Vasculiti nell'anziano

Journal club su Casi Clinici in Geriatria
Gruppo di Ricerca Geriatrica
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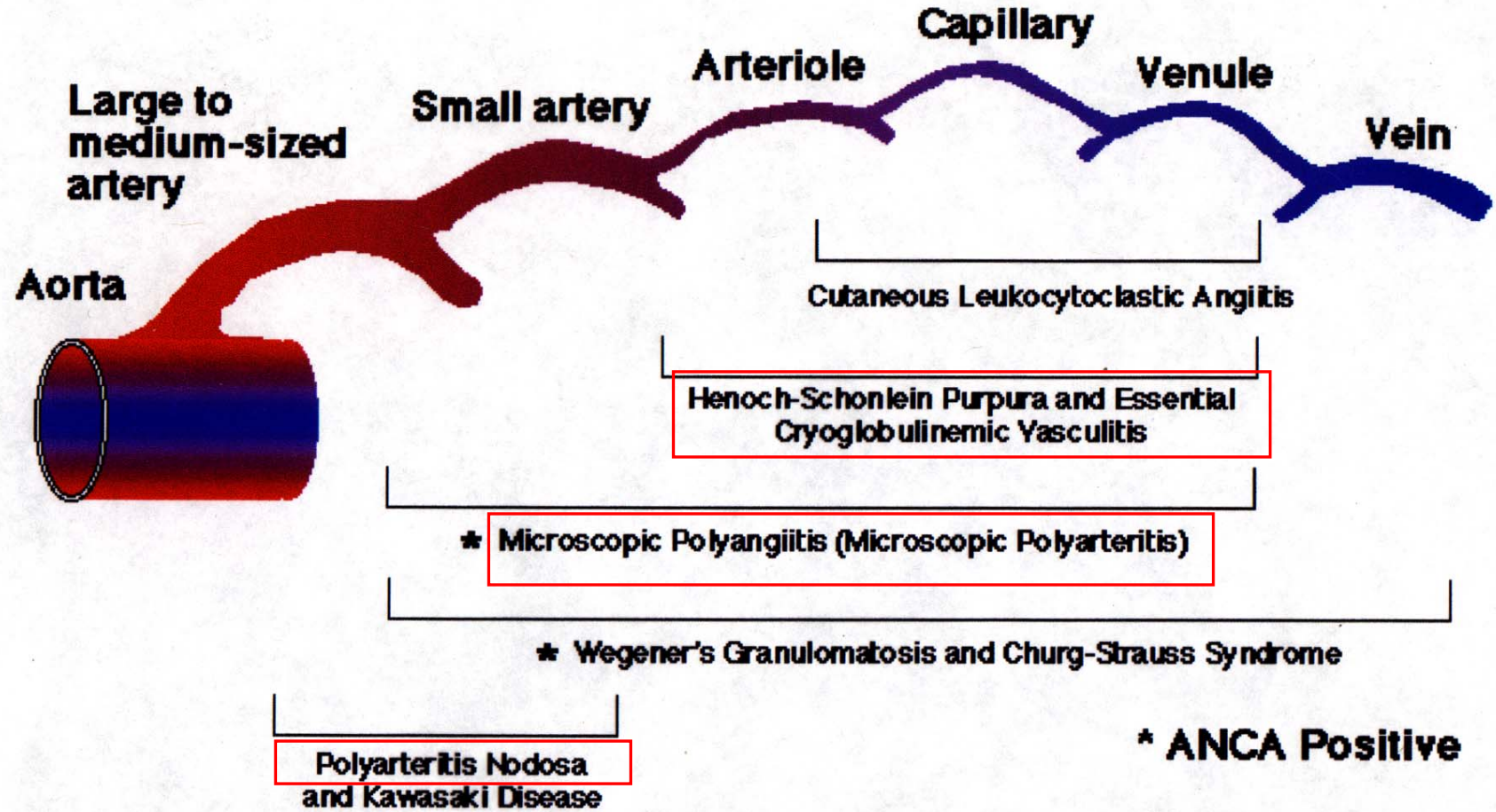
Divisione e Cattedra di Nefrologia

Spedali Civili di Brescia



Classification of systemic vasculitis adopted by the Chapel Hill Consensus Conference, 1992

Arterite di Horton (Arterite a cellule giganti GCA)

- Colpisce uno o più rami della carotide, in particolare **l'arteria temporale.**
- Malattia sistemica, può interessare le arterie in sedi multiple
- Età>50 anni, incidenza 6.9-28.6/100.000 persone/anno.
- Nel 30-50% dei pazienti si associa la Polimialgia Reumatica (PMR)
- Il 10- 15 % dei pazienti con PMR isolata evolve verso la Arterite di Horton
- Etiologia: ipotesi infettiva
- Patogenesi: risposta cellulo-mediana ad un antigene autologo nella sede della lesione arteritica.

Arterite di Horton (Arterite a cellule giganti GCA)

- **-sistemici**
- **-craniali**

Cefalea, più spesso temporale, mono o bilaterale

Disturbi visivi(amaurosis fugax, cecità mono o bioculare, difetti del campo visivo, diplopia transitoria)

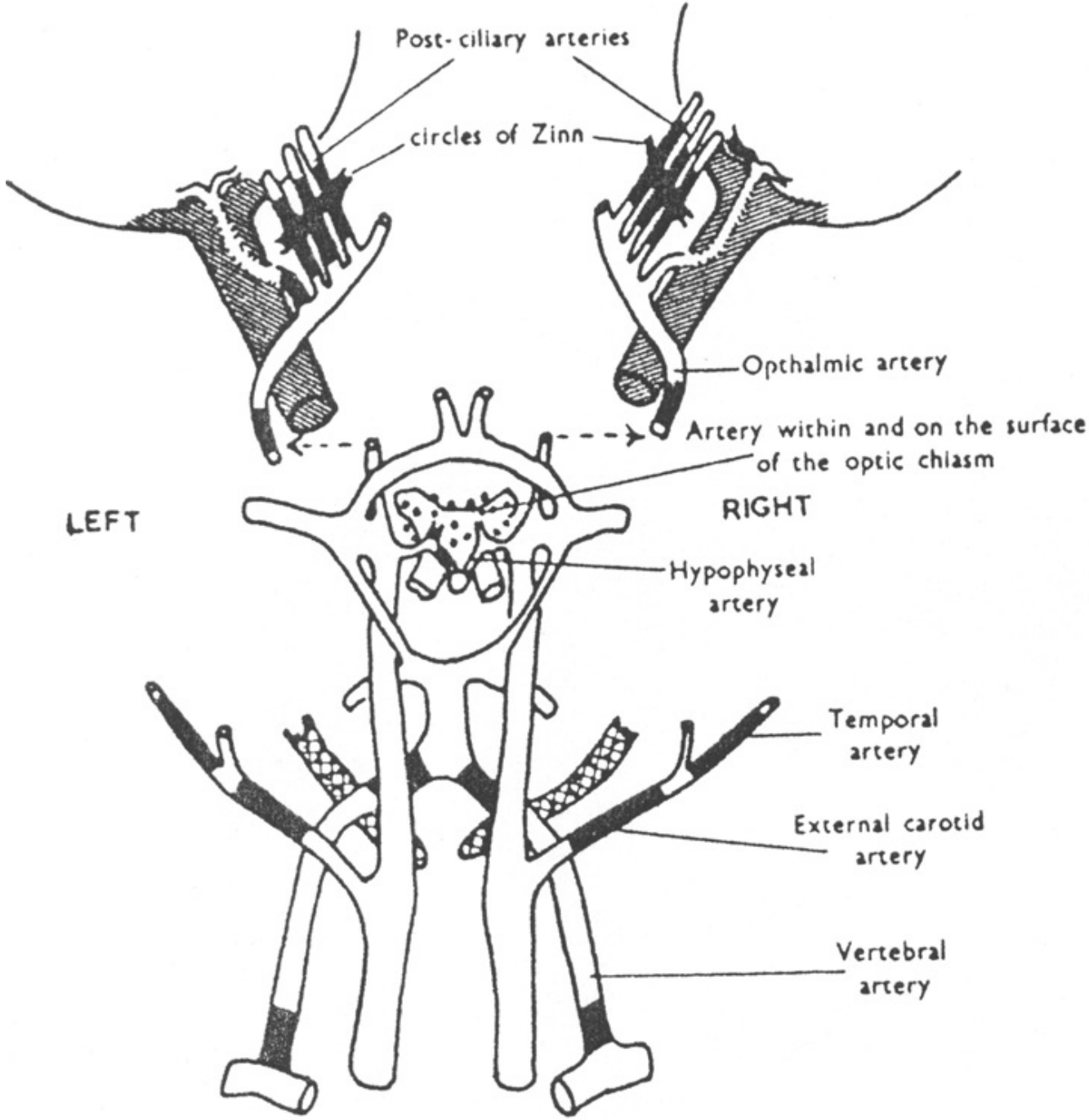
Algie facciali

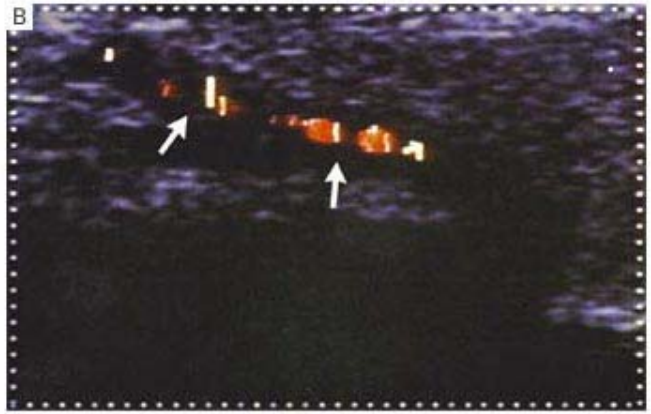
Carotidodinia

Faringodinia

- Manifestazioni dipendenti dalle arterie interessate dalla vasculite (ictus, infarti del miocardio, ischemie intestinali, claudicatio degli arti superiori ed inferiori)

- In alcuni pazienti il quadro clinico è dominato dai sintomi sistemici **(AT "occulta)**


Post-ciliary arteries
circles of Zinn
Opthalmic artery
Artery within and on the surface of the optic chiasm
LEFT
RIGHT
Hypophyseal artery
Temporal artery
External carotid artery
Vertebral artery



The NEW ENGLAND JOURNAL of MEDICINE

ACR Criteria for the Diagnosis of Giant Cell Arteritis

CRITERION	DEFINITION
Age ≥ 50	Development of symptoms or findings older than age 50
New headache	New onset or new type of localized pain in the head
Temporal Artery Abnormality	Tenderness to palpation or decreased pulsation of the temporal artery , unrelated to arteriosclerosis of cervical arteries
Elevated ESR	ESR ≥ 50 mm per hour according to the Westergren method
Abnormal findings on biopsy of temporal artery	Biopsy specimen shows vasculitis characterized by a predominance of mononuclear cell infiltrate or granulomatous inflammation, usually with multinucleated giant cells

10%-15% Of GCA Involve Extra-cranial Vessels

Clinical Presentation includes:

- **Aortic Arch Arteritis**
- **Aortic Dissection/Rupture**
- **Aortic Insufficiency**
- **Coronary Arteritis**

Aortic & Extra-Cranial Large Vessel Disease
Giant Cell Arteritis

Evans, Mayo Clinic, Ann Intern Med 1995

- **96** cases GCA
- **11** cases Thoracic Aortic aneurysm, dissection or both
  - CT, US, angiogram or autopsy
- **6/11** sudden death from thoracic dissection (type 1)
- **9/11** median of 5.8 years post GCA Dx
- **6/11** Abdominal aneurysm 2.5 years post Dx GCA

Giant Cell Arteritis

Location	Complications	Death
Cranial		
Carotid	**CVA**	+
Opthalmic	**Blindness, diploplia**	
Facial	**Jaw/tongue claudication**	
Extra-cranial		
Suclavian/axillary	**Arm claudication**	
Coronary	**Ischaemia/MI**	+
Aorta	**AI/ Aortic dissection/Aortic rupture**	+
Mesenteric	**Bowel Ischaemia**	+

PMR 15-55% develop GCA
GCA 40-60% have PMR symptoms

Giant Cell Arteritis

Differentiating Atherosclerosis & Inflammation

- Upper limb >> Lower limb
- Limited risk for Atherosclerosis
- Angiographic findings
- Prompt response to corticosteroid Rx

Giant Cell Arteritis

Differentiating Atherosclerosis & Inflammation

- Long segments of smooth arterial stenosis alternating with areas of normal or increased caliber vessels
- Smooth tapered occlusion
- Absence of irregular plaques & ulceration
- Anatomic distribution subclavian, axillary, brachial arteries & ascending, thoracic aorta

Perruquet, Archives Int Med, Feb 1986

Aortic & Extra-Cranial Large Vessel Disease
Giant Cell Arteritis

- Thoracic Aneurysm **RR=** 17.3 **(95% CI, 7.9-33)**
- Abdominal Aneurysm **RR =** 2.4 **(95% CI, 0.8-5.5)**
- Surgical Outcome poor

Kerr, J Thoracic and CV Surgery 2000

Giant Cell Arteritis
Aortic Dissection/Rupture
Literature Review (23 cases)

Presentation

- **Female:male = 19:4**
- **Catastrophic 46%; no known GCA**
- **GCA preceded in 54% (TA/PMR (8), PMR (3))**
- **ESR increased in 22/23**
- **Pathological confirmation 23/23**

- Inadequate Rx of GCA & HT increases risk for AD

Involvement

- **Diffuse in 89% vs "Skip lesion of TA"**
- **Proximal aorta 85%**

Mortality

- **80% in 2 weeks**

Hypertension

- **77%**

Liu, Shupak & Chiu Seminars Arthritis Rheum 1995

Giant Cell Arteritis
Aortic Insufficiency

- Case reports
- Klinghofer, A&R 1985
    - 6 cases; 2 +
- Abstract: Bowles, Hunder A&R 1984
    - proximal aortitis with dilatation of aortic ring
    - 14 females, 4 males TA from 1950-1980
    - AI at TA dx in 3; median 5 years post Dx in 13
    - CHF in 5/18; 3 patients died
    - GCA not implicated in AI clinically in any pt

Giant Cell Arteritis

Coronary Artery disease

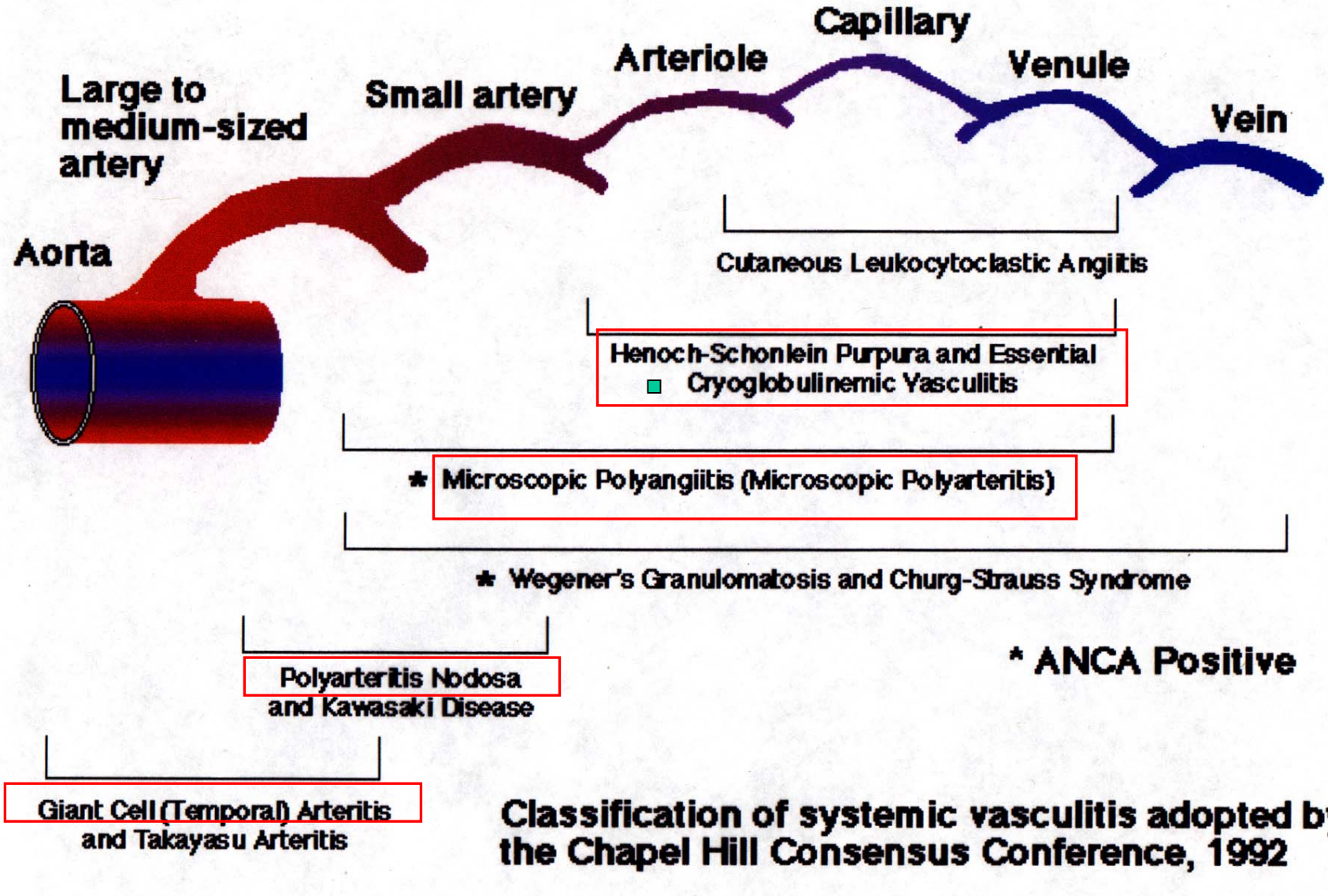
- Editorial Am Heart Journal 1980
  - Is GCA a Cardiologist's Blind Spot??
  - Dominance of Atherosclerosis overwhelms less common treatable disorders
  - Case reports; true prevalence of CAD in GCA is unknown
  - Controversy exists re relative risk CAD in GCA pts

Giant Cell Arteritis
Coronary Artery Disease

- Ray, Heart, 2005
  - population based retrospective cohort
  - RR **1.6** (95% CI 1.1-2.2) for CAD compared to OA
  - RR **2.1** (95% CI 1.5-3.0) for CAD compared to Normals

Pitfalls to Diagnosis

- *Do not think of the Diagnosis*
- False negative biopsy; ‘skip’ lesions
- Intimal proliferation may dominate over giant cells
- Normal ESR ~10%



Classification of systemic vasculitis adopted by the Chapel Hill Consensus Conference, 1992

POLIARTERITE NODOSA
(incidenza 0.6 x10^5, prevalenza 6 x 10^5)

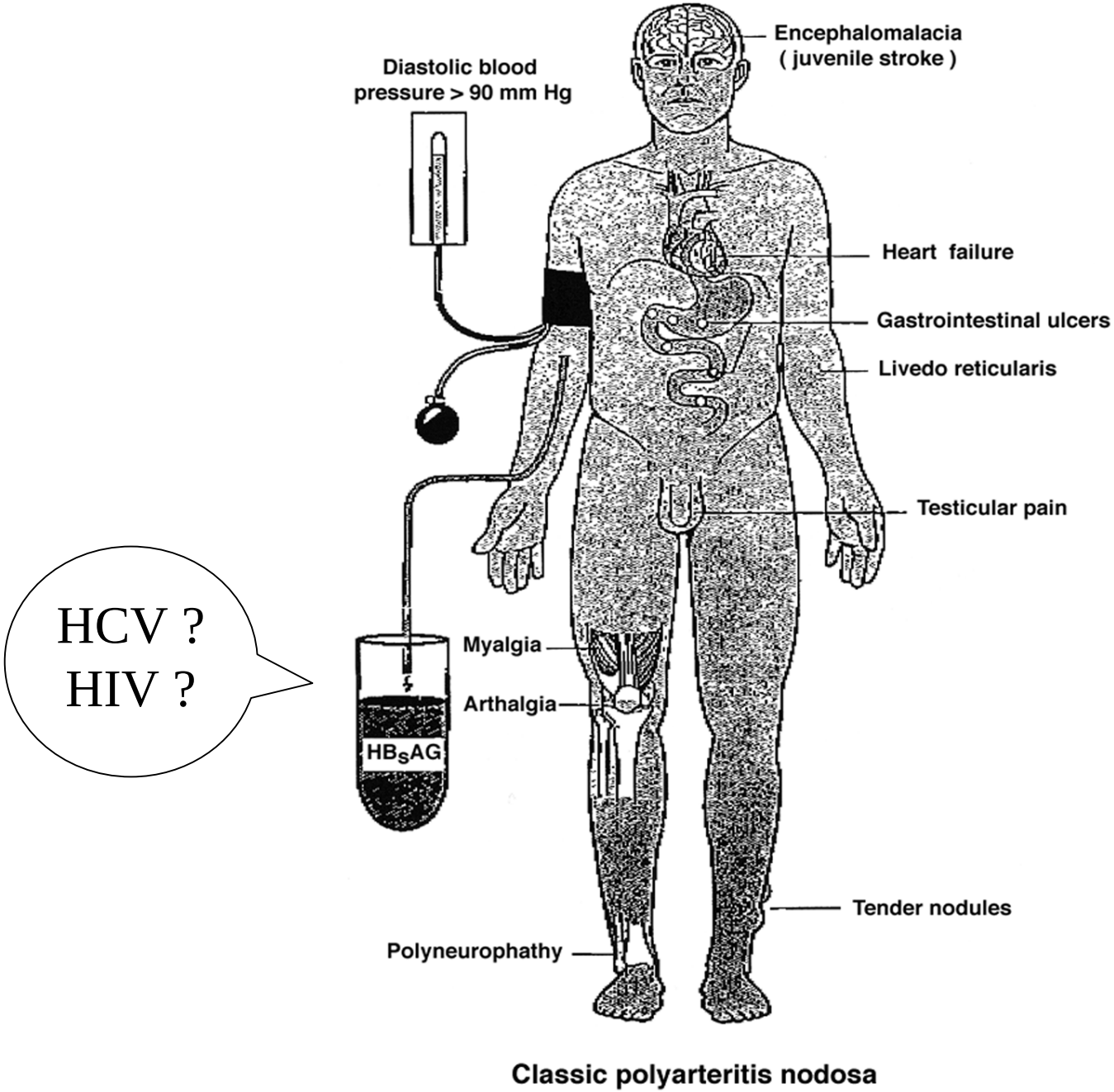
- Arterite necrotizzante del arterie di medio calibro, talora di arteriole
- Età media 40-45 anni
- 10-30 % associata a HBsAg e/o HCV
- Casi sporadici insorti dopo vaccini o altre infezioni
- Non predisposizione genetica nota

POLIARTERITE NODOSA
(criteri classificativi, almeno 3)

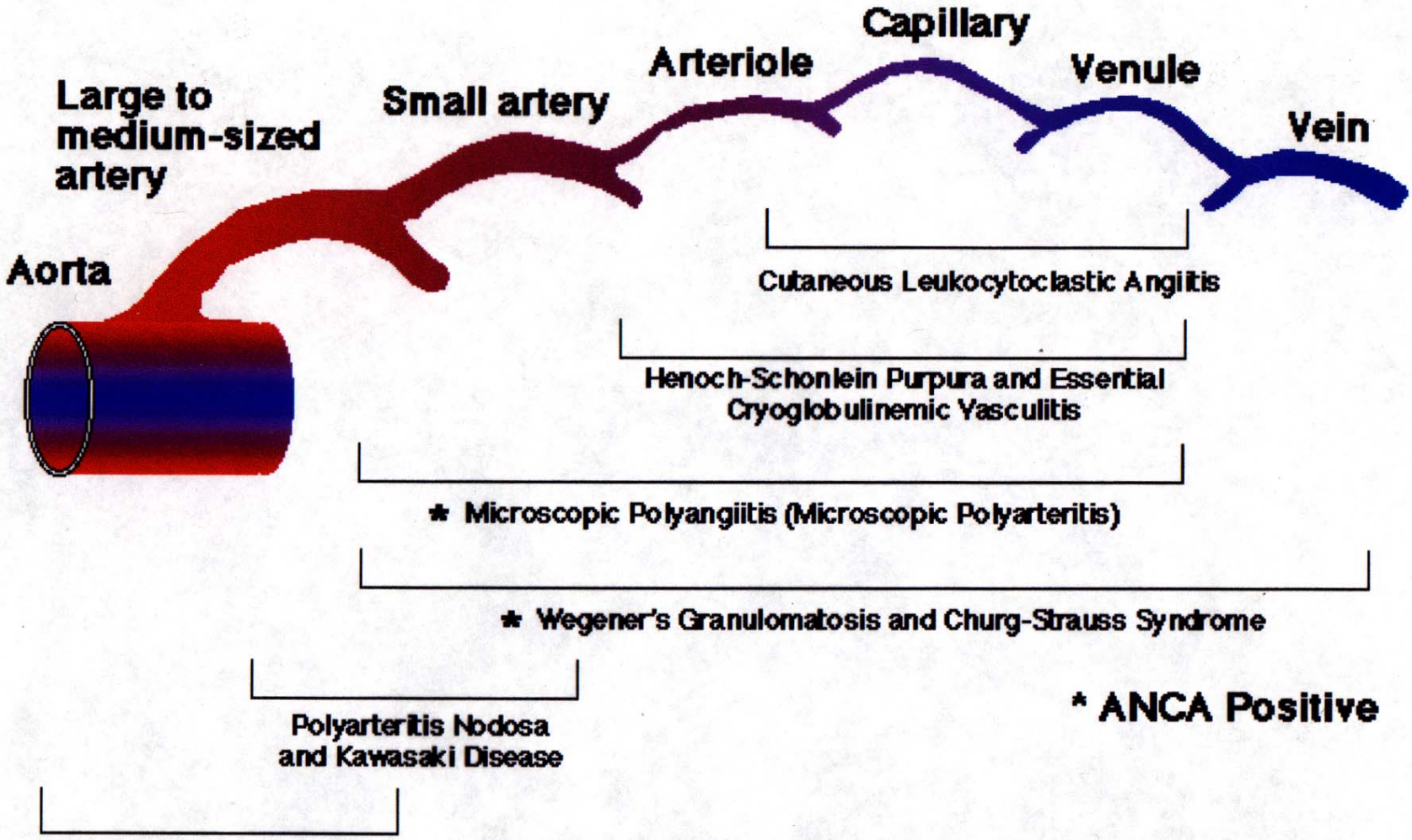
- Perdita di peso > 4 Kg
- Livedo reticularis
- Dolore testicolare
- Mialgie, astenia, dolore alle gambe
- Mono o polineuropatia
- PA diast > 90 mmHg
- ↑ creatinina
- HBsAg
- Arteriografia anomala
- Biopsia arteriosa (PMN nella parete)

Livedo reticularis

PN: dilatazioni aneurismatiche all'angiografia mesenterica

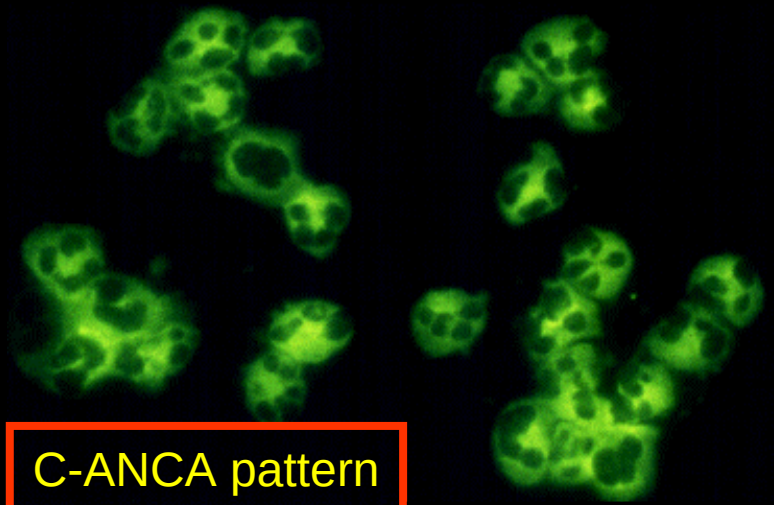


Classic polyarteritis nodosa



Classification of systemic vasculitis adopted by the Chapel Hill Consensus Conference, 1992

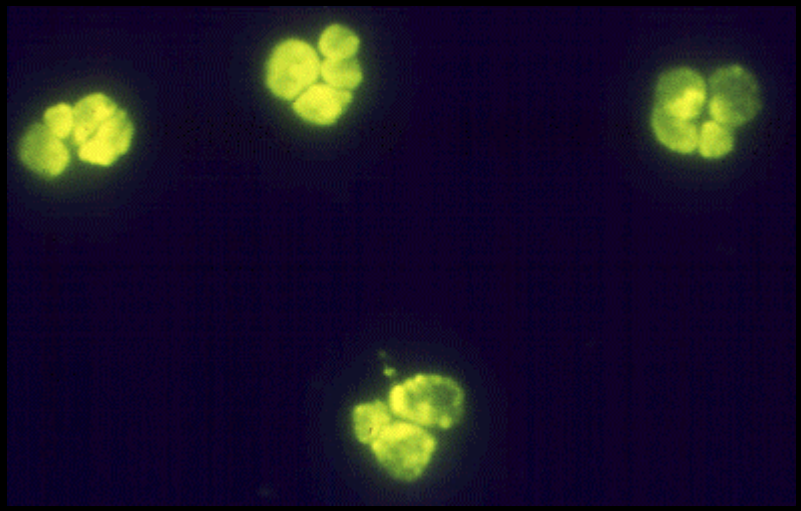
Indirect immunofluorescence microscopy



C-ANCA pattern

ELISA

Anti-proteinase 3 antibodies (anti-PR3)



P-ANCA pattern

Anti-myeloperoxidase antibodies (anti-MPO)

VASCULITI ANCA-POSITIVE

POSITIVITA' ANCA ⇨ **criterio SUFFICIENTE per porre la diagnosi ed iniziare la terapia**

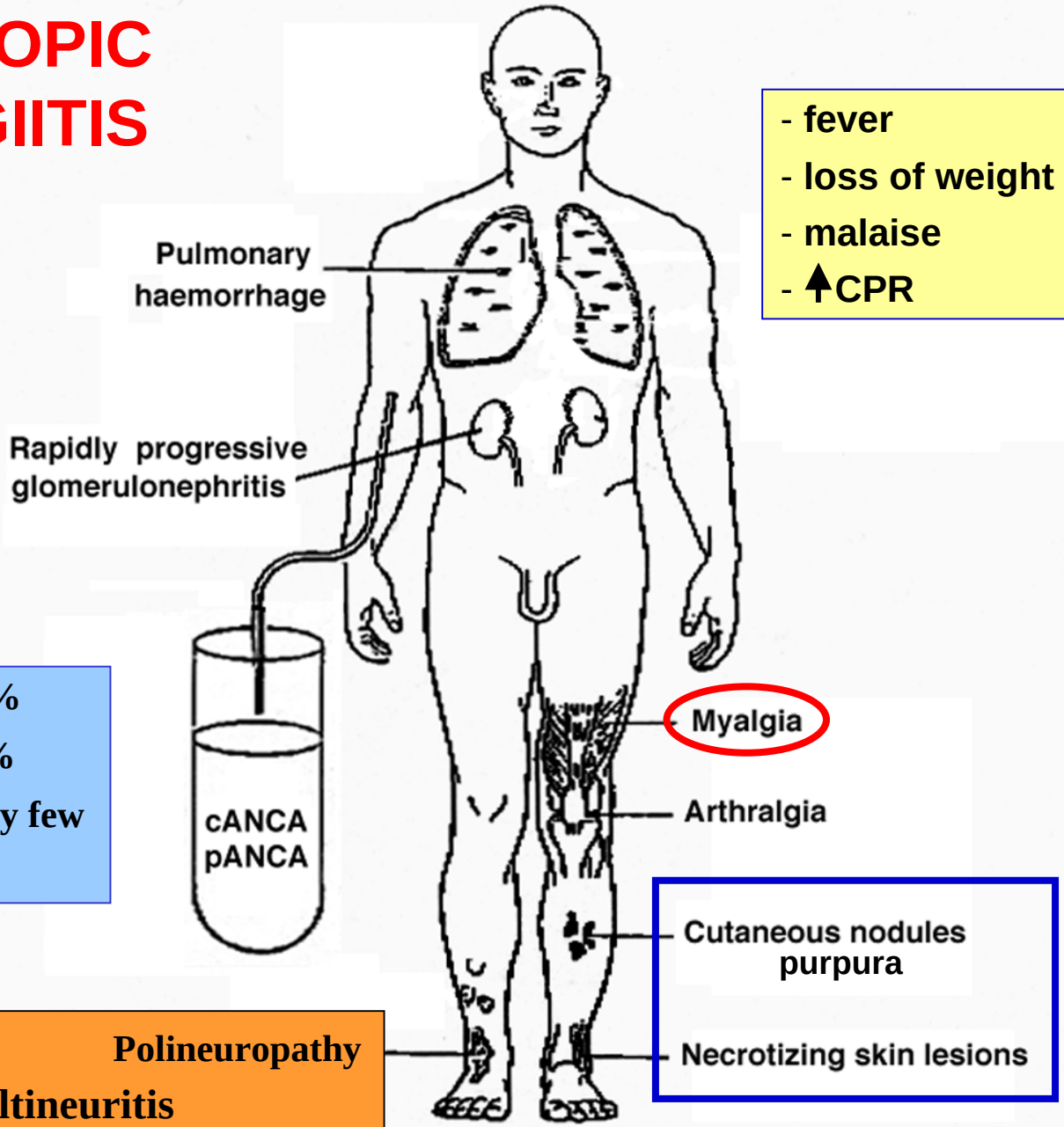
- in presenza di quadro clinico compatibile
- ANCA correttamente determinati

- a determinazioni incomplete (solo IFI, solo ELISA)
- appaiamenti sbagliati
- positività ad alto titolo doppia per entrambi gli antigeni (alto background, binding non specifico)
- titoli border-line in presenza di malattie acute

MICROSCOPIC POLYANGIITIS

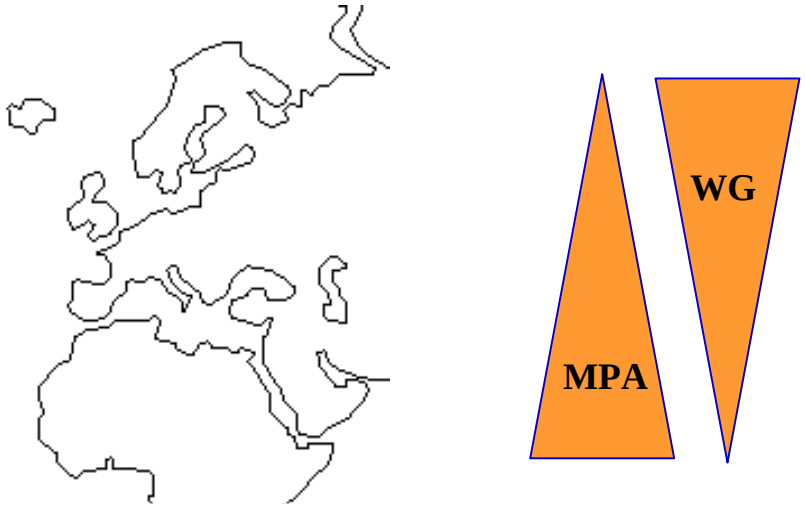
Old age
71.5+/- 9.8
(43-88)

- fever
- loss of weight
- malaise
- ↑CPR



P-ANCA/antiMPO 75%
C-ANCA/antiPR3 25%
P-ANCA+ (ANA -): very few
ANCA neg ?

ANNUAL INCIDENCE (per million) OF PRIMARY VASCULITIS IN DIFFERENT REGIONS IN EUROPE AND THE MIDDLE EAST



	Norway (Tromsø)	North Germany (Schleswig-Holstein)	UK (Norwich)	South Germany (Baden-Württemberg)	Spain (Lugo)	Kuwait (Kuwait City and Al-Jahra)
WG	10.5 (7.6-14.2)	8 (2-14)	10.6 (7.8-14.0)	6 (3-9)	4.9 (2.4-8.8)	0
MPA	2.7 (1.3-4.8)	3 (0-6)	8.4 (5.9-11.5)	2 (0-4)	11.6 (7.6-17.0)	25
PAN	0.5 (0.06-1.8)	1 (0-3)	0.0 (0.0-0.8)	2 (0-4)	0.9 (0.1-3.2)	16
CCS	0.5 (0.06-1.8)	0 (0)	3.1 (1.7-5.2)	1 (0-2)	0.9 (0.1-3.2)	NR
Total	13.7 (10.3-17.8)	12 (2-23)	18.9 (15.1-23.4)	11 (3-19)	18.3 (13.1-24.8)	47

WG: granulomatosi di Wegener; MPA: micropoliangioite; PAN: panarterite nodosa; CCS: sindrome di Churg Strauss.

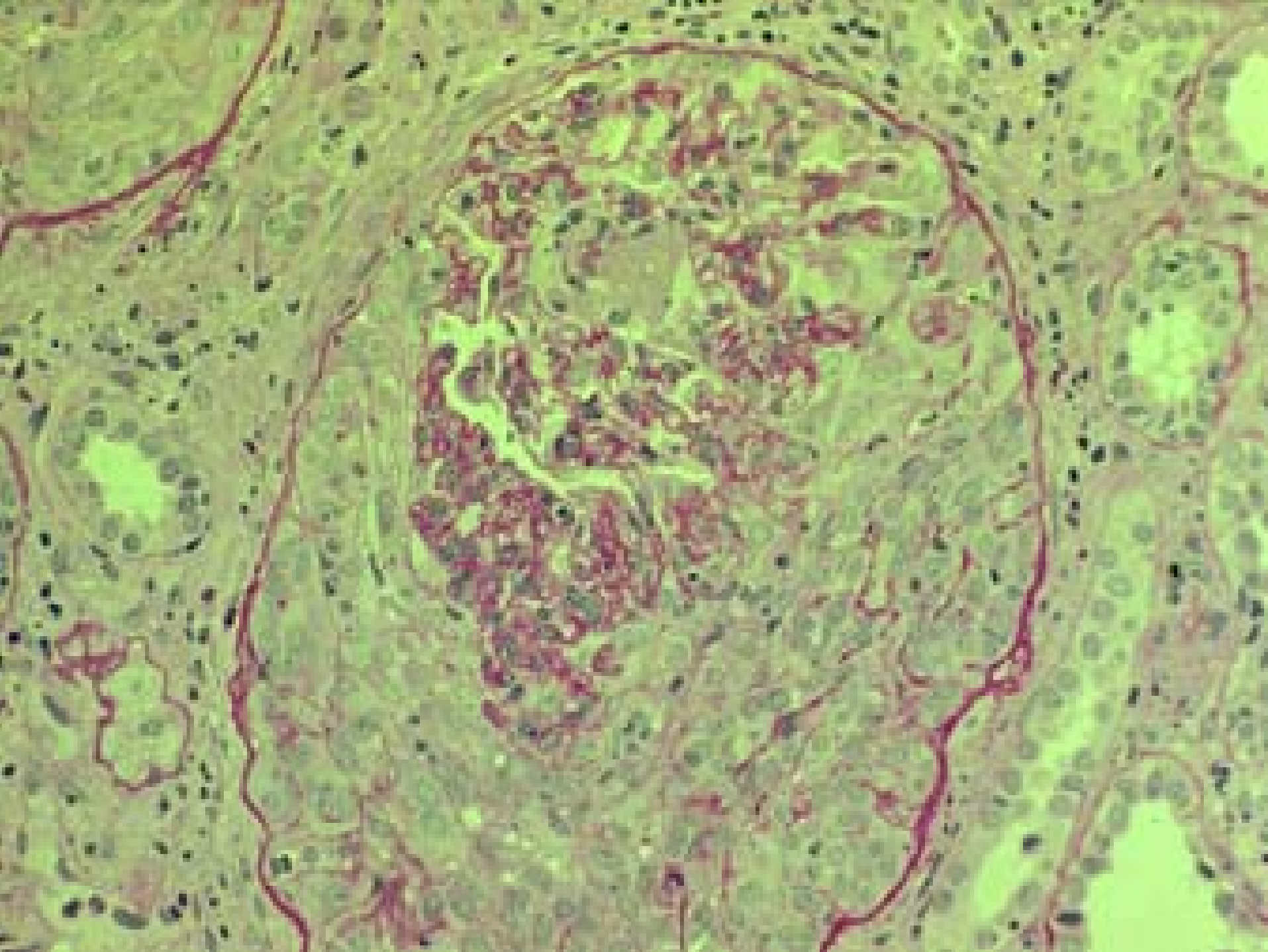
INCIDENCE OF ANCA-ASSOCIATED VASCULITIDES WITH RENAL INVOLVEMENT

Location, Country	Latitude	**Annual incidence** *(per million)*				Pupulation (millions)	Study period
		MPA	WG	CSS	Total		
1. Orebro, Sweden	59° N	**ND**	ND	ND	16.0	0.20 to 0.21	1975-1995
2. Lund, Sweden	55° N	**2.5**	2.1	ND	4.6	1.2	1971-1993
3. Norfolk, UK	52° N	**7.5**	7.9	1.3	18.0	0.41	1992-1997
4. Schlswig-Holstein, Germany	51° N	**2.7**	7.9	1.1	11.7	2.78	1988-2002
5. Devon, UK	50° N	**ND**	ND	ND	12.4	0.85	2 yrs
6. Lugo, Spain	43° N	**7.9**	3.0	1.3	12.2	0.21	1988-2001
7. Miyazaki, Japan	30° N	**14.8**	0	0	14.8	0.77	2000-2004
8. Al-Jahra, Kuwait	26° N	**20.9**	ND	ND	ND	0.12	1993-1996

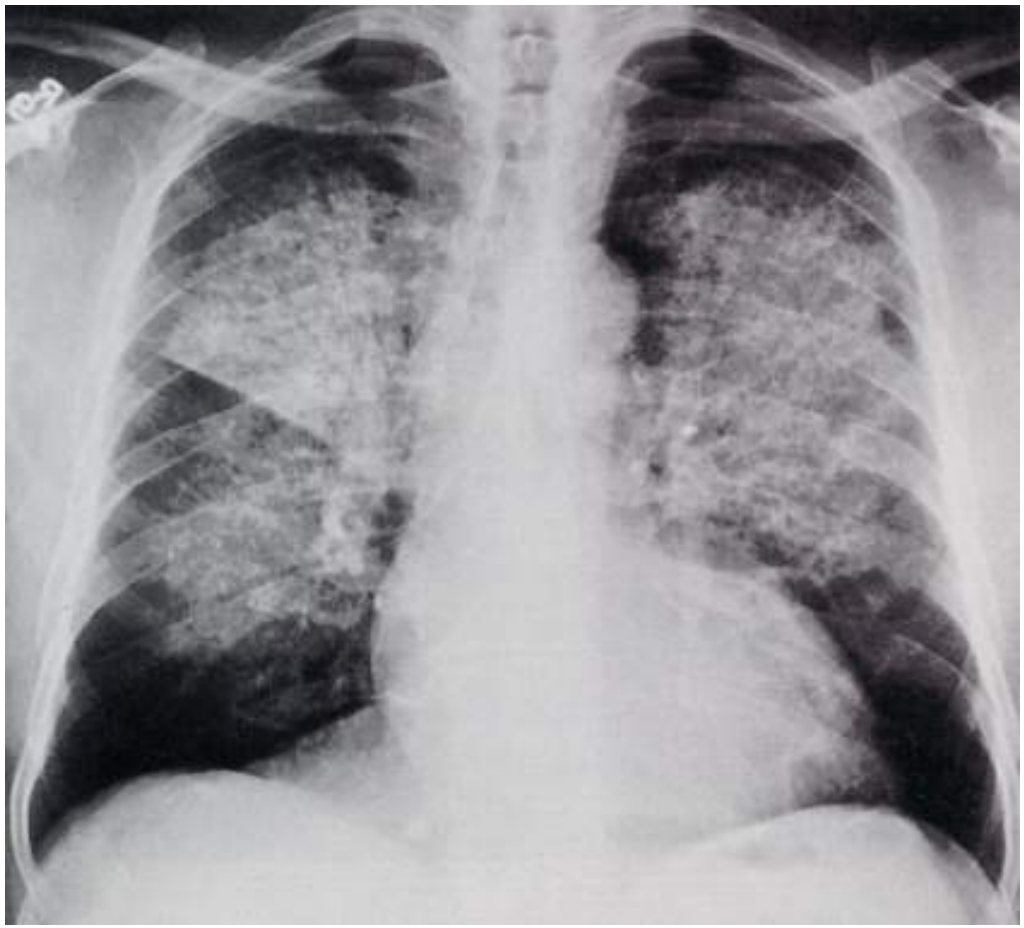
Definizione di sindrome pneumo-renale

Associazione di:

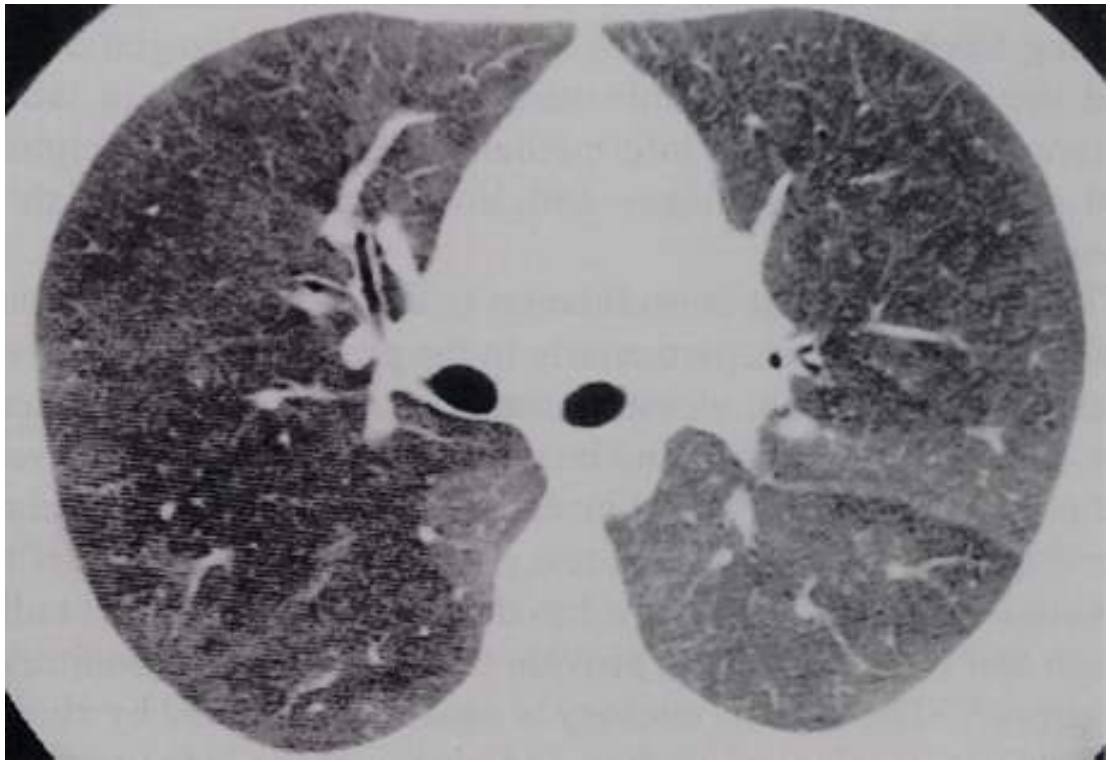
- Glomerulonefrite
  - ad impronta ematurica
  - con insufficienza renale a rapida progressione
- Emorragia polmonare diffusa
- Sintomi sistemici (febbre,perdita di peso,artromialgie etc) ed aumento indici di flogosi
- Vari gradi di severità
- Possibile dissociazione tra severità della malattia polmonare e renale

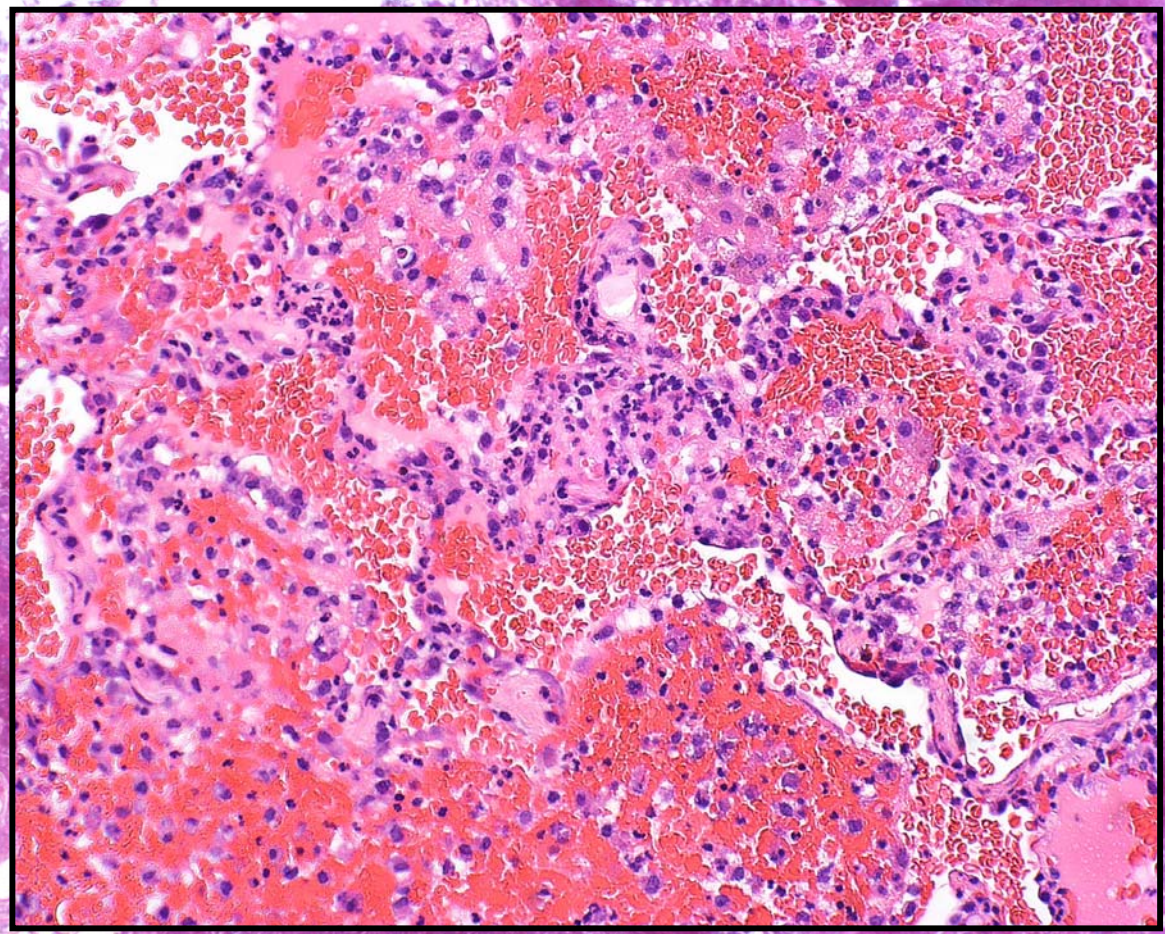


Emorragia alveolare



TAC di emorragia alveolare

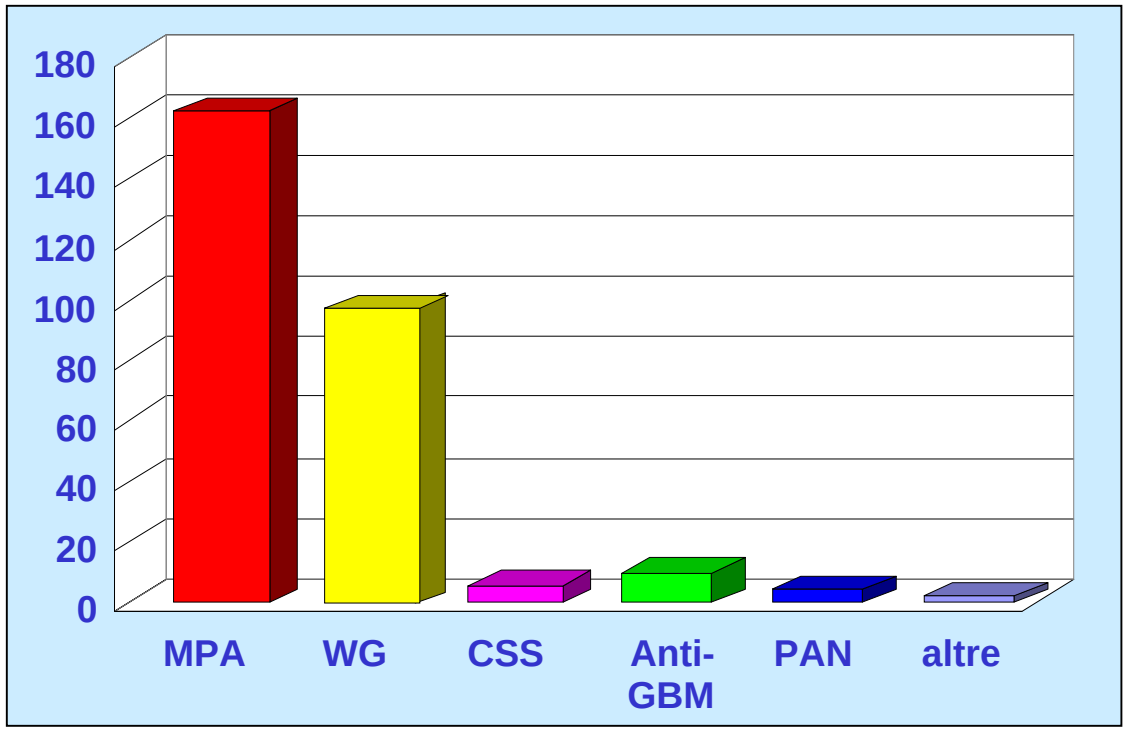




ANCA-ASSOCIATED VASCULITIS : OBSERVED CASES AT SPEDALI CIVILI OF BRESCIA

(Jan 1987- Nov 2007)

280 patients
WITH VASCULITIS



165 MPA +92 WG

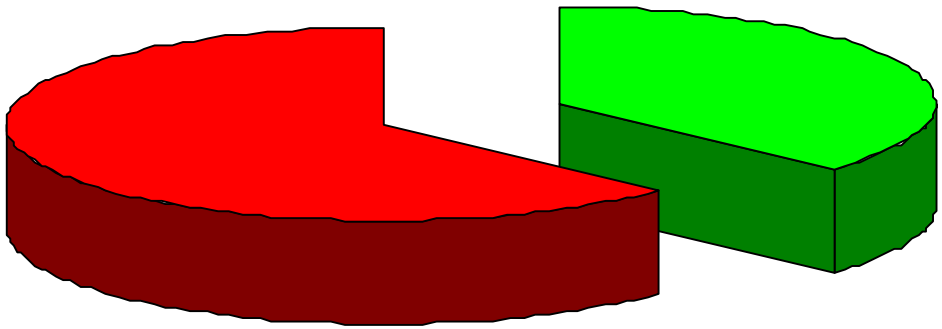
34/92 non C-ANCA/PR3+

- 17 p-ANCA/antiMPO+
- 17 ANCA negative

SILICA EXPOSURE IN PATIENTS WITH ANCA POSITIVE VASCULITIS

Period: January 1987 → November 2007

Diagnosis of ANCA positive vasculitis in 240 patients



Wegener's Granulomatosis 75 pts (36%)

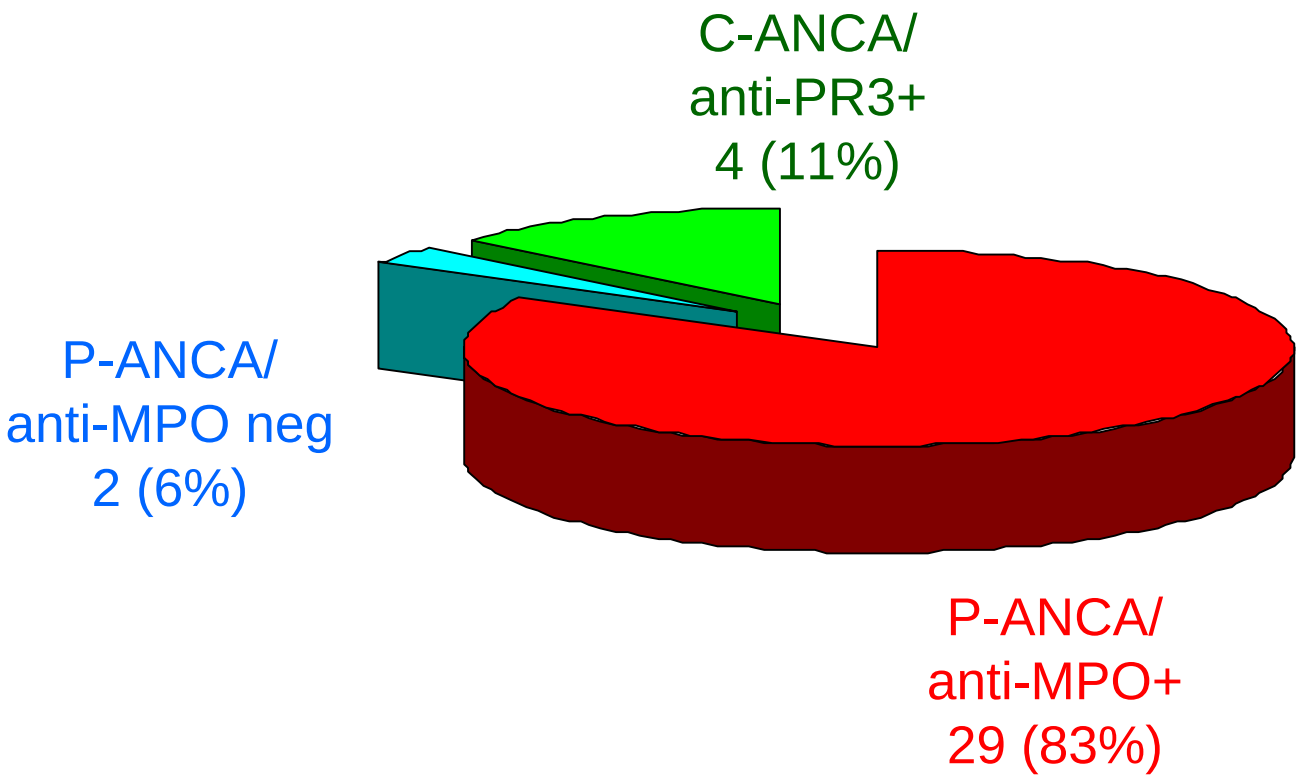
Micropoliangiitis 165 (64%)

35/165 (21%): Silica Exposure

13 patients: diagnosis of pulmonary silicosis time before the diagnosis of ANCA positive disease

22 patients: significant silica exposure

ANCA PATTERN IN SILICA EXPOSED PATIENTS WITH ANCA POSITIVE VASCULITIS



SILICA EXPOSURE IN SILICOTIC PATIENTS

Pt, age, gender	Activities/tasks with exposure to silica	Years of exposure
PD, 60, F	Ceramics (sanitary ware, finishing) Dental material (sand blasting, polishing)	7 15
PM, 66, M	Mining (Fe) Granite cutting Construction (excavation and sand processing)	2 7 8
DE, 70, M	Mining (coal)	11
AM, 68, F	Ceramics (finishing)	13
RE, 64, M	Grinding and blasting Mining (maintenance)	3 14
FG, 64, M	Cement (raw material processing) Steel mills (furnace repair)	9 6
FS, 69, M	Miner in tunnel Abrasive blasting	4 17
PO, 56, M	Mining (Fe) Miner in tunnel	3 21
ZP, 50, M	Mining (Fe) Miner in tunnels Metal polishing with abrasive products	11 3 2
FG, 71, M	Construction (demolition, masonry, tunnel construction)	40
VC, 69, M	Mining (coal9 and miner in tunnel	25
PA, 67, M	Mining (Fe) and miner in tunnel	21
PA, 52, M	Miner in tunnels	22

SILICA EXPOSURE IN NON-SILICOTIC PATIENTS

Pt, age, gender	Activities/tasks with exposure to silica	Years of exposure
GP, 63, M	Mining (Fe)	5
BB, 69, M	Construction (demolition, masonry, tunnel construction)	20
ZA, 63, M	Miner in tunnel	3
GL, 65, M	Mining (coal) Granite cutting	4 1
BG, 89, M	Mining (coal) Cast iron foundry (molding)	2 30
PA, 52, M	Miner in tunnel	22
GF, 68, M	Dental material (sand blasting, polishing)	20
NA, 72, M	Cast iron foundry (maintenance)	30
AS, 59, M	Construction (demolition, masinry)	45
MD, 71, M	Cast iron foundry (molding)	25
FGM, 73, M	Fedrrous and non ferrous foundries	38
MP, 65, F	Brass foundry (molding)	12
PA, 49, M	Cast iron foundry (molding) Construction	12
RL, 56, M	Miner in tunnels Ceramics	2 7
SP, 59, M	Non ferrous foundry (casting and abrasive blasting)	17
AA, 69, M	Miner in tunnels Tunnel construction	5 14
FB, 66, M	Ceramics (finishing)	35

AGRICULTURAL SILICA EXPOSURE

- Harvesting the crops* *(wheat, corn, grass, cotton, tobacco, potatoes, peanut)*

  - throught shaking clay, dirt, soil or sand off of the product as it is pulled from the ground

  - respirable quartz higher in sandy or sandy–loam soils than in clay soils

- Cattle breeding
- Working in a textile industry

Archer JD et al: Exposure to respirable crystallyne silica in eastern North Carolina farm workers.AIHA (Fairfax,VA)63:750-755.2002

Parks CG et al:Assessing exposure to crystalline silica from farm work:a population-based study in the southeastern United States.Ann Epidemiol13:385-392,2003

MPA in the context of other CHRONIC PULMONARY DISEASES

Previous pulmonary tubercolosis with fibrotic scars	20/99
Chronic bronchitis/emphysema/ bronchiectasis	14/99

Spedali Civili of Brescia (1988-1999)

Pulmonary Fibrosis in pts with MPA

162 patients with diagnosis of micropolyangiitis

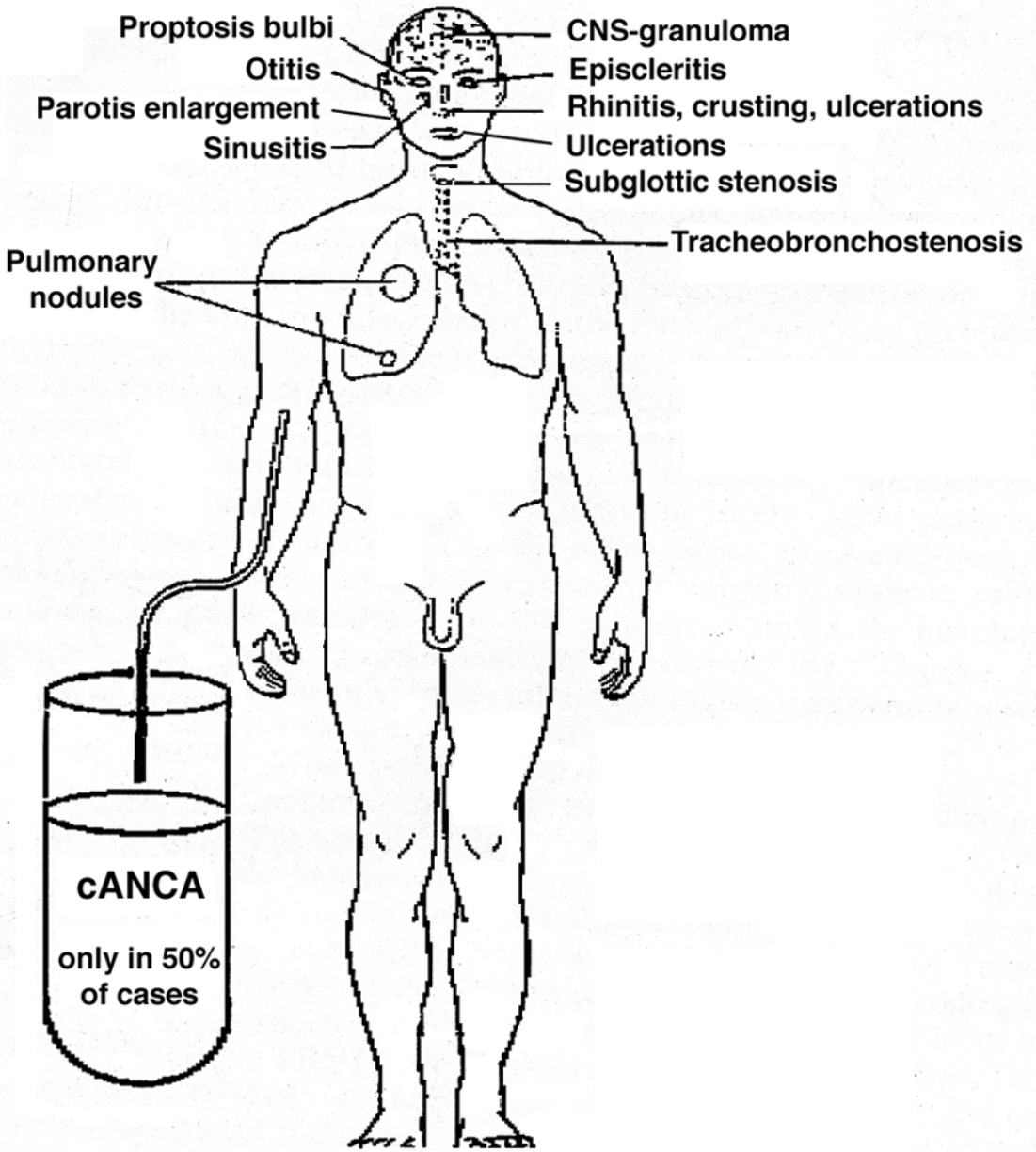
21 pts (13%) with pulmonary fibrosis at admission

- 20 pts P-ANCA/anti-MPO positive
- 1 pt C-ANCA/PR3 positive

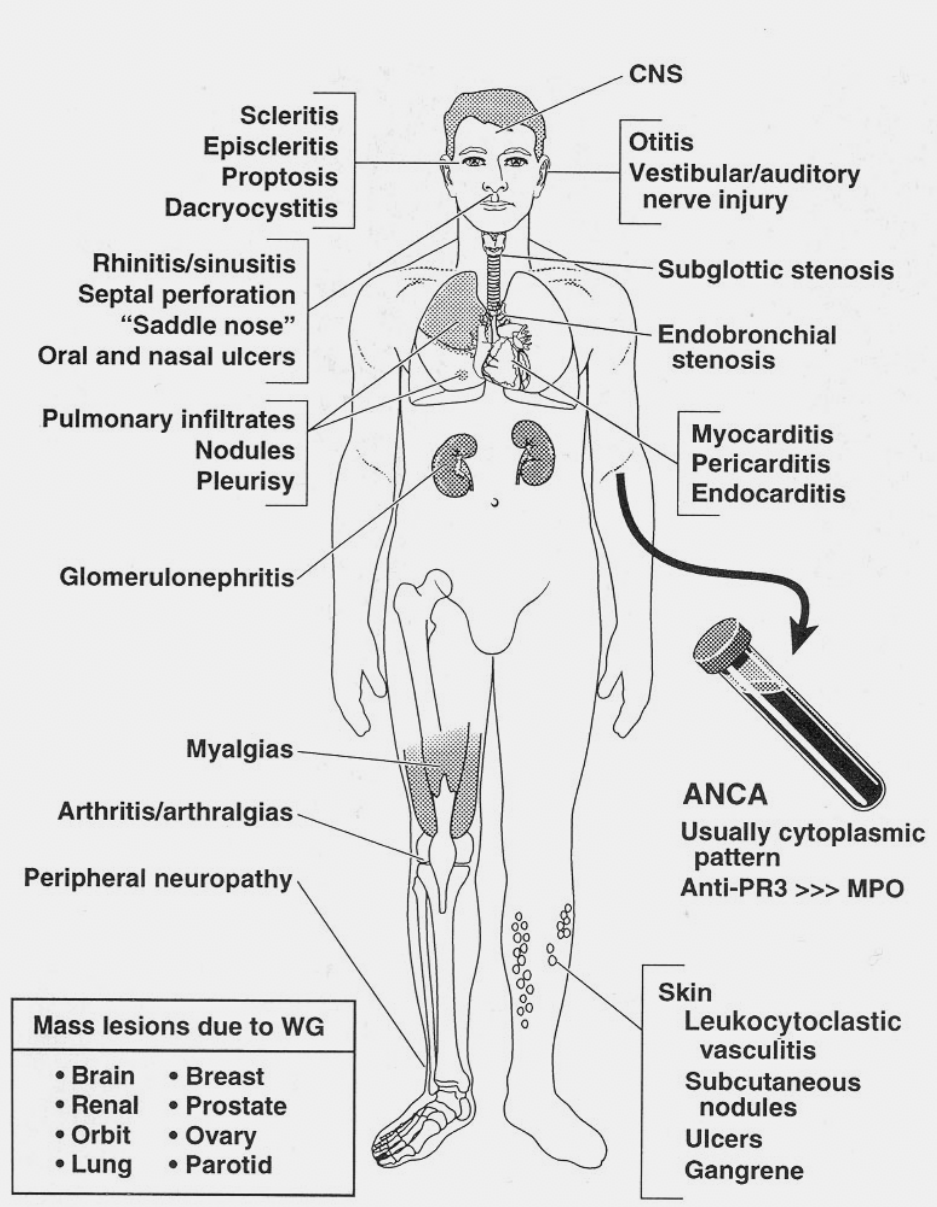
- Clinical and serological features of this subgroup
- Relationship between pulmonary fibrosis and MPA

Granulomatosi di Wegener

- Mal infiammatoria granulomatosa dell'apparato respiratorio
- Vasculite sistemica necrotizzante dei vasi di medio e piccolo calibro
- GNF necrotizzante (semilune)



Wegener's Granulomatosis: localized form



Wegener's Granulomatosis: generalized form

Vasculite di Churg-Strauss

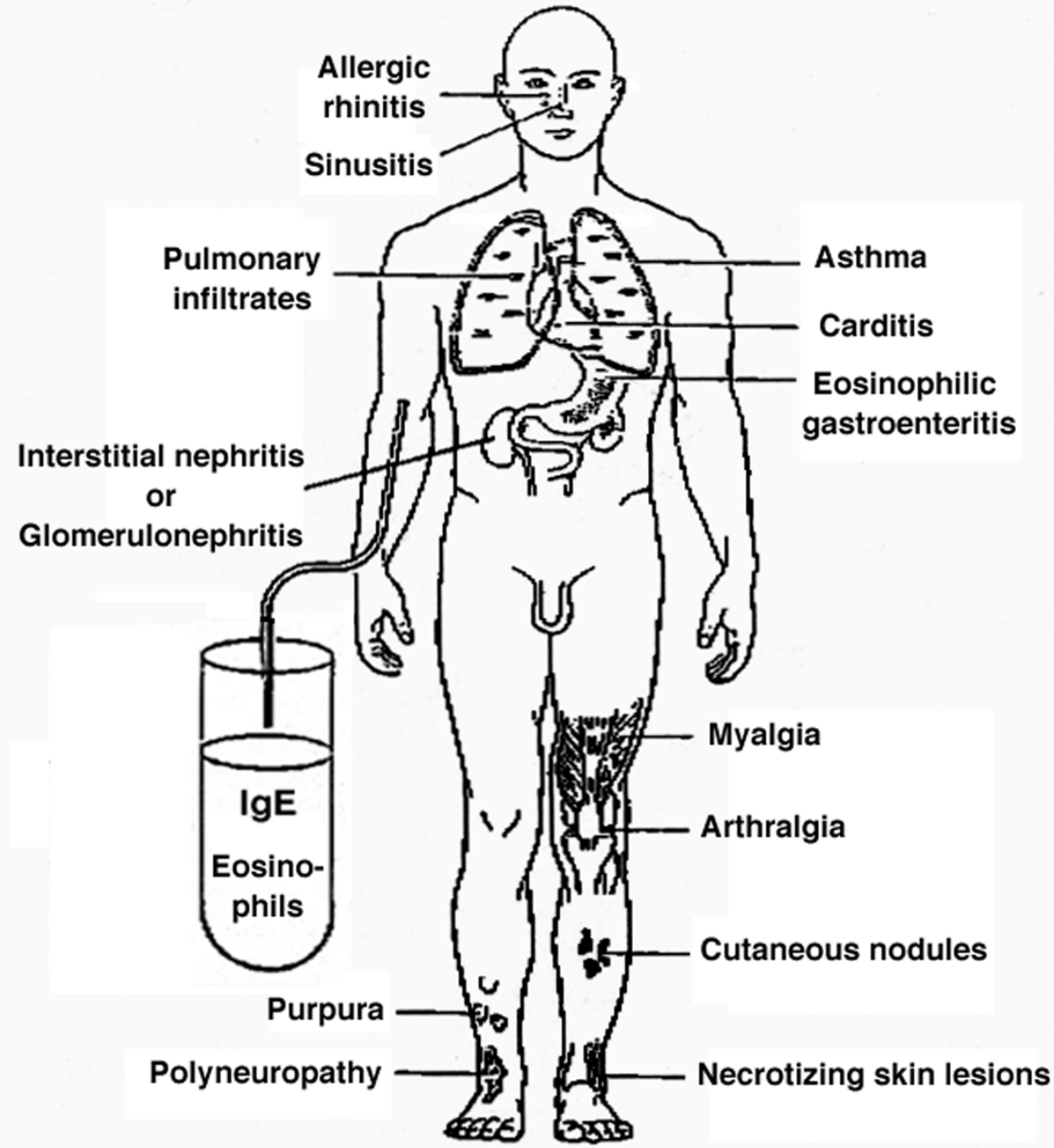
- Incidenza 0.3 x 10^5
- Granulomatosi allergica e vasculite di vasi di medio-piccolo calibro, con necrosi fibrinoide, infiltrazione eosinofila e aspetti granulomatosi.
- Organi colpiti: seni paranasali, polmone, cute, SN periferico, cuore, reni, intestino
- p-ANCA / MPO positivi nel 50 %

Vasculite di Churg-Strauss
Le 3 fasi della sindrome

- Prodromica: malattia atopica (rinite, asma) che può durare mesi o anni
- Eosinofilia ematica e tessutale
- Fase vasculitica:vasculite necrotizzante di polmone, cuore, cute, nervi periferici

Sindrome di Churg-Strauss (criteri di classificazione)

- Asma
- Eosinofilia > 10 %
- Mono o polineuropatia (distribuzione a calzini o a guanti)
- Infiltrati polmonari migranti
- Sinusite
- Eosinofilia tessutale (biopsia)



Churg-Strauss syndrome

Vasculiti: Crioglobulinemia

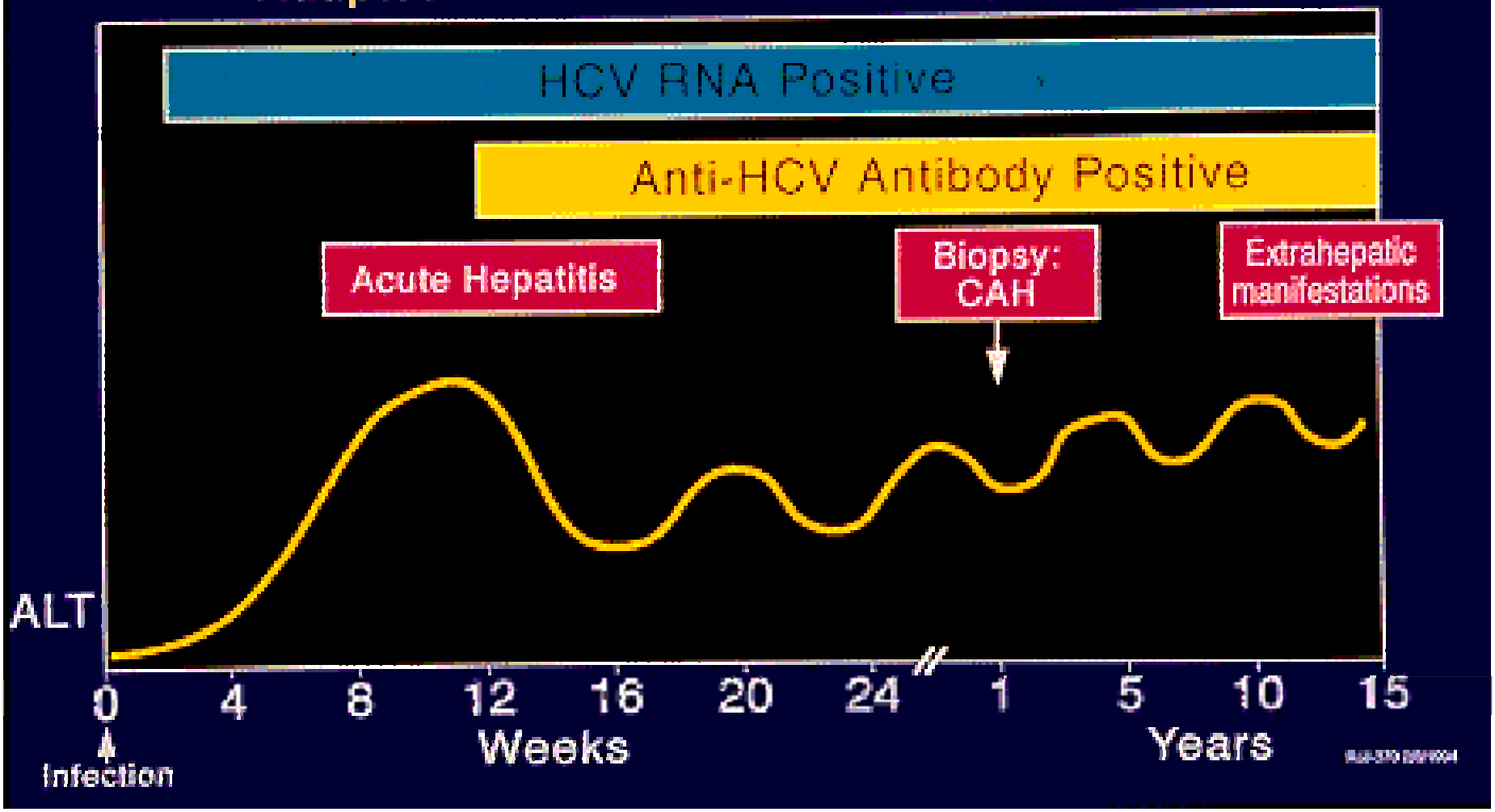
Crioglobulinemia: Immunoglobuline (Ig) che precipitano a temperature inferiori a 37°C, formando aggregati insolubili che si dissolvono riscaldando il siero.

Tipo I (rara): Ig monoclonale comunemente IgM (malattia di Waldestrom) anche IgG (mieloma multiplo o altre malattie linfoproliferative) non correlata ad epatite C

Tipo II e tipo III: (80% dei casi) Crioglobulinemia Mista per la presenza di due componenti IgG e IgM (nel tipo II IgM monoclonale, tipo III policlonali, IgM ha ruolo di fattore reumatoide)
si associa ad epatite C nel 90% dei casi

Clinical Course of HCV Infection

Adapted from Ann Int Med 1991; 115:647



Vasculiti: Crioglobulinemia Manifestazioni cliniche extrarenali

Studio multicentrico italiano crioglobulinemia hcv-correlata

- porpora (66% all'esordio)
- ulcere cutanee (0.7%→8% al f-up)
- febbre (16%), artralgie (39%)
- astenia (6.4%→31.5% al f-up)
- neuropatia (9.7%→28.7% al f-up)
- Dolori addominali (10%)
- Raynaud (5%)
- Interessamento cardiaco (angina, scompenso c-c) (0→6.8% al f-up),
- prevalente agli arti inferiori
- probabile conseguenza di ripetute poussée vasculitiche con necrosi ischemica
- in relazione a progressione dell'epatopatia e a interessamento sistemico
- probabilmente sottostimata, è risultato di sofferenza assonale ischemica e flogistica (quadri di percezione distorta con parestesie, disestesie, ipoestesie, ipostenia e iporeflessia; episodi comiziali, da vasculite encefalica)
- conseguenza di ipertensione arteriosa frequente e non controllata

Patologie autoimmuni: Crioglobulinemia Diagnosi

La diagnosi di sindrome crioglobulinemica viene posta in presenza di criocrito maggiore dell' 1% per almeno 6 mesi ed almeno 2 dei seguenti criteri:

- porpora
- astenia
- artralgie
- C4< 8 mg/dl
- positività del fattore reumatoide
- eventuale associazione con malattia cronica epatica
- malattia del connettivo o disordini linfoproliferativi
- processi vasculitici
- coinvolgimento renale,
- neuropatia periferica
- noduli linfomatosi nel midollo osseo

Porpora palpabile in vasculite (nell'esempio da crioglobulinemia)

Challenges in the management of microscopic polyangiitis: past, present and future

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Overt cerebral vasculitis in the context of MPA is rare and may be mimicked by hypertensive encephalopathy or infection, however there is increasing concern that MPA patients may suffer subclinical cerebral disease with nonspecific defects in neurocognitive function [28].

Dementia with rapidly progressive course in patients with Microscopic Polyangiitis: temporal aspects analysis

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Introduction

- If dementia with rapidly progressive course present at time of diagnosis of Microscopic Polyangiitis (MPA) could be due to vasculitic involvement of CNS small vessels remain an unresolved question. Suggested by single case reports it is in fact reported as "rare and uncommon" in main reviews

- The reasons for this persisting uncertainty include:

  → lack of clinical studies and histological confirm

  → inadequateness of neuroimaging to explore small vessel diseases

  → possible coexistence, because of old age of patients, of degenerative or vascular dementia

Aim of the study

- Reconstruct temporal relationship between MPA symptoms and dementia symptoms
in 22 out of 155 MPA patients who presented dementia with rapidly progressive course
in the acute phase of MPA

Methodology

- Time of clinical onset of MPA was reconstructed on the basis of:
  - clinical symptoms (malaise, loss of appetite and weight, fever,arthromyalgias)
  - laboratory data (hematuria, proteinuria, increased sCreatinine,increased CRP)

- Time course of dementia was reconstructed by description by cohabitant relatives of basic activity of daily living (Barthel Index, BI normal values 100). Relatives were asked to date and score 3 different times:
  - last time of "normality"
  - time of "worse"performance
  - time of recovery (if any).

- Pre-existing cardio-vascular risk factors and features of vasculitic diseases were determined by re-examining clinical records

- In 15 pts, with available images in hospital, brain CT scan and RMN were re-examined

Characteristics of the patients

		Mean	Standard deviation	Range
Patients	N° Age Sex P-ANCA/anti-MPO+ C-ANCA/anti-PR3+	22 78 M:9 F:13 20 2	8	63-89
Clinical Features	Weight loss Fever Arthralgia/Arthritis Myalgia RPGN Pulmonary Haemorrage Motor Mononeuritis	15/18 8/18 7/18 5/17 18/22 3/22 6/18		
Laboratory	s-Cr (mg/dl) Hb (g/dl) CRP (mg/l)	5.9 9.1 92.6	3.7 1.3 77.2	1.1-15.3 6.4-12.0 3-297
Vasculitis Activity Score	BVAS 1 BVAS 2	18.5 8.7	4.9 2.1	9-29 4-14

Pre-existing cardiovascular risk factors

	N° of pts
Hypertension	11/19 (58%)
Diabetes	2/19 (10%)
Congestive heart failure	1/19 (5%)
Atrial Fibrillation	2/19 (10%)

Brain CT scan and MRI re-examined (in 15/22patients)

		N° of patients
▲ Unspecific findings - Cortical sub-cortical atrophy - Leukoaraiosis - w/wo chronic lacunar infarcts		9
▲ Peculiar Findings - multiple lacunar infarcts - multiple lacunar + thromboembolic infarcts - HSV Encephalitis + PRES	 1 4 1	6

Results (1)

- Features of vasculitic diseases, pre-existing cardiovascular risk factors and neuro-imaging data are reported in Table.

- MPA related symptoms or altered laboratory tests in the **22 pts** were present 9.3 (range 1-31) months before diagnosis

In **<u>17 pts</u>** dementia was present at time of diagnosis of vasculitis, with a mean values of BI of 10 (range 0-45) and BI at 0 in 7 pts (fig 1).
In these patients BI values were still normal 7.5 months (range 1-29) before the diagnosis of vasculitis (fig 2).
In this group of pts development of dementia seems to parallel the development of vasculitis

In **<u>5 pts</u>** dementia developed 2 months (range 1-3) after the MPA diagnosis and treatment (fig 1 e 3)

Time of clinical onset of MPA and last time of normal Barthel Index (BI) in 17 patients with dementia at time of diagnosis of vasculitis

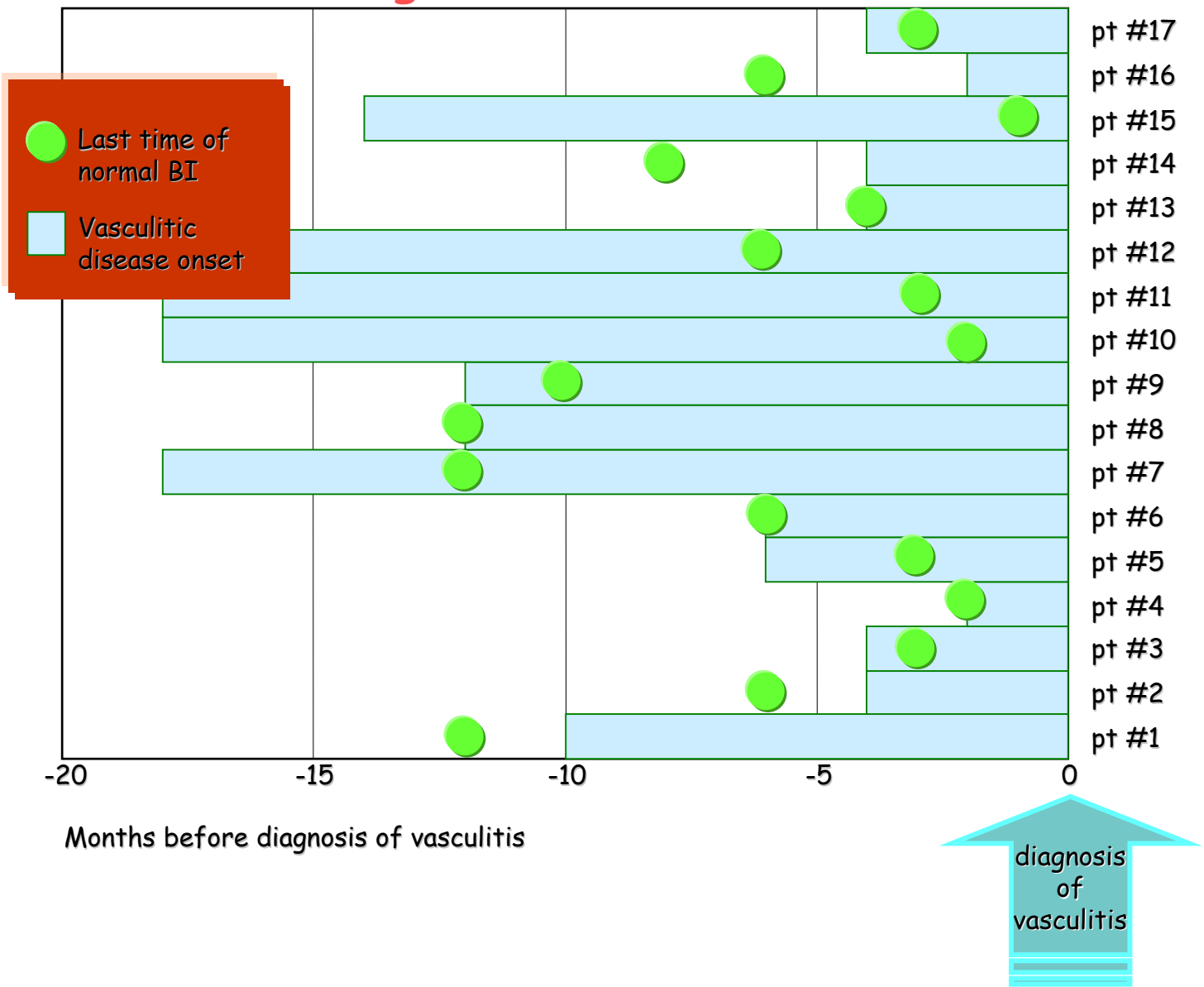

Fig. 2

Time of clinical onset of MPA and last time of normal Barthel Index (BI) in 5 patients who developed dementia after the MPA diagnosis

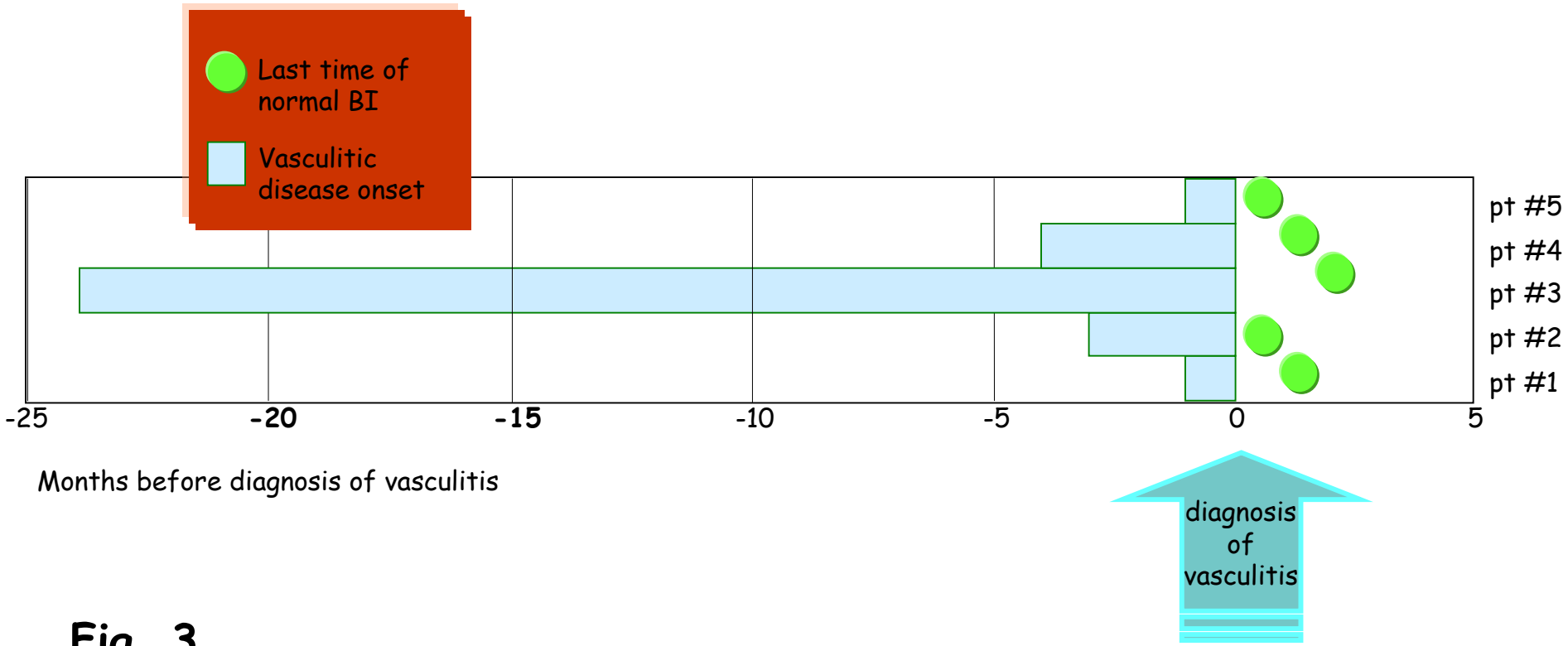

Fig. 3

Results (2)

- HSV related encephalitis and PRESS were diagnosed in 1 pt, 30 days after the start of treatment, no definite cause could be found in the other 4 pts
- A trend to partial recovery and stabilization was evident in most surviving patients during the follow -up
- In this group of MPA pts with cognitive impairment proportion of patients surviving at 3 years is around 20% (Fig. 4)
- Brain CT scan and RMN re-examined did'nt reveal acute lesions except in the patient who had HSV encefalitis and PRES (see Tables)

Conclusions

1- 22 out of 155 pts (15 %) with microscopic poliangiitis developed dementia in strict time relationship with the vasculitic disease.

2- In 17 pts development of dementia "paralleled" the development of vasculitis, whereas in 5 pts dementia developed during or after the hospitalization for the diagnosis and treatment of vasculitis.

3- Dementia in all pts had rapidly progressive course, was severe in many pts and only partially reversible.

4 - Available neuroimaging did not reveal acute lesions except in one pt who developed acute HSV encephalitis and PRES.

5- Prospective and wider application of neuropsyicological test and newer neuroimaging techniques are needed to better understand the relationship between the two diseases.