AFECCIÓN PULMONAR EN LAS VASCULITIS ANCA +

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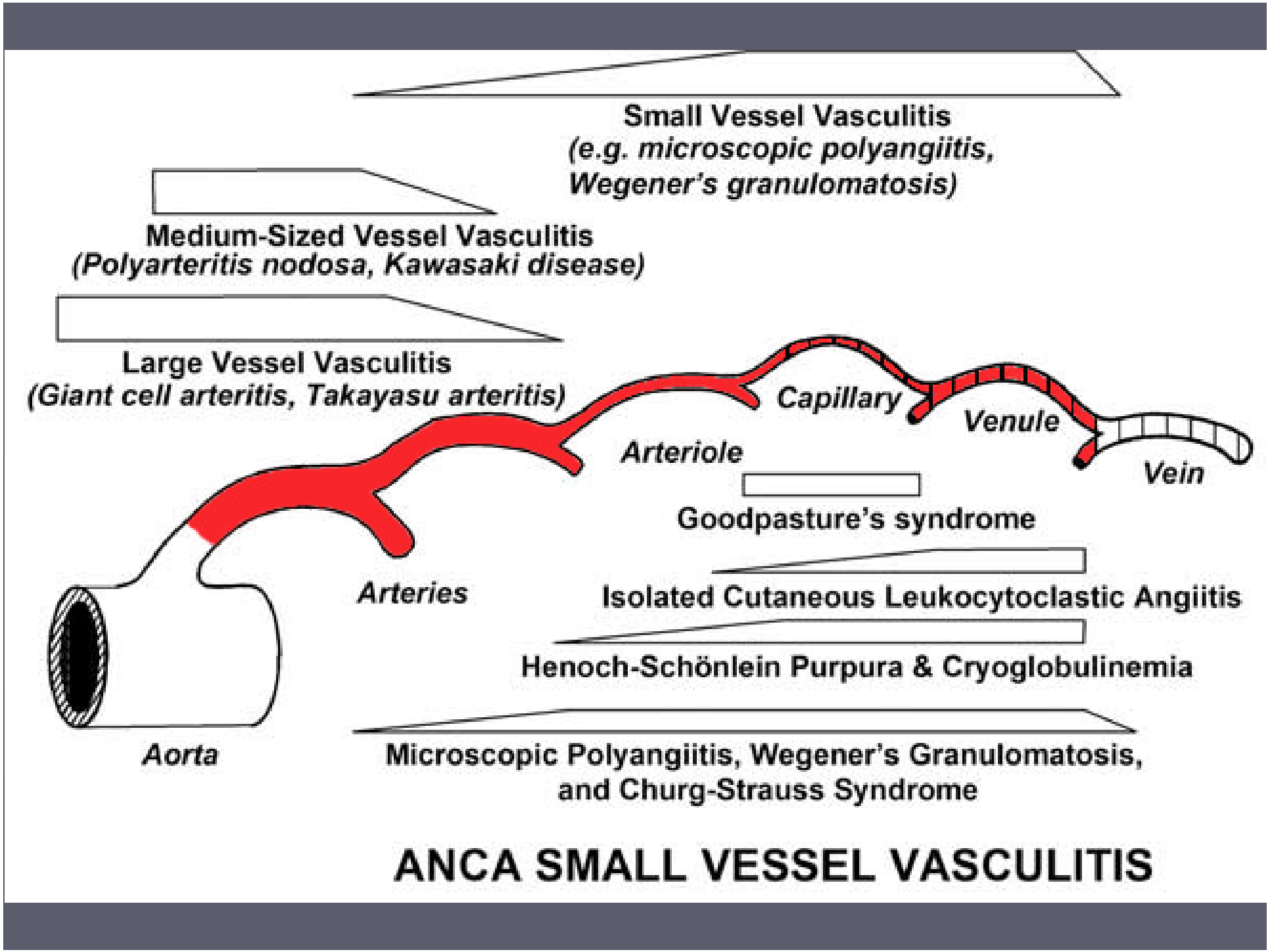
ANCA

- Anticuerpos IgG contra proteínas de los gránulos primarios de los neutrófilos.
- Antígenos detectados: MPO, PR3, elastasa, lactoferrina, catepsina G...
- Clínicamente relevantes: PR3-ANCA, MPO-ANCA; patogenéticos
- “Vasculitis asociadas a ANCA”: GW, PAM y Síndrome de Churg-Strauss

MÉTODOS DE DETECCIÓN

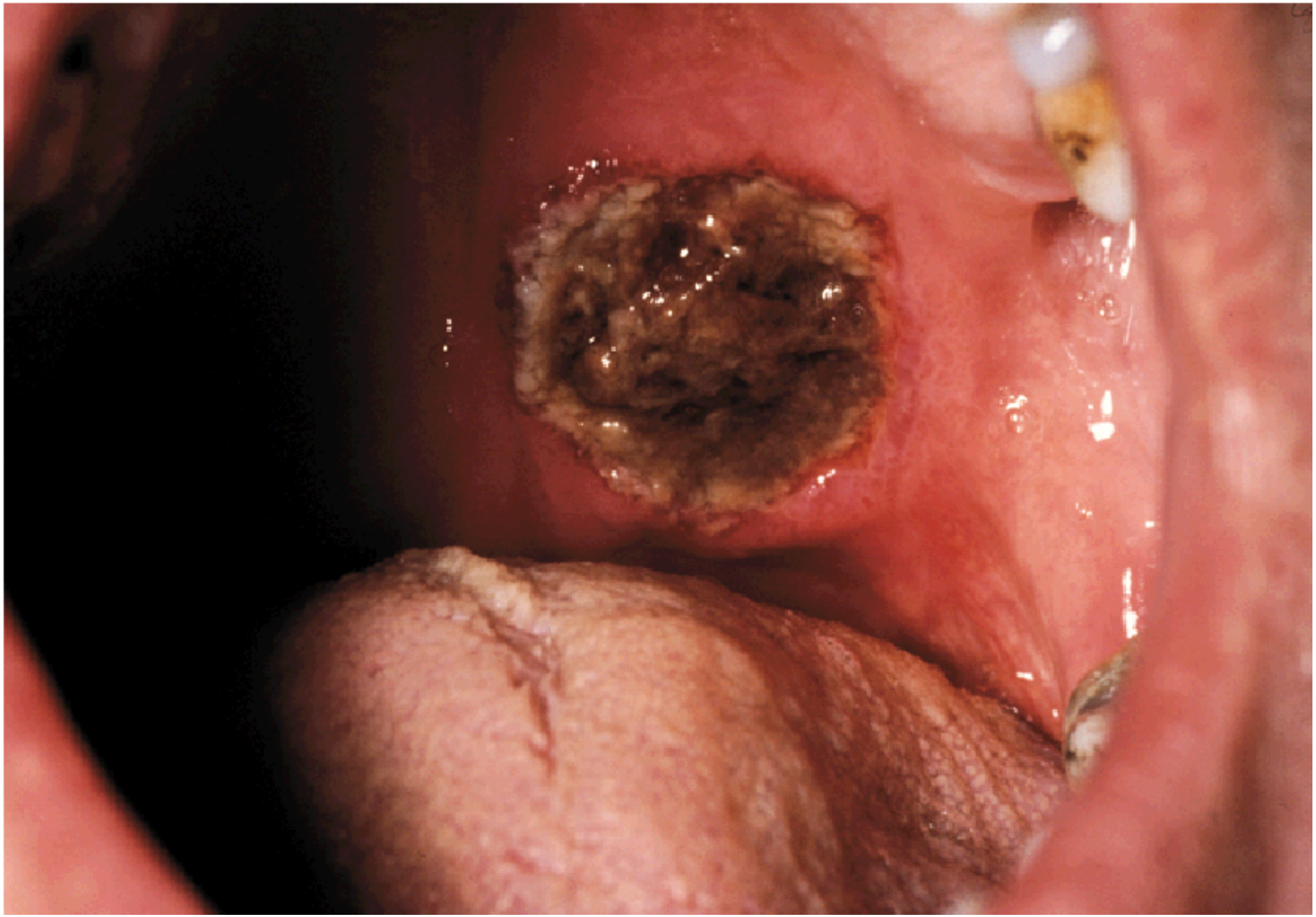
- Realizar ambas técnicas
- Combinación del resultados positivo de ambas pruebas (p.e., C-ANCA + PR3 ANCA)
- S = 70%, E = 99% para VAA



ANCA SMALL VESSEL VASCULITIS

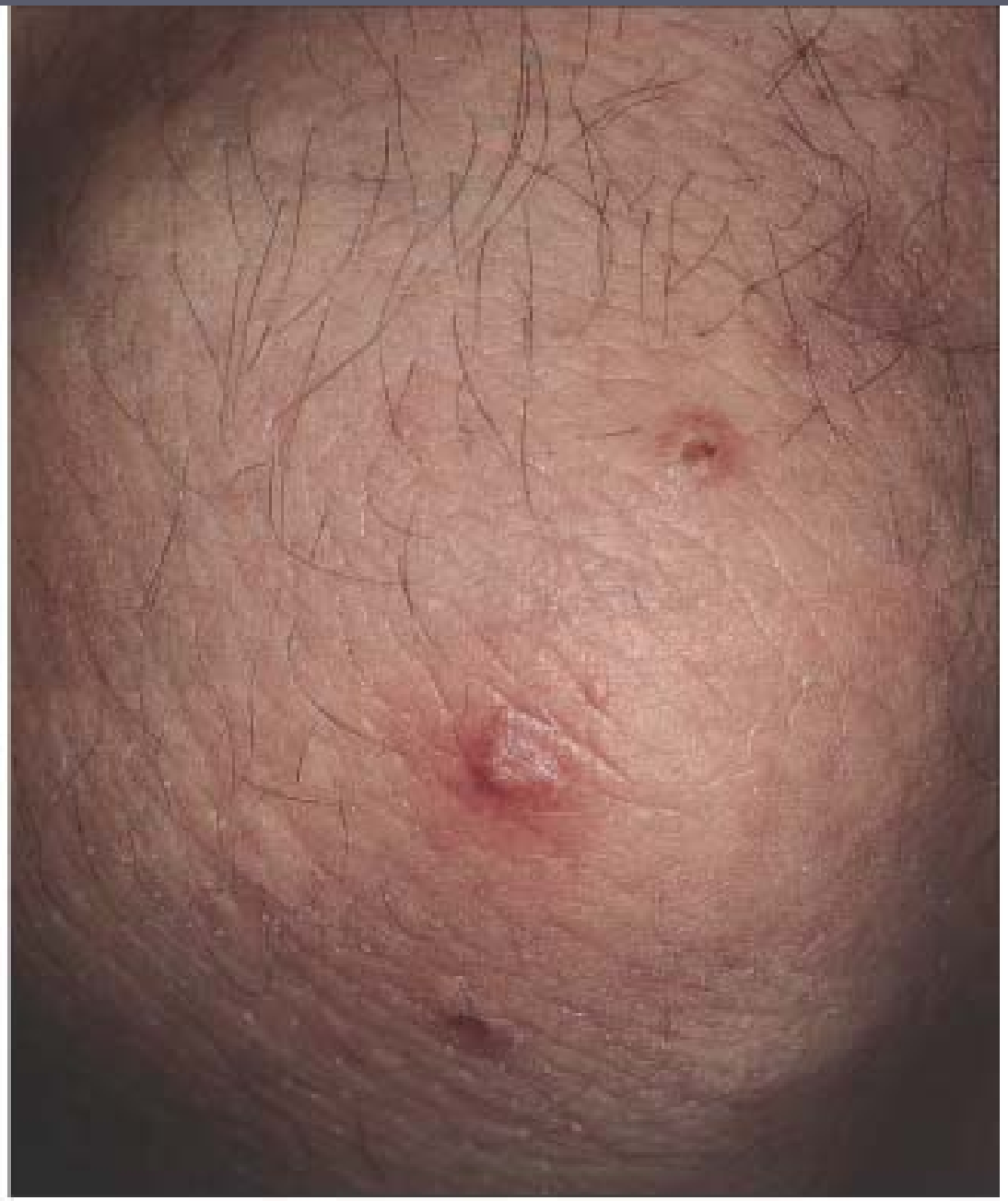
GRANULOMATOSIS DE WEGENER

- Tracto respiratorio (granulomas ☺)
- GNF necrotizante pauci-inmune 80%
- Capilaritis alveolar
- Piel, SNP, Intestino, Ojo
- C-ANCA + PR3 = 70-80%
- P-ANCA + MPO = 10%
- Forma limitada: ANCA 60%



POLIANGEITIS MICROSCOPICA

- Sintomas sistémicos previos al brote “explosivo”
- GNF necrotizante pauci-inmune 90%
- Capilaritis alveolar 50%
- Púrpura palpable 46% al inicio
- P-ANCA + MPO = 60%
- C-ANCA + PR3 =30%



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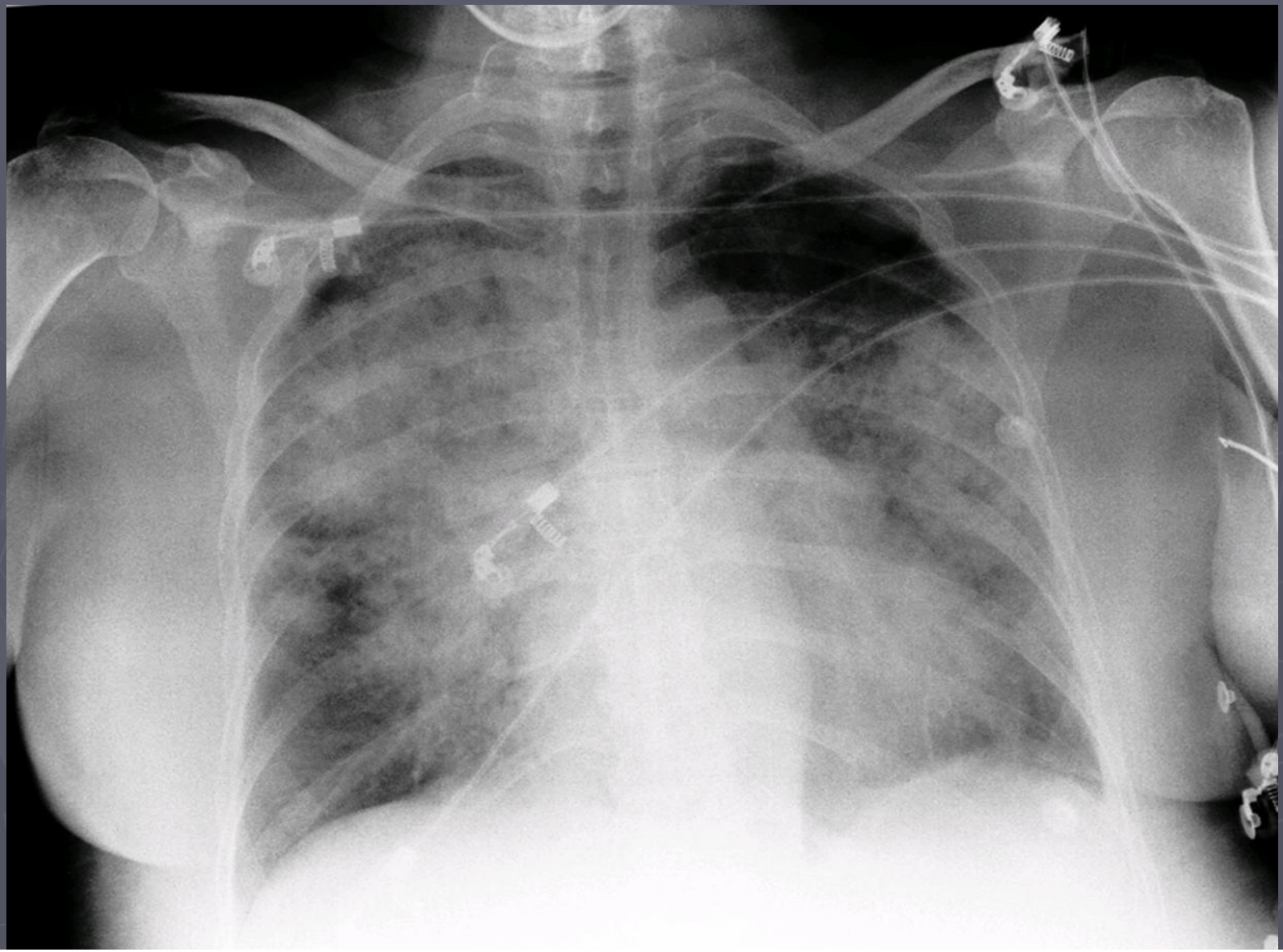

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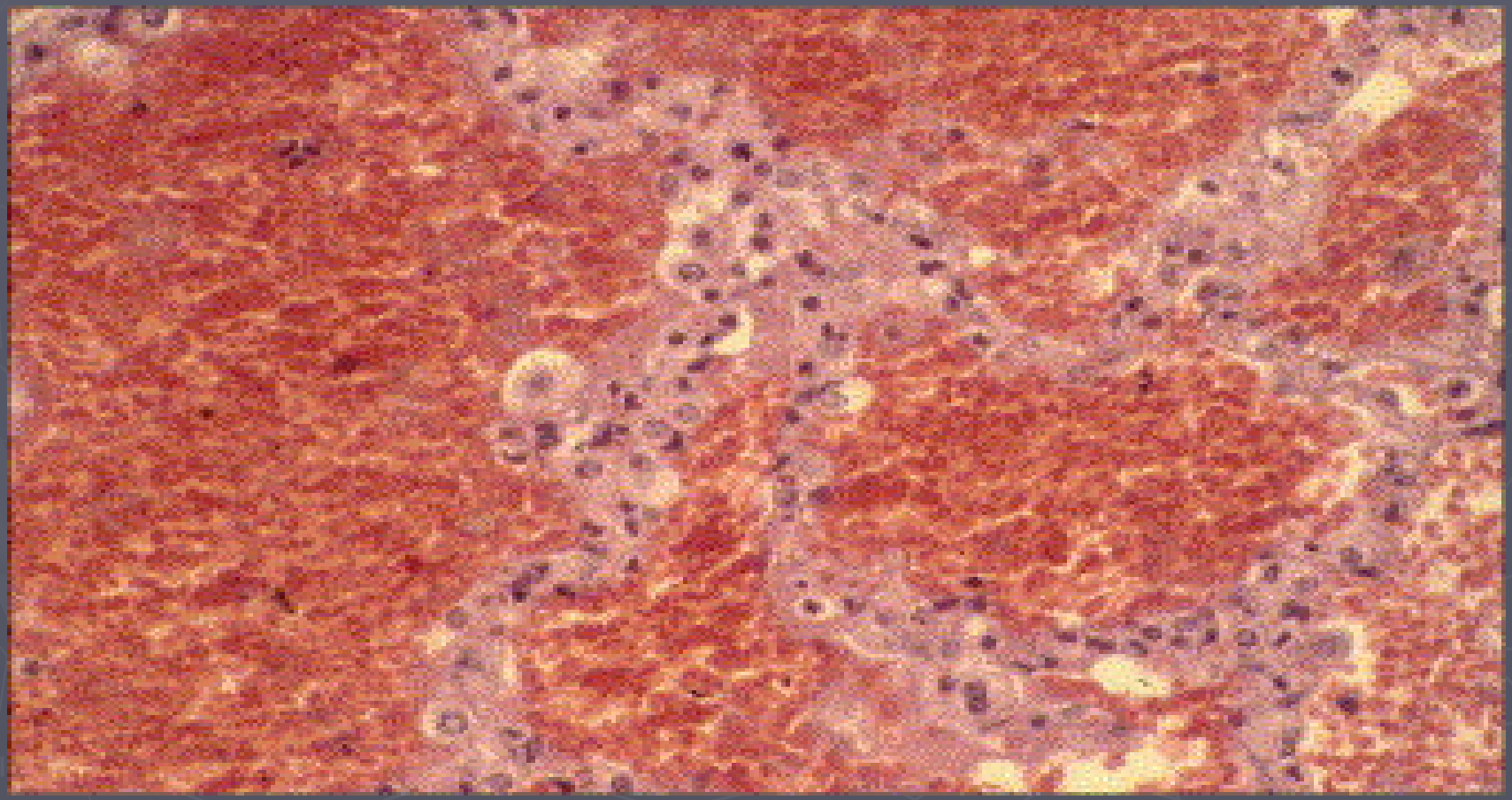

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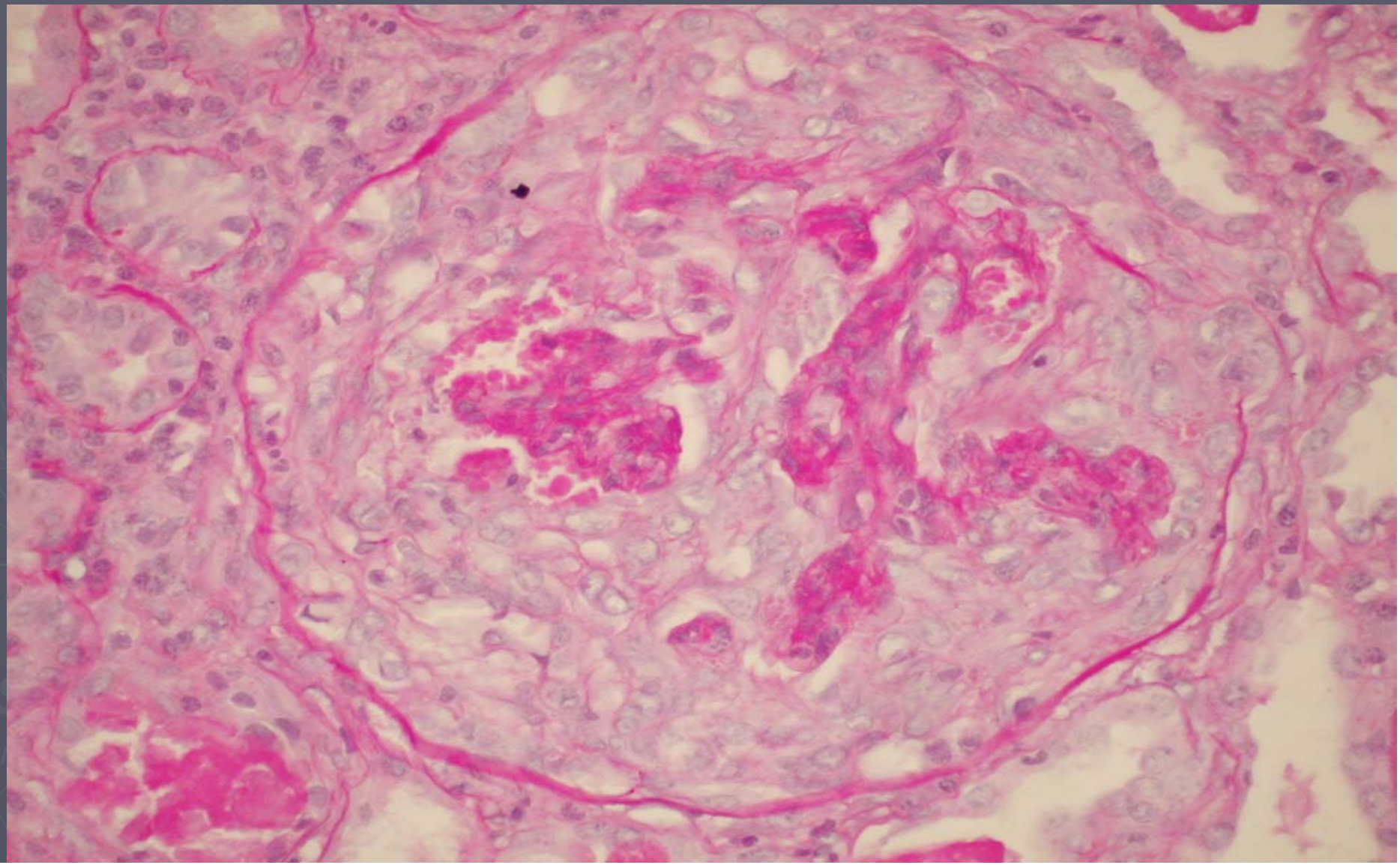


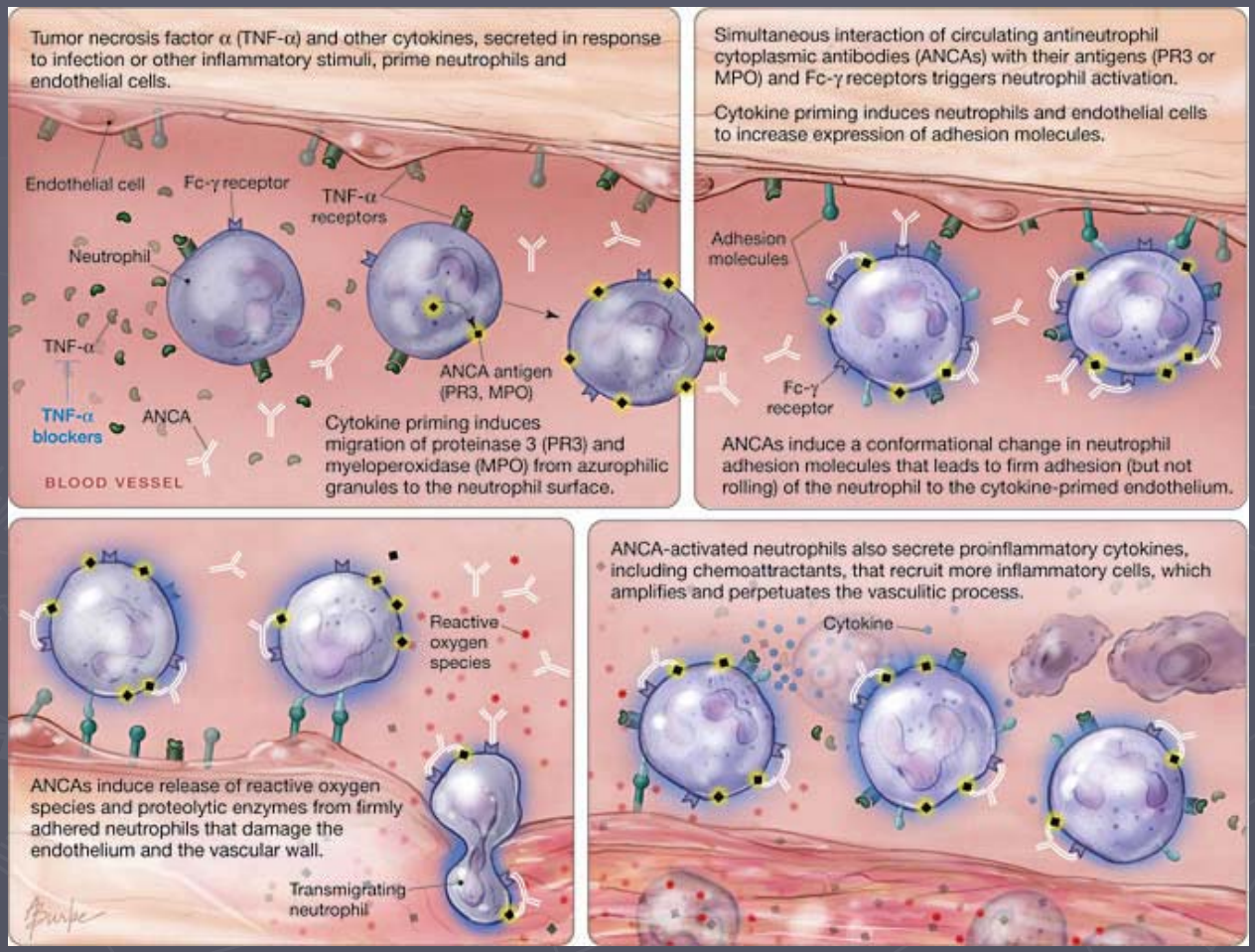
SÍNDROME DE CHURG-STRAUSS

- Asma tardío
- Eosinofilia, neumonías eosinofílicas
- Vasculitis sistémica con granulomas ricos en eosinófilos en tracto respiratorio
- Inflamación granulomatosa del miocardio
- Mononeuritis múltiple
- < GNF y capilaritis pulmonar que PAM y GW
- PR3-ANCA 30%; MPO-ANCA 30%

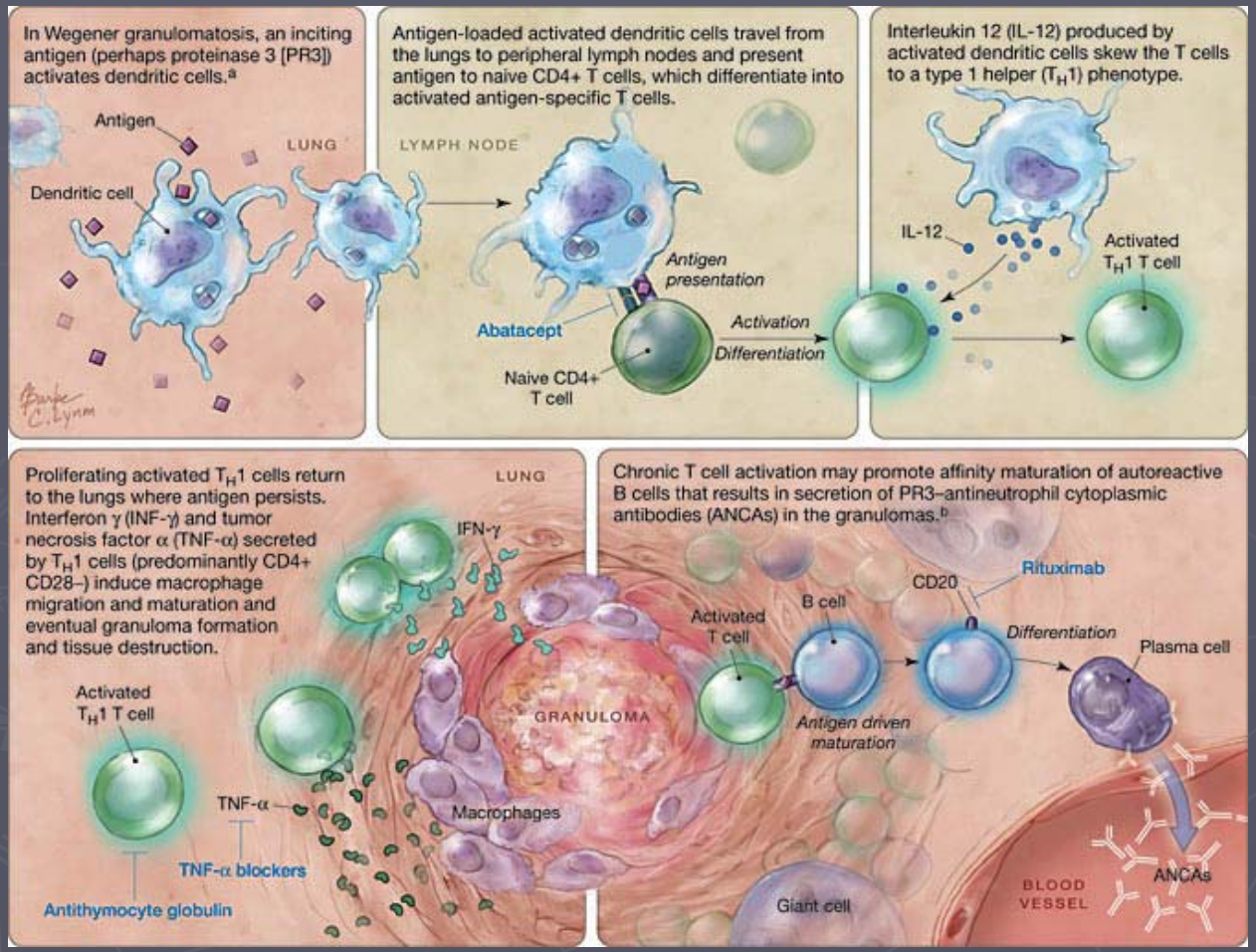
PATOGENIA

- ANCA can stimulate respiratory bursts in neutrophils to trigger the release of primary granule constituents (Falk et al., 1990).
- *In vitro* studies: ANCA can cause vascular damage by inducing a wide range of neutrophil effector functions such as release of cytokines and chemokines, and can adhere to cultured endothelial cells to cause their lysis.
- 2002: Xiao et al: murine anti-myeloperoxidase (MPO) IgG to Rag2−/−mice (which lack functioning T and B lymphocytes) and resulted in the development of focal necrotizing glomerulonephritis (FNGN) without immune deposits (indistinguishable from human ANCA-associated glomerulonephritis).

DAÑO VASCULAR



Inflam. Granulomatosa



PATOGENIA: PR3

- Pathogenic potential of ANCA against PR3 remains unproven, and these antibodies have not reproduced the typical granulomata or vasculitic lesions in any animal model

- PR3-directed autoimmunity involves the complementary peptide of PR3, which is encoded by the antisense strand of the PR3 gene. Exposure of the immune system to this peptide triggers the formation of antibodies that cross-react with PR3:

  - DNA sequences complementary to the PR3 gene have been identified in microorganisms including *Staphylococcus aureus*, which supports the role of infectious agents as triggers of PR3 autoimmunity via molecular mimicry

PATOGENIA: LINK INFECCIOSO

- Kain et al (2009) provided a novel molecular explanation for the origin and development of pauci-immune FNGN:

- Infection by fimbriated bacteria can trigger cross reactive autoimmunity to LAMP-2, which results in the production of autoantibodies that activate neutrophils and damage human microvascular endothelium *in vitro* and cause pauci-immune FNGN in rats.

S. de CHURG-STRAUSS

- Activation of Th1/Th2 lymphocytes, eosinophils (whose levels correlate with disease activity), the release of toxic products, and MPO-ANCA are therefore the main pathogenic factors in the CSS spectrum and apparently predominate in different phenotypes of the disease.

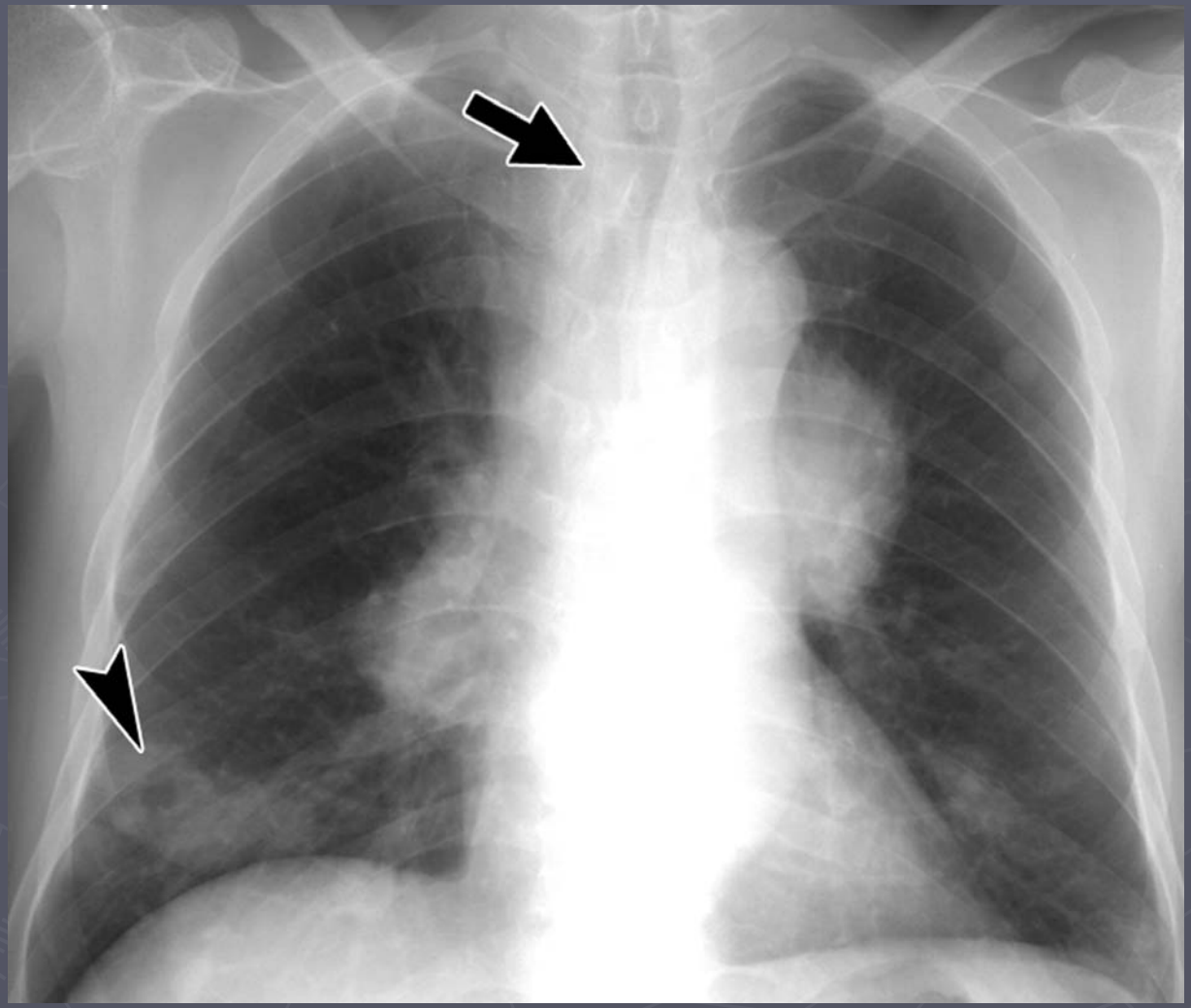
FORMAS CLINICAS DE AFECCIÓN PULMONAR

Condition	Abnormality
NGV	
Otorhinolaryngologic	Endobronchial granulomatous inflammation;
	Granulomatous nasal or paranasal inflammation; and
	Subglottic stenosis
Pulmonary	Symptomatic and asymptomatic pulmonary nodules and infiltrates;
	Pleuritis and pleural effusion;
	Pulmonary arterial hypertension; and
	Pulmonary fibrosis
MPA	
Pulmonary	Symptomatic and asymptomatic pulmonary infiltrates;
	Pleuritis and pleural effusion;
	Pulmonary hemorrhage and alveolitis;
	Pulmonary fibrosis; and
	Pulmonary arterial hypertension
CSS	
Otorhinolaryngologic	Allergic rhinitis;
	Nasal polyposis and obstruction; and
	Recurrent sinusitis
Pulmonary	Asthma; and
	Infiltrates and nodules

Granulomatosis Wegener

- Limitada a TRS o pulmones en 25% casos
- Afección traqueobronquial: exclusiva de GW
- Nodulos o infiltrados pulmonares: 85% casos
- HPD: 5% casos

ANCA-associated granulomatous vasculitis in 57-year-old man.



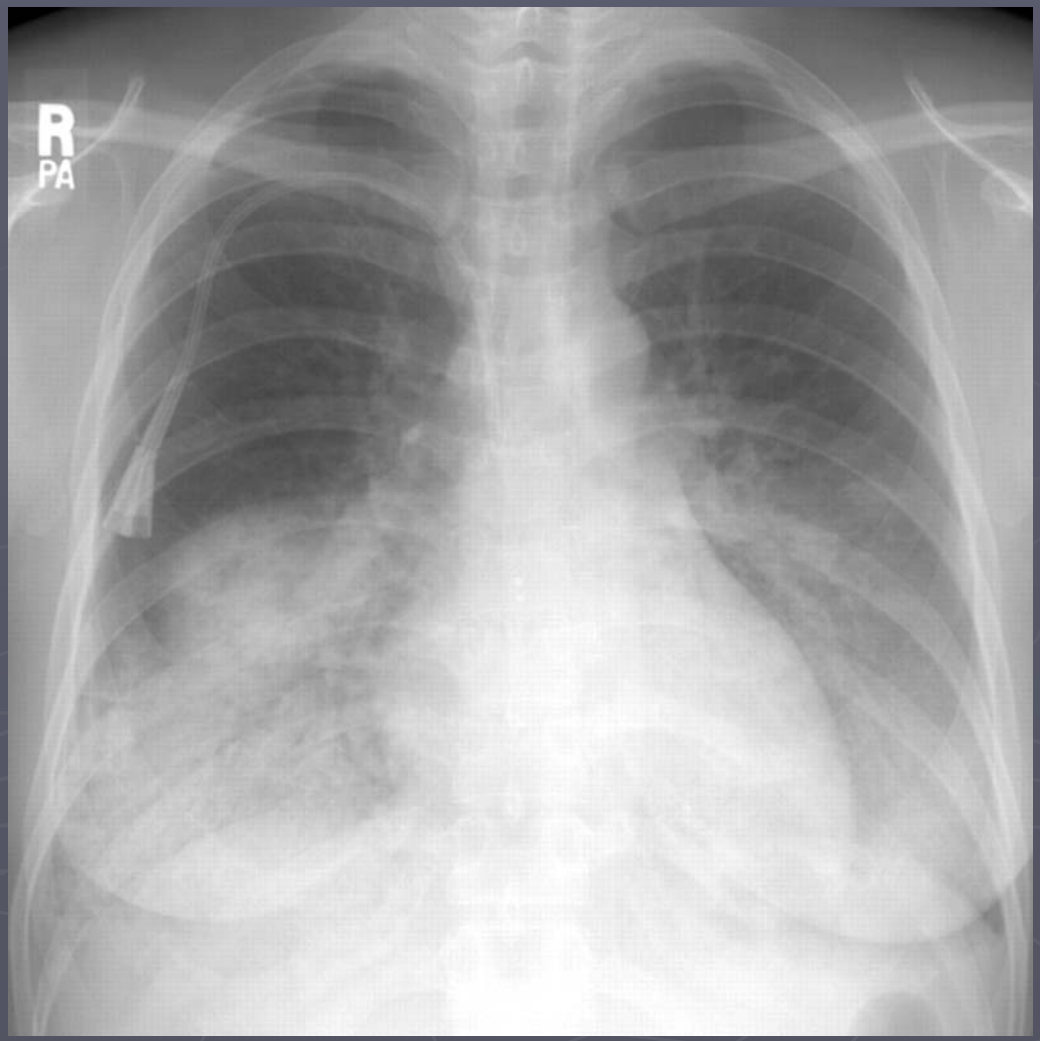
Chung M P et al. Radiology 2010;255:322-341

Radiology

PAM

- HAD: 25-55% casos
- Episodios repetidos de HAD: afección pulmonar intersticial = FPD

Microscopic polyangiitis in 33-year-old woman.



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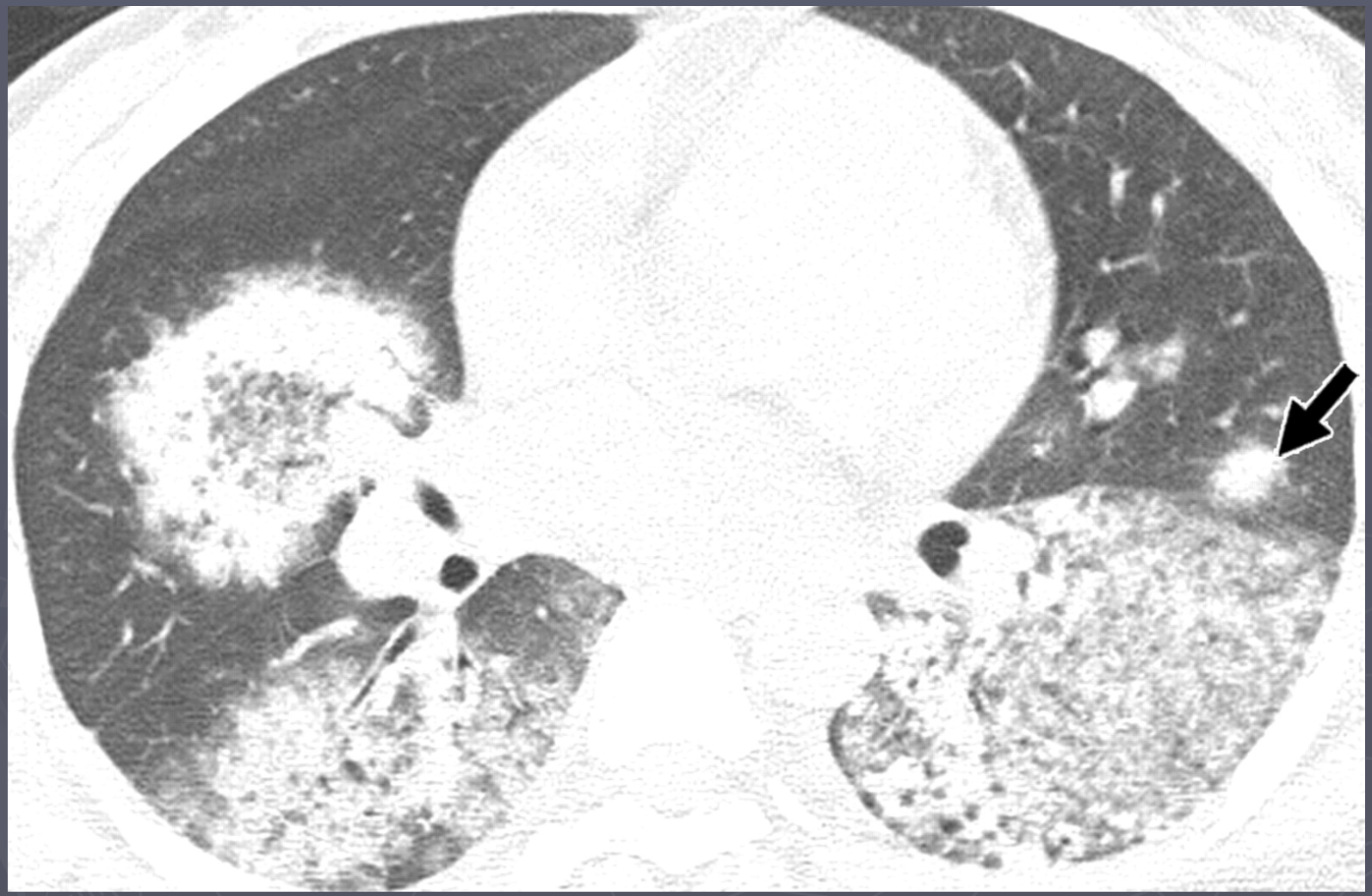

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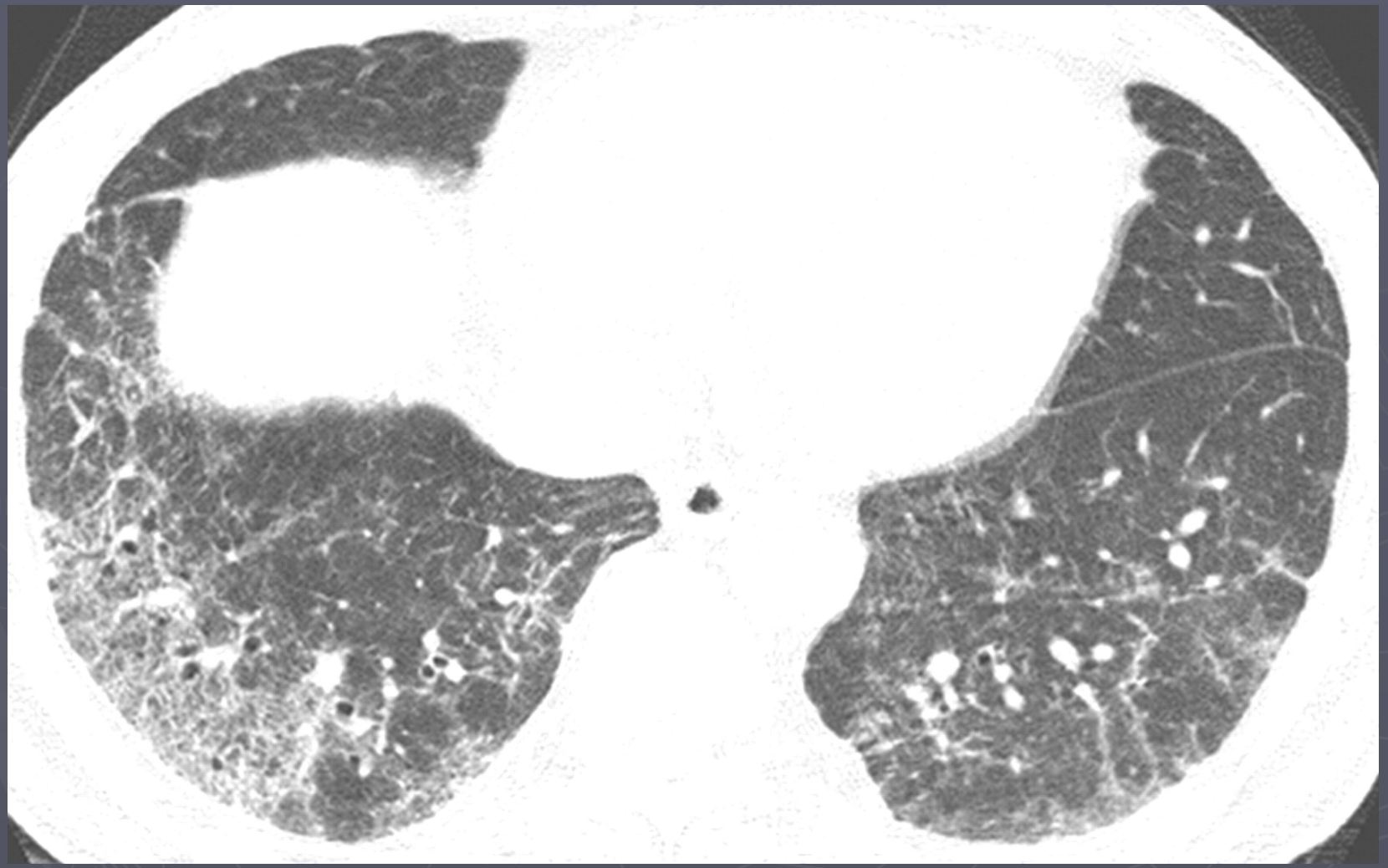
Radiology

Microscopic polyangiitis simulating interstitial pulmonary fibrosis due to repeated alveolar hemorrhage in 60-year-old man.



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Radiology

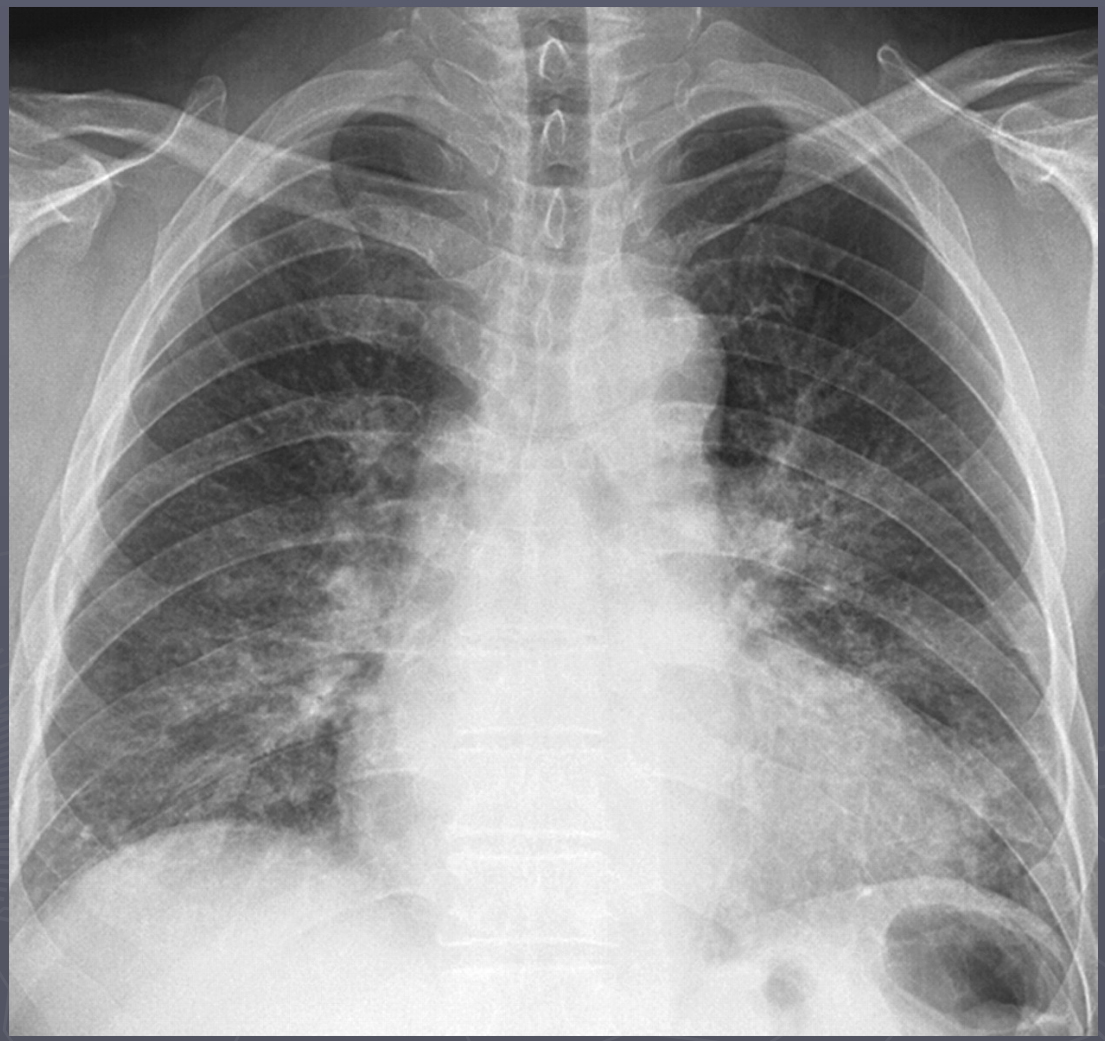
Sindrome de Churg-Strauss

- Infiltrados transitorios: 38-77% casos
- Nódulos pulmonares en TACAR: 63% casos
- Asma: 95% casos y antes de vasculitis (3-4 años)

Síndrome de Churg-Strauss

- Obstrucción nasal, sinusitis recurrente y poliposis nasal
- Tratamiento prolongado del asma con cortocioides puede enmascarar la forma completa

CSS in 63-year-old woman.



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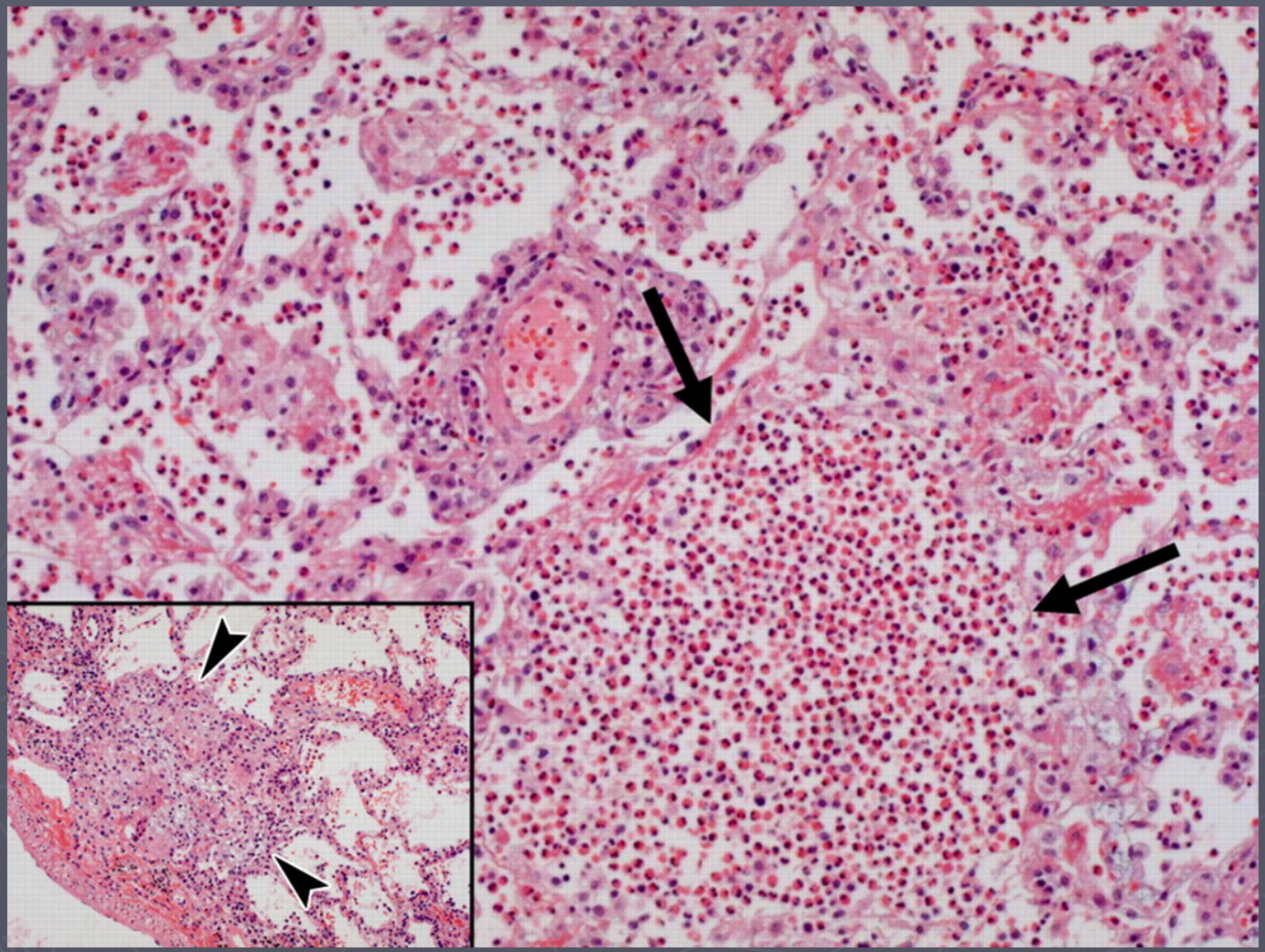

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Radiology

Funcionalismo Pulmonar

- Patrón restrictivo (afección intersticial difusa) y obstructivo (formas traqueobronquiales de GW y S. Churg-Strauss)
- Más frecuente: Reducción de la capacidad de difusión de CO. Pero puede aumentar notablemente en casos de HAD

Pronóstico de las complicaciones pulmonares

- PAM: elevada mortalidad en el primer año sin tratamiento.
- GW: mortalidad en función de la presentación
- Empleo de esteroides e IS: 90% remisión en 6 meses
- Recidiva: 50% casos
- 10% pacientes: refractarios a tto. IS

Pronóstico de las complicaciones pulmonares

- Factores asociados a elevada mortalidad:

- Más de 60 años
- Afección pulmonar y renal simultáneas
- Afección cardiaca en el S. Churg-Strauss
- Mayor índice de actividad de la enfermedad

Pronóstico de las complicaciones pulmonares

- Pagnoux et al (Arthritis Rheum 2008):

- Dos cohortes de pacientes USA y Francia
- Edad=predictivo de resistencia terapeutica
- PR3-ANCA y afección pulmonar=predictivos de recidiva

Pronóstico de las complicaciones pulmonares

- Chen et al (Medicine 2008):

- Infecciones pulmonares y edad: factores predictivos independientes de muerte en 234 pacientes

Pronóstico de las complicaciones pulmonares

- HAD: principal causa de hospitalización e ingreso en UCI en pacientes con vasculitis ANCA + con afección pulmonar
- Holguin et al (Am J Med Sci 2008):

- 65 pacientes con HAD
- Insuf. Respiratoria, hemoptisis, tabaquismo e IRA=predictivos de ingreso en UCI

Pronóstico de las complicaciones pulmonares

- Khan et al (Chest 2007):

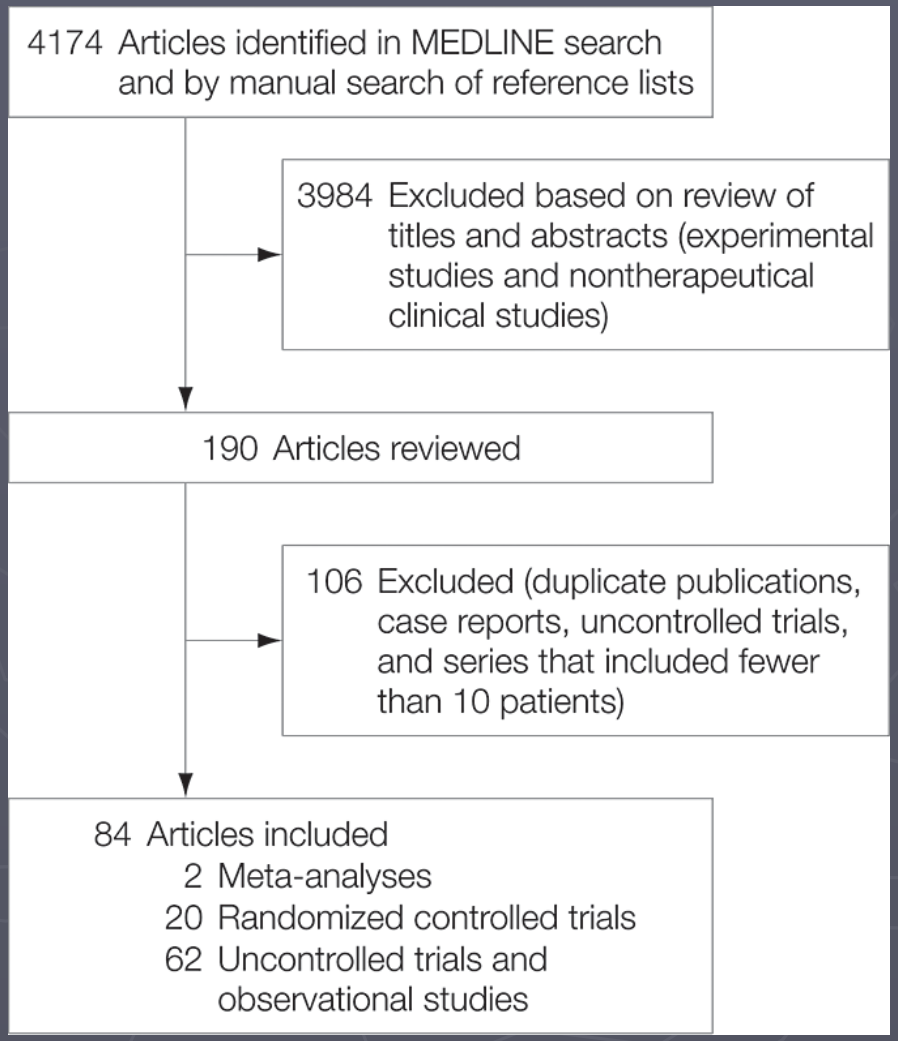
- 38 pacientes con formas graves de vasculitis ANCA + en que la HAD fue el factor principal de ingreso en UCI
- Mortalidad a los 28 dias: 11% (shock séptico)

TRATAMIENTO

- Grupo EUVAS:

- Diferentes subgrupos de pacientes según localización y severidad de las AAV (PAM y GW)
- Diferentes revisiones sistemáticas (pronóstico, tratamiento, ...)

Process for Study Inclusion



Bosch, X. et al. JAMA 2007; 298:655-669

Localized Disease

- Patients with symptoms restricted to the upper and/or lower airways, without constitutional symptoms or systemic vasculitis

Localized Disease

- **Remission Induction and Maintenance**

* RECOMMENDATION : Owing to its favorable response rates and the favorable adverse-effect profile: use cotrimoxazole alone or in combination with corticosteroids

Generalized Non–Organ-Threatening Disease (Early Systemic Disease)

- EUVAS: patients with localized WG with constitutional symptoms or with multifocal WG or MPA without threatened organ function
- Serum creatinine levels must be lower than 1.7 mg/dL (other authors: lower than 2.5 mg/dL)
- Possible lung involvement, but PO2 higher than 70 mm Hg and DLCO more than 70%

Generalized Non–Organ-Threatening Disease (Early Systemic Disease)

- **Remission Induction**

* RECOMMENDATION: To induce remission, methotrexate plus corticosteroids can be used instead of cyclophosphamide. When methotrexate is used as maintenance therapy, the likelihood of relapses is high: rigorous monitoring for early detection

Generalized Non–Organ-Threatening Disease (Early Systemic Disease)

- **Remission Maintenance**

***Azathioprine**-63 pat- (2.0 mg per kilogram per day) vs. **Methotrexate**-63 pat- (0.3 mg per kilogram per week initially and progressively increased every week by 2.5 mg, to 25 mg per week). Duration: 12 months:

23 patients who received azathioprine and 21 pat who received methotrexate had a relapse (P=0.71)

Adverse events: 29 AZA vs 35 MTX (P=0.29)

Pagnoux et al (NEJM 2008;359:2790-2803)

Generalized Organ-Threatening Disease (Generalized Disease)

- EUVAS: WG or MPA with constitutional symptoms, threatened organ function, and serum creatinine levels lower than 5.7 mg/dL

Generalized Organ-Threatening Disease (Generalized Disease)

- **Remission Induction:** Pulse cyclophosphamide with oral corticosteroids can be used to induce remission

  * **Scheme**: Start with 1 mg/kg per day of oral prednisone plus 0.6 to 0.7 g/m2 (15 mg/kg; maximal dose: 1 g/m2) IV pulse cyclophosphamide (every 3 weeks for 6 months). Prednisone should be tapered to 10 mg by 6 months and maintained at this dose until month 15, when it should be tapered to 7.5 mg and maintained for at least 3 more months followed by local practice.

Generalized Organ-Threatening Disease (Generalized Disease)

- **Remission Induction** (Ann Intern Med 2009;150:670-680):

* The pulse cyclophosphamide regimen induced remission of ANCA-associated vasculitis as well as the daily oral regimen
  at a reduced cumulative cyclophosphamide dose and caused fewer cases of leukopenia.

Generalized Organ-Threatening Disease (Generalized Disease)

- **Remission induction**: trial **RAVE:**

- RTX (375 mg/m2 administered intravenously once weekly for 4 weeks), compared to cyclophosphamide (2 mg/kg per day administered orally), in inducing disease remission in patients with severe AA V.

* A 6-month induction of remission phase was followed by 12-month remission maintenance therapy.

* All patients received 1-3 g of methylprednisolone intravenously and 1 mg/kg per day of prednisone administered orally.

* 99 pat (64%) (RTX) and 98 pat (55%) (CYC): achieved the primary outcome of disease remission with no prednisone therapy at month 6 (the difference was not significant) .

Generalized Organ-Threatening Disease (Generalized Disease)

- **Remission Maintenance**: combination of azathioprine and daily prednisone effectively maintains remission

  *__Scheme__: 2 mg/Kg of azathioprine should be started when cyclophosphamide is discontinued. At 6 months it should be reduced to 1.5 mg/kg per day and maintained for at least 6 more months

  *Useful alternatives: leflunomide and mycophenolate mofetil

Generalized Organ-Threatening Disease (Generalized Disease)

- **Remission maintenance** (N Engl J Med 2008;359:2790-803):

- Once remission was achieved: oral azathioprine (63 pat.) (at a dose of 2.0 mg per kilogram of body weight per day) or methotrexate (63 pat.) (at a dose of 0.3 mg per kilogram per week, progressively increased to 25 mg per week) for 12 months.

* **Primary end point**: adverse event requiring discontinuation of the study drug: 7 AZA and 12 MET.

* **Conclusion**: The two agents are similar alternatives for maintenance therapy

Severe Renal Vasculitis and Immediately Life-Threatening Disease

- Constitutional symptoms plus vital organ failure plus creatinine > 5.7 + pO2 < 70 mmHg
- Patients with rapidly progressive renal failure with and without diffuse alveolar hemorrhage have traditionally received a greater immunosuppressive load such as daily pulses of methylprednisolone (1 g) and IV cyclophosphamide (3-4 mg/kg per day) over brief periods. However, the evidence supporting this practice is scarce

Severe Renal Vasculitis and Immediately Life-Threatening Disease

- Despite use of immunosuppressants, only 50% of patients presenting with advanced renal failure maintain independent renal function at 1 year

Severe Renal Vasculitis and Immediately Life-Threatening Disease

- **Jayne et al**: 137 patients with severe renal vasculitis (serum creatinine >5.7 mg/dL) were randomly assigned to undergo plasma exchange (7) or receive pulsed methylprednisolone (3 g).

- Primary end point was dialysis independence at 3 mo.

- Two-thirds of these patients were dialysis-dependent on presentation. All patients were treated with the standard remission induction regimen (oral CYC and PDNSLN)

Severe Renal Vasculitis and Immediately Life-Threatening Disease

- Jayne et al (cont.):
- recovery of independent renal function at 3 months was significantly higher in the plasma exchange group (69% vs 49%)

  CONCLUSION: plasma exchange is, at present, the best complement to immunosuppressants in advanced renal disease

*** The role of intravenous methylprednisolone in addition to plasma exchange for this indication and the role of plasma exchange for other severe vasculitic manifestations, such as diffuse alveolar hemorrhage, requires further study

Tratamiento Estenosis Subglótica

- Inicio reciente: Tto de enfermedad localizada
- Enfermedad traqueo-bronquial grave: corticoides y ciclofosfamida sistémicos y traqueostomia en algunos casos

Tratamiento Estenosis Subglotica

- Hoffman et al (J Rheumatol 2003):

  - Procedimientos locales (iny de metilprednisolona intralesional y dilataciones mecánicas o con balón): no necesidad de más traqueostomias en estos pacientes

SÍNDROME DE CHURG-STRAUSS

Score de 5 factores para predecir la mortalidad en los pacientes con síndrome de Churg-Strauss:

- Insuficiencia renal (creatinina > 1,58 mg/dl)
- Proteinuria > 1 gr/dia
- Sangrado gastrointestinal, perforación, infarto intestinal y/o pancreatitis
- Afectación del sistema nervioso central
- Miocardiopatía

Se otorga 1 punto por cada factor presente. Se definen tres tipos de scores:

0, cuando no se observa ningún factor

1, cuando 1 factor está presente

2, cuando 2 o mas factores están presentes

SÍNDROME DE CHURG-STRAUSS

* RECOMMENDATION:

Start high doses of corticosteroids (1 mg/kg per day), tapering them when the patient improves. In patients with a 5-factors score equal to or greater than 1 or when corticosteroids fail, cyclophosphamide should be introduced to induce remission, which may be maintained with another less toxic drug.

FUTURE DIRECTIONS

- The agents that have accumulated the highest evidence are not as effective and safe as would be desirable
- Research should focus on clarifying and consolidating the evidence for new immunosuppressants and those biological agents that have been initially successful (rituximab and infliximab).

FUTURE DIRECTIONS

- High-quality, comparable evidence requires studies following homogeneous guidelines. Definitions of disease activity (eg, remission, relapse), disease states (eg, localized, early systemic), and treatment protocols (eg, same regimen of corticosteroids tapering) should be systematic and consistent.

TERAPIA FUTURA

- Bloquear otras citoquinas diferentes a TNF-α
- Interferir la relación entre el neutrófilo y el endotelio (moléculas de adhesión)
- Modular señales intracelulares