# Approche clinique, classification, nomenclature des vascularites

Luc Mouthon

Service de Médecine Interne, hôpital Cochin,

Centre de Référence Maladies Systémiques Autoimmunes Rares d'Ile de France

Assistance publique-Hôpitaux de Paris, Paris

Université Paris Descartes, Inserm U1016, Institut Cochin, Paris

AMMAIS - Casablanca – 18 novembre 2017

# Conflicts of interest

- **Consultant**: Actelion, CSL Behring, LFB Biotechnologies, Lilly, Pfizer, Octapharma
  - Financial support to ARMIIC
- **Investigator**: Actelion, CSL Behring, Pfizer
- **Financial support (grants to ARMIIC)**: Actelion, CSL Behring, GSK, LFB Biotechnologies, Pfizer
- **Invited conference**: SOBI, Roche, Actelion, CSL Behring, Octapharma, GSK, LFB Biotechnologies, Pfizer, Lilly, UCB pharma

# Approche clinique, classification, nomenclature des vascularites

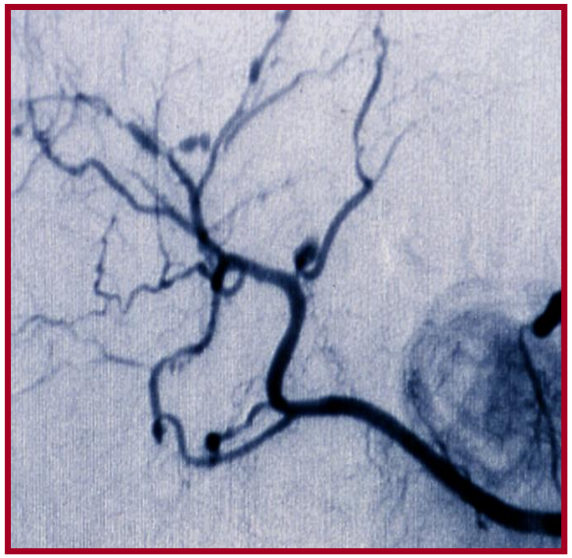
- Introduction
- Classification
  - Gros vaisseaux
  - Vaisseaux de moyen calibre
  - Vaisseaux de petit calibre
- Conclusion

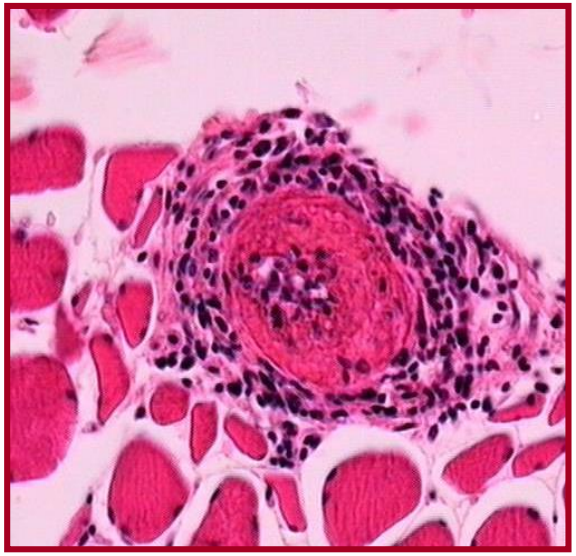
# Introduction

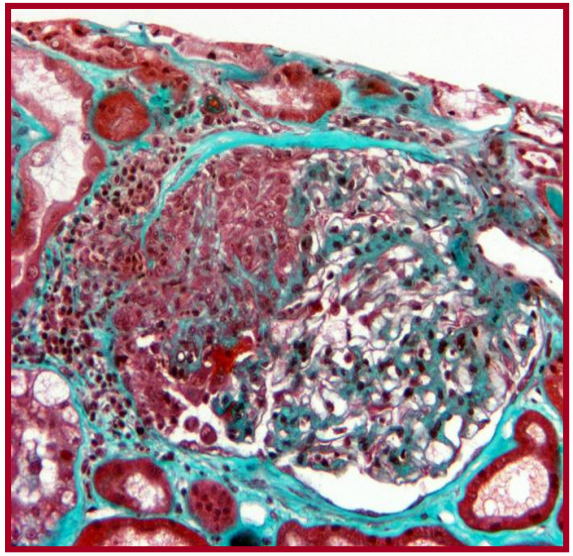
# VASCULARITES : DÉFINITION

**Atteinte inflammatoire des vaisseaux sanguins artériels et veineux :**

→ **Ischémie et nécrose des tissus à distance**







- Diagnostics différentiels
- Vascularites secondaires

# Expression clinique des vascularites

**Arthralgies inflammatoires**
**Polyarthrite**

**Multinévrite**
**Polyneuropathie**

**Néphropathie**

**AVC**
**Epilepsie**
**Démence**

**Hémorragie digestive**
**Perforation**

**Purpura**
**Raynaud**
**Nécroses**
**Thromboses**

**Hémorragie alvéolaire**
**Nodules**
**Infiltrats**

# Progrès thérapeutiques

- Artérite à cellules géantes: tocilizumab (anti-IL6R) dans les formes réfractaires
- Takayasu: anti-TNF$\alpha$ dans les formes réfractaires
- Kawasaki: Imunoglobulines intraveineuses + aspirine
- PAN : anti-TNF$\alpha$ si mutation ADA2
- Cryoglobulinémies: nouveaux anti-viraux C/rituximab
- Vascularites ANCA-positives: rituximab
- Vascularites hypocomplémentémiques: rituximab

# Classification

# Classifications anatomo-cliniques

- Schönlein (1837), Henoch (1868)
- Kussmaul et Maier: 1866
- Horton: 1932
- Wegener: 1939
- Zeek: 1952
- Churg et Strauss: 1951
- Kawasaki: 1967

# Classifications des vascularites

- American College of Rheumatology (ACR) 1990
  - Vascularites prouvées
  - Ce qui différencie les vascularites les unes des autres
- Chapel Hill Consensus Conference Nomenclature of Vasculitides
  - 1994
  - Révisée en 2012
- Les critères de classification ne sont pas des critères diagnostiques

# 1990 ACR Classification: limitations !

Summary of ACR criteria and their limitations [12–18].

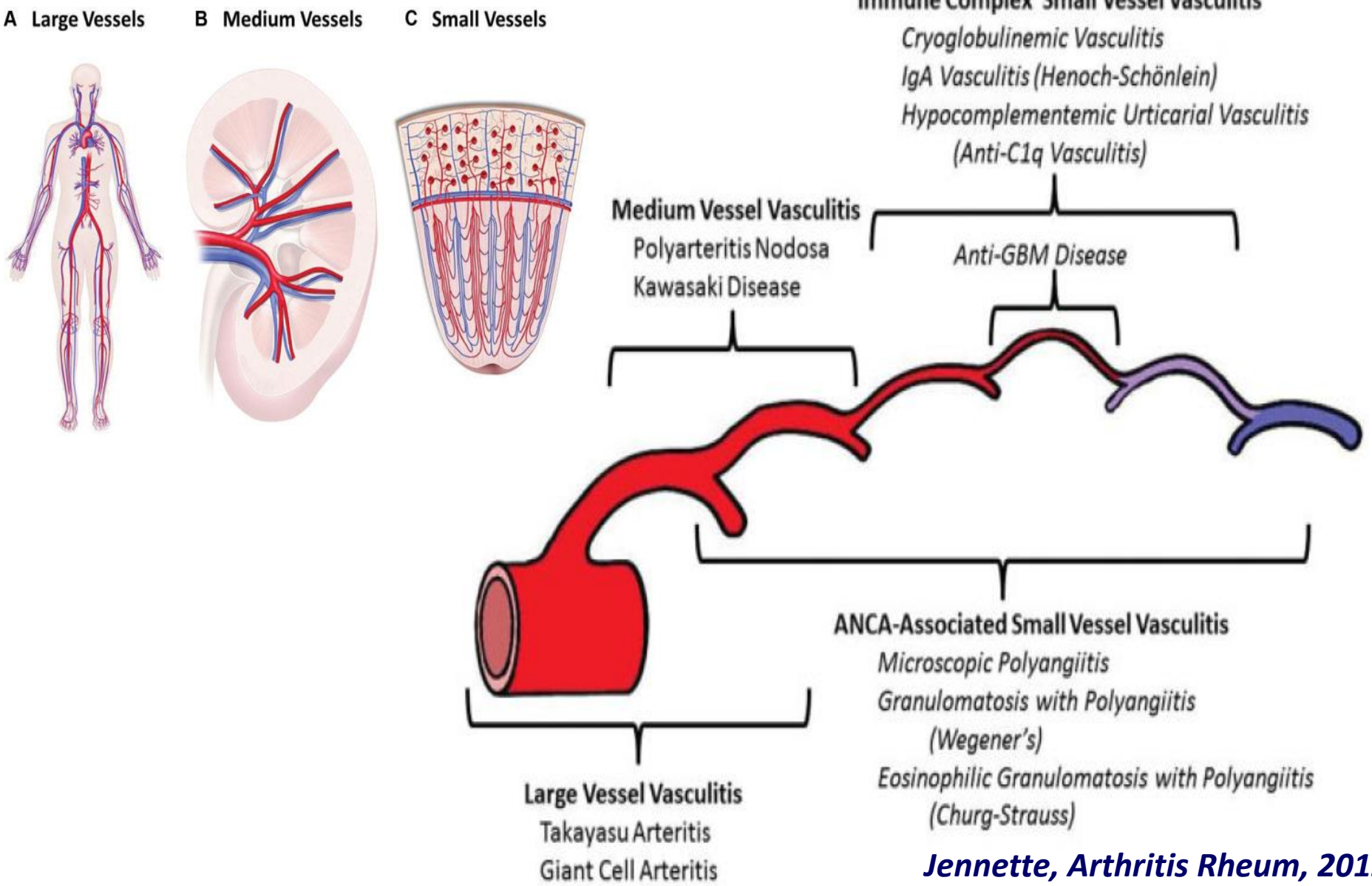
| Type of Vasculitis | Sensitivity | Specificity | Limitations |
|---|---|---|---|
| GCA | 93.5% | 91.2% | Temporal artery biopsy is an important diagnostic tool but is not an obligatory criterion. |
| TAK | 90.5% | 97.8% | Newer imaging modalities, such as CT PET maybe useful, but are not included |
| GPA | 88.2% | 92% | No clear discrimination between GPA and MPA, or other mimics of GPA. Does not incorporate ANCA test. |
| EGPA | 85% | 99.7% | No inclusion of common features such as cardiac manifestations and rash. Does not incorporate ANCA test. |
| PAN | 82.2% | 86.6% | No absolute requirement for arteriography, or biopsy findings. No clear discrimination between PAN and MPA. |
| IgAV | 87.1% | 87.7% | Do not distinguish between IgAV from allergic reactions, or infectious related purpura. Common features; arthritis and nephritis are excluded. Age set as important criteria, but almost 30% of patients were above the age of 20. |
| Hypersensitivity vasculitis | 71% | 83.9% | Difficult to distinguish from IgAV |
| Microscopic polyangiitis | | | Not recognized by ACR |

Pas maladie de Behcet, pas ANCA, IgA, cryo, anti-GBM

# 1994 Chapel Hill CC nomenclature

- Nomenclature +++
  - Pas de critères de classification
  - Pas de critères diagnostiques
- Se basait sur la taille des vaisseaux
- Se basait sur l'histologie
- Incluait les ANCA
- Distinguait Polyangéïte microscopique (MPA) de Périartérite noueuse (PAN)

# Chapel Hill nomenclature: revision




*Jennette, Arthritis Rheum, 2012*

# 2012 Chapel Hill Conference Consensus nomenclature: la chasse aux éponymes

| Abbreviation | Definition | Previous terminology |
|---|---|---|
| GPA | Granulomatosis with polyangiitis | Wegener's granulomatosis |
| EGPA | Eosinophilic granulomatosis with polyangiitis | Churg–Strauss |
| MPA | Microscopic polyangiitis | |
| IgA vasculitis | IgA vasculitis | Henoch–Schonlein purpura |

| Other new terminology and minor modifications | Previous terminology |
|---|---|
| Anti-GBM disease | Goodpastures disease |
| Cutaneous arteritis | Cutaneous PAN |
| Cutaneous leukocytoclastic angiitis | |
| Hypocomplementemic urticarial vasculitis | |

***Jennette, Arthritis Rheum, 2012***

# 2012 Chapel Hill Conference Consensus (CHCC) nomenclature

- Formes localisées de vascularites des petits vaisseaux

  GPA et EGPA

- Variable Vessel Vasculitis

  Behcet, Cogan

- Single-organ vasculitis

  peau, testicules, SNC, SNP, rein

- Vascularites secondaires (PR, lupus, virus)

***Jennette, Arthritis Rheum, 2012***

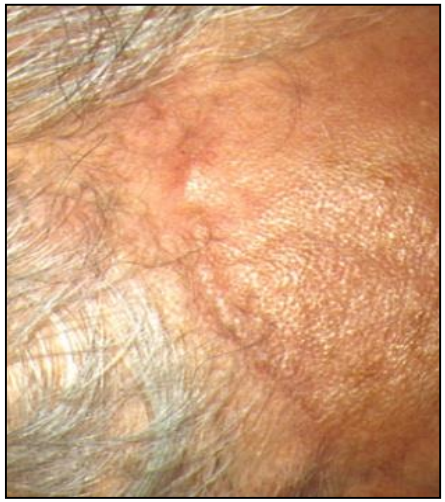
# Gros vaisseaux

# Artérite à cellules géantes (maladie de Horton)
# Critères ACR 1990

| |
|---|
| Age de début > 50 ans |
| Céphalée d'installation récente |
| Anomalie des artères temporales (Sensibilité de l'artère temporale à la palpation ou diminution ou abolition du pouls temporal non lié à une athérosclérose cervicale) |
| Accélération de la VS > 50 mm à la 1ère h |
| Anomalie de la biopsie d'artère temporale (Vascularite caractérisée par une prédominance d'éléments mononucléés ou inflammation granulomateuse avec cellules géantes multinucléées) |

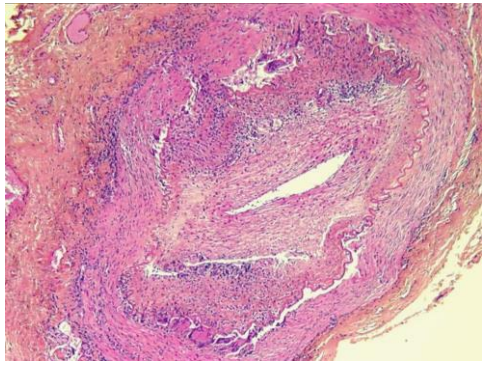
**Maladie de Horton si au moins 3 des 5 critères sont présents avec une sensibilité de 93,5% et une spécificité de 91,2%.**

# Giant cell arteritis



- Giant cell arteritis (GCA) is a large-vessel vasculitis occuring exclusively in patients older than 50 years.

- GCA specifically involves aorta and external carotid arteries and their branches, responsible for temporal headaches, jaw claudication and scalp tenderness.



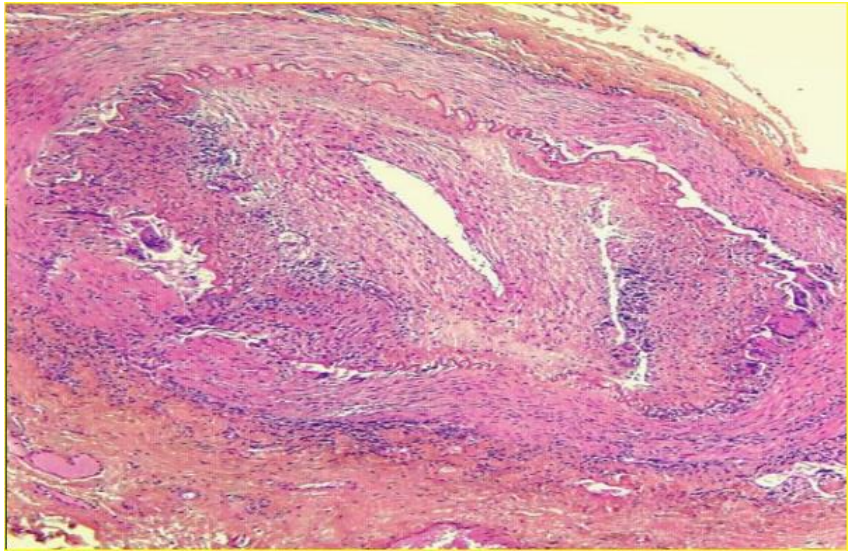
- Visual loss represents the most severe complication.

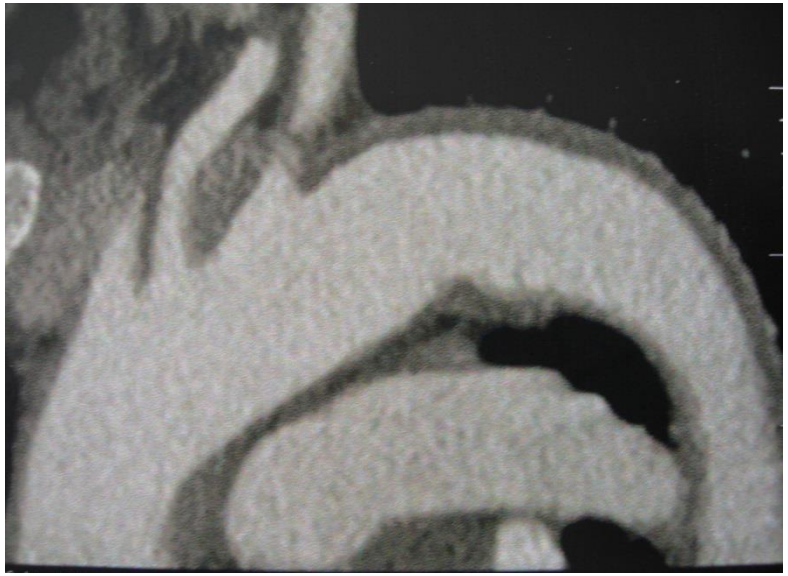
- Today there is no validated biomarker in GCA and the diagnosis is made upon temporal artery biopsy.

Ly KH et al. Autoimmunity Reviews, 2010

# GIANT CELL ARTERITIS

BAT

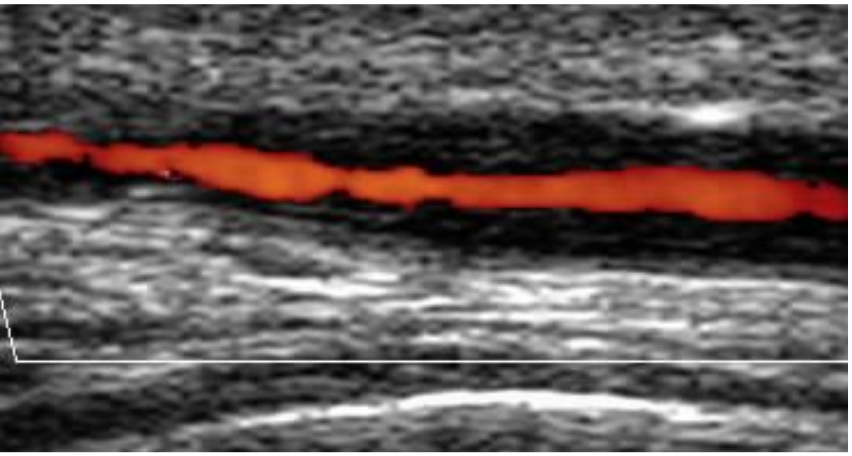


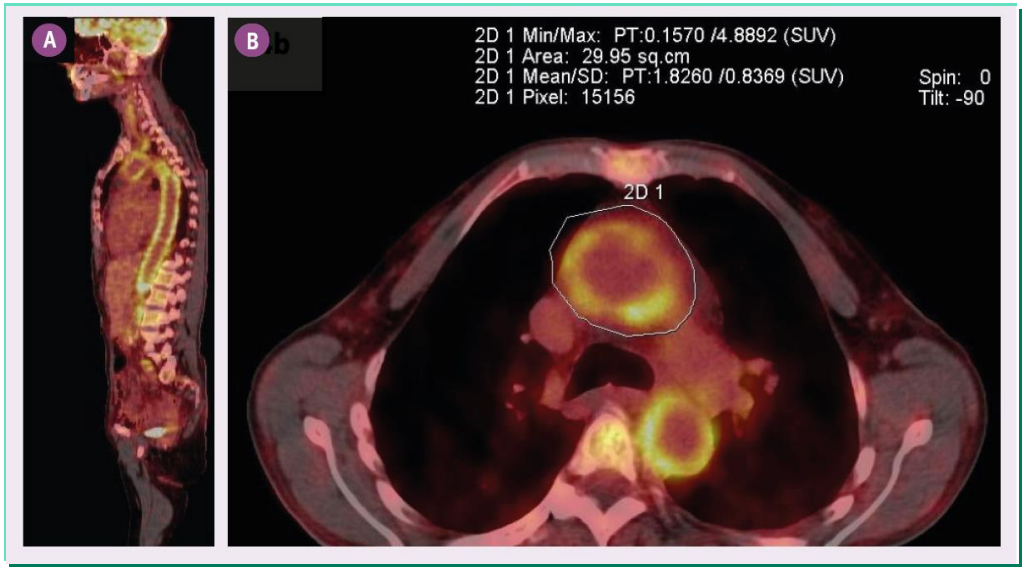


IRM

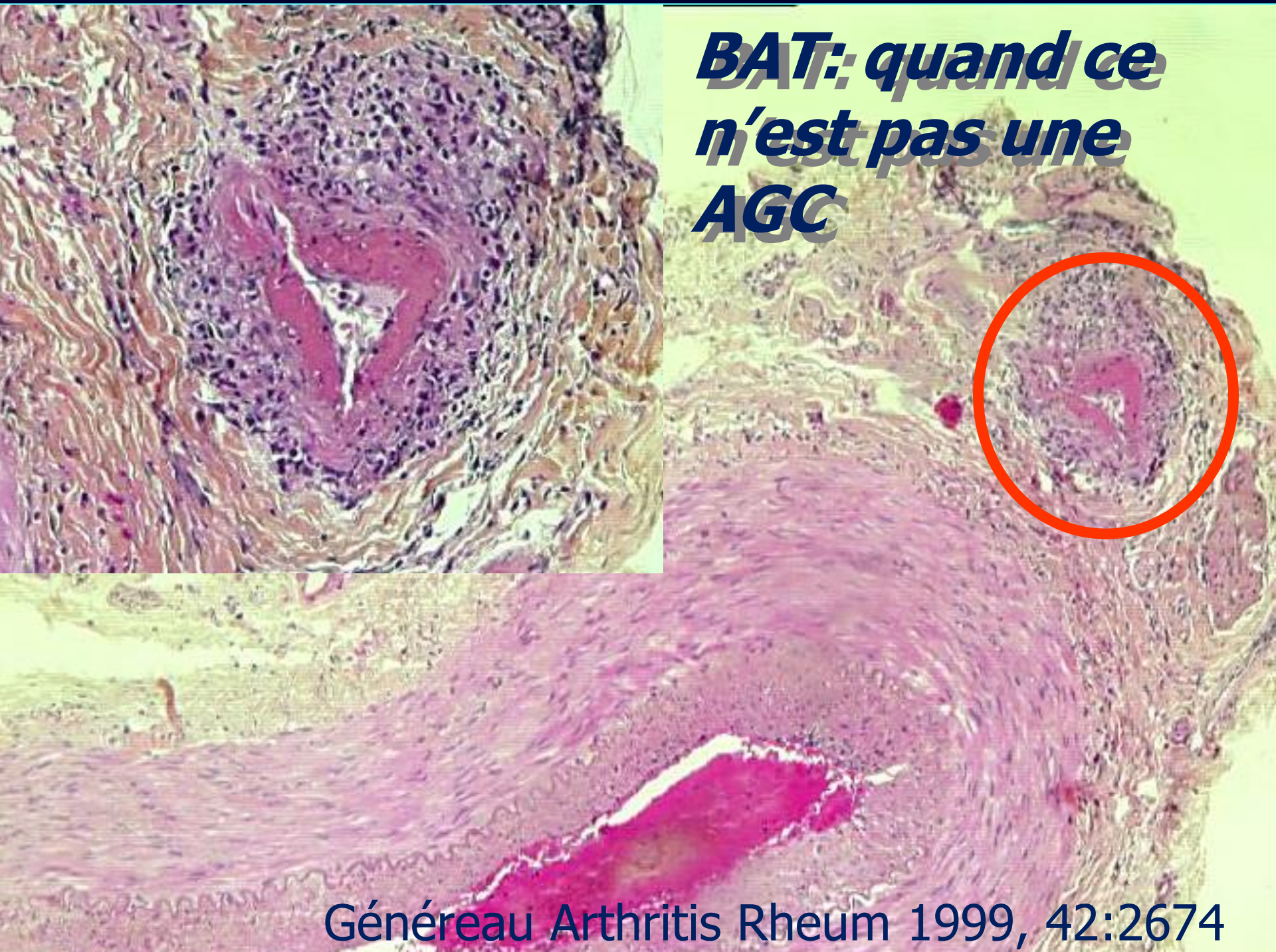
TEP scanner

Echo-doppler



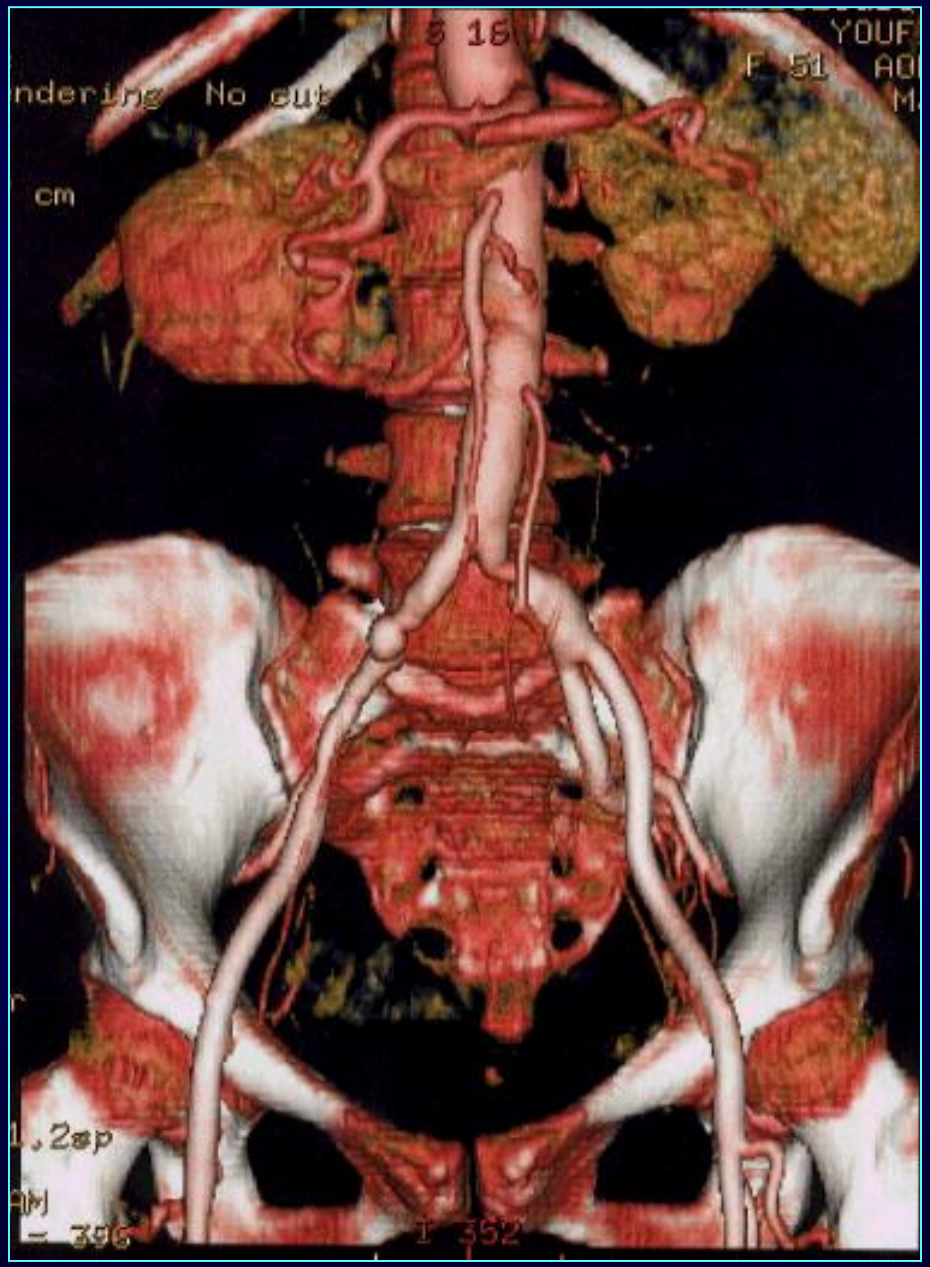


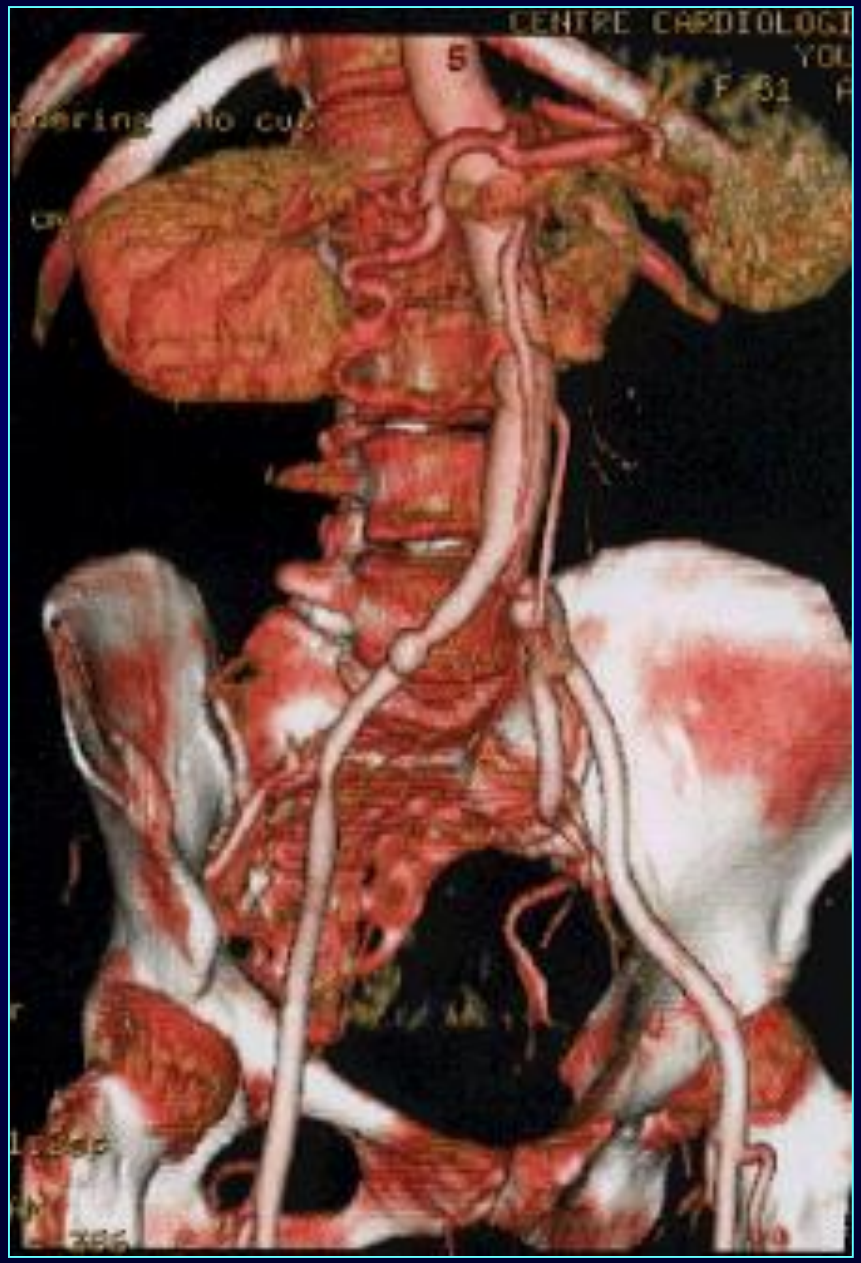
# BAT: quand ce n'est pas une AGC



Généreau Arthritis Rheum 1999, 42:2674

# TAKAYASU



# Takayasu

**Box 1** | 'Red flags' for Takayasu arteritis

In patients under 40 years of age there are a number of clinical findings that might indicate a diagnosis of Takayasu arteritis:

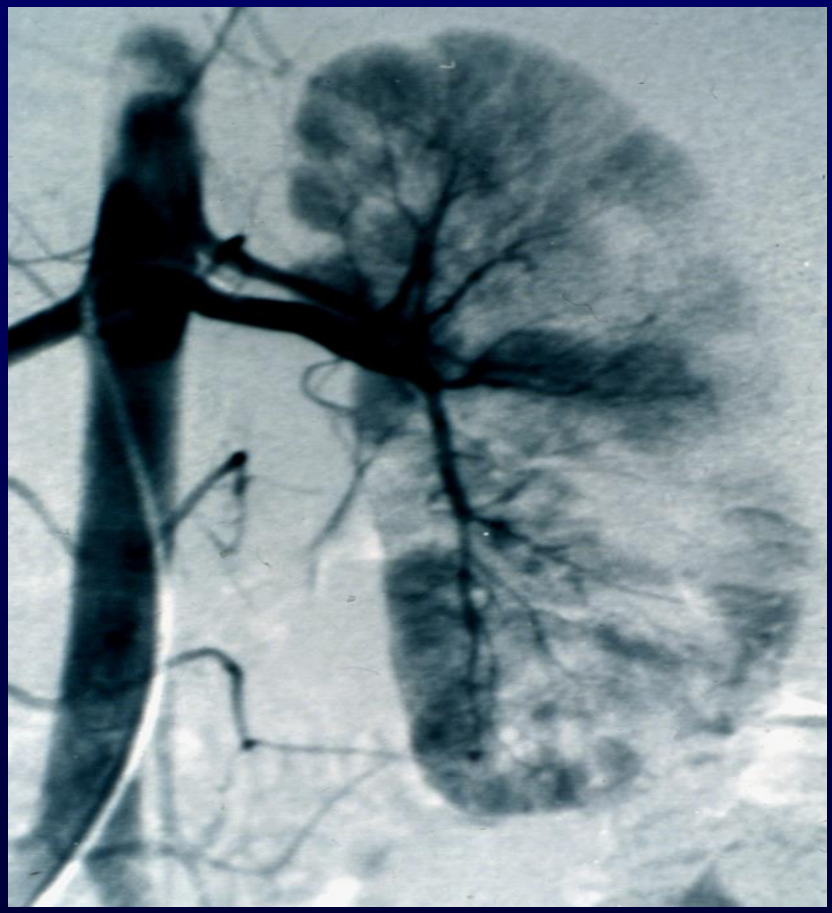
- An unexplained acute phase response (raised erythrocyte sedimentation rate or C-reactive protein levels, or both)
- Carotidynia
- Hypertension
- Discrepant blood pressure between the arms (>10 mmHg)
- Absent or weak peripheral pulse(s)
- Limb claudication
- Arterial bruit
- Angina

Mason, J. C. *Nat. Rev. Rheumatol.* 6, 406–415 (2010); doi:10.1038/nrrheum.2010.82

# Vaisseaux de moyen calibre

# *PAN : 1990 ACR CRITERIA*

- Weight loss < 4kg
- Livedo reticularis
- Testicular pain or tenderness
- Mono- or polyneuropathy
- Diastolic BP > 90 mm Hg
- Elevated BUN or creatininemia
- Hepatitis B virus
- Biopsy of small or medium-sized artery containing PMN



**3 of 10 criteria should be present**

# Polyangéite microscopique vs. PAN

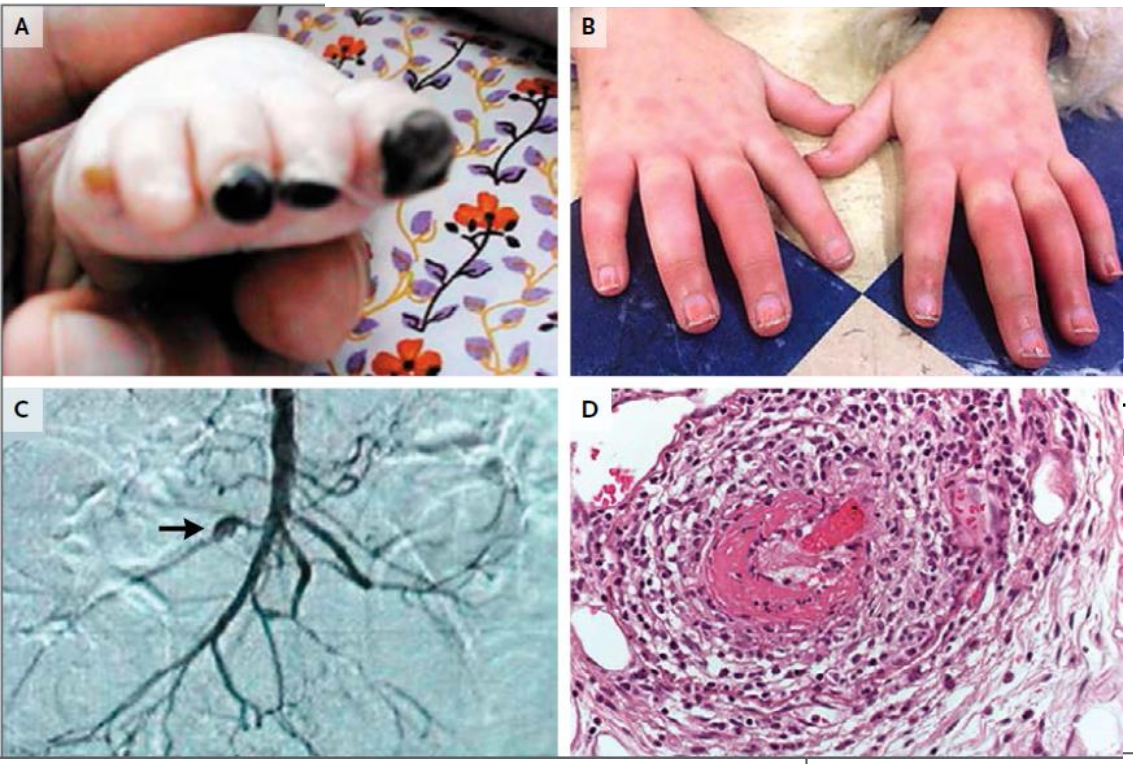
| | MPA | PAN |
|---|---|---|
| Vaisseaux | Petits | Moyens |
| Granulomes | Non | Rare |
| VHB | Non | Rare |
| ANCA | > 50% | Non |
| Atteinte glomérulaire | Oui | Non |
| Atteinte vasculaire rénale | Non | Oui |
| Atteinte pulmonaire | Oui | Non |

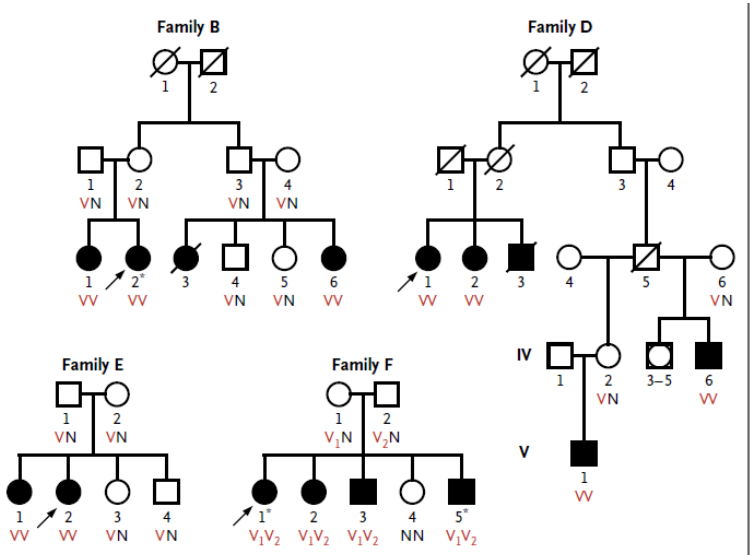
The NEW ENGLAND JOURNAL of MEDICINE

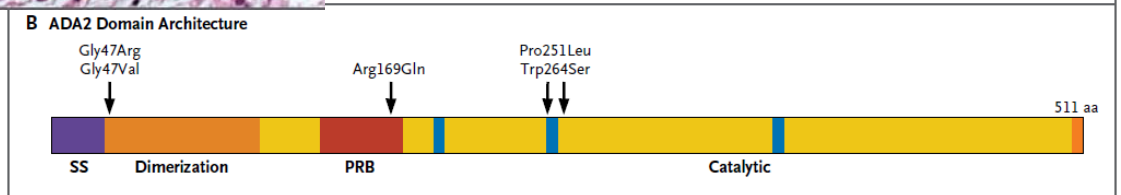
ORIGINAL ARTICLE

# Mutant Adenosine Deaminase 2 in a Polyarteritis Nodosa Vasculopathy

N ENGL J MED 370;10 NEJM.ORG MARCH 6, 2014

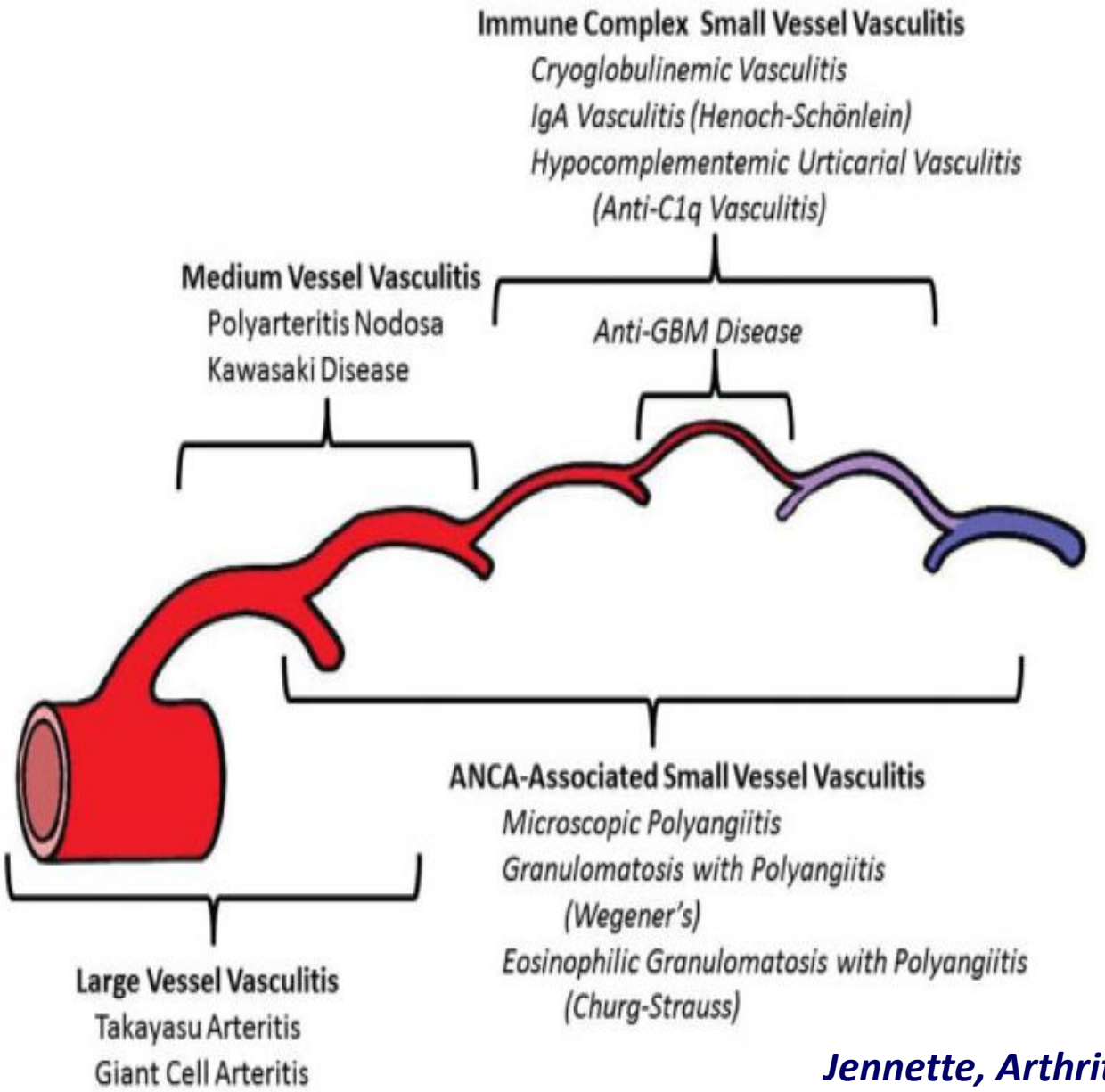


# Vaisseaux de petit calibre

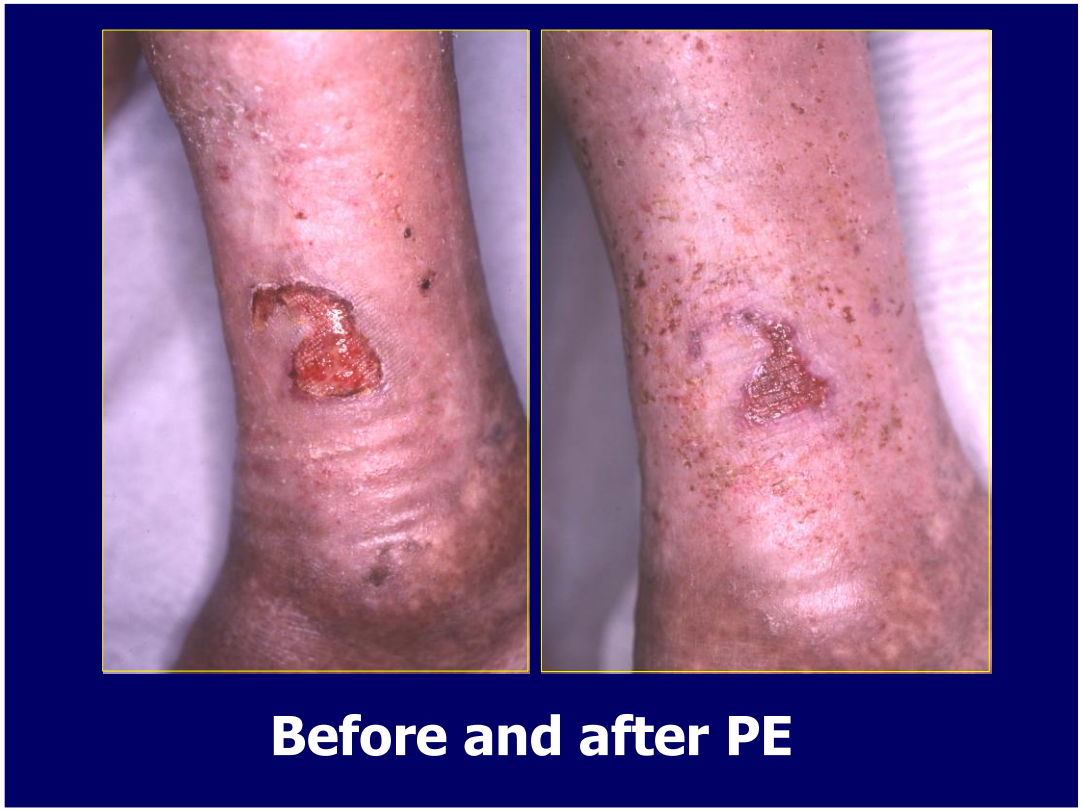
# Chapel Hill nomenclature: revision




***Jennette, Arthritis Rheum, 2012***

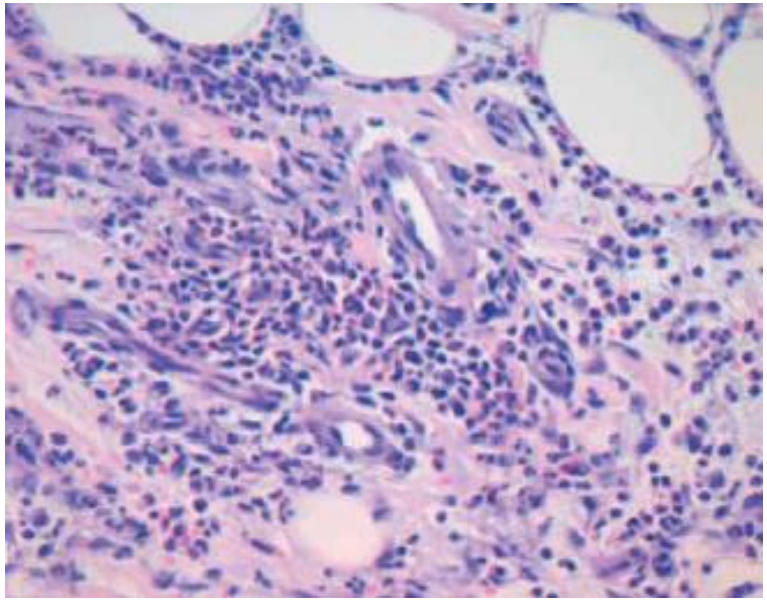
# Cryoglobulines

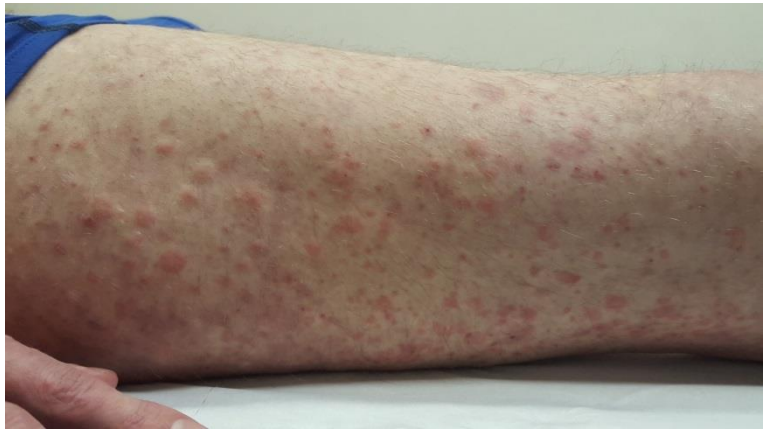
- Protéines sériques
- Immunoglobulines
- Précipitent < 37°C et se resolubilisent à 37°C




1. VHC
2. Lymphoproliferation
3. Sjögren
4. Essentielle

# Vascularites urticariennes hypocomplémentémiques: Critères diagnostiques



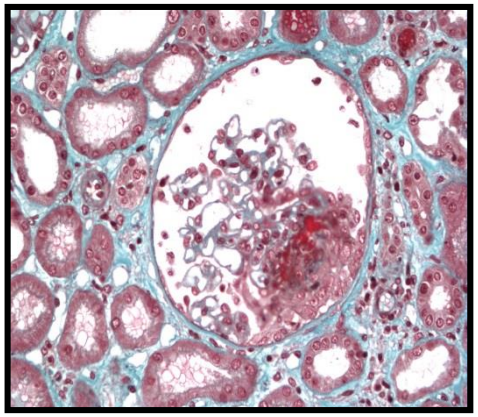


| Critères diagnostiques SVUH |
|---|
| **Critères majeurs** |
| Urticaire chronique |
| Hypocomplémentémie |
| **Critères mineurs** |
| Vascularite leucocytoclasique |
| Arthralgies/arthrites |
| Uvéite/épisclérite/conjonctivite |
| Glomérulonéphrite |
| Douleur abdominale |
| Anticorps anti-C1q |

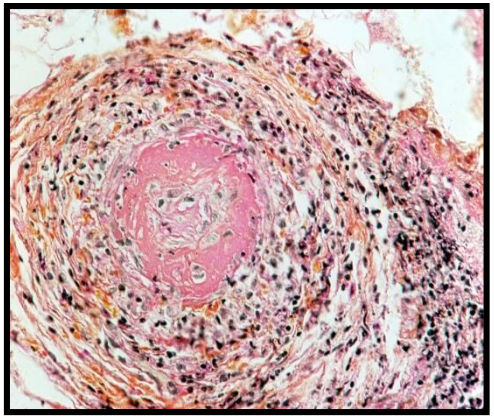
**2 critères majeurs et au moins 2 des 6 critères mineurs**

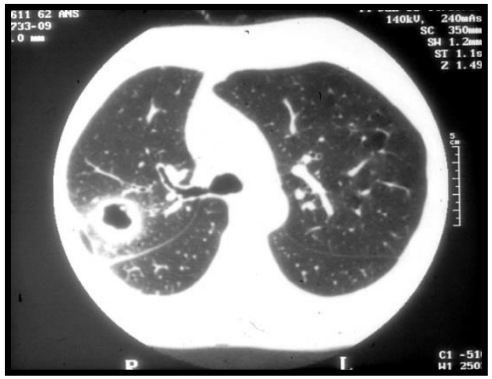
*Agnello, J Invest Dermatol, 1976*
*McDuffie, Mayo Clin Proc, 1973*
*Schwartz , Mayo Clin Proc, 1982*

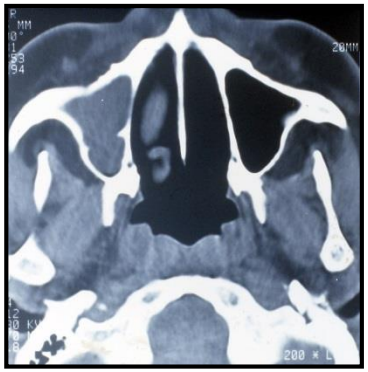
# ANCA-associated vasculitides



- Vascular necrosis and perivascular inflammation in small vessels
- Systemic disease because of renal and lung involvements

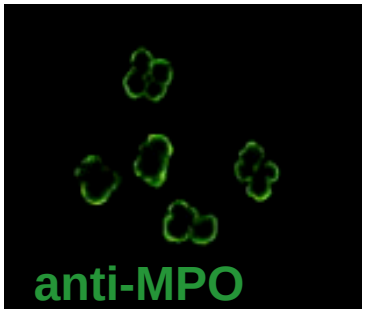


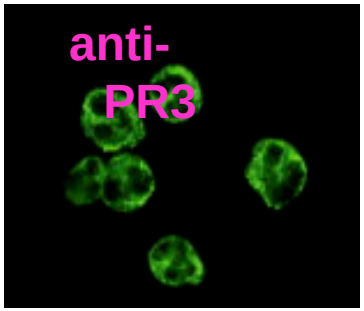




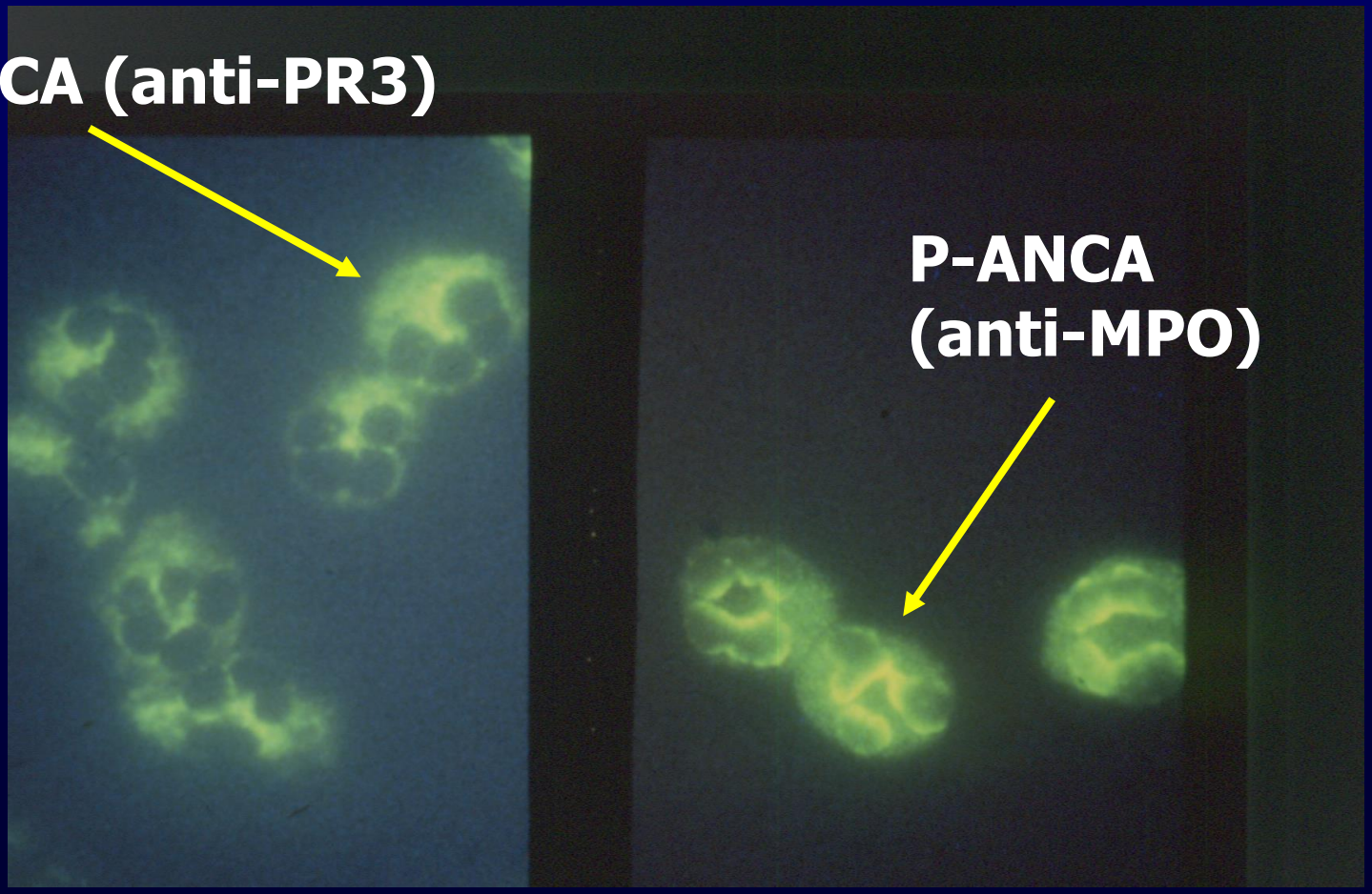
- Diagnostic value of ANCA

| | anti-MPO | anti-PR3 |
|---|---|---|
| Wegener's granulomatosis | 10 % | 85 % |
| Microscopic polyangiitis | 60 % | 30 % |
| Churg-Strauss | 31 % | <10 % |

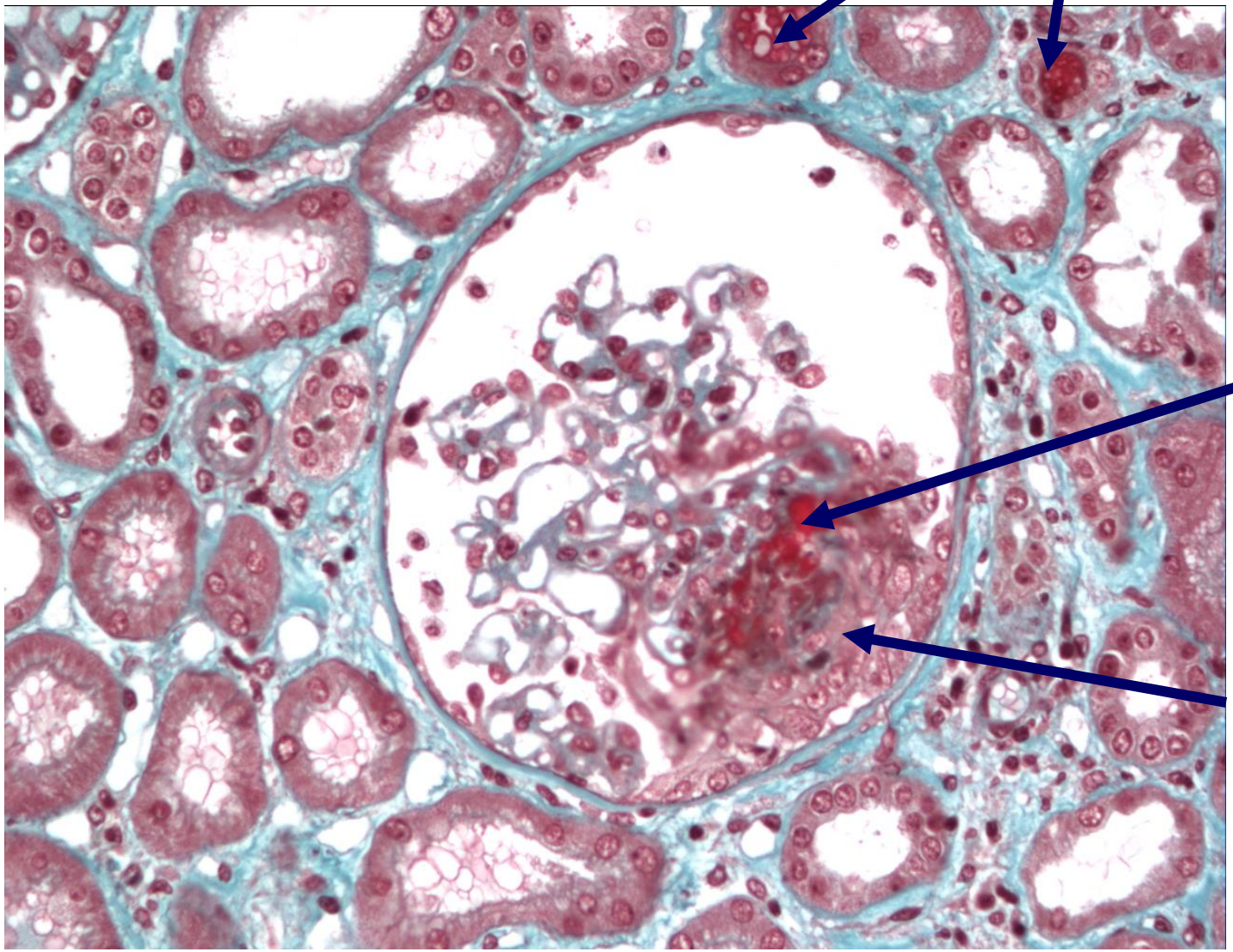


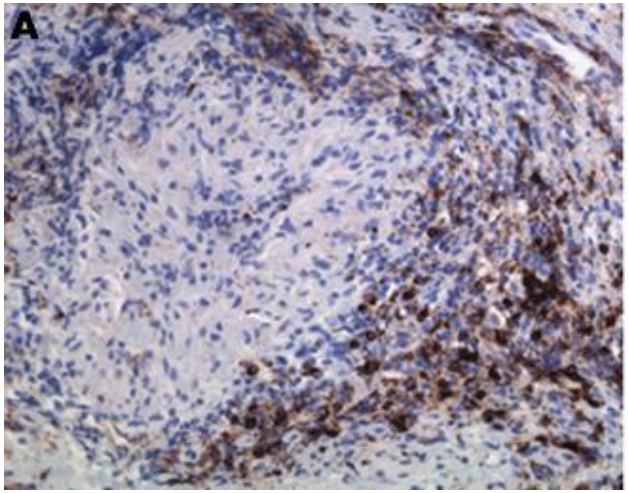
# *ANCA IN SYSTEMIC VASCULITIS*



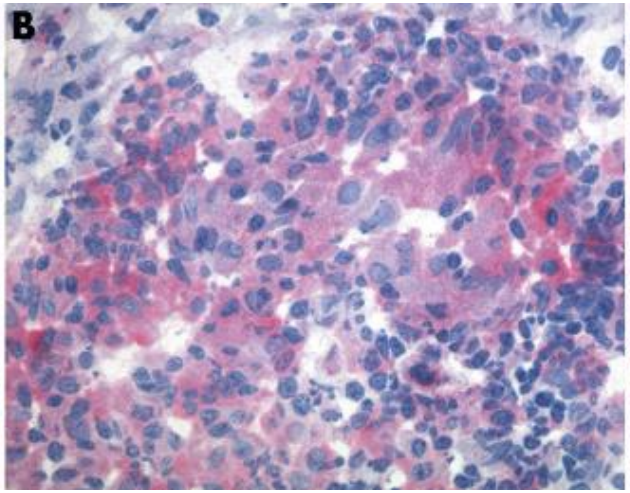
# Polyangéite microscopique



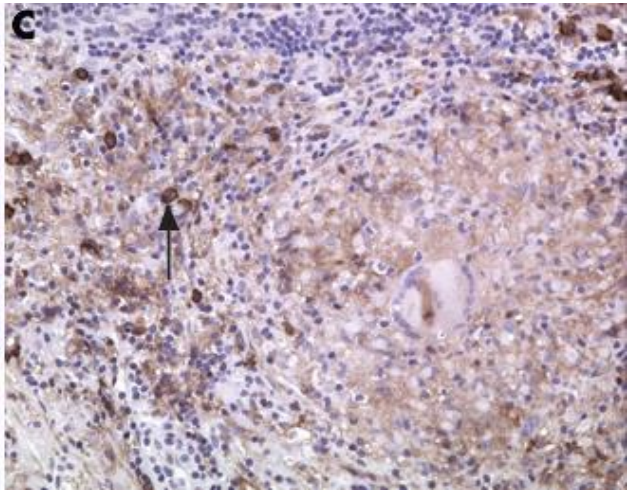
# B lymphocyte maturation in Wegener's granulomatosis




CD20 expression in an endonasal lesion from a case of Wegener's granulomatosis



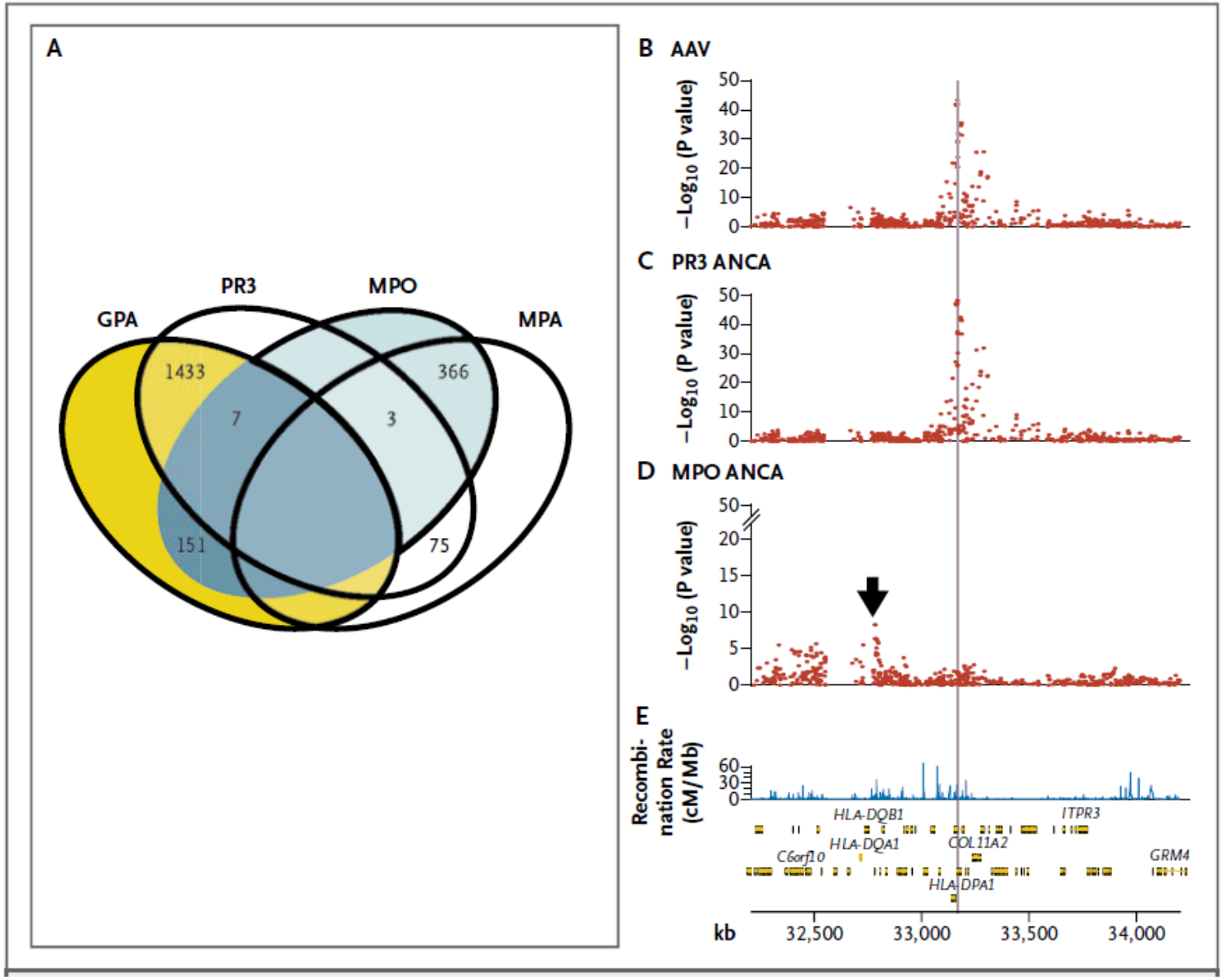

PR3 expression in a WG endonasal lesion




CD38 expression in a WG endonasal lesion

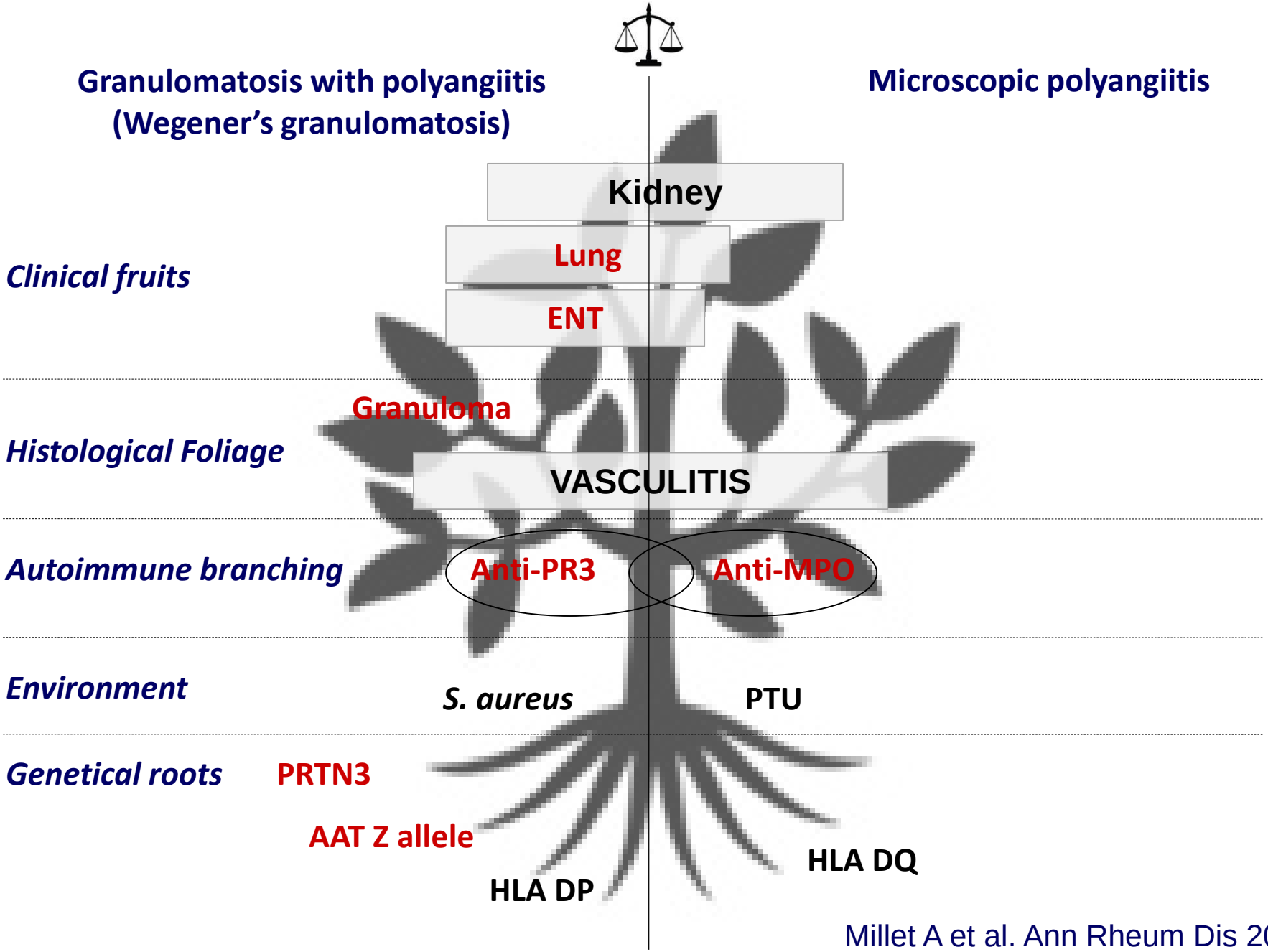
Voswinkel J et al. Ann Rheum Dis 2006;65:859–864

# Relationships between Clinical Subtype and ANCA Specificity in ANCA-Associated Vasculitis and Associations of the MHC Locus with Proteinase 3 ANCA and Myeloperoxidase ANCA



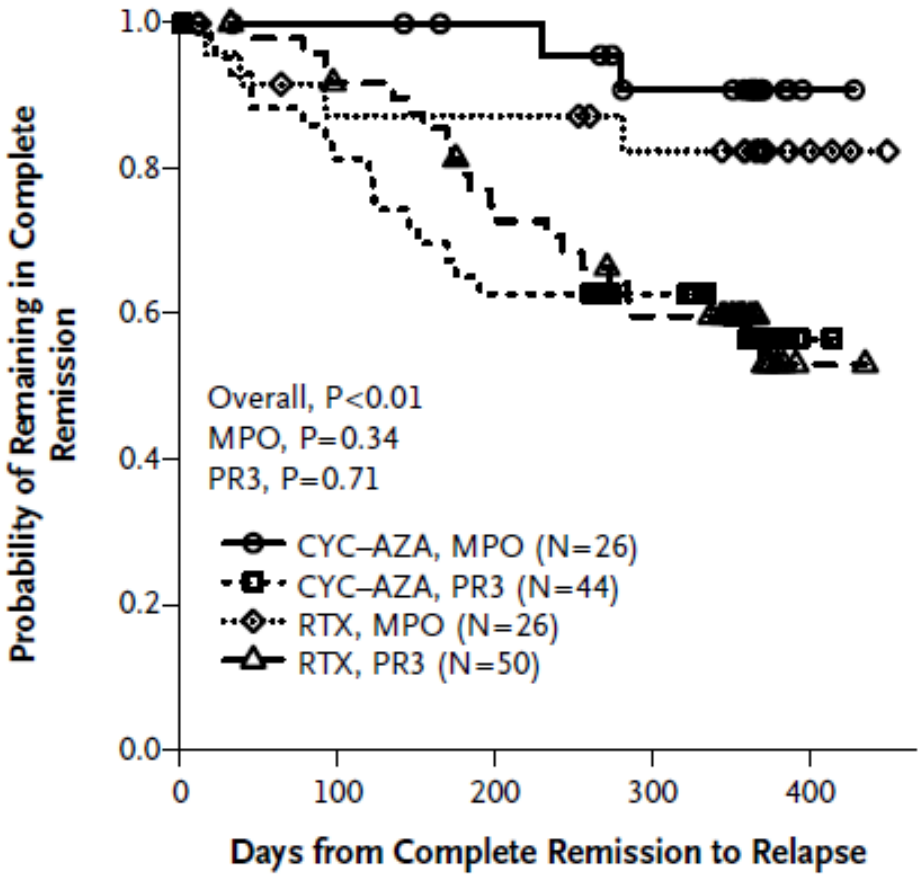

Lyons PA et al, NEJM 2012

# *ANCA-associated vasculitis Tree of knowledge*




Millet A et al. Ann Rheum Dis 2013

# RAVE: Time to first relapse after complete remission according to treatment and baseline type of ANCA




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| CYC–AZA, MPO | 26 | 26 | 24 | 19 | 2 |
| CYC–AZA, PR3 | 44 | 36 | 28 | 25 | 2 |
| RTX, MPO | 26 | 21 | 21 | 18 | 4 |
| RTX, PR3 | 50 | 45 | 35 | 28 | 2 |

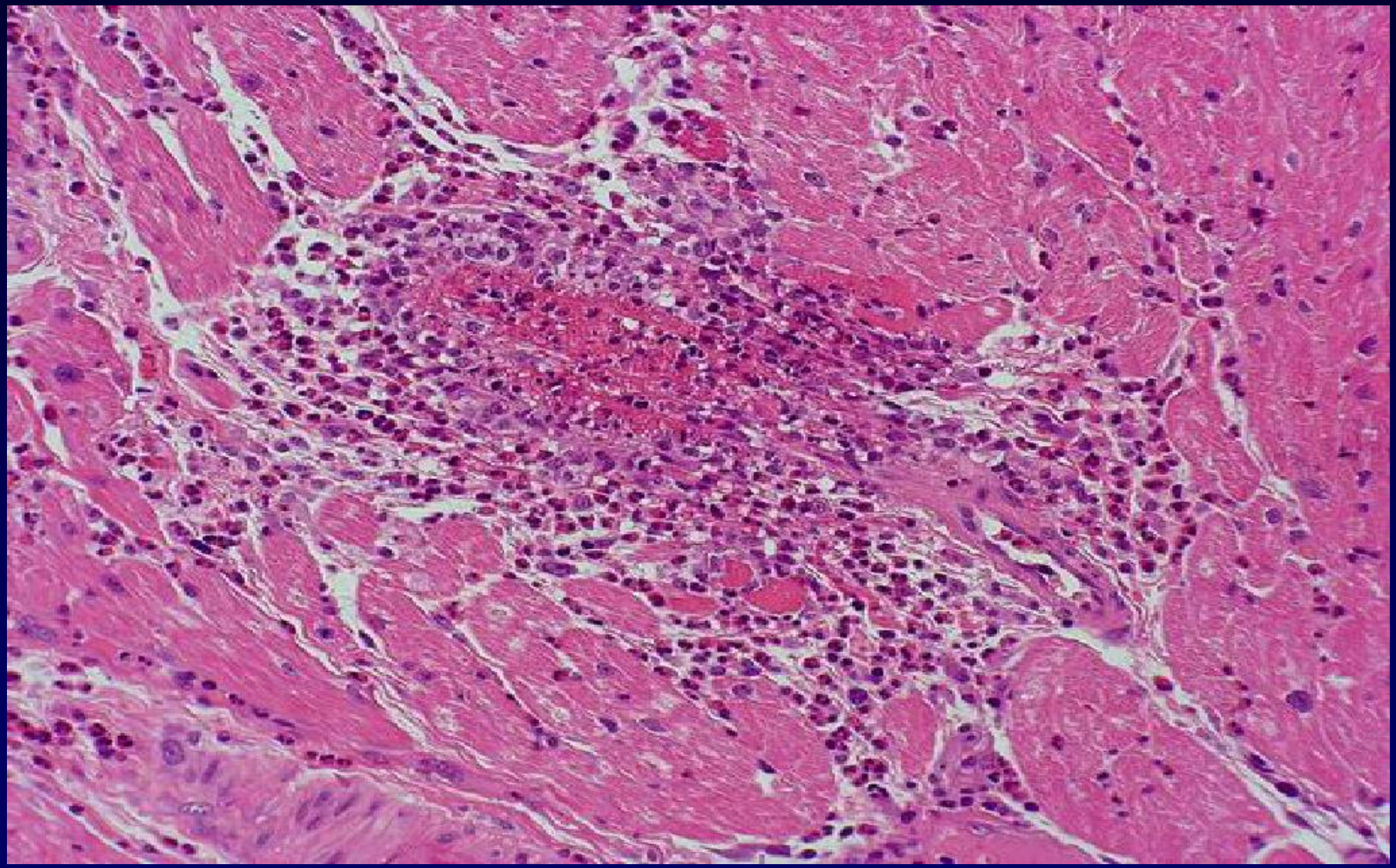
Specks U et al. NEJM 2013

# Churg Strauss syndrome: ACR criteria

| |
|---|
| Asthma |
| Eosinophilia |
| Neuropathy, mono or poly |
| Pulmonary infiltrates, non fixed |
| Paranasal sinus abnormalities |
| Extravascular eosinophils |

4 out of 6 criteria should be present.

Masi et al, 1990 Arthritis Rheum



Courtesy, G Gregorini

# CHURG-STRAUSS SYNDROME

Churg-Strauss syndrome.
One disease
Two phenotypes ?
Analysis of patients included in the
French Vasculitis Group protocols

Churg-Strauss syndrome.
Clinical study and
long-term follow-up of 96 patients
Loïc Guillevin et al.
Medicine, 1999; 78:26 - 37

# CHURG-STRAUSS SYNDROME

| ANCA+ | p < | odd ratio |
|---|---|---|
| Kidneys | 0.0005 | 19.6 |

| ANCA neg. | p < | odd ratio |
|---|---|---|
| Heart | 0.0002 | 12 |

# Conclusion

- Intérêt pour les biopsies+++
- Expertise du pathologiste
- Diagnostic quelquefois difficile
- ACG: BAT vs Echo-doppler
- Limites des critères de l'ACR
- Nomenclature révisée de Chapel Hill
  - Chasse aux éponymes
  - Arrivée des anti-GBM, Behcet, Cogan
- Vascularites ANCA: groupe hétérogène
- Spécificité des ANCA (anti-MPO ou PR3) > classification (MPA, GPA)
- Pronostic: PR3-ANCA

Groupe Français d'Etude des Vascularites

CMR
CENTRE MALADIES RARES
VASCULARITES I SCLÉRODERMIES
GOUGEROT-SJÖGREN I LUPUS

Hôpital Cochin, Paris, France

www.vascularites.org

Luc.mouthon@cch.aphp.fr

Centre de Référence pour les maladies systémiques autoimmunes rares d'Ile de France