II Curs de Malalties Autoimmunes
Societat Catalana de Reumatologia

26 i 27 de setembre de 2014

Vasculitis de vas gran, mitjà i petit: perles diagnòstiques

José Hernández Rodríguez

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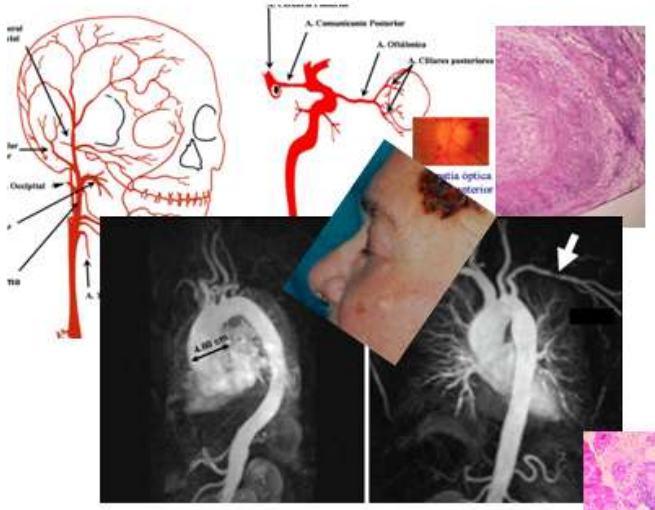
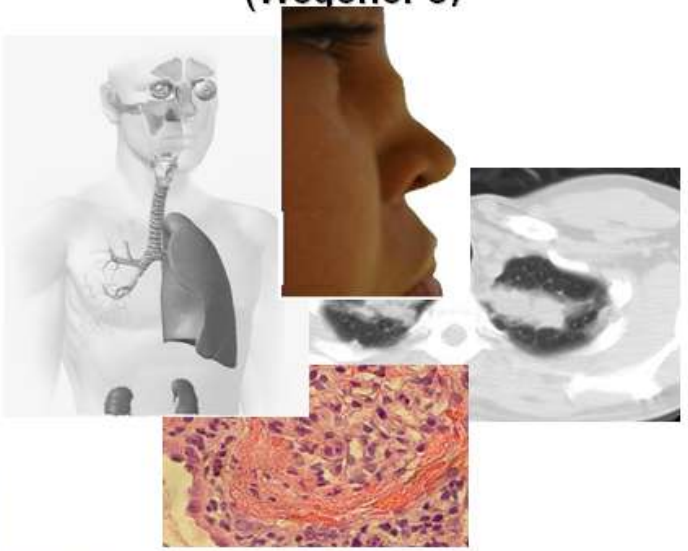
Hospital Clínic. IDIBAPS
Universitat de Barcelona

Diagnostic pearls in vasculitis

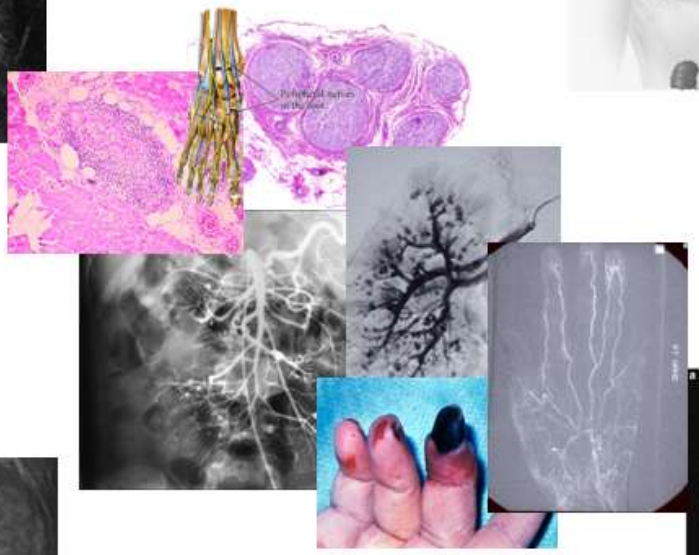
Giant cell arteritis



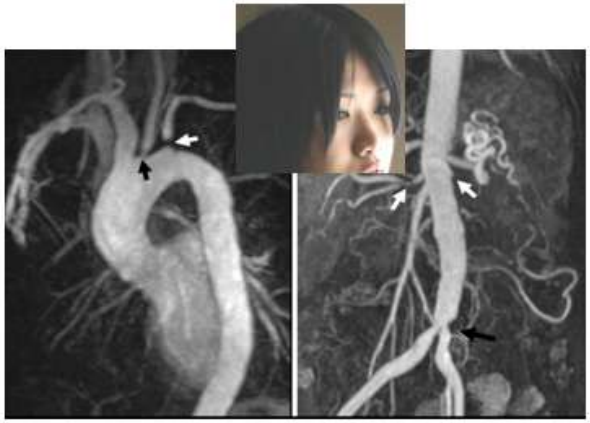
Granulomatosis with polyangiitis (Wegener's)



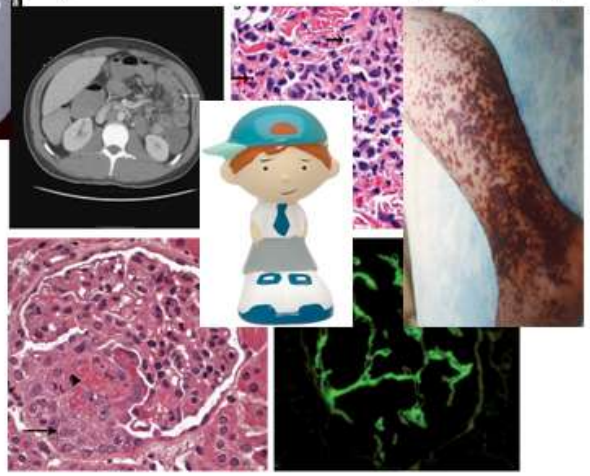
Polyarteritis nodosa



Takayasu's arteritis



IgA vasculitis (Henoch-Schönlein purpura)

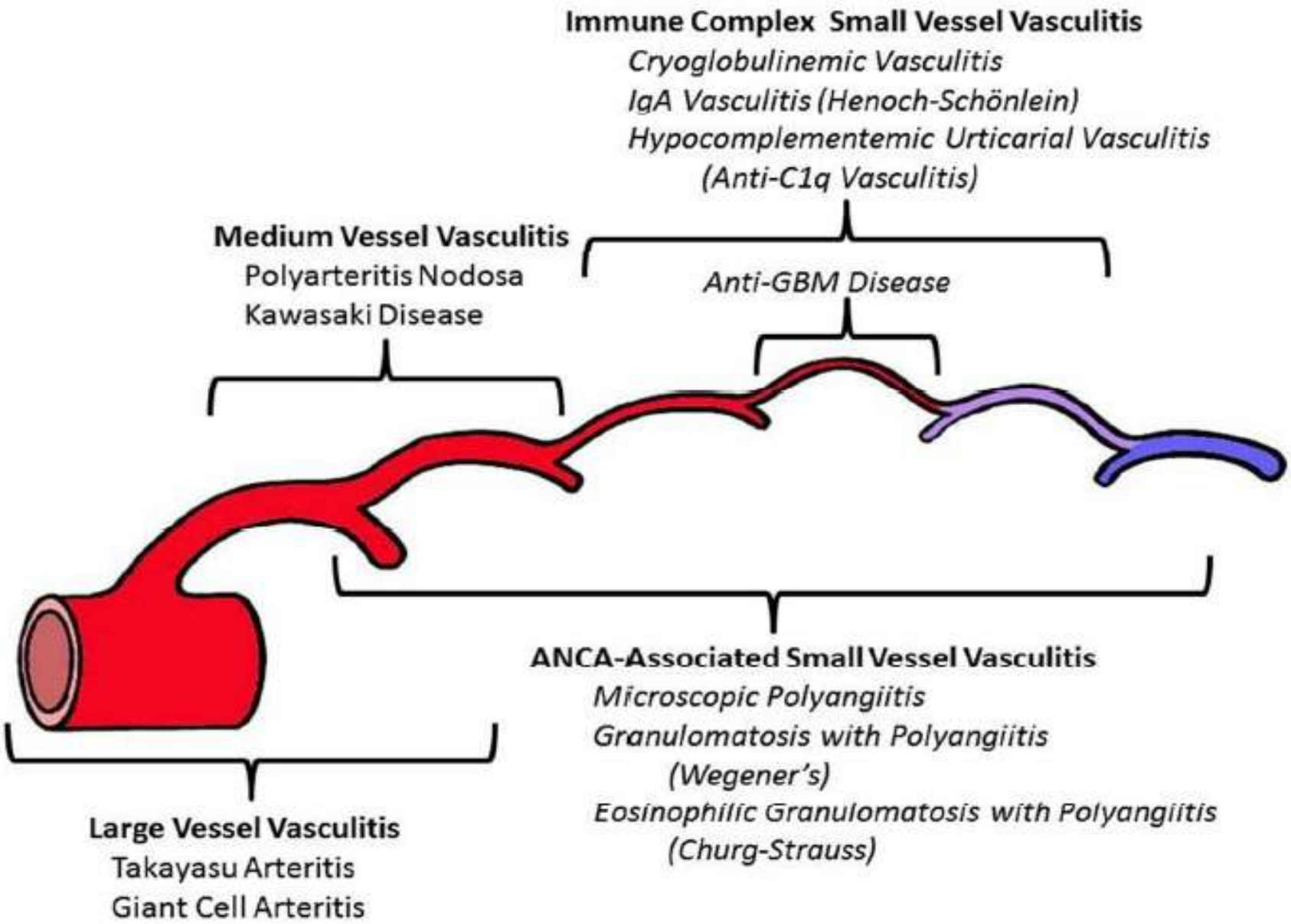


ACR classification criteria - 1990

- **Clinical features**
- **Laboratory** (ESR, eosinophilia, microhematuria, HBV serology…)
- **Imaging changes**
- **Histology**

(Chapel Hill 1994)

Classification and nomenclature for systemic vasculitis (Chapel Hill 2013)



ACR/EULAR endorsed study to develop new diagnostic and classification criteria for primary systemic vasculitis (DCVAS)

ClinicalTrials.gov **Identifier:**NCT01066208

Sponsor:
University of Oxford
Collaborators:
American College of Rheumatology
The European League Against Rheumatism (EULAR)
The Vasculitis Foundation

Condition

Wegener's Granulomatosis
Microscopic Polyangiitis
Churg Strauss Syndrome
Polyarteritis Nodosa
Giant Cell Arteritis
Takayasu Arteritis

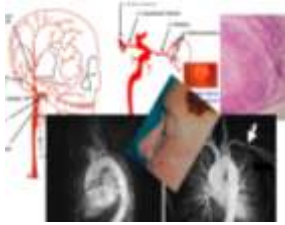
Study Type: Observational

Study Design: Observational Model: Case Control
Time Perspective: Prospective

Estimated Enrollment: 3588

Study Start/Completion Date: January 2011/December 2015

Trial status: Enrollment ongoing



Giant cell arteritis

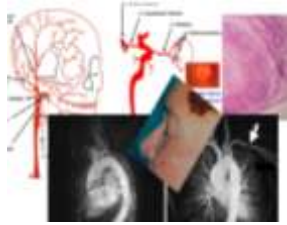
1990 CLASSIFICATION CRITERIA

1. Age at disease onset >=50 years
2. New headache
3. Temporal artery abnormality
4. Elevated erythrocyte sedimentation rate (≥50 mm/hour)
5. Abnormal artery biopsy

* For classification at least 3 of these 5 criteria must be present.
3 or more criteria: sensitivity 93.5% and specificity 91.2%

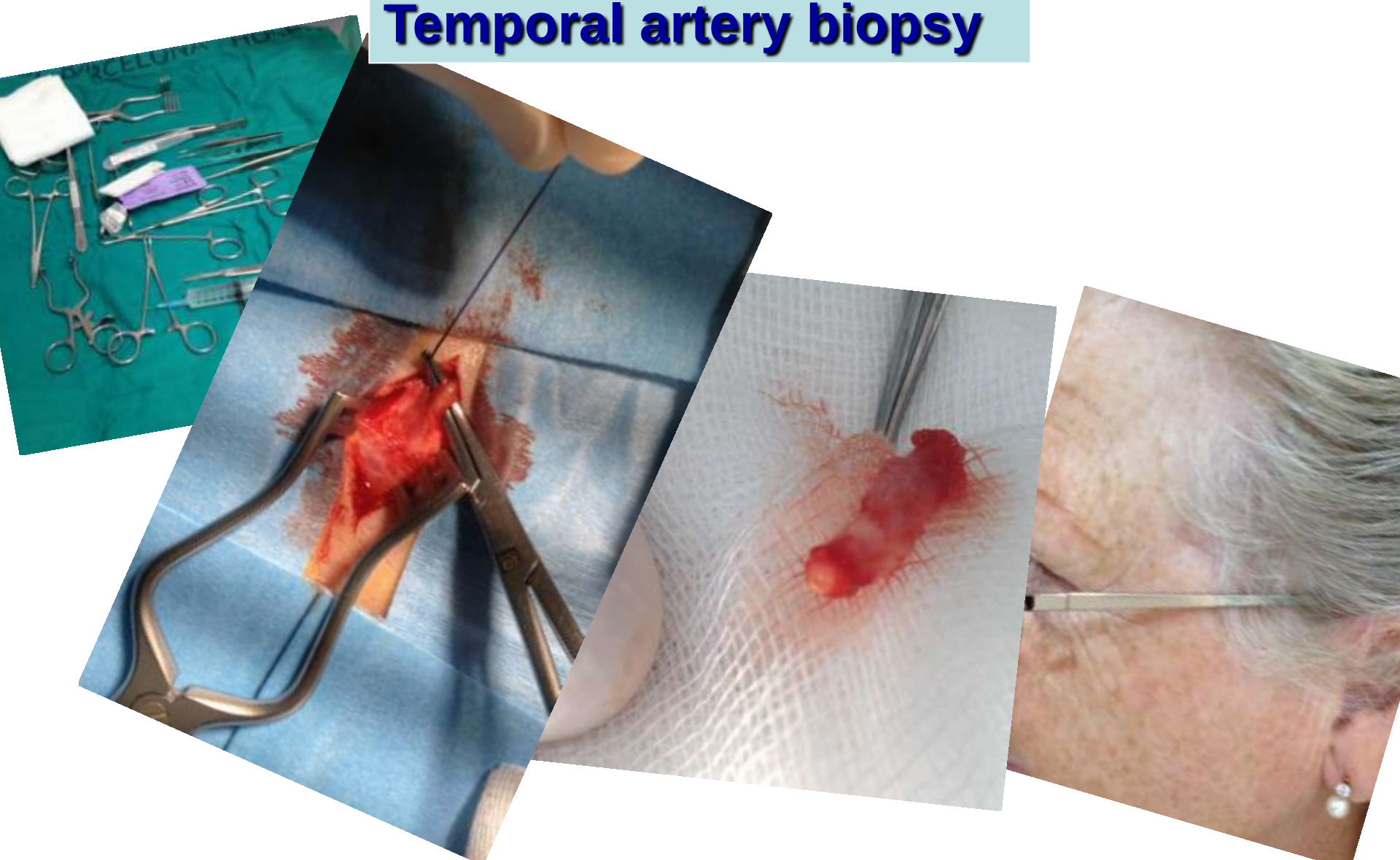
Hunder GG et al. Arthritis Rheum 1990

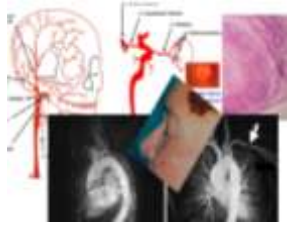
Temporal artery biopsy
or
color-doppler ultrasonography?



Giant cell arteritis

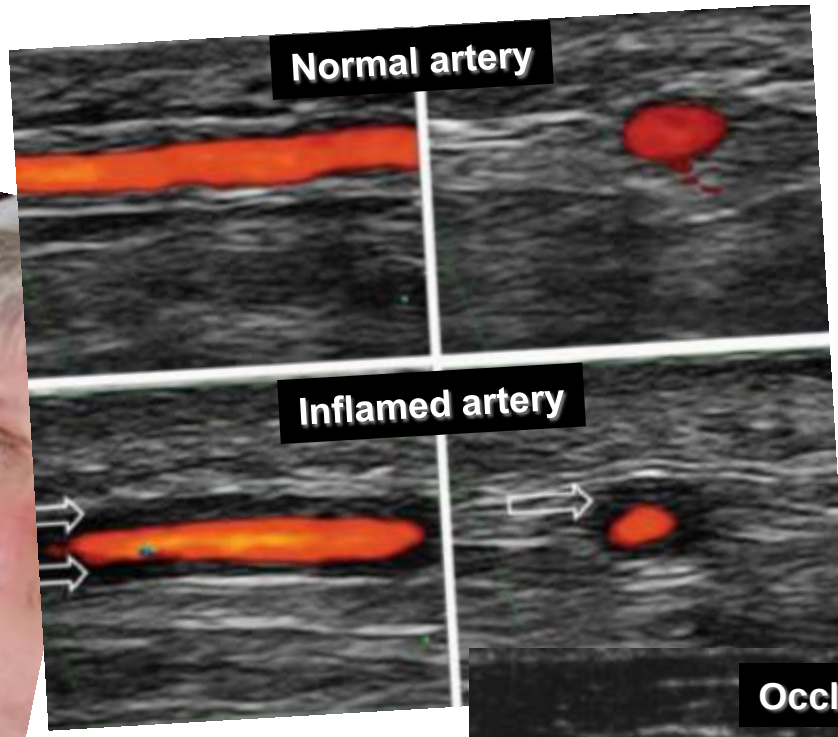
Temporal artery biopsy

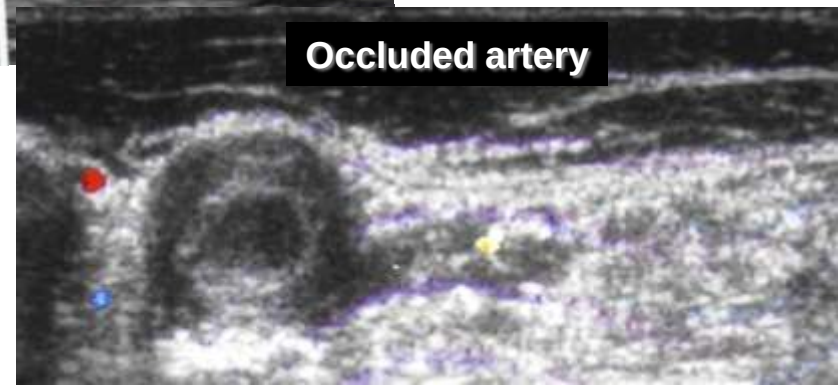


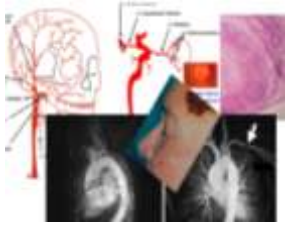


Giant cell arteritis

Color-doppler ultrasonography

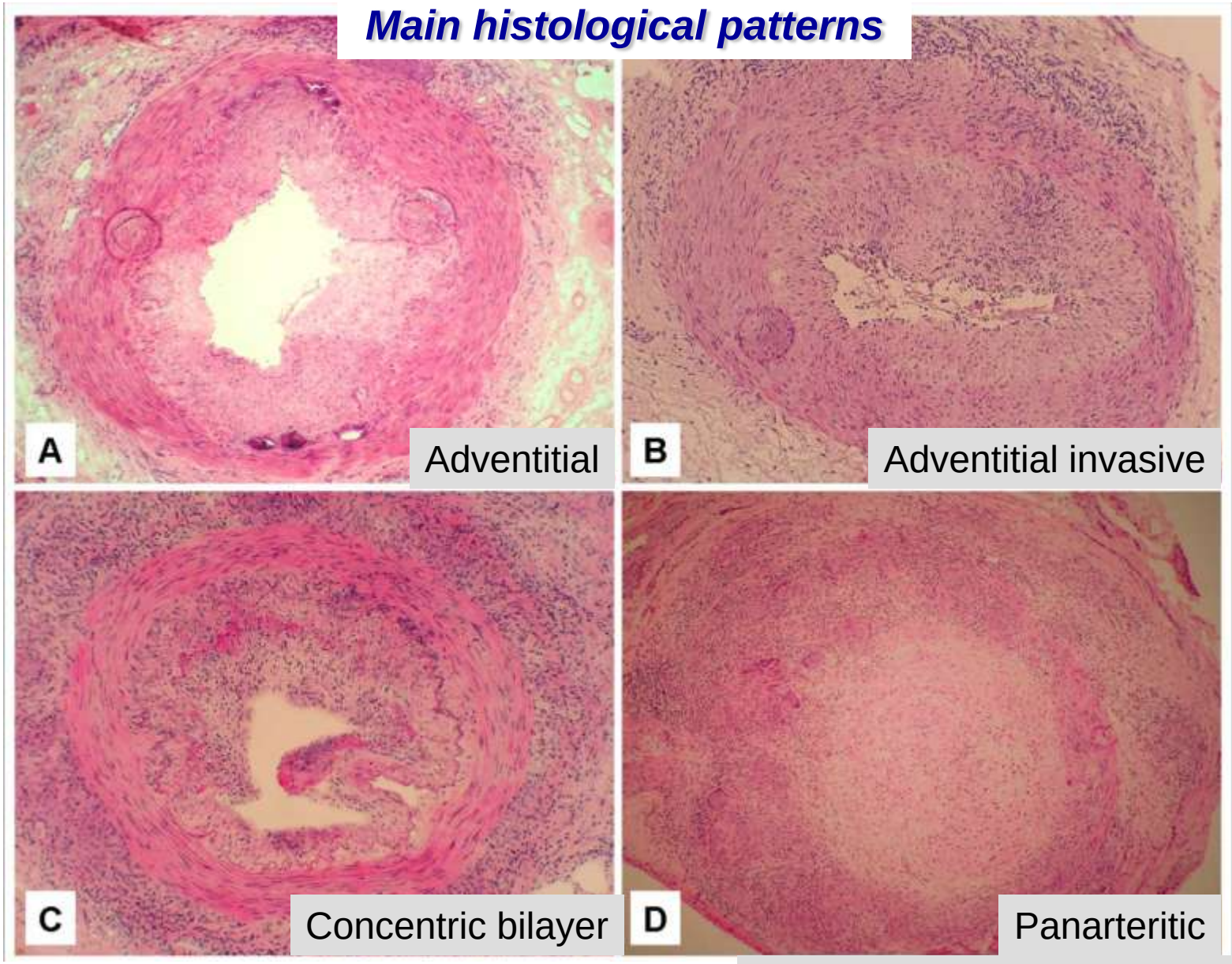






Giant cell arteritis **Temporal artery biopsy**

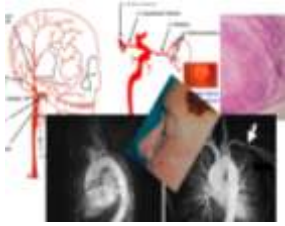
Main histological patterns



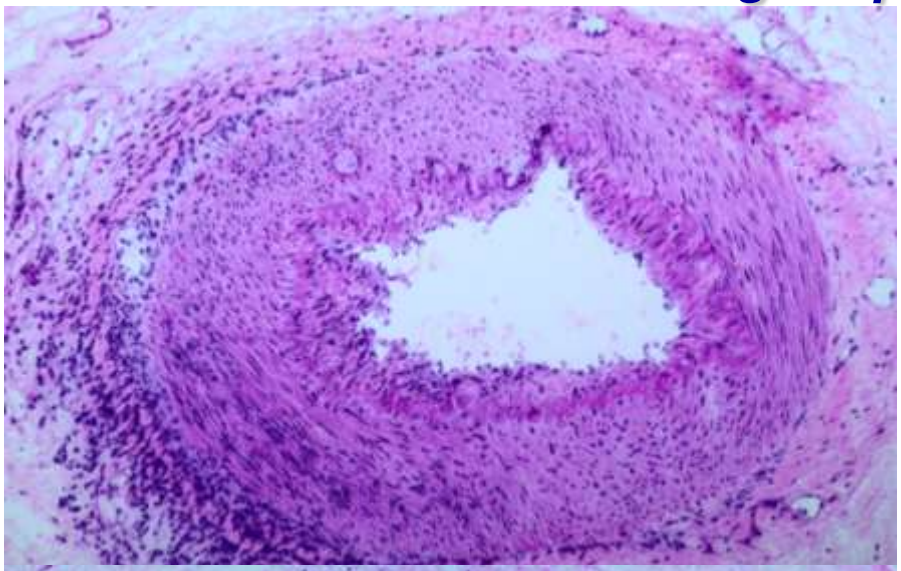
Hernández-Rodríguez J et al. ***Arthritis Rheum*** 2005 (abstract)

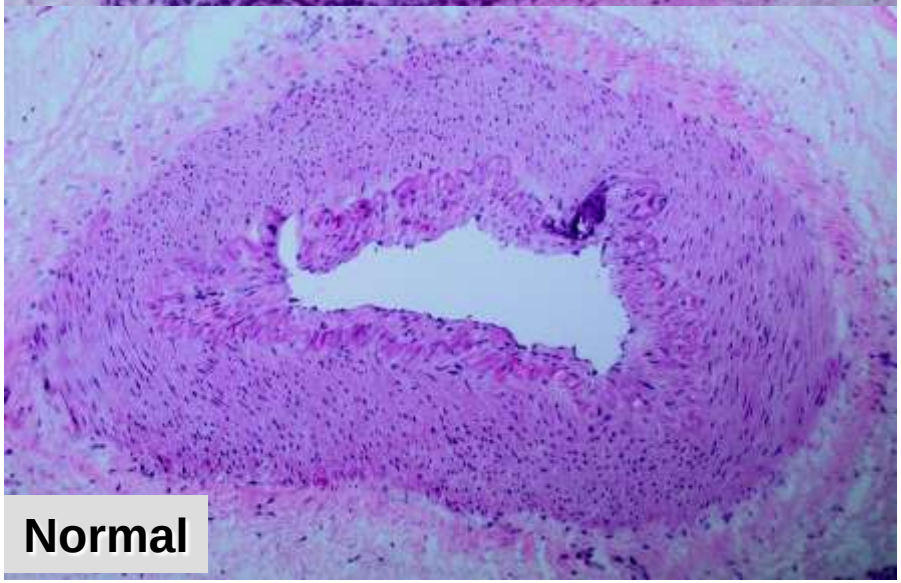
Giant cell arteritis

Temporal artery biopsy



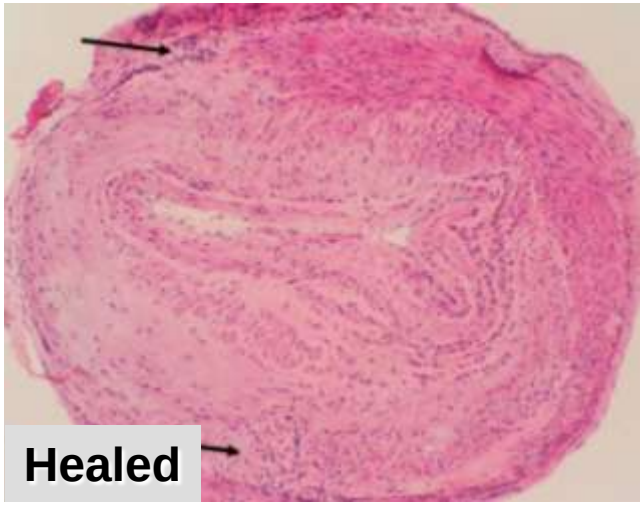
Other histological patterns in GCA





Normal

Small vessel vasculitis
(vasa vasorum or distal)

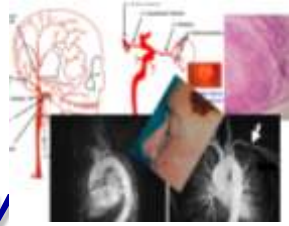


Healed

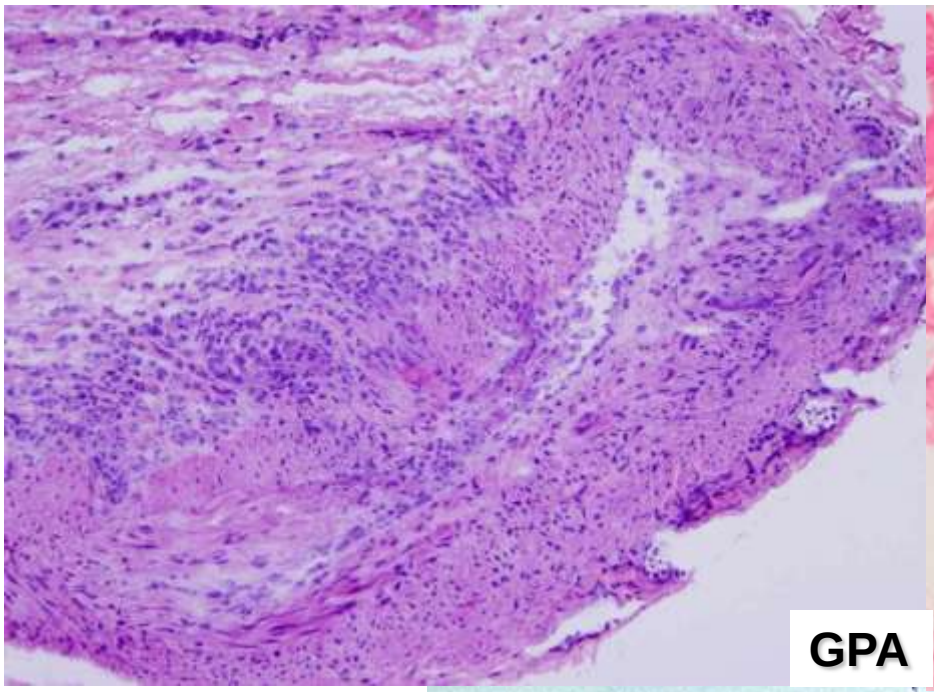
Hernández-Rodríguez J et al. ***Arthritis Rheum*** 2005 (abstract)

Diagnostic pearls in vasculitis

Giant cell arteritis **Temporal artery biopsy**

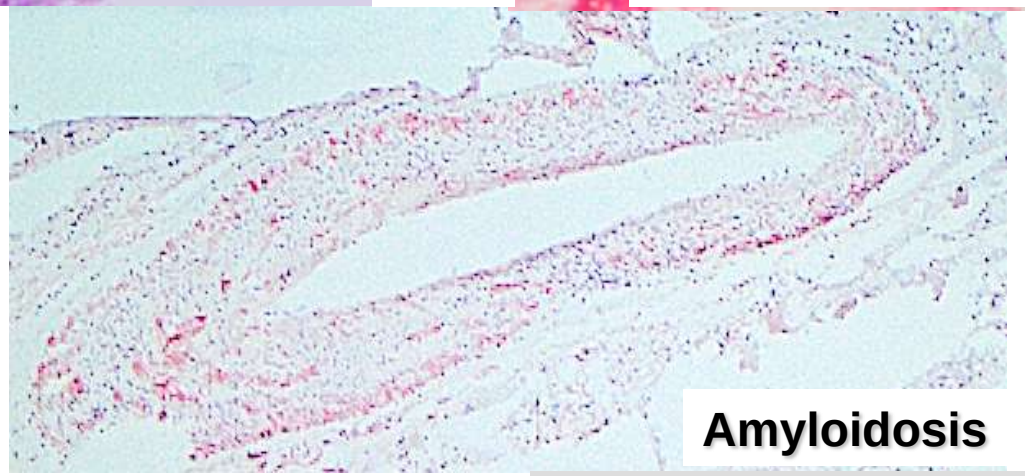


Other vasculitis/diseases involving the temporal artery



GPA

Small/medium vessel vasculitis



Amyloidosis

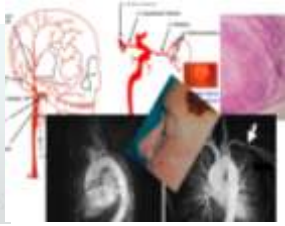
Hernández-Rodríguez J et al. ***Arthritis Rheum*** 2005 (abstract)

Giant cell arteritis

Color doppler ultrasound

↑specificity

↓sensibility



ORIGINAL ARTICLE

Salvarani C et al. ***Ann Intern Med*** 2002

Inflamed Temporal Artery

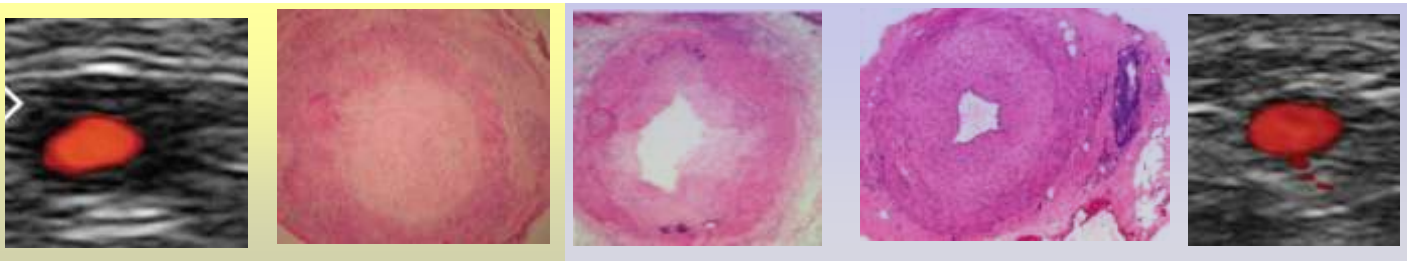
Histologic Findings in 354 Biopsies, With Clinical Correlations

Alberto Cavazza, MD, Francesco Muratore, MD,† Luigi Boiardi, MD,†*
*Giovanna Restuccia, MD,† Nicolò Pipitone, MD,† Giulia Pazzola, MD,† Elena Tagliavini, MD,**
Moira Ragazzi, MD, Giulio Rossi, MD,‡ and Carlo Salvarani, MD†*

Am J Surg Pathol • Volume 38, Number 10, October 2014

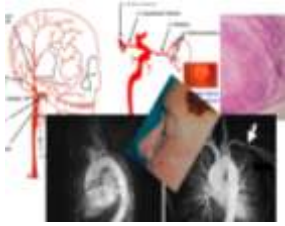
TABLE 4. Demographic and Clinical Characteristics at Diagnosis of TMI, ILA, VVV, and SVV in 317 Patients With GCA

Variables	TMI (n = 253)	ILA (n = 18)	VVV (n = 19)	SVV (n = 27)	P*
	80%		20%		
Halo on CDS of temporal arteries	84/116 (72.4)	1/7 (14.3)	2/12 (16.7)	6/22 (27.3)	< 0.0001
	84/116 (72.4%)		9/41 (22%)		



US might avoid TAB if halo sign is present

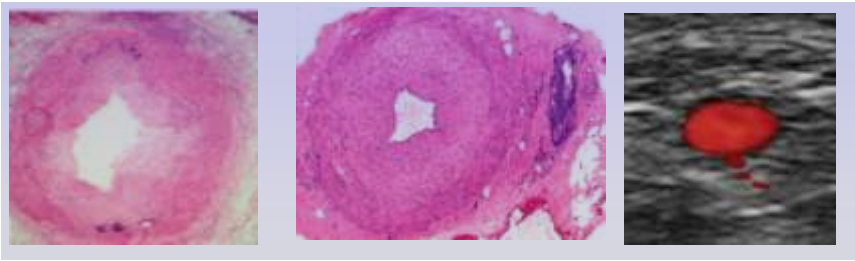
The absence of halo in US does not rule out GCA and TAB is still warranted



Giant cell arteritis

Pearl

The temporal artery biopsy is still the goal standard for the diagnosis of GCA, mainly in these forms without panarteritic involvement and slight intimal hyperplasia degree, and also for diagnosing those forms characterized for small vessel vasculitis surrounding a spared temporal artery



Polyarteritis nodosa

1990 CLASSIFICATION CRITERIA

1. Weight loss ≥4 kg
2. Livedo reticularis
3. Testicular pain or tenderness
4. Myalgias, weakness or leg tenderness
5. Mononeuropathy or polyneuropathy
6. Diastolic BP >90 mm Hg
7. Elevated BUN (>40 mg/dl) or creatinine (>1.5 mg/dl)
8. Hepatitis B virus
9. Arteriographic abnormality (visceral arteries)
10. Biopsy of small or medium-sized artery containing granulocytes

* For classification, at least 3 of these 10 criteria must be present.
3 or more criteria: sensitivity 82.2% and specificicy 86.6%.

Lightfoot RW Jr, et al. Arthritis Rheum 1990

It is still as frequent as we thought?
Does it really exist?

Polyarteritis nodosa

First complete decription – Kussmaul and Maier

Description of microscopic polyarteritis – F. Wohlwill
periarteritis + glomerulonephritis

Description of allergic granulomatosis/angiitis and periarteritis nodosa – Churg and Strauss
periarteritis + asthma + cutaneous rash + eosinophilia

Classification of necrotizing vasculitis – Pearl M. Zeek

1 Hypersensitivity angiitis;
2 Allergic granulomatous angiitis;
3 Rheumatic arteritis;
4 Periarteritis nodosa
5 Temporal arteritis

Polyarteritis nodosa

ACR classification criteria →Hepatitis B virus

Chapel Hill Nomenclature Vasculitis →No ANCA

→ **Annual incidence** → ACR 4-9 cases/million inh

→ CHCC 0-0.9 cases/million inh

→ **HBV vaccination 90's** → before >33% HBV

→ after <10% HBV

Revised Chapel Hill Nomenclature Vasculitis →No HBV

Polyarteritis nodosa (PAN)	Necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with antineutrophil cytoplasmic antibodies (ANCAs).
Vasculitis associated with probable etiology	Vasculitis that is associated with a probable specific etiology. The name (diagnosis) should have a prefix term specifying the association (e.g., hydralazine-associated microscopic polyangiitis, hepatitis B virus–associated vasculitis, hepatitis C virus–associated cryoglobulinemic vasculitis, etc.).

Classification algorithm of necrotizing vasculitis

Polyarteritis nodosa

… after Chapel Hill 2012

HBV-associated vasculitis

Watts R et al. ***Ann Rheum Dis*** 2007

Hernández-Rodríguez J et al. ***J Autoimmun*** 2014

Polyarteritis nodosa

PAN caused by Adenosine Deaminase 2 (ADA2) deficiency

The NEW ENGLAND JOURNAL of MEDICINE

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.

Navon-Elkan P et al. ***N Engl J Med*** 2014

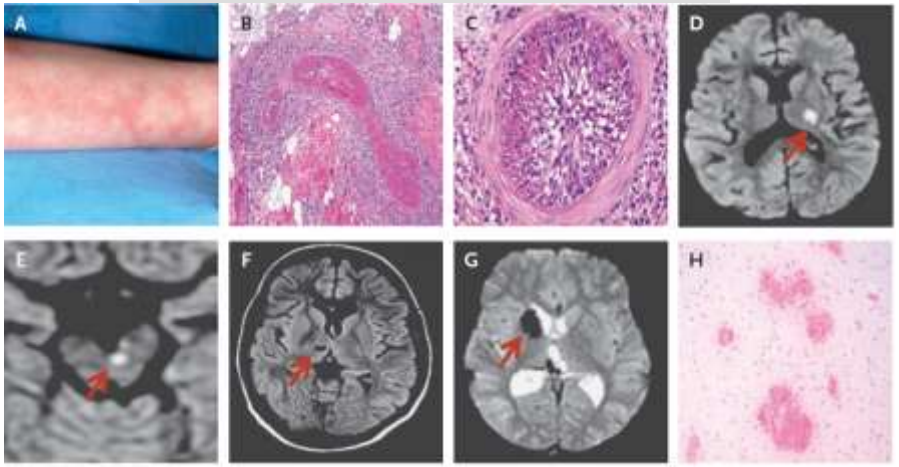
The NEW ENGLAND JOURNAL of MEDICINE

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

Zhou Q et al. ***N Engl J Med*** 2014



PAN caused by Adenosine Deaminase 2 (ADA2) deficiency

ORIGINAL ARTICLE

Elkan PN et al. ***N Engl J Med*** 2014

Mutant Adenosine Deaminase 2 in a Polyarteritis Nodosa Vasculopathy

ORIGINAL ARTICLE

Zhou Q et al. ***N Engl J Med*** 2014

Early-Onset Stroke and Vasculopathy Associated with Mutations in ADA2

Patients

24 patients with PAN (5 families and simple cases)
Age onset 2 m-59 yrs (4 ≥16 y.o.)

9 patients and their 8 families
Age onset 5 m-5 yrs

Clinical features

Gastrointestinal, renal, neurological (peripheral neuropathy, CNS) and cutaneous

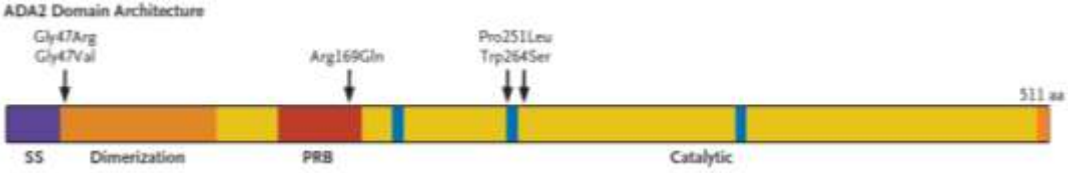
Recurrent fevers + strokes/visual complications + livedo racemosa vasculitis (4/9) + hepatosplenomegaly + high acute phase reactants + hipogammaglobulinemia (>IgM)

Biopsy findings

Systemic inflammatory vasculopathy/vasculitis (in skin, liver and brain biopsies)

Genetic result

Recessive mutations in *CECR1* (cat eye syndrome chromosome region, candidate 1)
CECR1 → gene encoding adenosine deaminase 2 (ADA2)



ADA2 circulating levels

Marked reduction in the levels of ADA2 and ADA2-specific enzyme activity in the blood

In vivo and in vitro studies

Expression in human embryonic kidney 293T cells revealed low amounts of mutant secreted protein

Knockdown of a zebrafish ADA2 homologue caused intracranial hemorrhages and neutropenia — prevented by coinjection with nonmutated human *CECR1*.
Monocytes from patients induced damage in cocultured endothelial-cell layers

Diagnostic pearls in vasculitis

Classification algorithm of necrotizing vasculitis

Clinical diagnosis of primary systemic vasculitis

Fulfils ACR or Lanham criteria for Churg-Strauss syndrome

Yes → Churg-Strauss syndrome

No → ACR criteria for Wegener's granulomatosis

Yes → Wegener's granulomatosis

No → Histology compatible with CHCC for Wegener's granulomatosis

Yes → Wegener's granulomatosis

No → Histology compatible with CHCC for microscopic polyangiitis and Wegener's surrogate markers

Yes → Wegener's granulomatosis

No → No histology. Wegener's surrogate markers and positive serology for PR3 or MPO

Yes → Wegener's granulomatosis

No → Clinical features and histology compatible with small vessel vasculitis. No Wegener's surrogate markers

Yes → Microscopic polyangiitis

No → No histology. No Wegener's surrogate markers. Surrogate markers for microscopic polyangiitis and positive serology for PR3 or MPO includes renal-limited vasculitis

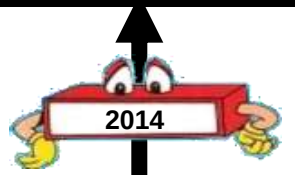
Yes → Microscopic polyangiitis

No → Histology compatible with CHCC for polyarteritis nodosa or typical angiographic features of PAN

Yes → Polyarteritis nodosa

No → Unclassifiable

ADA2 deficiency?



Polyarteritis nodosa

… after Chapel Hill 2012

HBV-associated Vasculitis

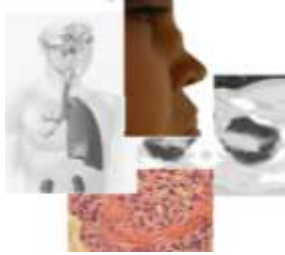
Watts R et al. ***Ann Rheum Dis*** 2007

Polyarteritis nodosa

Pearl

PAN is an extremely rare disease
… after excluding HBV, ANCA, cryoglobulins, other autoimmune diseases (SLE, RA…) and ADA2 related vasculitis.

Granulomatosis with polyangiitis (Wegener)



1990 CLASSIFICATION CRITERIA

1. Nasal or oral inflammation
2. Abnormal chest radiograph
3. Urinary sediment with microhematuria/red cell casts
4. Granulomatous inflammation on biopsy

*For classification, at least 2 of these 4 criteria must be present.
2 or more criteria: sensitivity 88.2% and specificity 92.0%

Leavitt RY et al. Arthritis Rheum 1990

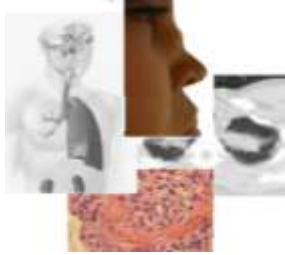
1994 Chapel Hill …
Very often associated to ANCA presence

2012 Revised Chapel Hill…

ANCA-associated vasculitis (AAV)	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries), associated with myeloperoxidase (MPO) ANCA or proteinase 3 (PR3) ANCA. Not all patients have ANCA.

How to diagnosis the limited forms of granulomatosis with polyangiitis (Wegener's)

ANCA-associated vasculitides



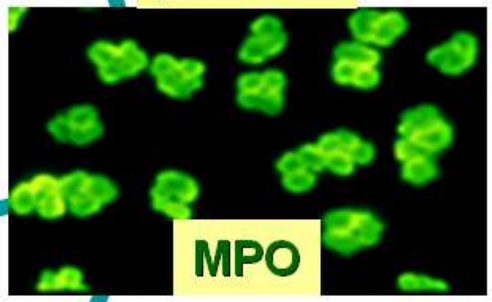
GPA
(WEGENER)

MPA
MICROSCOPIC
POLYANGIITIS

ANCA

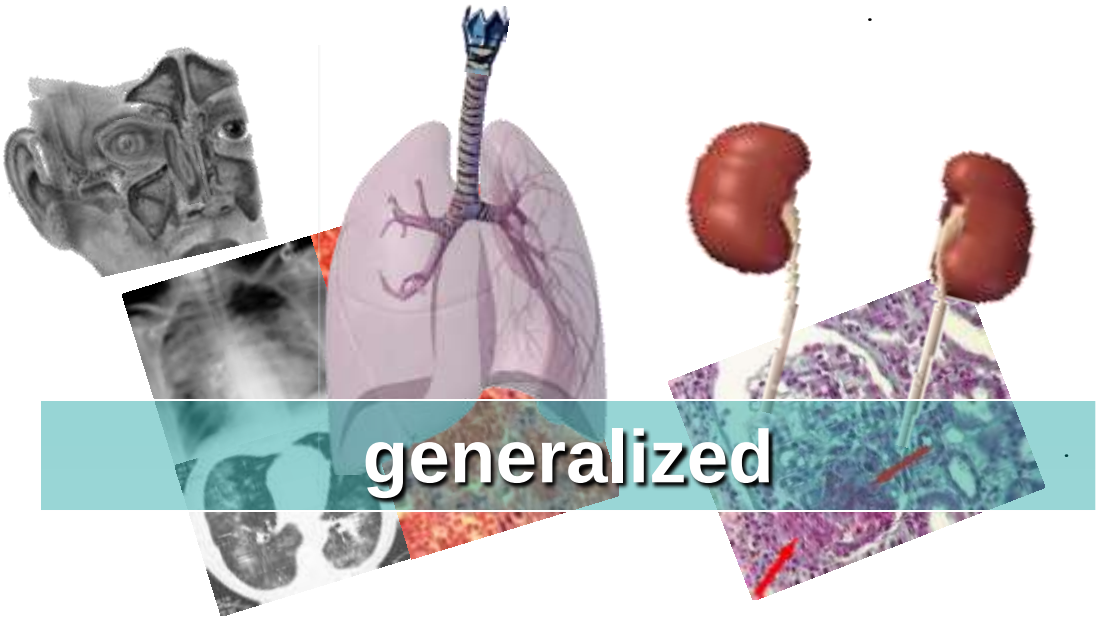
c-ANCA

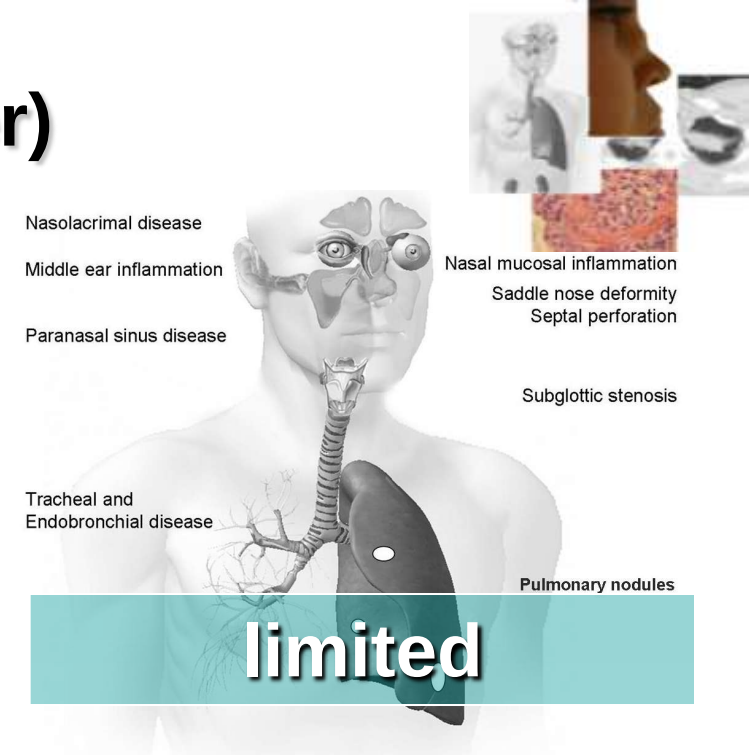
p-ANCA



EGPA
(CHURG-STRAUSS)

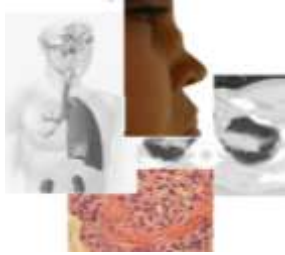
GPA (Wegener)

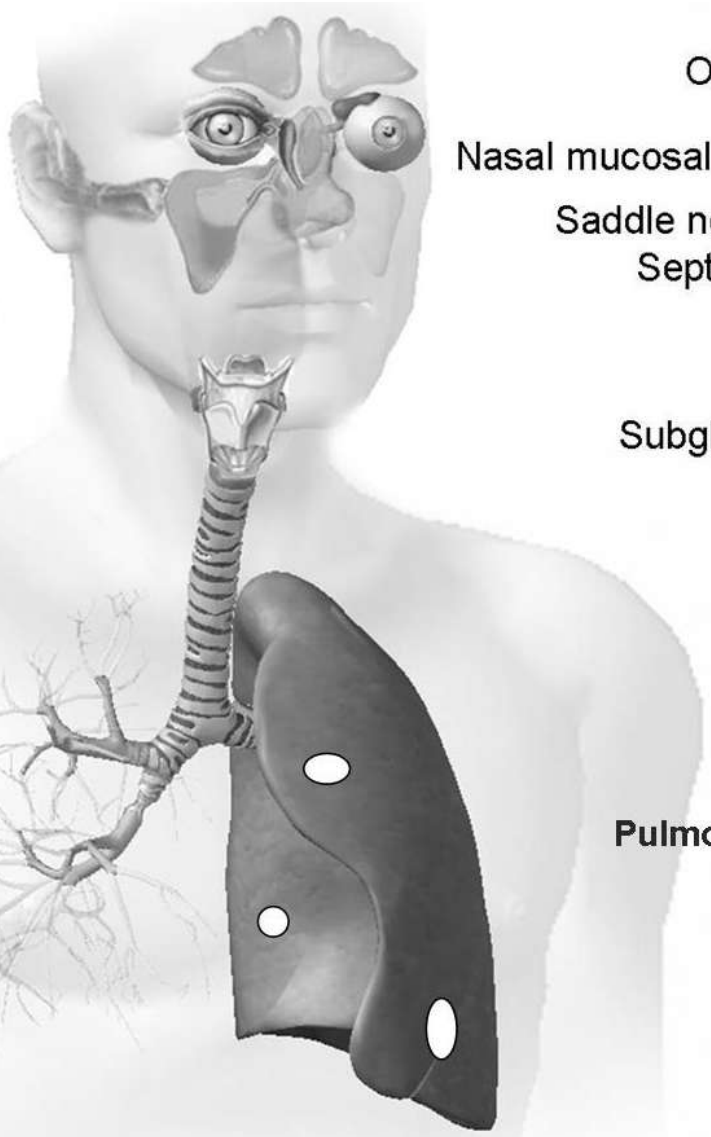




ANCA positivity	GPA (Wegener)		MPA	EGPA
cANCA / PR3	40-90%		10-20%	0-10%
	80-95% generalized	40-75% limited		
pANCA / MPO	0-10%		60-85%	30-60%

Limited GPA (Wegener)





8% Nasolacrimal disease

20-60% Middle ear inflammation

72-92% Paranasal sinus disease

32% Tracheal and
43% Endobronchial disease

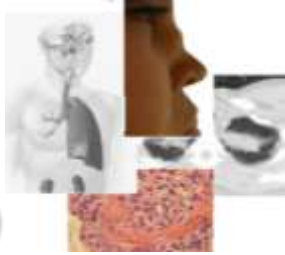
Orbital disease 2-15%

Nasal mucosal inflammation 72-92%

Saddle nose deformity
Septal perforation 10-25%

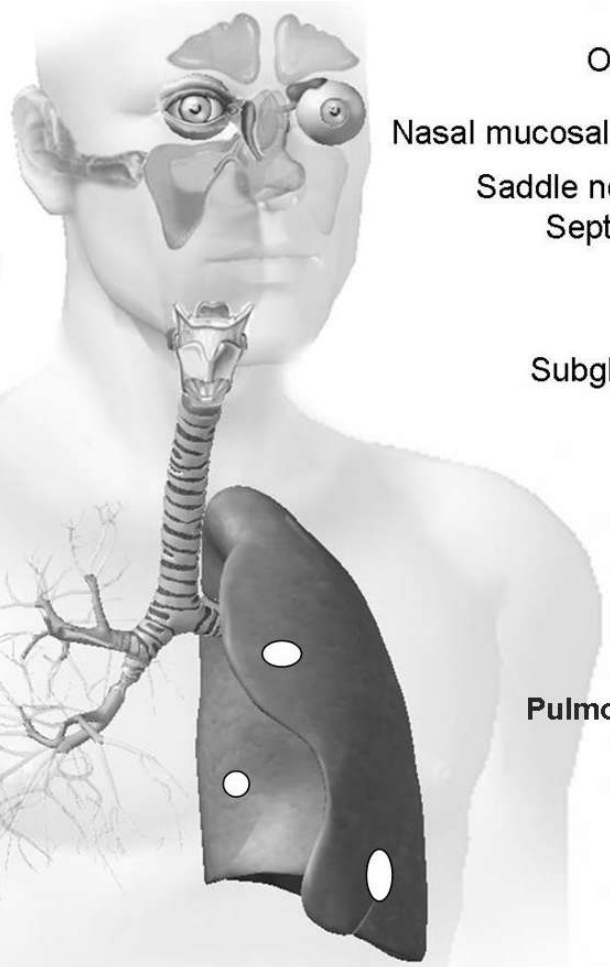
Subglottic stenosis 7-23%

Pulmonary nodules 40-70%



Limited GPA (Wegener)

Yield of biopsies (vasculitis and/or granuloma)



Nasolacrimal disease

Middle ear inflammation

55% Paranasal sinus disease

18% Tracheal and Endobronchial disease *

Orbital disease — 27-85% vasculitis; 62-91% granuloma & necrosis; 54% triad

Nasal mucosal inflammation

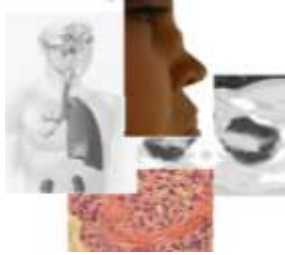
Saddle nose deformity — 3-20% *

Septal perforation

Subglottic stenosis — 5% *

Pulmonary nodules — 7% transbronchial bx; 90% open lung bx

* Most of samples with normal or nonspecific acute and chronic inflammation



Limited GPA (Wegener)

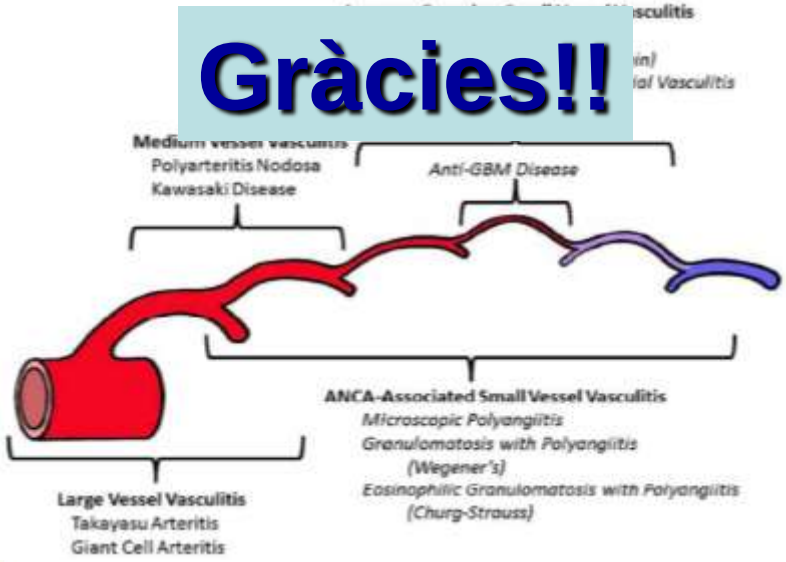
Pearl

In limited GPA (ENT, upper airway and/or orbital involvement alone), a positive biopsy showing vasculitis/granuloma and/or a positive ANCA will be determinant to make the final diagnosis.

However, most patients (>50%) with will have a negative/non-specific biopsy and absence of ANCA, and after ruling out other (infectious, cancer…) conditions these have to be treated accordingly to avoid further established tissue damage.

In the meantime, repeated biopsies and new ANCA determination are recommended.

Gràcies!!


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