SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

università di ferrara
DA SEICENTO ANNI GUARDIAMO AVANTI.

LA DIAGNOSI PRECOCE IN REUMATOLOGIA

Ferrara 16 Giugno 2012

Quadri di apertura delle vasculiti sistemiche

Andrea Lo Monaco

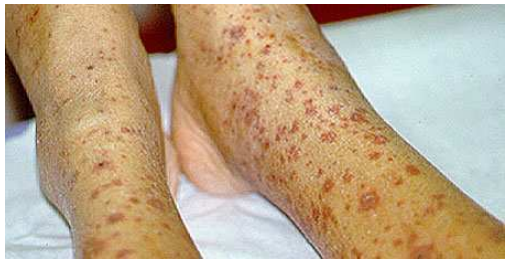
UOC di Reumatologia

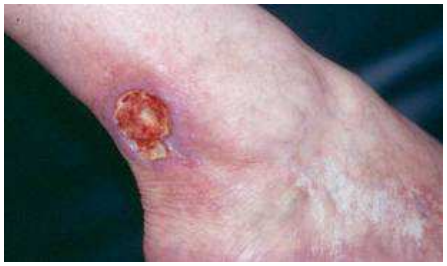
Vasculitis is
simply inflammation directed at blood vessels
identified by
histologic examination

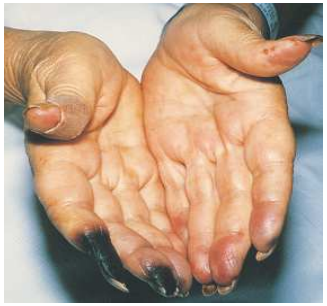
…anyway…

Few diseases in clinical medicine cause as much diagnostic
and therapeutic consternation as vasculitis

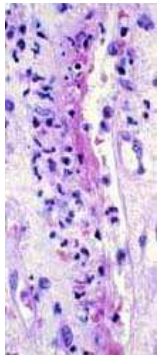
“vasculitis presents as a *mosaic* of clinical and *histologic findings* due to varied pathogenic mechanisms”



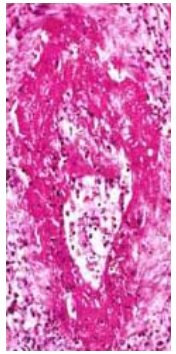




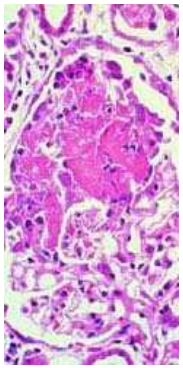
Necrotizing Venulitis



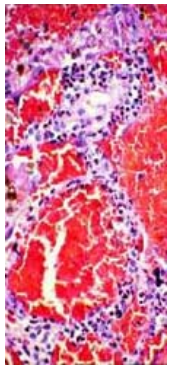
Necrotizing Arteritis

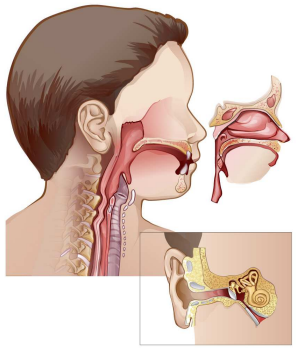


Glomerular Capillaritis



Pulmonary Capillaritis





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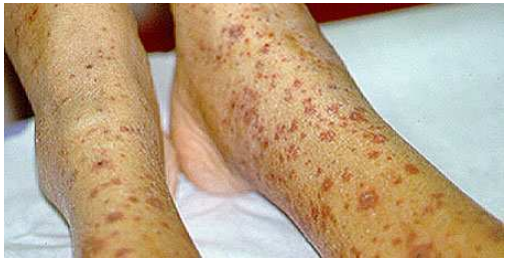
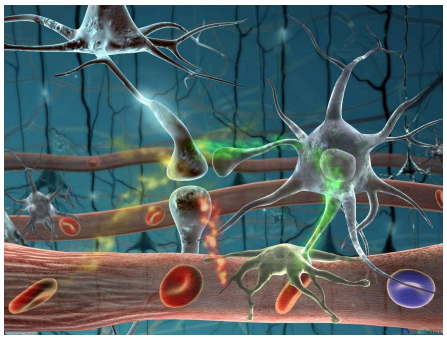
CEPHALEA

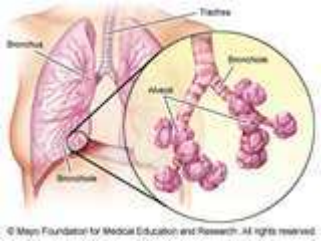


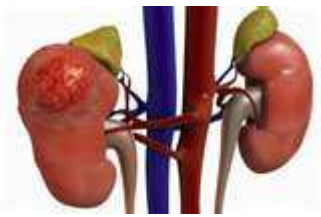
SKIN

SYSTEMIC VASCULITIS



CNS & PNS





LUNG & RENAL DISEASE

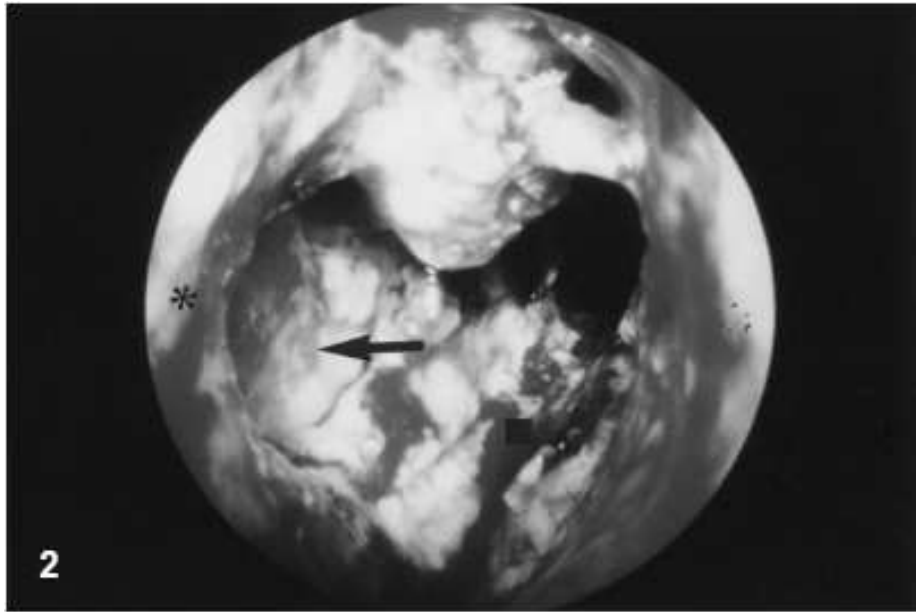
INQUADRAMENTO:

Primitive **Secondarie**

TABLE 3. Factors Associated with Vasculitis

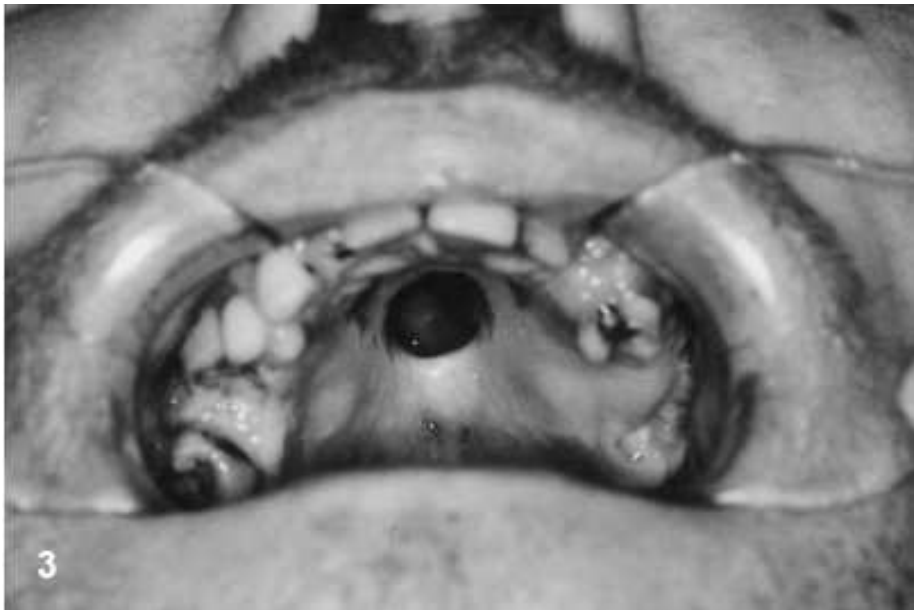
Disease State or Associated Factor	Specific Entity or Agent
Gene polymorphisms	MHC, ICAM-1, IL-Ra, eNOS
Chronic infection	Bacteria (Neisseria sp, Staphylococcus aureus, Streptococcus sp, Mycobacteria sp), rickettsia (Rocky Mountain Spotted fever), virus (Hepatitis viruses A, B, & C, Hantavirus, Herpesviridae, parvovirus B19, and human immunodeficiency virus), fungus, protozoa (malaria), helminthic infections (gnathostomiasis, schistosomiasis)
Drugs	Insulin, antibiotics (penicillin, sulfonamides, chloramphenicol, streptomycin), anticonvulsants (hydantoin), diuretics (thiazides, furosemide), analgesics (aminosalicylic acid, phenylbutazone), phenothiazine, vitamins, quinine, streptokinase, tamoxifen, oral contraceptives, serum (sickness), propylthiouracil, potassium iodide, granulocyte colony stimulating factor (GCSF), leukotriene inhibitors (montelukast), interferons (IFN-γ/α), nicotine patches, TNF inhibitors
Vaccines	Anti-influenza, anthrax, hepatitis B
Chemicals, environmental agents, external factors	Insecticides, petroleum products, particulate silica (quartz, granite, sandstone, and grain dust), solvents, farm work, drug abuse (cocaine), radiocontrast media, protein A column pheresis, arthropod assaults, prolonged exercise, coronary artery bypass surgery, coral ulcers
Allergy	Food allergens (milk proteins, gluten), drug allergy, atopy, hyposensitization antigen
Connective tissue diseases	Systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, mixed connective tissue disease, scleroderma, dermatomyositis/myositis, relapsing polychondritis, ankylosing spondylitis, primary biliary cirrhosis, adult Still disease
Other systemic inflammatory diseases	Behçet disease, sarcoidosis, inflammatory bowel disease
Chronic disease	Cryoglobulinemia, hyperglobulinemic states, cystic fibrosis, bowel-bypass syndrome, alpha-1 anti-trypsin deficiency, St. Jude aortic valve replacement, diabetes mellitus, chronic hepatitis (viral, alcoholic), endocarditis, Wiskott-Aldrich syndrome, Hemolytic anemia
Immunodeficiency states	Primary combined immunodeficiency, acquired immunodeficiency syndrome (AIDS)
Cancer, lymphoproliferative disorders	Hodgkin disease, mycosis fungoides, chronic lymphocytic leukemia, B- and T-cell lymphomas, myeloma, adult T-cell lymphoma/leukemia, Waldenström macroglobulinemia, angioimmunoblastic lymphadenopathy, Hairy cell leukemia
Cancer, solid tumors/carcinomas	Lung, colon, renal, breast, prostate, head and neck squamous cell carcinoma, nasopharyngeal carcinoma, Barrett esophagus

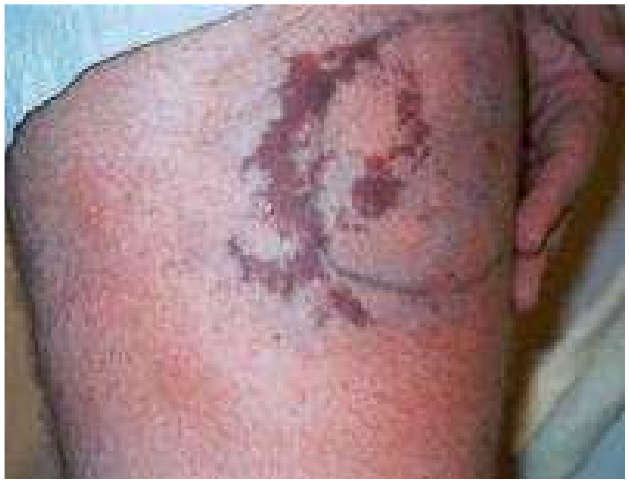
From (7, 13, 32, 33, 63–81, 94, 95).
eNOS, endothelial nitric oxide synthetase; MHC, major histocompatibility complex.



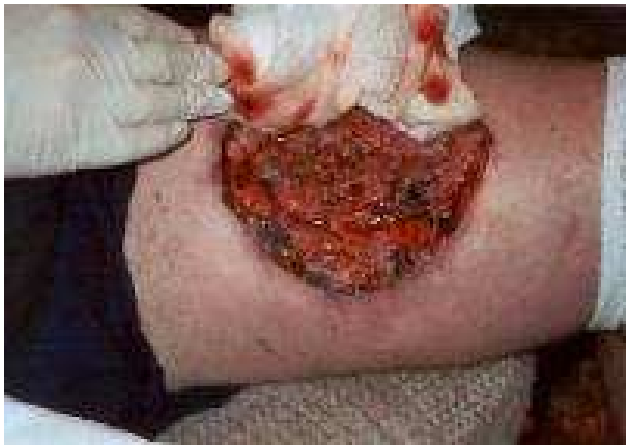
Nasal cocaine abuse causing an aggressive midline intranasal and pharyngeal destructive process mimicking midline reticulosis and limited Wegener's granulomatosis

J Rheumatol. 1990 Jun;17(6):838-40



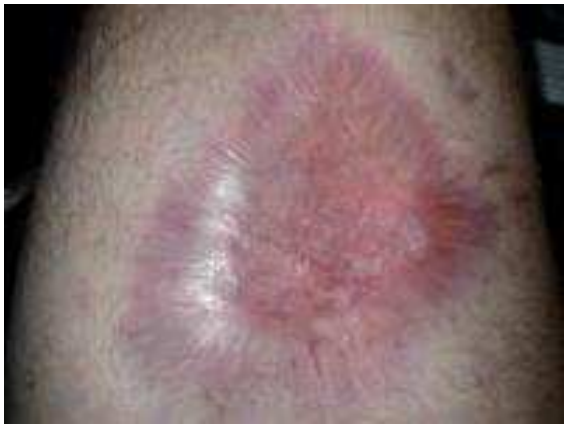


3°GIORNO



11° GIORNO

Brown Recluse Spider

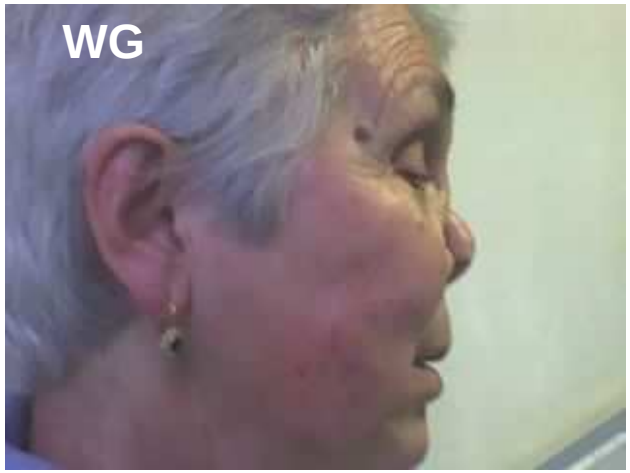


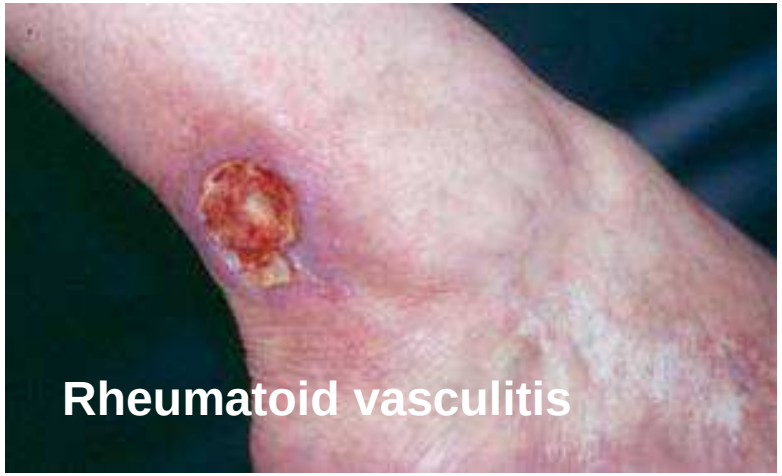
1 ANNO

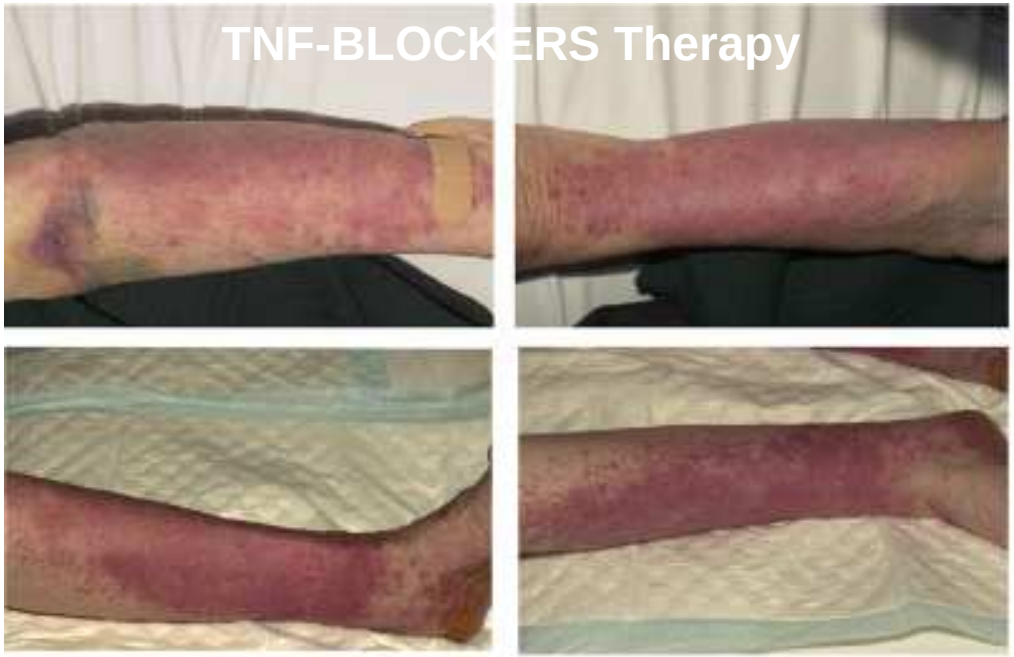
Arch Dermatol. 2005;141:595-597

Comparison of Colchicine, Dapsone, Triamcinolone, and Diphenhydramine Therapy for the Treatment of Brown Recluse Spider envenomation: a double-blind, controlled study in a rabbit model.

Patologia & Complicanza & Terapia





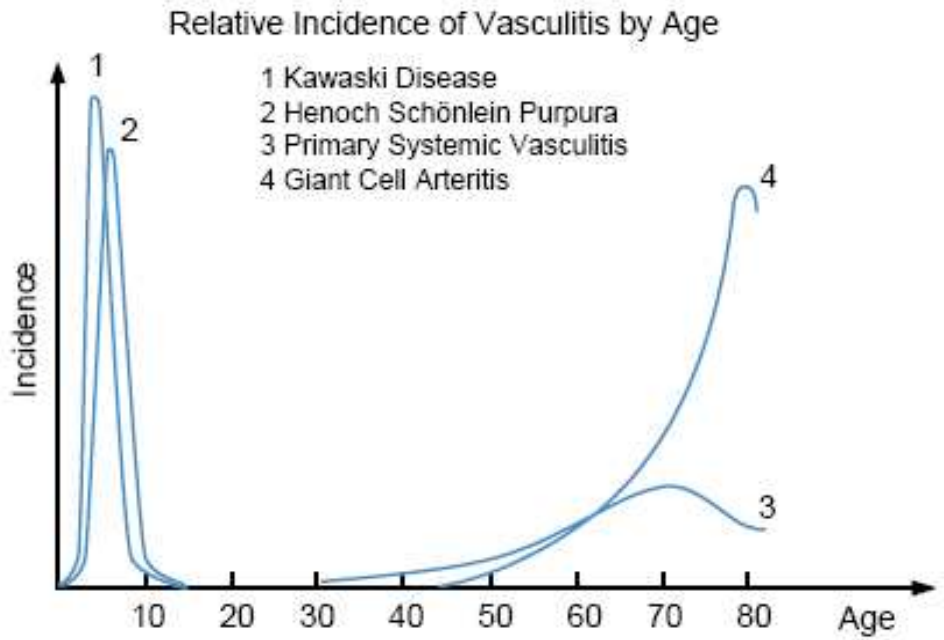


What is known about the epidemiology of the vasculitides?

Richard A. Watts* DM, FRCP

BEST PRACTICE & RESEARCH
Vol. 19, No. 2, pp. 191–207, 2005

GCA è la vasculite <u>più frequente</u>:	**53/100.000 (caucasian >70 yrs)**
Poliarterite nodosa	**0-0,9/milione**
Takayasu	**0-2/milione**
Primary vasculitis (PV):	**20/milione**
Kawasaki	**90/100.000 < 5 yrs**
Henoch-Shönlein	**70/100.000 4-7 yrs**



PV>70 yrs 60/milione

DIFFERENZE GEOGRAFICHE ED ETNICHE

Table 2. Prevalence of primary systemic vasculitis in Europe (per million population).

	Date	Population	WG	CSS	MPA	PAN	Overall
Norway	31/12/1998	467 964	95				
UK	2000	429 000	109	38	28		177*
Germany (North)	1994	449 498	58	7	9	9	
Germany (South)	1994	426 485	42	2	0	2	
Sweden	31/12/1995	–	56	–	–	–	–
Sweden	1/1/2003	287 479	157	7	66	28	257
France	2002	1 093 515	24	11	25	31	90

See text for abbreviations. *Data from Watts et al, unpublished data, 2004, and Refs. 6–9,67.

Takayasu “comune” in Giappone ed India (WG & GCA “molto rare”)

Panarterite nodosa: **77/milione** Alaskan Indians (HBV endemico)
45/milione Kuwait

AAV: **rare nella popolazione di colore**

How do patients present?

1. FLU-LIKE SYMPTOMS:	Fever, polymyalgia, polyarthralgia, headache, malaise, anorexia, weight loss
2. Signs of systemic inflammation	CRP, ESR, anaemia, leucocytosis, thrombocytosis, etc…
3. Signs of organ damage	Dyspnoea, cough, haemoptysis, haematuria, proteinuria, raised serum creatinine, etc…

“SPECIFIC” SYMPTOMS RELATED TO SPECIFIC VASCULITIS

Names Proposed by the Chapel Hill Nomenclature System

Jennette JC et al: Arthritis Rheum 1994; 37:187-192

Table 1 The Chapel Hill nomenclature

Large vessel vasculitis	
Giant cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. Often involves the temporal artery. Usually occurs in patients older than 50 and often is associated with polymyalgia rheumatica.
Takayasu arteritis	Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 50.
Medium sized vessel vasculitis	
Polyarteritis nodosa	Necrotising inflammation of medium sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules.
Kawasaki disease	Arteritis involving large, medium sized, and small arteries, and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children.
Small vessel vasculitis	
Wegener's granulomatosis	Granulomatous inflammation involving the respiratory tract, and necrotising vasculitis affecting small to medium sized vessels (that is, capillaries, venules, arterioles, and arteries). Necrotising glomerulonephritis is common.
Churg-Strauss syndrome	Eosinophil rich and granulomatous inflammation involving the respiratory tract, and necrotising vasculitis affecting small to medium sized vessels, and associated with asthma and eosinophilia.
Microscopic polyangiitis	Necrotising vasculitis, with few or no immune deposits, affecting small vessels (that is, capillaries, venules, or arterioles). Necrotising arteritis involving small and medium sized arteries may be present. Necrotising glomerulonephritis is very common. Pulmonary capillaritis often occurs.
Henoch-Schönlein purpura	Vasculitis, with IgA dominant immune deposits, affecting small vessels (that is, capillaries, venules, or arterioles). Typically involves skin, gut, and glomeruli, and is associated with arthralgias or arthritis.
Essential cryoglobulinaemic vasculitis	Vasculitis, with cryoglobulin immune deposits, affecting small vessels (that is, capillaries, venules, or arterioles), and associated with cryoglobulins in serum. Skin and glomeruli are often involved.
Cutaneous leucocytoclastic angiitis	Isolated cutaneous leucocytoclastic angiitis without systemic vasculitis or glomerulonephritis.

Modified from reference 3.

Large Vessel Vasculitis

Giant Cell Arteritis
Takayasu Arteritis

Medium-Sized Vessel Vasculitis

Polyarteritis Nodosa
Kawasaki Disease

Small Vessel Vasculitis

Microscopic Polyangiitis
Wegener's Granulomatosis
Churg-Strauss Syndrome
Henoch-Schönlein Purpura
Cryoglobulinemic Vasculitis
Cutaneous leukocytoclastic vasculitis (CLA)

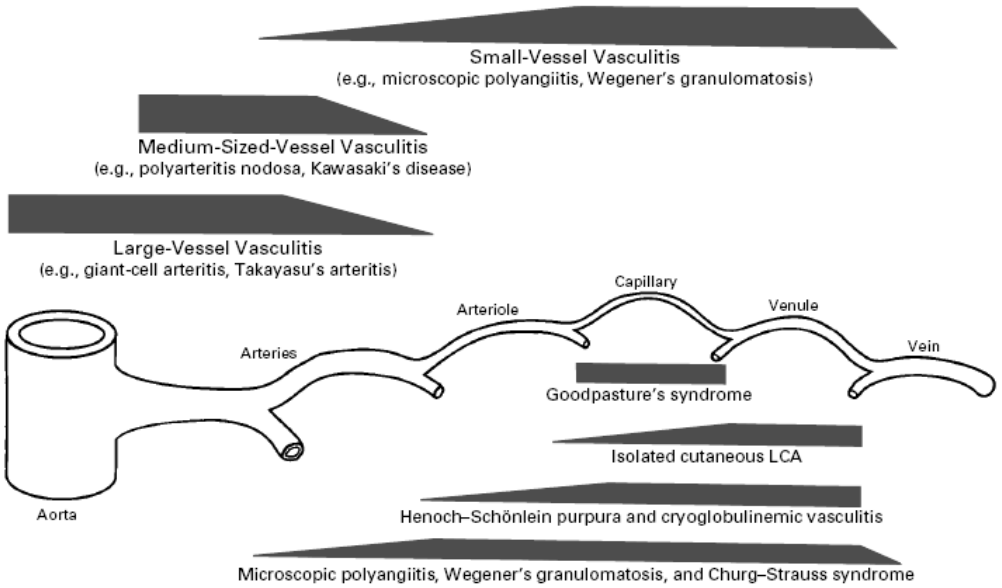
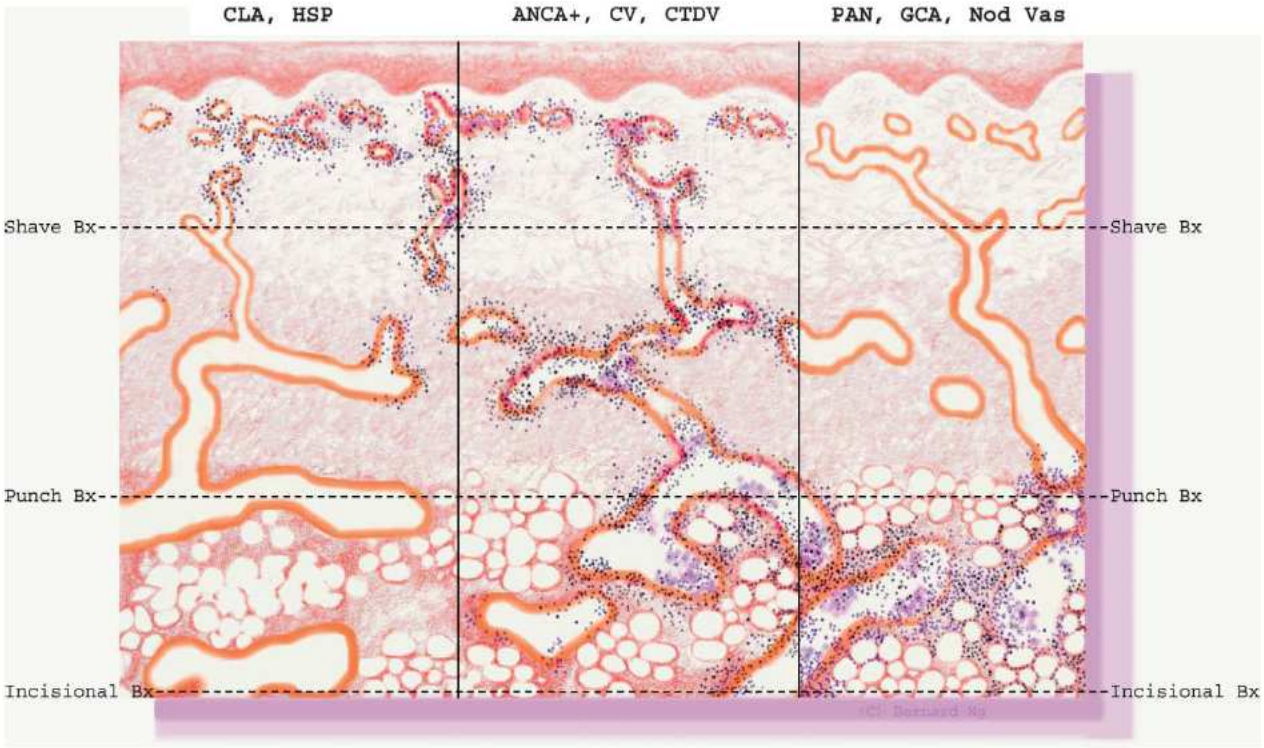


Figure 1. Preferred Sites of Vascular Involvement by Selected Vasculitides.
The widths of the trapezoids indicate the frequencies of involvement of various portions of the vasculature. LCA denotes leukocytoclastic angiitis.

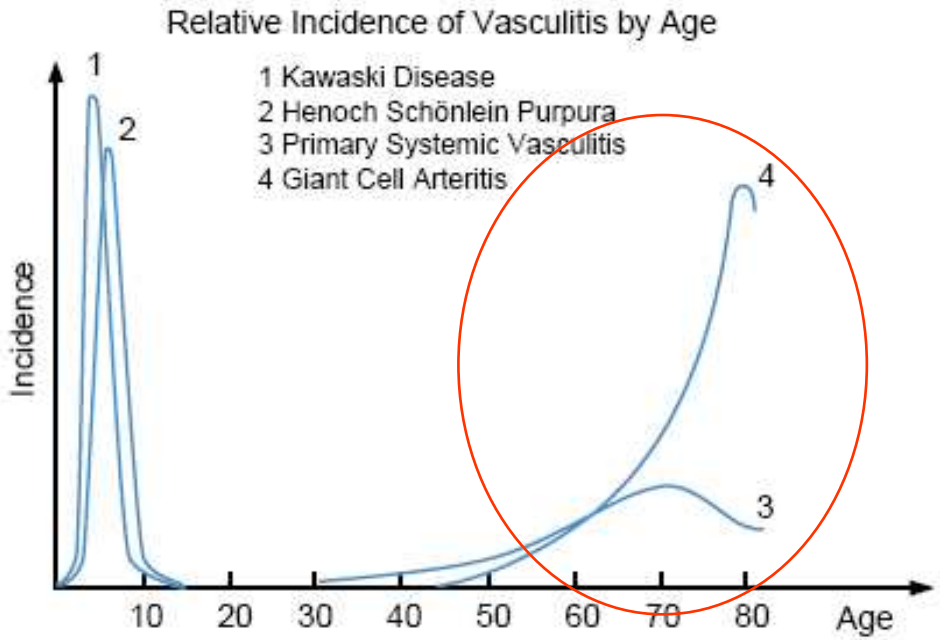
Indicazioni:
-cliniche
-terapeutiche



Typical features

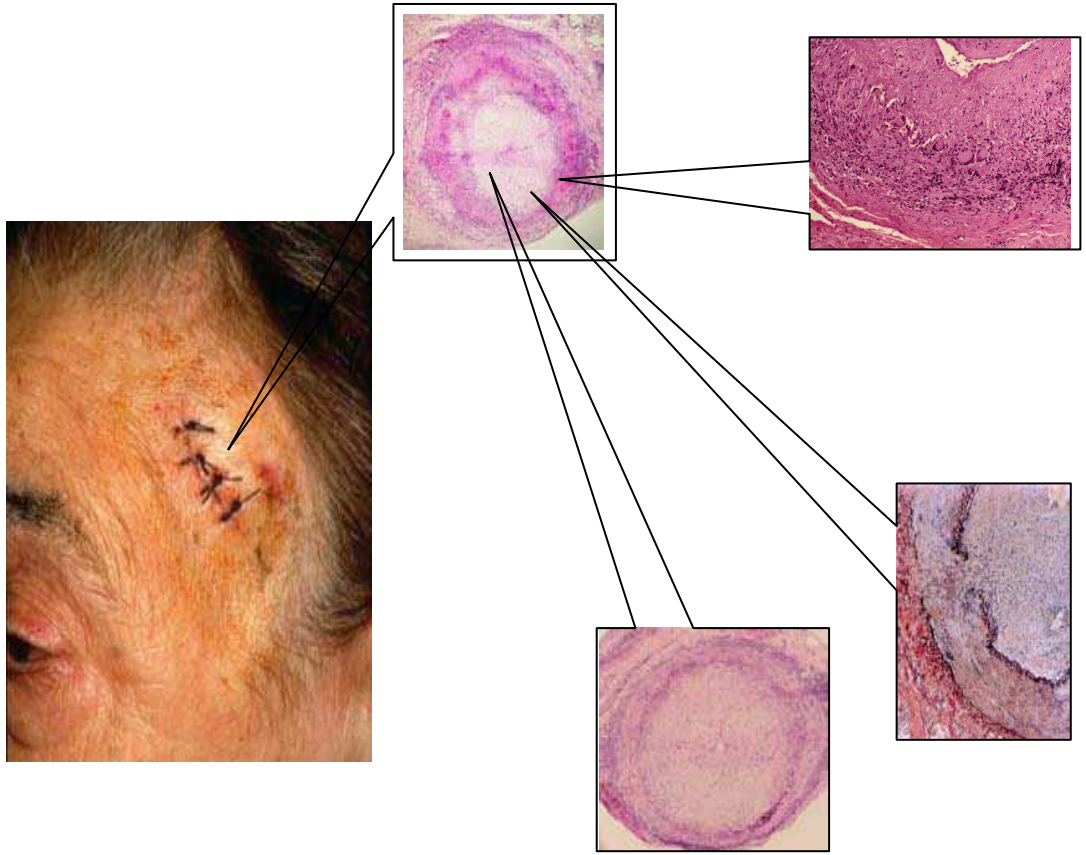
LARGE VESSEL VASCULITIS:
(aorta and its major branches)

- •FEVER (FUO), WEIGHT LOSS, ANAEMIA
- • ↑ ESR AND CRP
- •ISCHAEMIA & ANEURYSM
- •CEPHALEA & VISUAL LOSS (Horton's arteritis)
- •AGE AT THE ONSET [<40 yrs >50 yrs (>65 yrs)]



Giant Cells Arteritis

NEW HEADACHE
ESR/CRP
VISUAL LOSS!!!!!



1990 ACR criteria

1. Age at disease onset >=50 years

Development of symptoms or findings beginning at age 50 or older

2. New headache

New onset of or new type of localized pain in the head

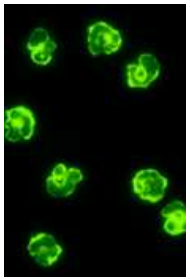
3. Temporal artery abnormality

Temporal artery tenderness to palpation or decreased pulsation, unrelatd to arteriosclerosis of cervical arteries

4. Elevated erythrocyte sedimentation rate

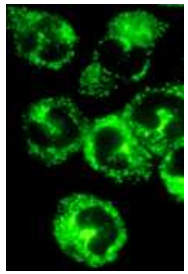
Erythrocyte sedimentation rate >=50 mm/hour by the Westergren method

5. Abnormal artery biopsy



ANCA-ASSOCIATED VASCULITIS (AAV)

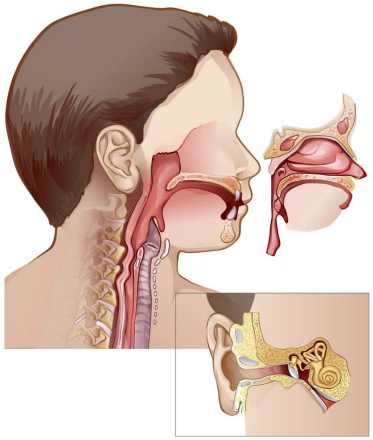
PRIMARY VASCULITIS



WG **CSS** **MPO**

"…a continous spectrum of tissue changes from pure necrosis and granuloma formation to pure angiitis with intermediate combination…

Typical features



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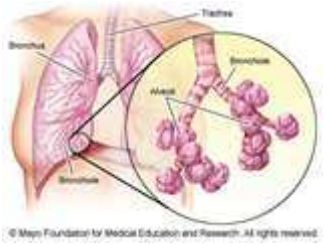
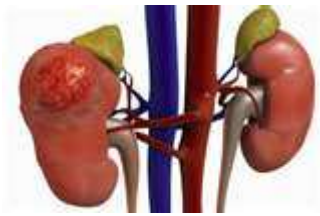
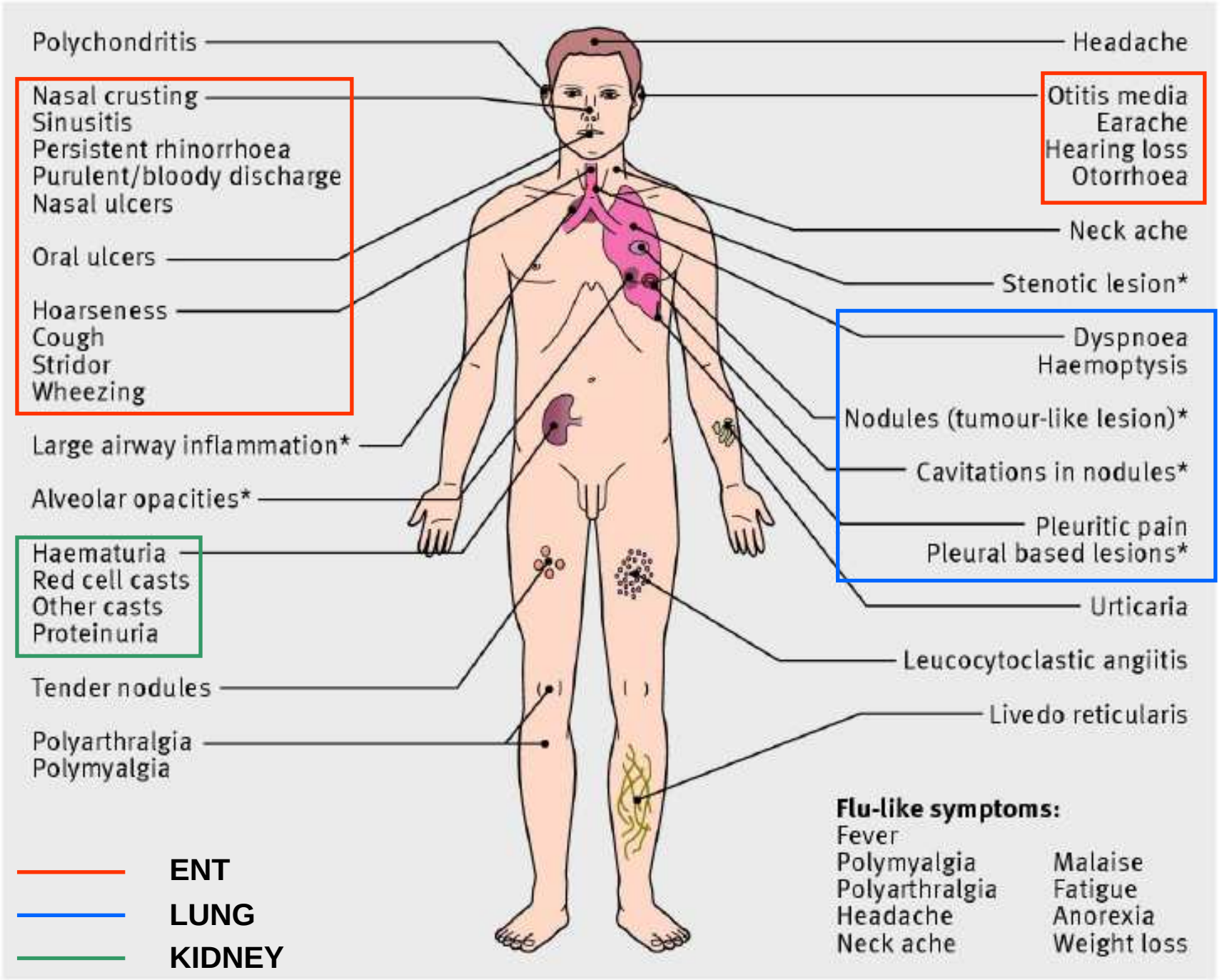




LUNG & RENAL DISEASE

Jacob Churg


Polychondritis
Nasal crusting
Sinusitis
Persistent rhinorrhoea
Purulent/bloody discharge
Nasal ulcers
Oral ulcers
Hoarseness
Cough
Stridor
Wheezing
Large airway inflammation*
Alveolar opacities*
Haematuria
Red cell casts
Other casts
Proteinuria
Tender nodules
Polyarthralgia
Polymyalgia
Headache
Otitis media
Earache
Hearing loss
Otorrhoea
Neck ache
Stenotic lesion*
Dyspnoea
Haemoptysis
Nodules (tumour-like lesion)*
Cavitations in nodules*
Pleuritic pain
Pleural based lesions*
Urticaria
Leucocytoclastic angiitis
Livedo reticularis
Flu-like symptoms:
Fever
Polymyalgia
Polyarthralgia
Headache
Neck ache
Malaise
Fatigue
Anorexia
Weight loss
ENT
LUNG
KIDNEY

Shared features

Skin lesions [porpora di Henoch-Schonlein & Cryoglobulinemic Vasculitis]

Mononeuritis multiplex/polyneuropathy

Fatigue

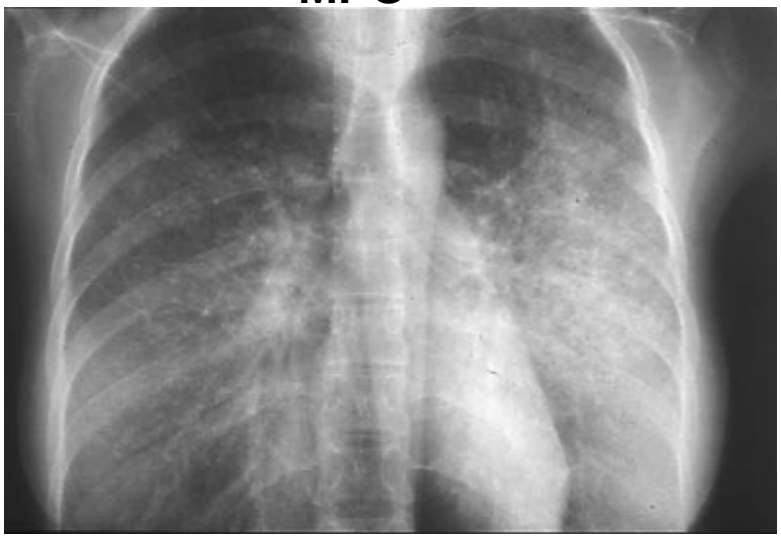
Arthralgia/arthritis

Response to corticosteroids

Life-threatening involvement

- Alveolar haemorragies [nephro-pulmonary syndrome, mortality 40-90%]
- Intestinal ischaemia
- Cardiac involvement (eosinophilic coronary arteritis)

MPO



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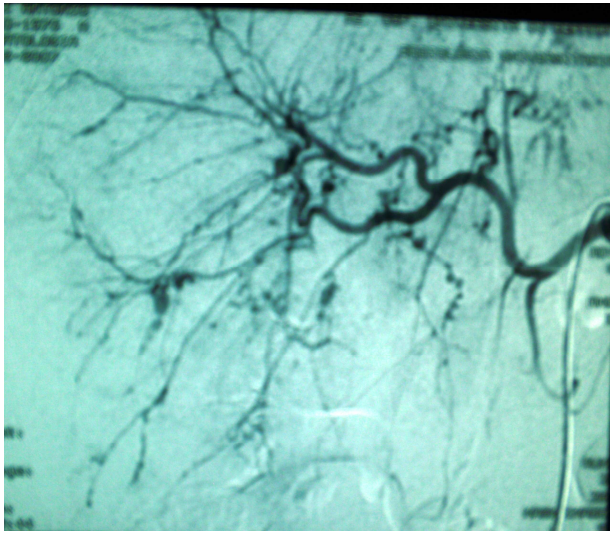

Two major issues for diagnosis

- ANTI-NEUTROPHIL CYTOPLASM ANTIBODY-**ANCA**
- HISTOLOGY

Anti-neutrophil cytoplasm antibody-ANCA

"The clinical setting in which the test is performed is crucial for interpreting the results…"

When to do that!! (to avoid low pre-test propability)

- Acute/chronic destructive *upper airway disease*
- *Pulmonary inflammatory disease*
- *Renal inflammatory disease (active urine sediment o RPGN)*
- *Skin vasculitis*
- *Mononeuritis multiplex*
- *"Red eye", Retro-orbital mass*

EULAR Recommendations for the Management of Primary Small and Medium Vessel Vasculitis

Chetan Mukhtyar[1], Loic Guillevin[2], Maria C. Cid[3], Bhaskar Dasgupta[4], Kirsten de Groot[5], Wolfgang Gross[6], Thomas Hauser[7], Bernhard Hellmich[8], David Jayne[9], Cees G. M. Kallenberg[10], Peter A. Merkel[11], Heiner Raspe[6], Carlo Salvarani[12], David G. I. Scott[13], Coen Stegeman[10], Richard Watts[14], Kerstin Westman[15], James Witter[16], Hasan Yazici[17], Raashid Luqmani[1] for the European Vasculitis Study Group

Statements

2. We recommend that ANCA testing (including both indirect immunofluorescence and ELISA) should be performed in the appropriate clinical context.

[Level of evidence 1A, Grade of recommendation A]

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

ANCA in the diagnosis of neutrophil-mediated inflammation

Ivo Lochman [a,*], Vlastimil Král [b], Alexandra Lochmanová [c], Julius Lupač [d], Ladislav Cebecauer [e]

[a] Department of Immunology and Allergy, Institute of Public Health, Ostrava, Czech Republic
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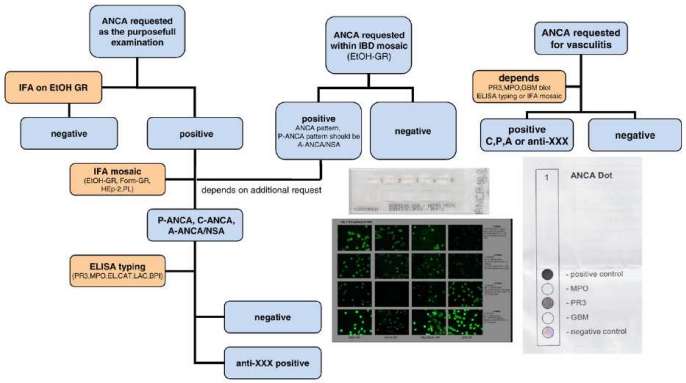


Fig. 1. ANCA diagnosis chart in the DIA of IPH, Ostrava.

AAV: 20/milione
Nord america ed nord europa:
WG 13/100.000
MPO 4.8/100.000

overview of IIFA results		
result	count	percent
negative	4909	93.22
marginal	4	0.08
weak pos	46	0.87
positive	307	5.83
total	5262	100.00

ANCA typ	freq	percent
C	43	12.04
P	56	15.69
PC	4	1.12
A	252	70.59
AP	2	0.56
total	357	100.00

Anti-neutrophil cytoplasma antibody-ANCA

PITFALLS

Conditions can be associated with ANCA pos

- Acute/Chronic infections
- Inflammatory bowel disease
- Autoimmune liver diseases
- Drugs (hydralazine, penicillamine, phenytoin, allopurinol, sulphasalazine, minocycline, cefotaxime, ciprofloxacin, thioridizine and clozapine)

Histologic signs of acute (active) vasculitis

Dermal small vessels (venules and arterioles) (2 of 3* criteria needed)

Angioinvasive **inflammatory infiltrates**

Destruction of vessel wall by inflammatory infiltrate

Intramural and/or intraluminal fibrin deposition (‘‘**fibrinoid necrosis**’’)

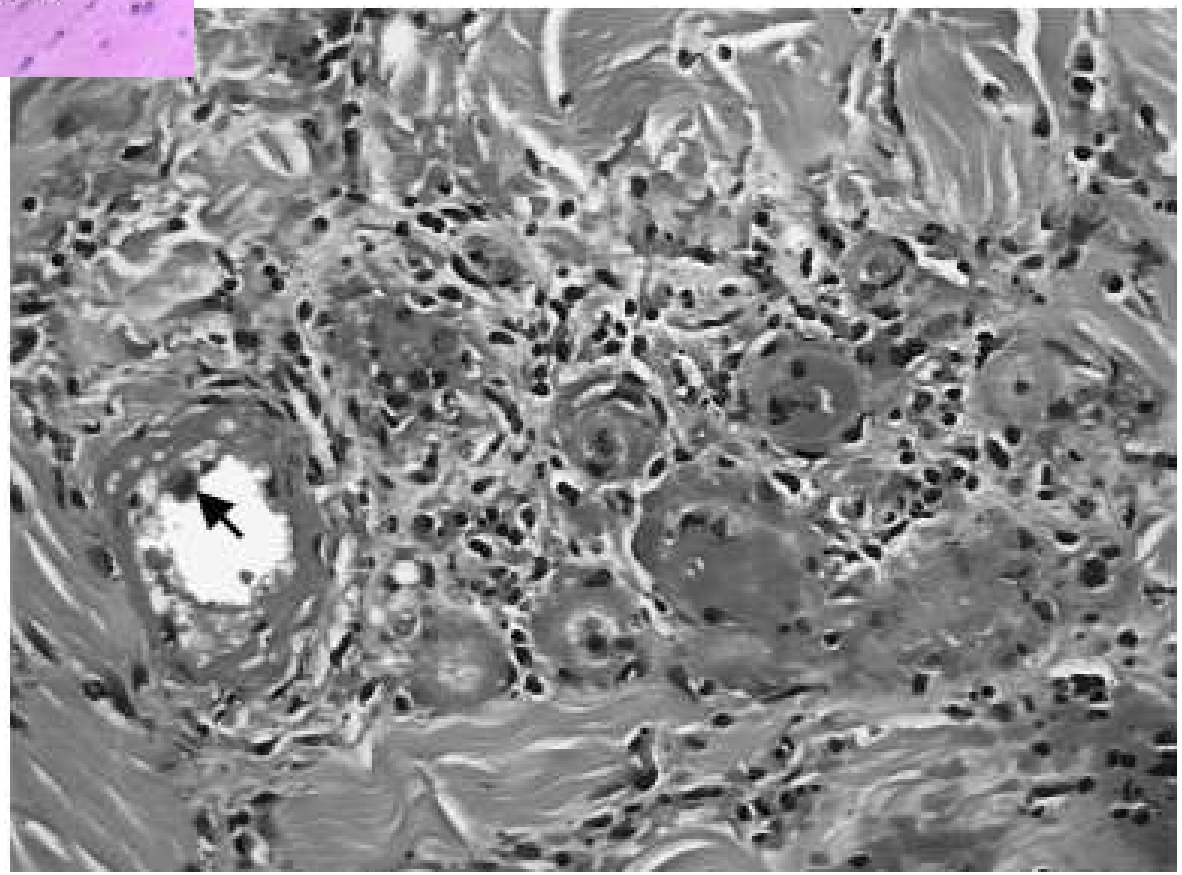
Dermal-Subcutaneous muscular vessels

(small arteries and veins)

*__Infiltration of muscular vessel wall__ by inflammatory cells

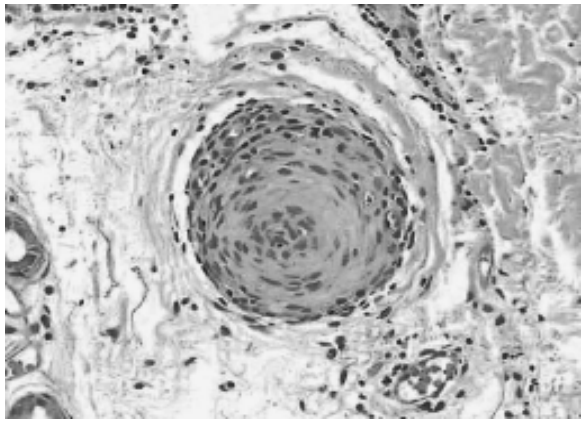
*__Intramuraland/or intraluminal fibrin deposition__ (‘‘fibrinoid necrosis’’)‡

(both* criteria needed)

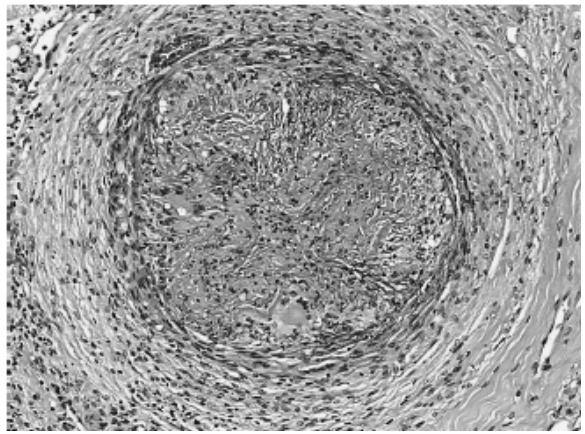


Histologic sequelae of vasculitis (chronic signs and healed lesions of vasculitis)

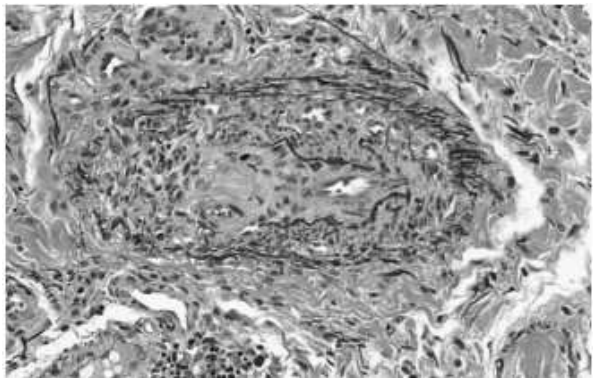
-Lamination (**onion-skinning**) of vessel wall constituents (concentric proliferation of pericytes and smooth muscle cells)



-Luminal obliteration (**endarteritis obliterans**) Intimal or medial proliferation of cellular elements leading to luminal occlusion with preservation of the internal elastic lamina



-**Segmental or complete loss of elastic lamina** in medium and large vessels associated with acellular scar tissue



MODERN PATHOLOGY (2012) 25, S31–S38

Necrotizing granulomatous inflammation: what does it mean if your special stains are negative?

Marie-Christine Aubry

Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

What is the significance of necrotizing granuloma that looks infectious but in which no organism is identified?

MODERN PATHOLOGY (2012) 25, S31–S38
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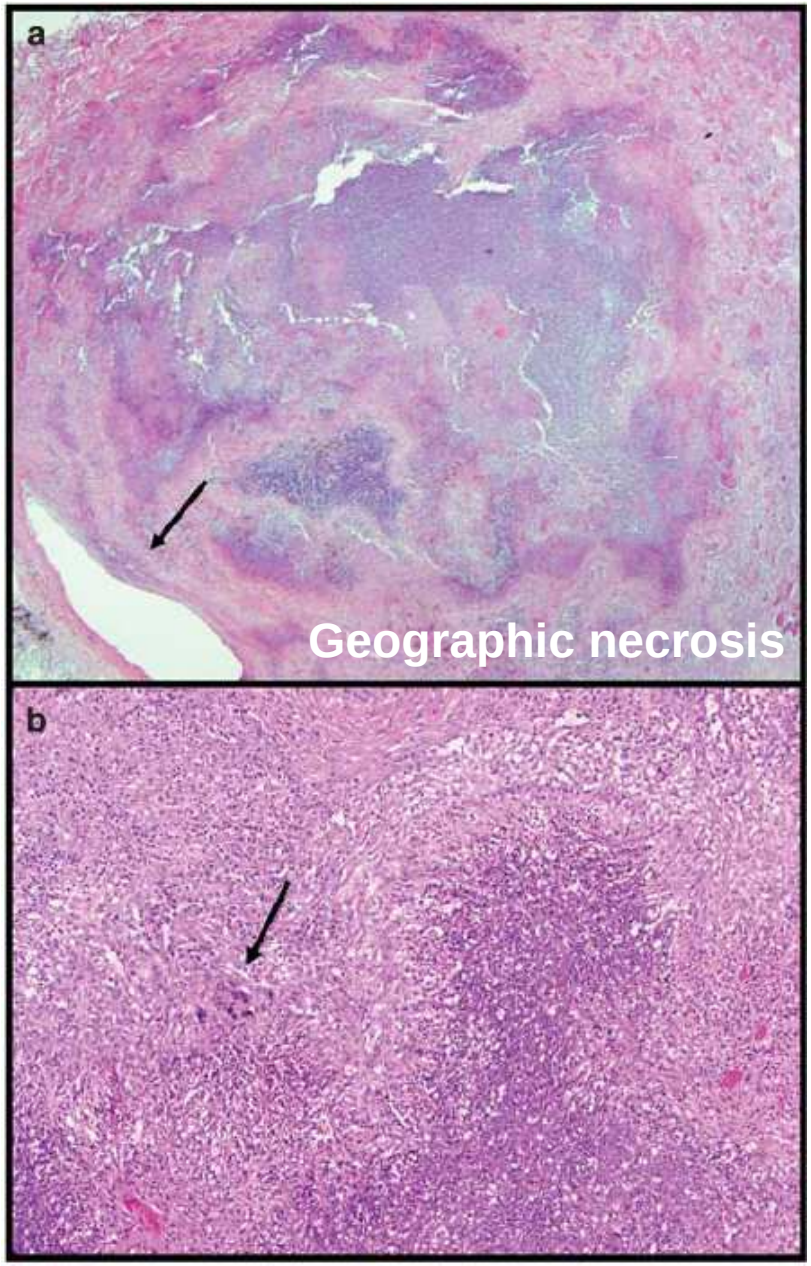
S31

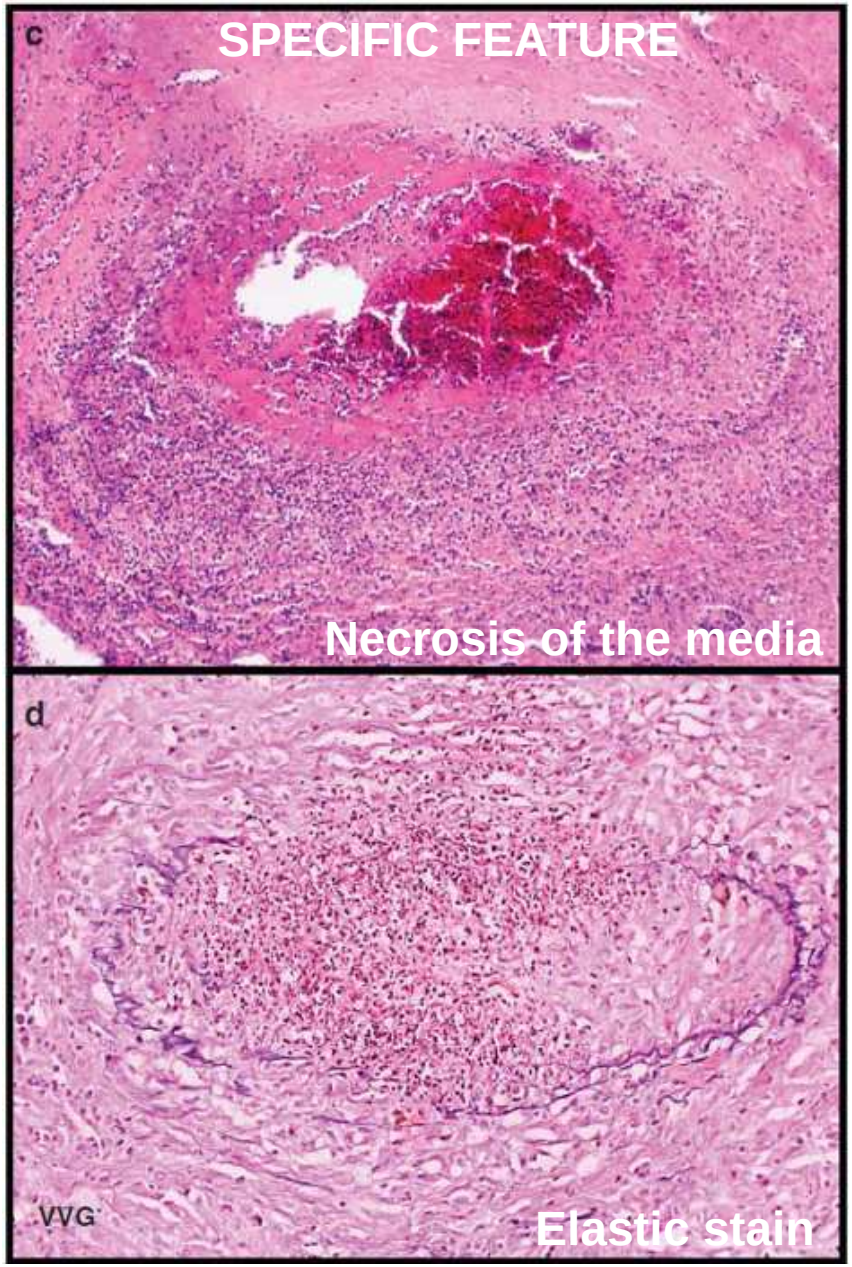
Many granulomas remains unexplained

-**Ulbright and Katzenstein** looked at 86 consecutive necrotizing granulomas presenting as single nodules:
•61 (71%) were infectious,
•3 (3%) were WG (1) and hyalinizing granuloma (2)
•22 (26%) remained unexplained after clinical, radiological and microbiological correlation.

-**Mayo Clinic**
50% infectious
13% other
39% remained unexplained after clinical, radiological and microbiological correlation.

MODERN PATHOLOGY (2012) 25, S31–S38





"…a true necrotizing vasculitis characterized by fibrinoid necrosis of the media associated with necrotic neutrophils is not seen and **is a specific feature of a true vasculitis such as WG."**

MC Aubrie

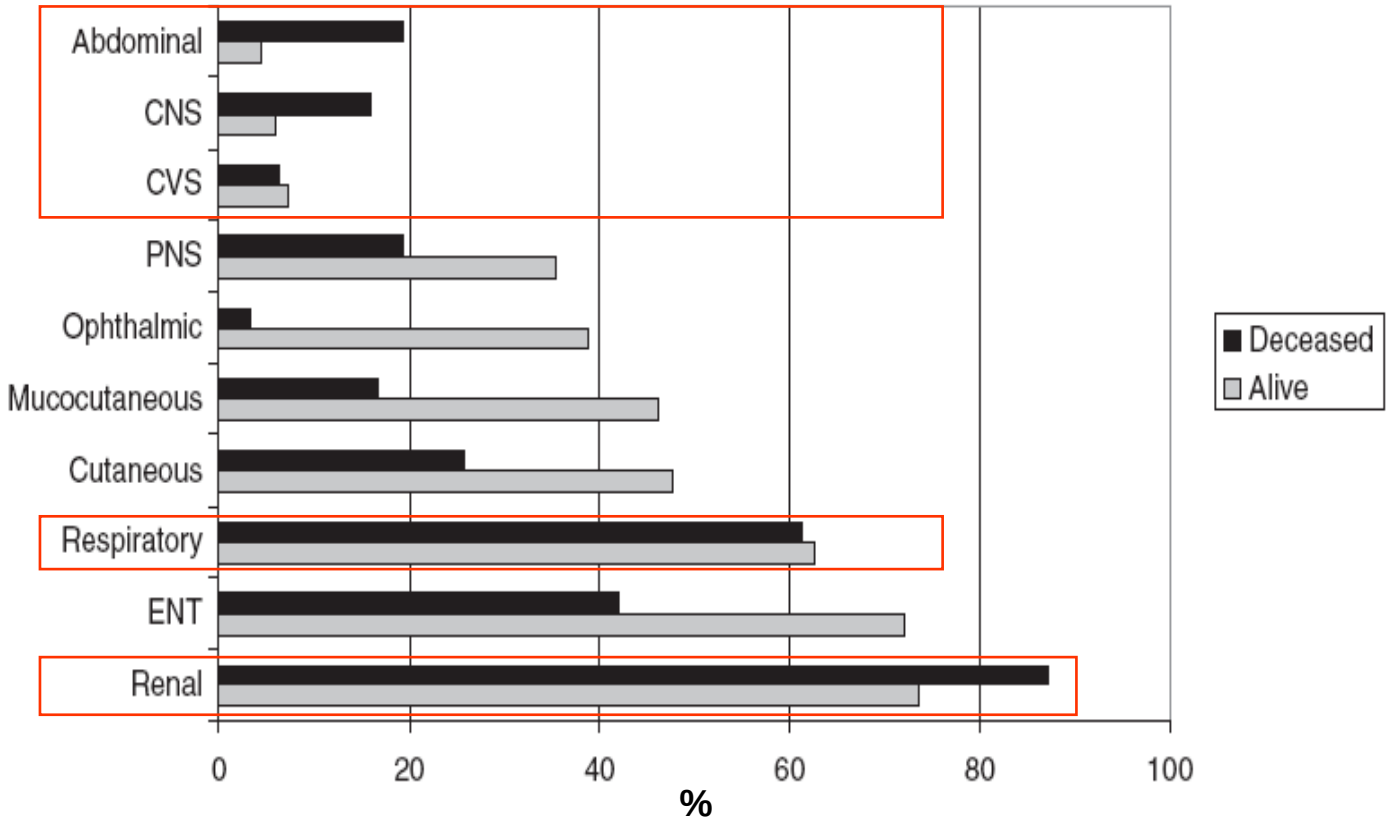
What features are most helpful in separating infectious granulomatous disease from other lesions such as WG?

COMBINATION OF MULTIPLE FEATURES

1. **FIBRONIOD NECROSIS OF THE MEDIA**
2. "DIRTY" NECROSIS DUE TO INTENSE Nø NECROSIS WITH NUCLEAR DEBRIS
3. SAVINGS OF LIMPH NODE (involved in infectious granuloma)
4. ELASTIC STAIN IN PERIPHERAL VESSELS (Verhoeff von Gieson stain)

MODERN PATHOLOGY (2012) 25, S31–S38

Mortality = organ involvement



Conclusions

•Systemic vasculitis are very rare![an in-depth DD is mandatory!]

•ANCA should be performed in the appropriate clinical context **(low pre-test probability)**

•Early diagnosis→early treatment!!

I have a dream…

•Dedicated pathologist [Neurologist, dermatologist, ORL, etc…]

•**Quality of ANCA detection: IIF plus EIA**

CLASSIFICAZIONE

Vasculitis's History

Karl von Rokitansky. Handbuch der pathologischen Anatomie. Braumiller & Seidel, Wien 1842.

Kussmaul A & Maier R. Dtsch Arch Klin Med, Freiburg 1866.

Graf E. Beitr Pathol Anat Allg Pathol 1896

Lüpke F. über Periarteriitis nodosa bei Axishirschen. Verh Dtsch Ges Inn Med 1906.

Gruber GB. Zur Frage der Periarteriitis nodosa…..Virchows Arch 1925.

Klinge F. Die Eiweissüberempfindlichkeit der Galenke…. Beitr Pathol Anat Allg Pathol 1929.

Masugi M & Isibasi T. über allergische…. Beitr Pathol Anat Allg Pathol 1936

Horton BT et al. Undescribed form of arteritis of temporal vessels. Proc Staff Meet Mayo Clin 1932.

Churg J, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. Am J Pathol 1951

Pearl Zeek. Periarteritis nodosa: critical review. Am J Clin Pathol 1952.

Infection era ***Allergic era*** **Immunologic era**

…CHCC is imperfect in a number of ways.

Coombs & Gell classification

TABLE 5. Pathogenic Mechanisms Implicated in Cutaneous Vasculitis

Pathogenic Mechanism*	Vasculitic Syndrome	Vasculitis Pattern	In Situ Blood Vessel	Serologic Studies	References
Direct infection	Rickettsial infections	Lymphocytic small vessel	Intra-endothelial *Rickettsia* species, T cells	IgG to Rickettsia species	(138, 255–257)
Type I Anaphylactic	Eosinophilic vasculitis	Eosinophilic small vessel	MBP, ICAM, ↓ mast cells/tryptase	↑ Eos, ↑ MBP, ↓ Neut, ↑ ESR, ↓ C	(146, 147)
	Churg-Strauss Syndrome (CSS)	Eosin-/neutrophilic mostly small and medium	ECP, ↑ Eos, ExGr with eosinophilic necrosis	↑ Eos, ↑ IgE, p-ANCA, ↑ ESR, ↑ IFN-α, ↑ IL-2	(145, 258–260)
Type II Cytotoxic-cytolytic antibody	Wegener granulomatosis (WG)	Neutrophilic mostly small and medium	ExGr with basophilic necrosis, CD4+CD25-	cANCA, ↑ ESR, ↑ WBC, ↑ CRP, ↑IFN-α, ↑ IL-2, lymphopenia, ↑ CD4+CD25+	(151, 258, 261–263)
	Microscopic polyangiitis (MPA)	Neutrophilic mostly small and medium	No ExGr, CD4+CD25-	pANCA, lymphopenia, ↑ CD4+CD25+	(144, 151, 264)
Type III Immune complex	Henoch-Schönlein Purpura (HSP)	Neutrophilic small vessel	IgA IC, MAC	↑ IgA	(189)
	Cutaneous leukocytoclastic angiitis (CLA/LCV/ hypersensitivity vasculitis)	Neutrophilic small vessel	IC, MAC, NE, ICAM-1, E-selectin, VLA	↓ C, ↑ , IΛ−1β, ↑ IL-2, ↑ Il-2r, ↑ IL-8, ↑ TNΦ-α, ↑ VEGF	(86, 88, 170–172, 179, 265)
	Cryoglobulinemic vasculitis (CV)	Neutrophilic mostly small and medium	IgG-mRF immune deposits	↓ C, Hepatitis C virus, ↑ Cryocrit	(266)
	Polyarteritis nodosa (PAN)	Neutrophilic medium	IC, MAC, E-selectin, ICAM	↓ C, Hepatitis B virus, ↑ IFN-α, ↑ IL-2	(174, 188, 258, 267)
Type IV Delayed hypersensitivity	Giant cell arteritis (GCA)	Granulomatous medium vessel	↑ CD3+/CD4+, ↑ activated CD68+, IL-1b, VEGF, PDGF, IL-2, IFN-γ	↓ CD3+/CD8+, ↑ activated CD68+, Il-1β, TNFα, IL-6	(193)
	Chronic graft-vs.-host disease	Lymphocytic small vessel†	↓ microvessel density, CD8+, GMP-17, Granzyme B	↑ vWF	(204, 205, 211)
	Sneddon Syndrome	Lymphocytic medium vessel†/endarteritis obliterans	T-cells, ↑ SMC, ↑ collagen	AECA	(47, 268, 269)

Adapted from Schmitt and Gross[270] and Jennette.[271]
*Coombs and Gell classification[130].
†Endothelialitis.
ANCA, antineutrophil cytoplasmic antibodies; pANCA, perinuclear and cANCA-cytoplasmic; AECA, antiendothelial antibodies; CRP, C-reactive protein; EBV, Epstein-Barr virus; ECP, eosinophilic cationic protein; Eos, eosinophils; ESR, erythrocyte sedimentation rate; ExGr, extravascular granulomas; GMP-17, granule membrane protein 17, marker of activated effector cytotoxic T cells; IC, immune complexes; MAC, membrane attack complex, C5b-9; MBP, major basic protein; MRF, monoclonal rheumatoid factor; Neut, neutrophils; NE, neutrophil elastase; SMC, smooth muscle cells; VEGF, vascular endothelial growth factor; VLA, very late activation antigen; vWF, von Willebrand factor.

ASPETTI ISTOPATOLOGICI GENERALI

EPIDEMIOLOGIA

Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *BMJ* 1958;2:265-70.

56 pts:
82% within 1 yr
>90% within 2 yrs

Renal failure
Respiratory failure

RESOURCES AND GENERAL INFLAMMATION ON SYSTEMIC VASCULITIS

http://vasculitis.med.jhu.edu John Hopkins Vasculitis Center

www.vasculitis.org European Vasculitis Study Group

www.clevelandclinic.org/arthritis/vasculitis/default.htm Cleveland Clinic Center for Vasculitis

www.vascularite.com Groupe Français d'Etude des Vascularites

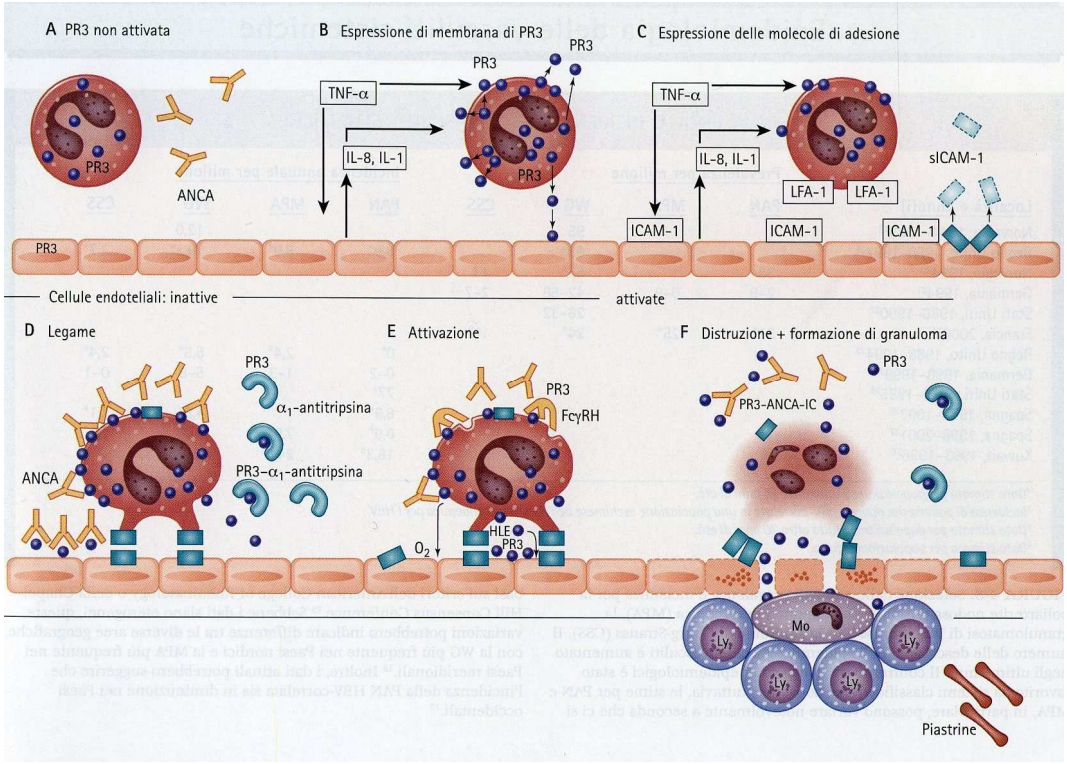
www2.ccf.org/inssys/default.htm International Network for the Study of Vasculitis

www.rheumatology.org American College of Rheumatology

www.wgassociation.org Wegener's Granulomatosis Association

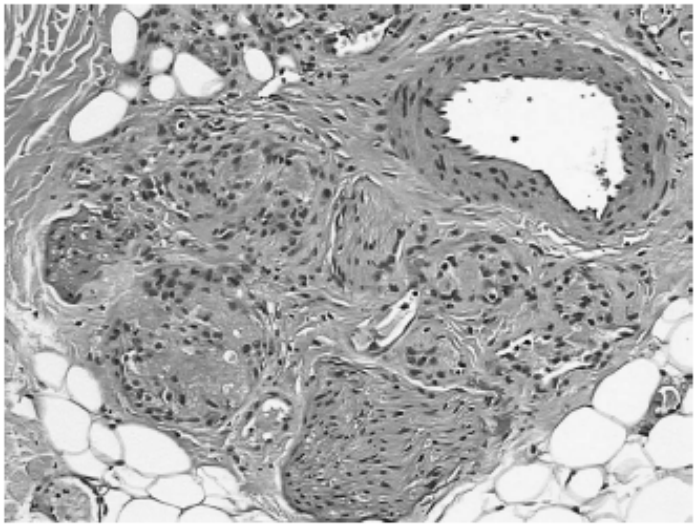
Table 5 EUVAS disease categorization of ANCA associated vasculitis

Category	Definition
Localized	Upper and / or lower respiratory tract disease without any other systemic involvement or constitutional symptoms
Early systemic	Any, without organ-threatening or life-threatening disease
Generalized	Renal or other organ threatening disease, serum creatinine < 500 µmol/L (5.6 mg/dl)
Severe	Renal or other vital organ failure, serum creatinine > 500 µmol/L (5.6 mg/dl)
Refractory	Progressive disease unresponsive to glucocorticoids and cyclophosphamide

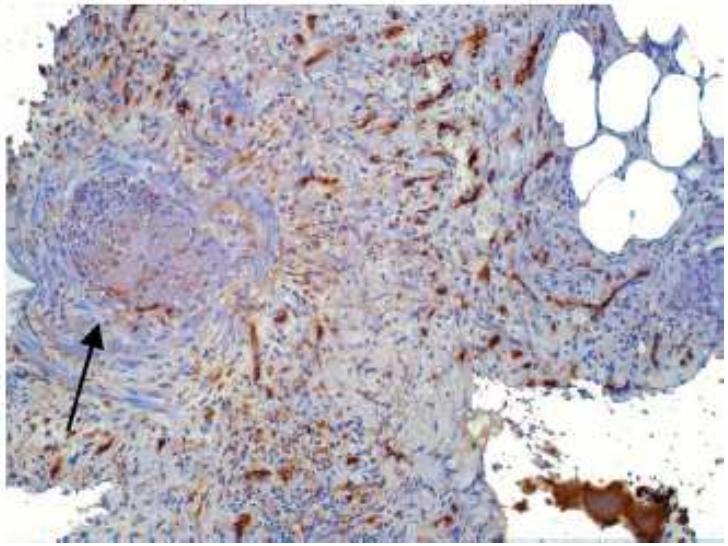

A PR3 non attivata
B Espressione di membrana di PR3
C Espressione delle molecole di adesione
PR3
ANCA
TNF-α
IL-8, IL-1
PR3
PR3
PR3
TNF-α
IL-8, IL-1
LFA-1
LFA-1
sICAM-1
ICAM-1
ICAM-1
ICAM-1
PR3
Cellule endoteliali: inattive
attivate
D Legame
E Attivazione
F Distruzione + formazione di granuloma
PR3
α1-antitripsina
PR3–α1-antitripsina
ANCA
PR3
FcγRH
O2
HLE
PR3
PR3
PR3-ANCA-IC
Mo
Ly
Piastrine

Histologic sequelae of vasculitis (chronic signs and healed lesions of vasculitis)

-Reactive **angioendotheliomatosis**



-**Neo-vascularization** of the adventitia



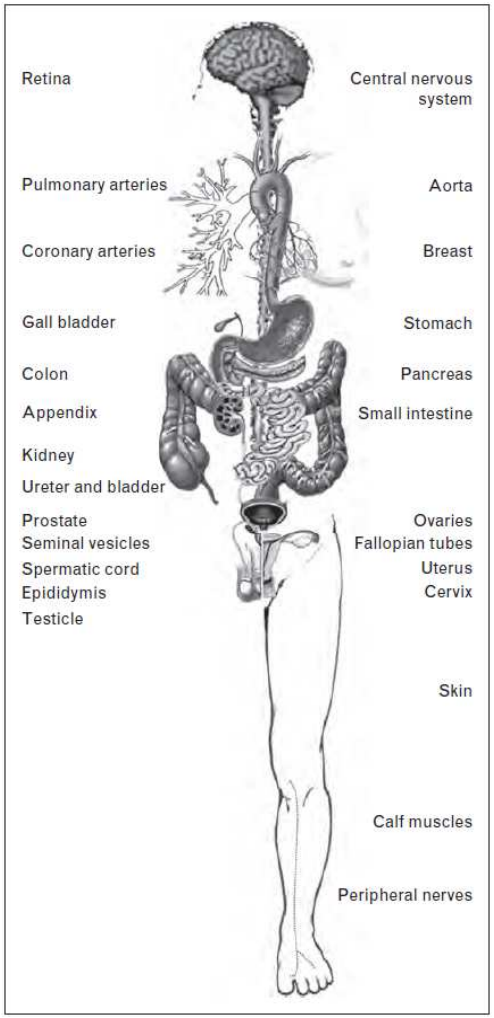
REVIEW

Updating single-organ vasculitis

José Hernández-Rodríguez[a] *and Gary S. Hoffman*[b]

KEY POINTS

- Single-organ vasculitis (SOV) is defined by vascular inflammation confined to an isolated organ and for which no signs of vasculitis beyond this focus emerges over a period of at least 6 months.
- SOV may involve territories in a diffuse/multifocal fashion (e.g. central nervous system and skin) or may be limited to single (focal) sites (e.g. gynecologic, testicular, and gastrointestinal structures, breasts, and the aorta).
- In focal forms of SOV, vasculitis is often unexpectedly found in surgical or biopsy procedures for other (unrelated) suspected processes, laboratory findings are usually normal, and surgical excision is frequently sufficient to achieve cure.
- SOV should be named/classified by organ affected and histological features (pattern of inflammation and vessel size involved).
- Long-term follow-up is warranted, because in rare cases with follow-up beyond 6 months vasculitis may evolve into a systemic disease.



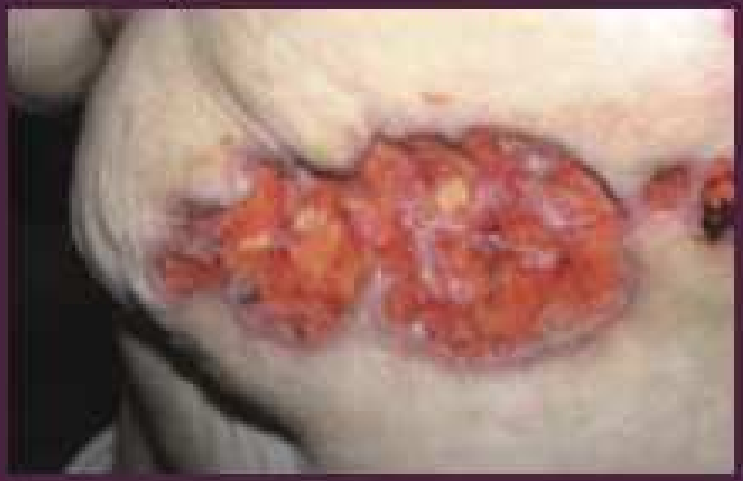
Vasculitis	Main clinical characteristics	ENT/URT manifestations
ANCA-associated vasculitides (small-sized vessels)		
Granulomatosis with polyangiitis (GPA; Wegener's granulomatosis)	• Three main target organs: ENT/URT, kidney (pauci-immune glomerulonephritis) and lungs (alveolar haemorrhage, parenchymal nodules) • Two forms: localized/limited/non-severe/early systemic/non-systemic GPA and systemic/severe/generalized GPA • Mainly associated with anti-PR3 C-ANCA	• Serous otitis media: recurrent and/or chronic, possibly evolving to mastoiditis • Middle-ear granulomatous lesions/tumours • Conductive hearing loss • Sensorineural hearing loss • Rhinitis: almost constant, with nasal obstruction, crusting and epistaxis • Sinusitis: sinus pain, frequently erosive (with bony erosion) and/or atrophic • Nasal and/or sinus mucosa granulomatous inflammation, tumour and/or ulcers • Anosmia/hyposmia • Nasal cartilage erosion: saddle nose deformity, septum perforation, fistula • Tongue ulcerations or infarctions • Gingiva ulcerations or strawberry-like hypertrophy • Sub-glottic stenosis
Churg–Strauss syndrome (eosinophilic granulomatosis with polyangiitis; EGPA)	• Prior history of pseudo-allergic sinus polyposis and/or late-onset asthma • Eosinophilia and eosinophilic tissue infiltration • Anti-MPO P-ANCA in up to 1/3 of patients • Cardiomyopathy: main factor of poor prognosis (more frequent in ANCA-negative patients)	• Pseudo-allergic rhinitis, possibly with some crusting or epistaxis • Nasal polyps • Anosmia or hyposmia • Sinusitis (non-erosive)
Microscopic polyangiitis (MPA)	• Target organs: lungs (alveolar haemorrhage) and kidneys (pauci-immune glomerulonephritis) • Mainly associated with antiMPO P-ANCA	• Non-specific rhinitis or sinusitis, in up to 1/3 of patients, not erosive

White Tail Spider

Alleged white tail spider bite

Case 4

A woman, 55 years of age, presented with a painful ulcer, increasing in size, on her left lower flank. It began as small, painful papule after the patient had spent the day gardening. A neighbour had said she heard that there were white tail spiders in the area.



Changes adjacent to vasculitis indicative of subtype or etiology

-**Lamellar or storiform fibrosis**

Erythema elevatum diutinum, granuloma faciale, or inflammatory pseudotumor

-**Palisading (necrotizing) granulomatous dermatitis** (‘‘Winkelmann granuloma’’)

-**‘‘Red’’ extravascular granuloma** (eosinophils, flame figures)

Churg-Strauss syndrome, rheumatoid nodules

-**‘‘Blue’’ extravascular granuloma** (neutrophils, nuclear dust)

Wegener granulomatosus, rheumatoid vasculitis, Churg-Strauss syndrome (rarely)

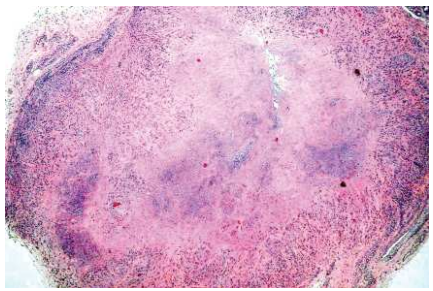
-**Vacuolar interface dermatitis** (sometimes dermal mucin deposition)

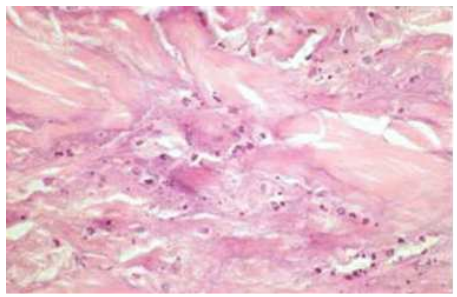
Connective tissue disease, for example, lupus erythematosus, dermatomyositis

-**‘‘Pustular’’ dermatosis with intraepidermal or subepidermal neutrophilic abscesses**

Infectious trigger

“RED”





“BLU”

1990 Criteria for the Classification of Takayasu Arteritis

Back To Classification Criteria

1. Age at disease onset < 40 years

Development of symptoms or findings related to Takayasu arteritis at age ≤40 years

2. Claudication of extremities

Development and worsening of fatigue and discomfort in muscles of 1 or more extremity while in use, especially the upper extremities

3. Decreased brachial artery pulse

Decreased pulsation of 1 or both brachial arteries

4. BP difference >10 mm Hg

Difference of >10 mm Hg in systolic blood pressure between arms

5. Bruit over subclavian arteries or aorta

Bruit audible on auscultation over 1 or both subclavian arteries or abdominal aorta

6. Arteriogram abnormality

Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lowe extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental

* For purposes of classification, a patient shall be said to ahve Takayasu arteritis if at least 3 of these 6 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 90.5% and a specificity of 97.8%. BP = blood pressure (systolic: difference between arms).

PAN

1. Weight loss ≥4 kg

Loss of 4 kg or more of body weight since illness began, not due to dieting or other factors

2. Livedo reticularis

Mottled reticular pattern over the skin or portions of the extremities or torso

3. Testicular pain or tenderness

Pain or tenderness of the testicles, not due to infection, trauma, or other causes

4. Myalgias, weakness or leg tenderness

Diffuse myalgias (excluding shoulder and hip girdle) or weakness of muscles or tenderness of leg muscles

5. Mononeuropathy or polyneuropathy

Development of mononeuropathy, multiple mononeuropathys, or polyneuropathy

6. Diastolic BP >90 mm Hg

Development of hypertension with diastolic BP higher than 90 mm Hg

7. Elevated BUN or creatinine

Elevation of BUN >40 mg/dl or creatinine >1.5 mg/dl, not due to dehydration or obstruction

8. Hepatitis B virus

Presenece of hepatitis B surface antigen or antibody in serum

9. Arteriographic abnormality

Arteriogram showing aneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibromuscular dysp
other noninflammatory causes

10. Biopsy of small or medium-sized artery containing PMN

Histologic changes showing the presence of granulocytes or granulocytes and mononuclear leukocytes in the artery

* For classification purposes, a patient shall be said to have polyarteritis nodosa if at least 3 of these 10 criteria are p
The presence of any 3 or more criteria yields a sensitivity of 82.2% and a specificicy of 86.6%. BP = blood pressure;
blood urea nitrogen; PMN = polymorphonuclear neutrophils.

*Lightfoot RW Jr, Michel BA, Bloch DA, Hunder GG, Zvaifler NJ, McShane DJ, et al. The American College of Rheum
1990 criteria for the classification of polyarteritis nodosa. Arthritis Rheum 1990;33:1088---93.*

WG

1. Nasal or oral inflammation
Development of painful or painless oral ulcers or purulent or bloody nasal discharge
2. Abnormal chest radiograph
Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities
3. Urinary sediment
Microhematuria (>5 red blood cells per high power field) or red cell casts in urine sediment
4. Granulomatous inflammation on biopsy
Histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole)

* For purposes of classification, a patient shall be said to have Wegener's granulomatosis if at least 2 of these 4 criteria are present. The presence of any 2 or more criteria yields a sensitivity of 88.2% and a specificity of 92.0%
Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33:1101---7.

1990 Criteria for the Classification of Churg-Strauss Syndrome (Traditional Format), Their Sensitivity And Specificity Versus Other Defined Vasculitis Syndromes

Asthma
Eosinophilia >10%
Neuropathy, mono or poly
Pulmonary infiltrates, non-fixed
Paranasal sinus abnormality
Extravascular eosinophils

* For classification purposes, a patient shall be said to have Churg-Strauss syndrome (CSS) if at least 4 of these 6 criteria are positive. The presence of any 4 or more of the 6 criteria yields a sensitivity of 85% and a specificity of 99.7%. (See Table 3 for criteria definitions.)
Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094---100.