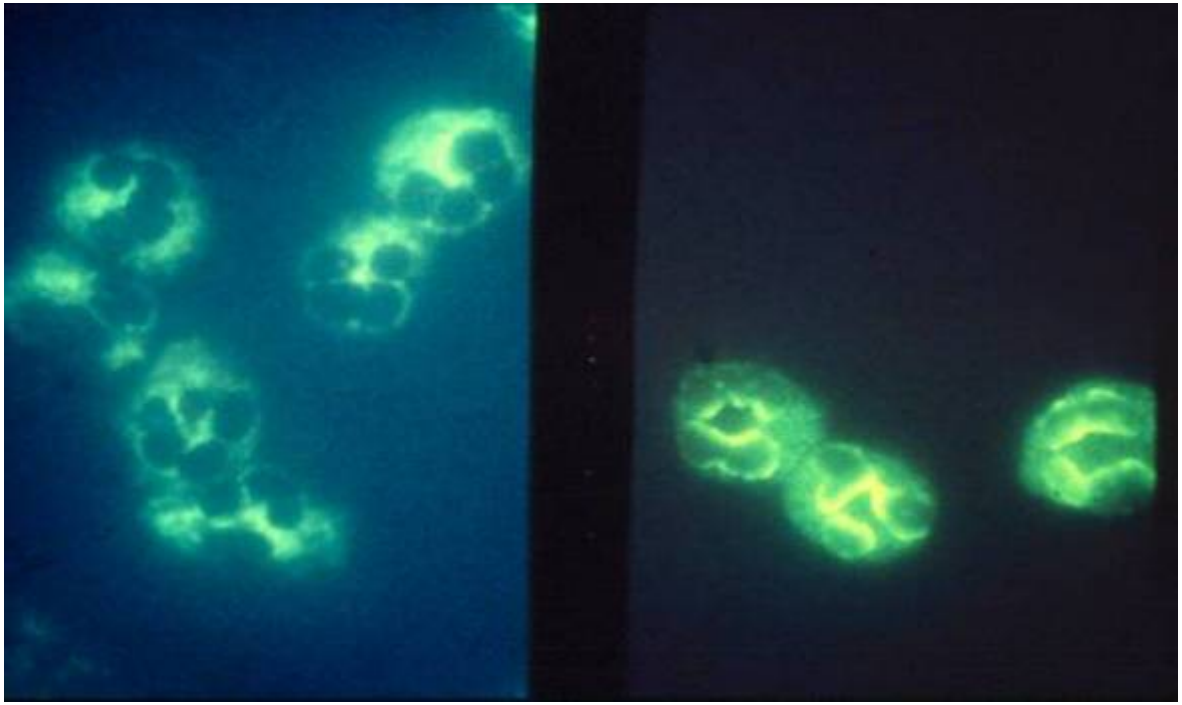
- CRP 125, Creatinine 353

What is next?

ANCA

C ANCA

GPA



P ANCA

MPA

EGPA

C-ANCA : 90% PR3 proteinase 3

P-ANCA : MPO myeloperoxydase

cANCA antiPR3

ANCA

- Systemic GPA = 90%
- Localized GPA = 50%
- Microscopic polyangiitis >75%
- Eosinophilic GPA <40%

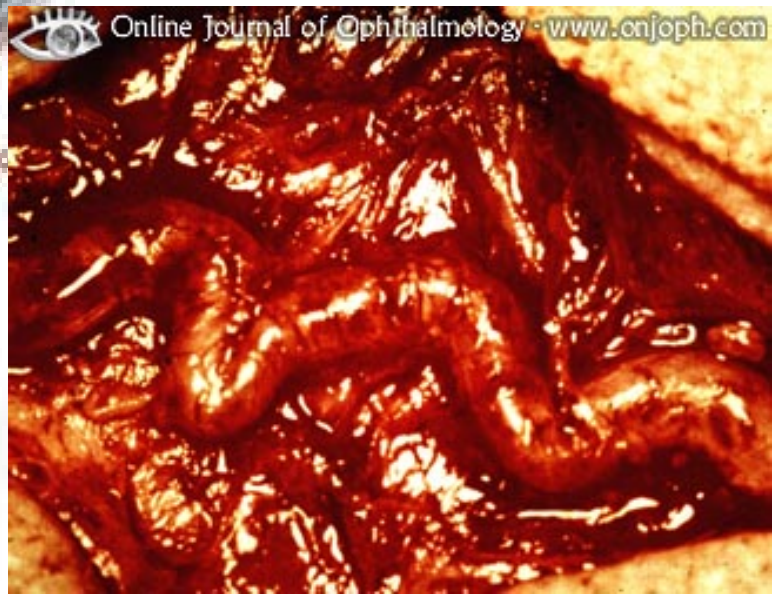
pANCA antiMPO

Referrals for ?vasculitis

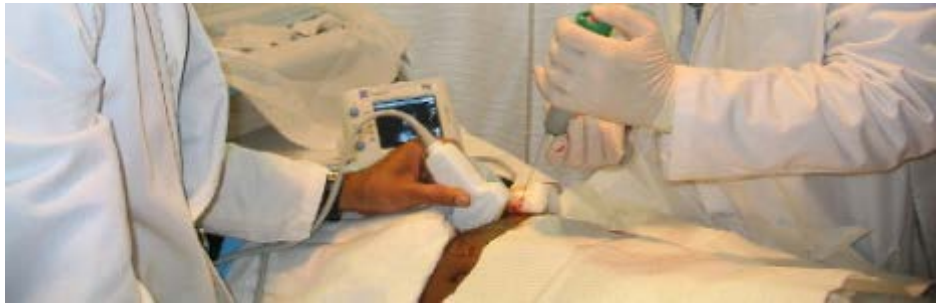
- W 60 years old
- 2 months history of fatigue, anemia and weakness
- Rapid-onset SDRA with alveolar hemorrhage and AKI

- CRP 125, Creatinine 353, cANCA+

What is next?



Biopsy



Study name / acronym	Patient numbers	Inclusion criteria	Studied intervention	Primary end points	Main results/conclusions
CYCAZAREM (Jayne et al. EUVAS, 2003)	144	Newly-diagnosed GPA, MPA or renal-limited disease, with at least one major organ involved (but creatinine level <500 micmol/l)	All induced with oral CYC and GC until remission (3-6 months) then randomized for maintenance with oral azathioprine (2 mg/kg) or continuation of oral CYC (1.5 mg/kg) until month 12 (then azathioprine for all until month 18)	Relapse (major or minor) and adverse events at month 18	No difference in relapse and adverse event rates at 18 months: CYC-based induction can be stopped after remission is achieved - At longer-term (8.5 yr), 52% had relapse in the azathioprine group versus 36% in the CYC (subHR 1.63, 95% CI 0.99–2.71; P=0.06). Same rates of side effects or deaths
CYCLOPS (De Groot et al. EUVAS, 2009)	149	Newly-diagnosed GPA, MPA with renal disease (creatinine 150-500 micmo/l)	Pulse (IV mainly) CYC (15 mg/kg) vs oral CYC (2 mg/kg/day) until remission + (in both arms) GC and 3-month consolidation of CYC after remission, then azathioprine until month 18	Time to remission	Pulse IV CYC induces remission as well as daily oral CYC, at a reduced cumulative CYC dose (8.6 vs 18 g) and caused fewer leucopenia - At longer term (4.3-yr follow-up), no difference in survival but the rate relapse was lower in the daily oral group (HR 0.50, 95% CI 0.26–0.93)
RAVE (Stone et al. USA, 2010)	197	New or relapsing ANCA+ severe GPA or MPA (but creatinine <354 micmol/l and no life-threatening manifestation)	RTX (375 mg/m^2 weekly x 4) vs oral CYC then azathioprine + (in both arms) GC (aiming to stop at month 6)	Complete remission off GC at 6 months	RTX is not inferior to CYC-azathioprine sequence at month 6 (and 18), and superior to CYC-azathioprine for relapsing OR PR3-ANCA+ patients patients at month 6 but only not inferior at month 18 (RTX is superior at 6 and 18 months for PR3-ANCA+ AND relapsing patients). Similar infection rates in both arms.
RITUXVAS (Jones et al. EUVAS, 2010)	44 (3:1 ratio)	Newly-diagnosed ANCA+ GPA, MPA or kidney-limited disease with renal disease	RTX (375 mg/m^2 weekly x 4) + 2 IV pulses of CYC (15 mg/kg at day 1 and 15) vs IV CYC pulses only (15 mg/kg) for 3-6 months, then azathioprine + (in both arms) GC	Sustained remission and rates of severe adverse events at 12 months	RTX is not superior to CYC-azathioprine sequence at 6 and 24 months. Sustained-remission rates were high in both groups. Similar rates of early severe adverse events in both groups
MEPEX (Jayne et al. EUVAS, 2007)	137	Newly-diagnosed GPA or MPA with renal disease and creatinine >500 micmol/l	PLEX vs methylprednisolone pulses (IV 1 g for 3 days) + (in both arms) oral GC and oral CYC for 6 months, then azathioprine	Renal recovery at 3 months (dialysis independence)	24% reduction in risk of progression to ESRD with PLEX at 12 months - At longer term (4 yr): HR for PLEX compared to IV methylprednisolone for death or ESRD of 0.81 (95% CI 0.53–1.23) with a subHR for ESRD of 0.64 (95% CI 0.40–1.05)
CORTAGE Pagnoux et al, FVSG 2015)	108	Systemic necrotizing vasculitides (including 36 GPA and 44 MPA), patients' age >65 years	GC for 9 months and six 500-mg fixed-dose IV CYC pulses, every 2–3 weeks vs 26 months of GC and IV CYC 500 mg/m2, then azathioprine or methotrexate in both groups	>1 serious adverse event within 3 years of follow-up.	Less adverse events with the lower, fixed-dose CYC regimen (500 mg per pulse): 60% vs 78% (P=0.04). No significant difference in failure rates (11% with fixed-dose vs 14%), mortality (17% vs 24%) or relapses (44% with fixed-dose vs 29%; P=0.15.
NORAM (De Groot et al. EUVAS, 2005)	100	Newly diagnosed GPA or MPA, with creatinine level <150 micmol/l and no major organ involvement	Methotrexate (15 initially increased to 25 mg/week) vs daily oral CYC + (in both arms) oral GC All treatments stopped at month 12	Remission at month 6	For limited GPA, remission rate is not inferior with methotrexate compared to oral CYC, but remission was delayed in patients with more extensive or pulmonary disease, and relapse rate at 18 months was higher in the methotrexate group. Adverse events were less frequent with methotrexate, but for liver dysfunction

Study name / acronym	Patient numbers	Inclusion criteria	Studied intervention	Primary end points	Main results/conclusions
CYCAZAREM (Jayne et al. EUVAS, 2003)	144	Newly-diagnosed GPA, MPA or renal-limited disease, with at least one major organ involved (but creatinine level <500 micmol/l)	All induced with oral CYC and GC until remission (3-6 months) then randomized for maintenance with oral AZA (2 mg/kg) or continuation of oral CYC (1.5 mg/kg) until month 12 (then AZA for all until month 18)	Relapse (major or minor) and adverse events at month 18	No difference in relapse and adverse event rates at 18 months: CYC-based induction can be stopped after remission is achieved - At longer-term (8.5 yr), 52% had relapse in the AZA group versus 36% in the CYC (subHR 1.63, 95% CI 0.99–2.71; P=0.06). Same rates of side effects or deaths
WGET (WGET research group, 2005)	180	Newly-diagnosed (44%) or relapsing, limited (29%) or severe GPA	Standard therapy with GC and CYC (severe, then MTX or AZA for maintenance for 12 months) or MTX (limited, continued for 12 months after remission) with concurrent etanercept (25 mg subcutaneous, twice weekly) or placebo	Sustained remission (BVAS=0 for at least 6 months)	No significant differences between the etanercept and placebo groups (69.7% vs 75.3% sustained remission; P=0.39) – follow-up 27 months Solid cancers developed in 6 etanercept recipients (none in placebo group)
Metzler et al. (2007)	54	Generalized GPA	Induction with oral CYC and GC then maintenance with LEF (100 mg/day loading dose for 3 days, then 20 mg/day for 1 month, then 30mg/day) or MTX (7.5 mg/week oral for 1 month, then 15 mg/week for 1 month, then 20 mg/week)		Study terminated prematurely because of high rate of major relapses in the MTX group (13 vs 6 patients; P=0.037) – follow-up 21 months. No MTX patient but 4 LEF patients had to discontinue the study because of LEF-attributable adverse events (2 hypertension, 1 peripheral neuropathy, 1 leucopenia)
WEGENT (Pagnoux et al, FVSG, 2008)	126	Newly-diagnosed systemic GPA or MPA	MTX (0.3 mg/kg/week, oral or subcutaneous if not tolerated orally) vs oral AZA (2 mg/kg/d) for 12-16 months + all induced with IV CYC pulses and prednisone until remission (3-6 months) then 3 consolidation pulses before randomization for maintenance	Adverse events (severe and/or leading to study drug cessation) and relapse	No difference between the groups in relapse and adverse event rates (results of longer term follow-up are under analysis)
IMPROVE (Hiemstra et al, EUVAS, 2010)	165	Newly-diagnosed systemic GPA or MPA	Oral MMF (2 g/d) vs oral AZA (2 mg/kg/d) until month 42 + all induced with IV or oral CYC pulses and prednisolone until remission (3-6 months) then randomization for maintenance	Relapse-free survival and adverse events	MMF was less effective than AZA for maintaining disease remission (HR of relapse 1.69 (95% CI 1.06-2.70; P=0.03). Severe adverse events did not differ significantly between groups
MAINRITSAN (Guilevin et al, FVSG, 2015)	115	Newly-diagnosed (80%) or relapsing, severe GPA (76%), MPA (20%) or renal limited disease, with (94%) or without ANCA	Induction with IV CYC and GC, then maintenance with RTX (500 mg on days 0 and 14, months 6, 12, and 18) or AZA (2 mg/kg/day for 12 months, then 1.5 mg/kg/day for 6 months and 1 mg/kg/day for 4 months)	Rate of major relapse (with BVAS>0 and ≥1 major organ involvement and/or life-threatening disease) at month 28	Less major relapses with RTX (5%) vs AZA (29%; HR 6.61, 95% CI 1.56 to 27.96; P =0.002) at 28 months. - At 60 months, more major relapses in both arms, but still less in the RTX group
AZA-ANCA (Sanders et al., 2016)	131	Newly-diagnosed PR3-ANCA+ vasculitis	Oral CYC and GC for all then extended (1.5-2.0 mg/kg/day for 4 years after diagnosis then tapered by 25 mg every 3 months) or standard (1.5-2 mg/kg/day until 1 year after diagnosis then tapered by 25 mg every 3 months) azathioprine maintenance therapy if C-ANCA positive at remission (n=45/131)	Relapse-free survival at 4 years after diagnosis	No significant difference in relapse-free survival or relapse rates between study groups (and no difference between extended treatment in those ANCA-positive at remission and standard treatment in all patients, ANCA-positive or -negative at remission) – follow-up 45 months

Principles of treatment of severe, systemic GPA

CYCLOPHOSPHAMIDE

IV (pulse): 15 mg/kg at D1,15,29 then /3 wk

Oral (continuous): 2 mg/kg/day

RITUXIMAB

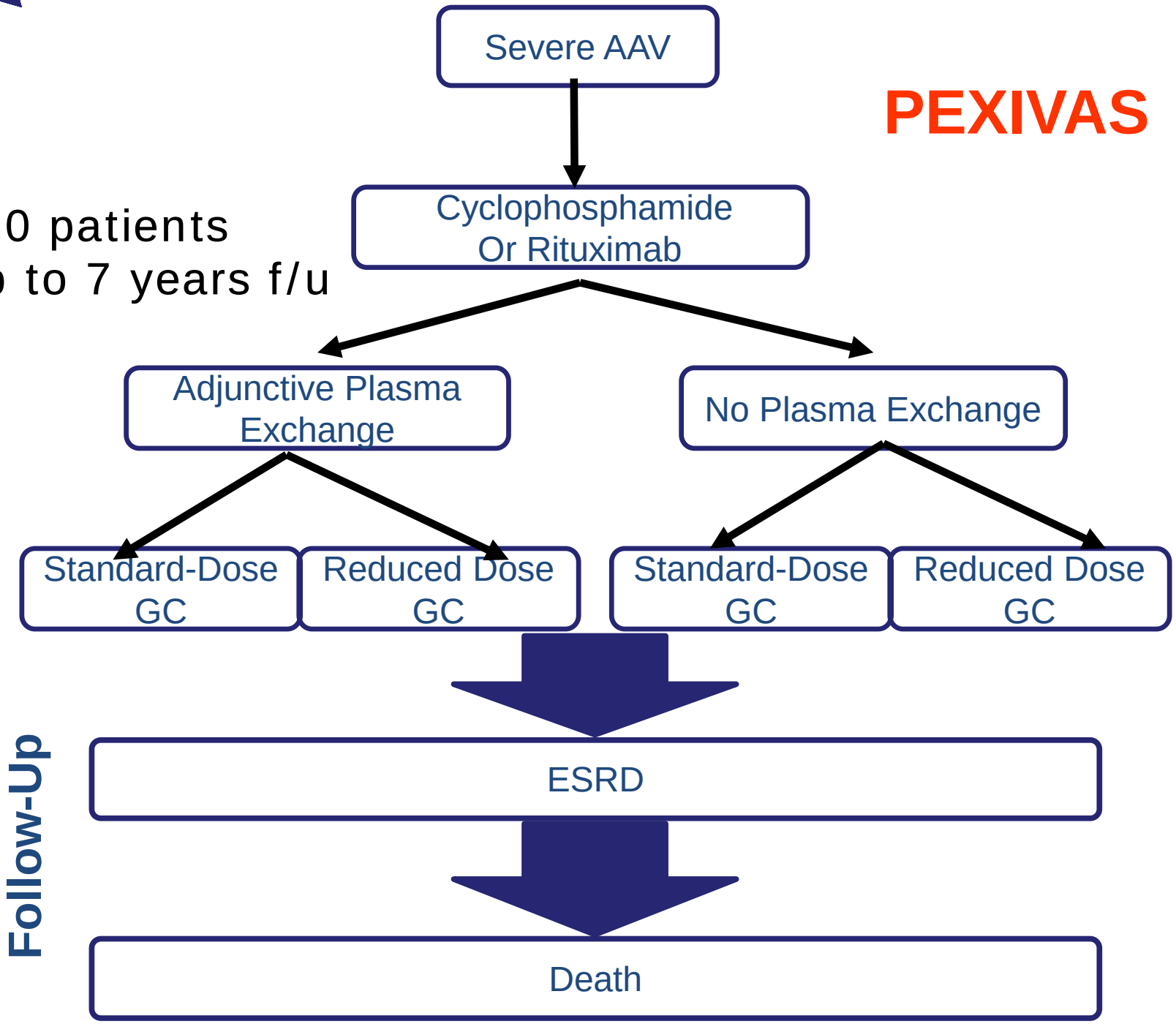
375 mg/m²/wk (or 1 g at D1 & 15)

± Plasma exchange?

INDUCTION ***MAINTENANCE***

PEXIVAS

700 patients
Up to 7 years f/u



Principles of treatment of severe, systemic GPA

CYCLOPHOSPHAMIDE

IV (pulse): 15 mg/kg at D1,15,29 then /3 wk

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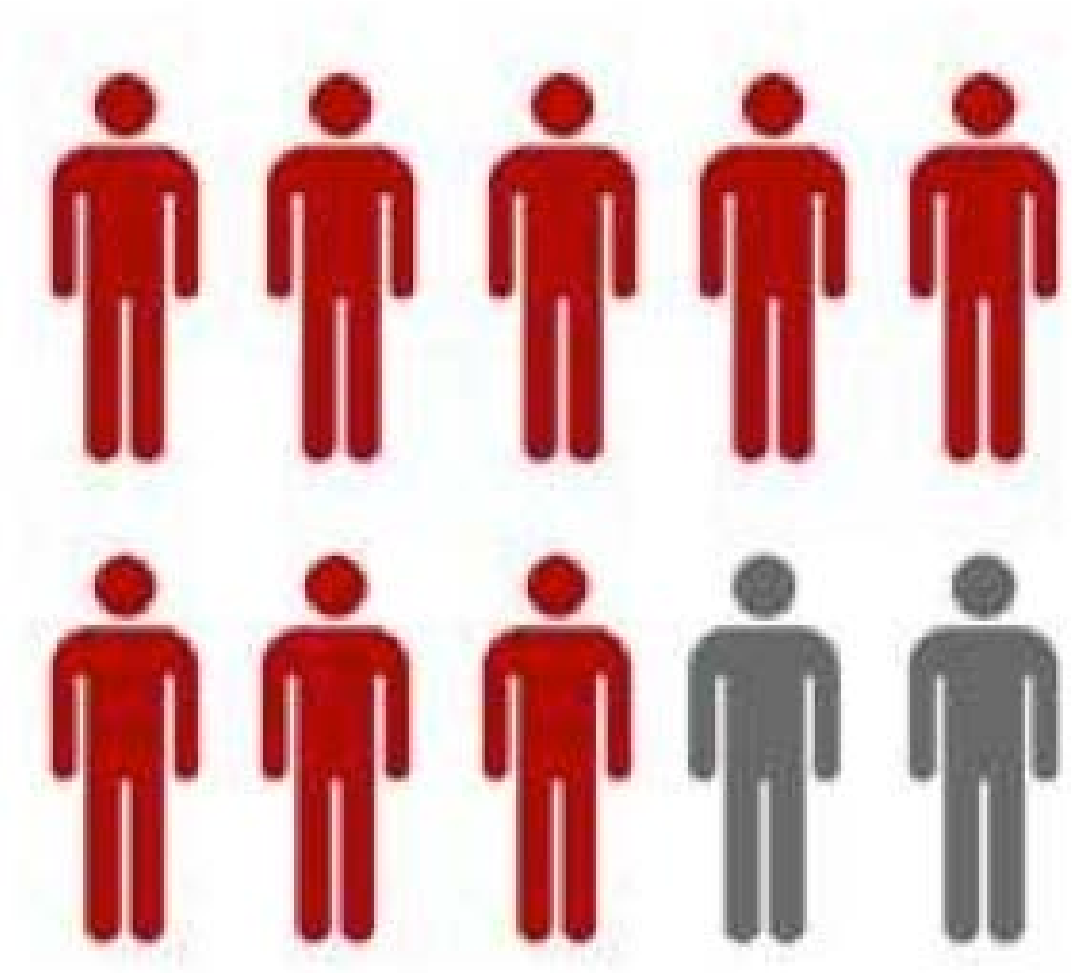
RITUXIMAB

375 mg/m²/wk (or 1 g at D1 & 15)

± Plasma exchange?

INDUCTION ***MAINTENANCE***

Remission 80-90% percent



Principles of treatment of severe, systemic GPA

CYCLOPHOSPHAMIDE

IV (pulse): 15 mg/kg at D1,15,29 then /3 wk

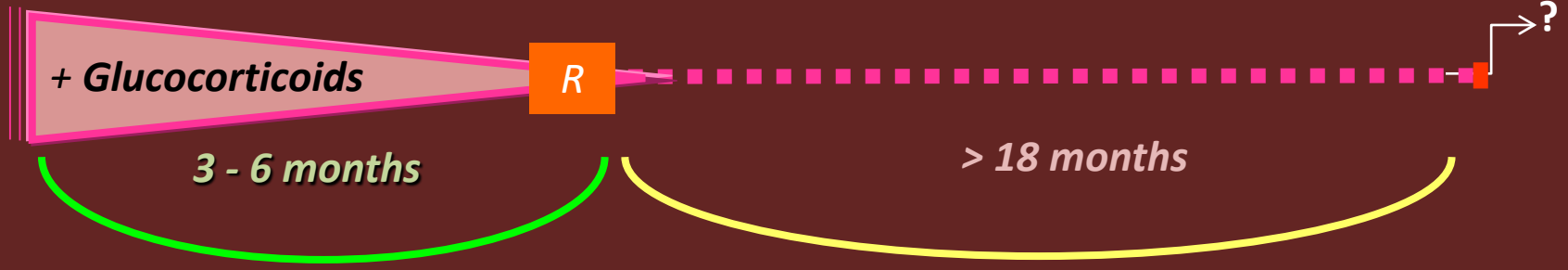
Oral (continuous): 2 mg/kg/day

- *AZATHIOPRINE* 2 mg/kg/day
- *METHOTREXATE* 0.3 mg/kg/wk
- *LEFLUNOMIDE* 20 mg/day
- *MYCOPHENOLATE MOFETIL* 2 g/day

?

RITUXIMAB

375 mg/m²/wk (or 1 g at D1 & 15)



± Plasma exchange?

INDUCTION ***MAINTENANCE***

Frequent relapses…

	Patients		Follow-up from Dg	Relapse rate	p
CYCAZAREM NEJM, 2003	WG, MPA	144	18 mo	AZA 15,5% vs. CYC 13,7%	NS
WGET NEJM, 2005	WG	180	27 mo	MTX 32,8% vs MTX/ETN 30,6%	NS
Langford Am J Med, 2003	WG	42	35 mo	52%	
WEGENT **Pagnoux, NEJM, 2009**	WG, MPA	126	37,3 mo	AZA 36,5% vs MTX 33,3%	NS
Sanders NEJM, 2003	WG, MPA	136	→ 5 yrs	AZA 42.3% vs. CYC 57.4%	NS

At 7 years, relapse rate 63.9% → 51.2% (445 patients)

Holle et al. Arthritis Rheum 2011 Jan;63(1):257-66

Principles of treatment of severe, systemic GPA

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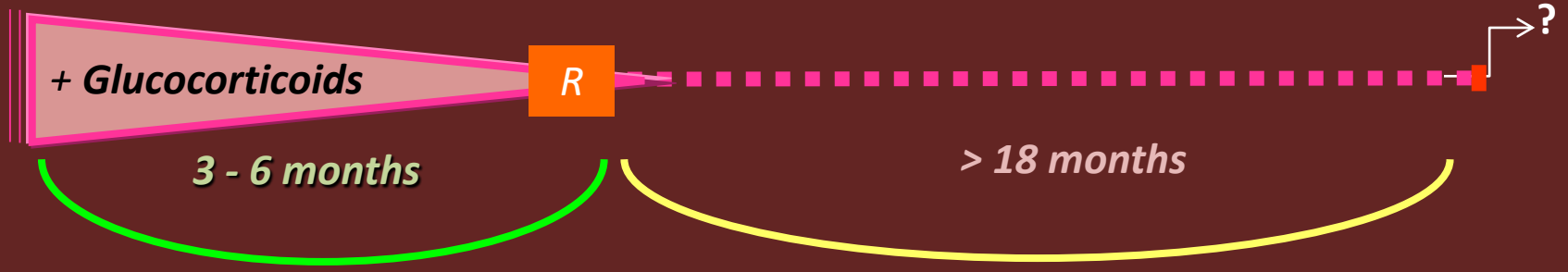
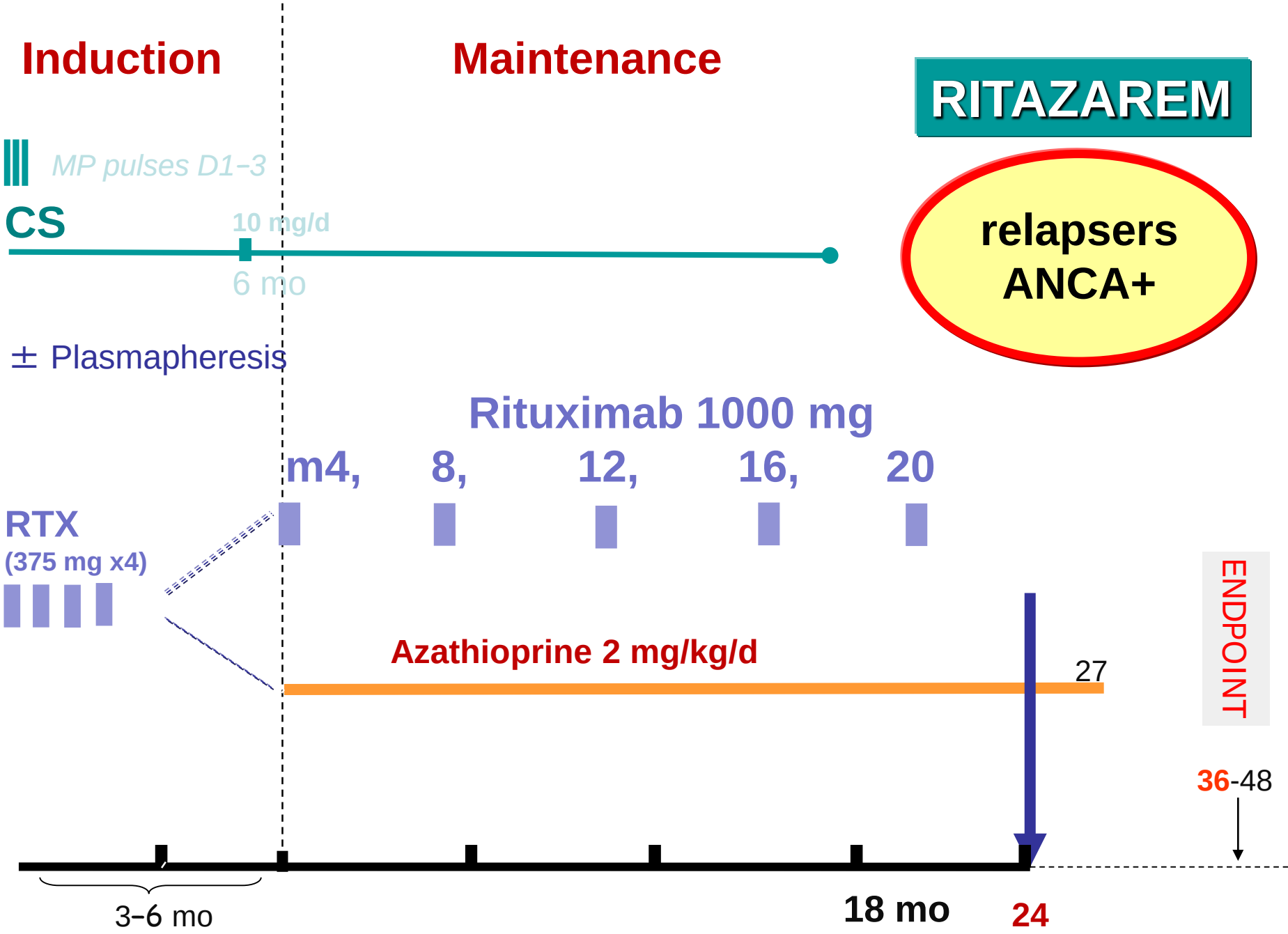
- *MYCOPHENOLATE MOFETIL* 2 g/day

→ ***? RITUXIMAB*** 500-1000 mg q4-6 months → ?



± Plasma exchange?

INDUCTION ***MAINTENANCE***


Induction
Maintenance
RITAZAREM
MP pulses D1–3
CS
10 mg/d
6 mo
relapsers
ANCA+
± Plasmapheresis
Rituximab 1000 mg
m4,
8,
12,
16,
20
RTX
(375 mg x4)
Azathioprine 2 mg/kg/d
27
ENDPOINT
36-48
3–6 mo
18 mo
24

Can we do better?

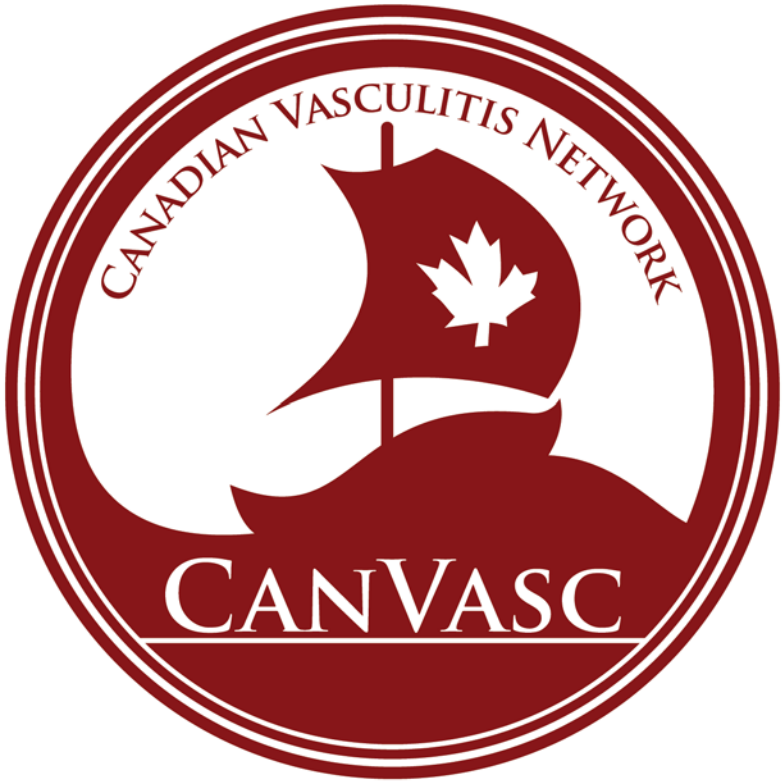
- Individualized treatments?

- Other agents instead of or in addition to others?

Two CCX168 Phase 2 Trials in AAV

	CLEAR Trial (Steroid Elimination/Sparing Design)	CLASSIC Trial (Added to Standard of Care)
Location	Europe	US and Canada
Treatment Groups	1. Placebo (of CCX168) + CYC/RTX + full Steroids 2. CCX168 30 mg BID + CYC/RTX + **low Steroids** 3. CCX168 30 mg BID + CYC/RTX + **no Steroids**	1. Placebo (of CCX168) + CYC/RTX + full Steroids 2. CCX168 **10 mg** BID + CYC/RTX + **full Steroids** 3. CCX168 30 mg BID + CYC/RTX + **full Steroids**
Patients	ANCA-associated vasculitis with/without renal disease (Step 3)	ANCA-associated vasculitis with/without renal disease (from initiation)
Duration	12 weeks with 12-week follow-up	12 weeks with 12-week follow-up
Study Size	60 patients	Up to ~45 patients
Prim. Endpoint	BVAS response at Week 12	BVAS response at Week 12
	n, BVAS % change, and, in the tients with renal disease activity, parameters	BVAS remission, BVAS % change, and, in the subgroup of patients with renal disease activity, renal outcome parameters

Less is **more.**
—Ludwig Mies van der Rohe



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