Small Vessel Vasculitis

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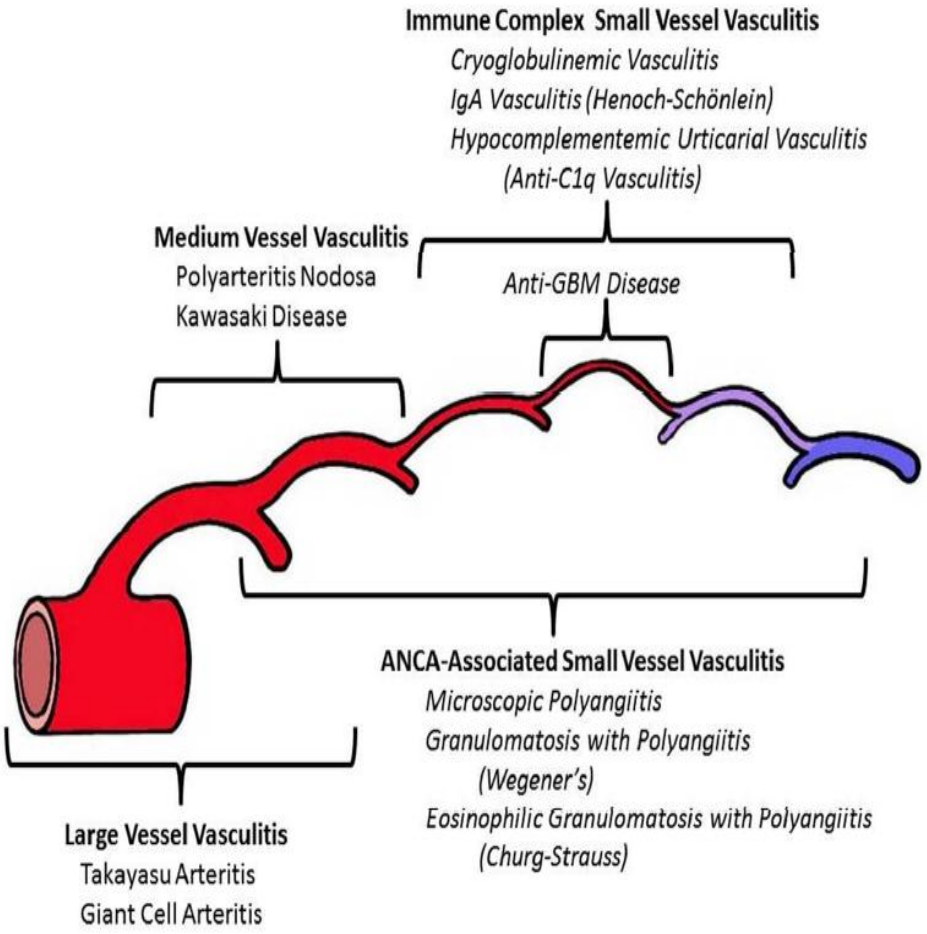
Chapel Hill Consensus definitions of vasculitis 2012



Jennette et al Arthritis Rheum. 2013 Jan; 65(1):1-11

Overview

- HSP (IgA Vasculitis)
- ANCA associated vasculitides (AAV)

HSP
IgA Vasculitis

HSP classification criteria [Ozen S et al 2010, Ann Rheum Dis. 2010;69:798-806.]

Purpura, predominantly lower limb OR diffuse* (mandatory) PLUS 1 out of 4 of:

1. abdo pain
2. IgA on biopsy
3. haematuria/proteinuria
4. arthritis/arthralgia

– *If diffuse (ie atypical distribution) then IgA deposition on biopsy required

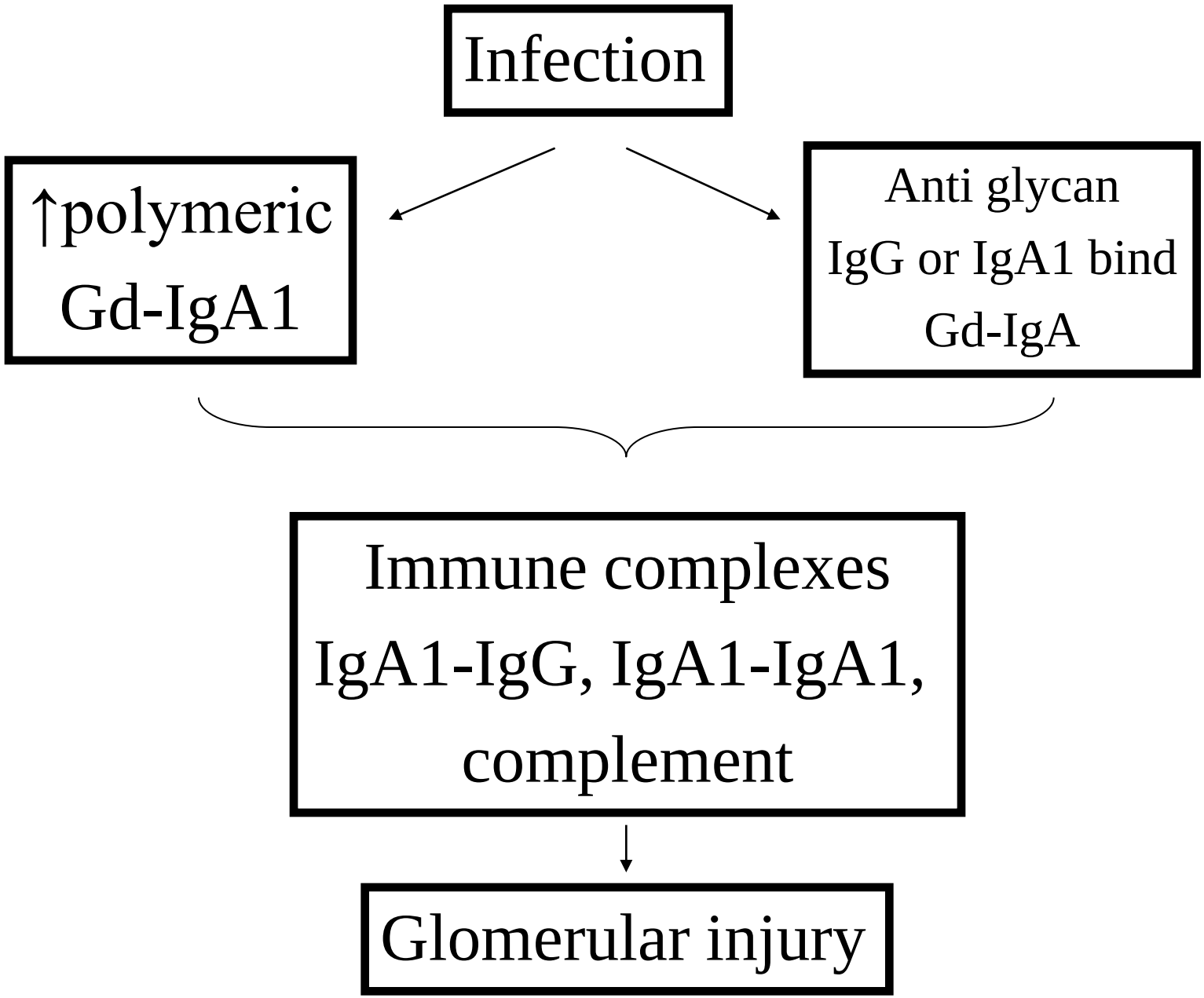
Sn 100% Sp 87%

Epidemiology: UK

- Incidence is estimated at 20.4 per 100,000 children in the UK
  - Indian subcontinent: 24 per 100, 000
  - White Caucasians: 17.8 per 100,000
  - Afro-Caribbean: 6.2 per 100,000
- Peak onset age 4 to 5 years of age, M>F
- Higher incidence during winter and the early spring

Pathogenesis
nature and nurture…

Lau KK et al. Ped Neph 2010:25:19-26

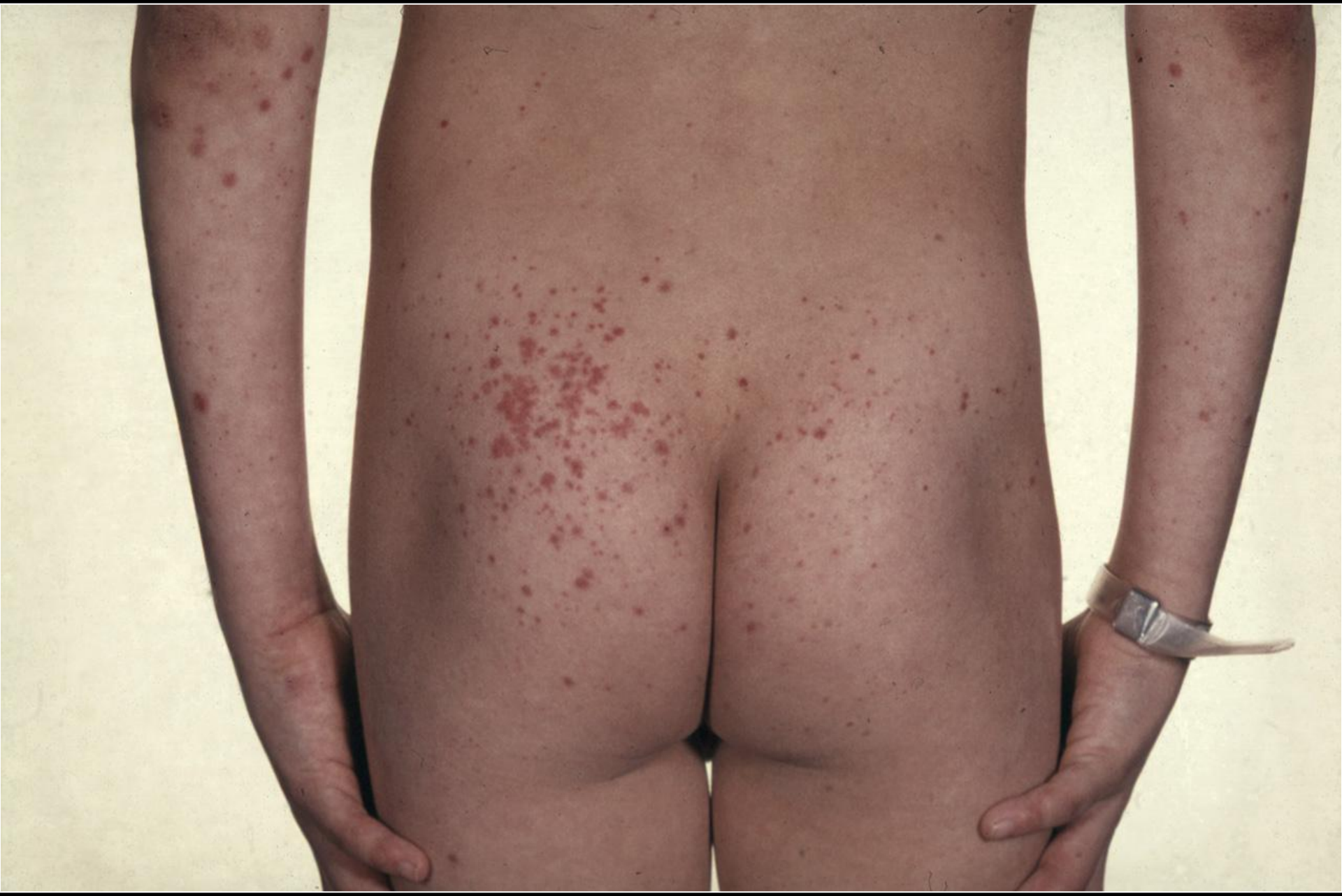

Infection
↑polymeric Gd-IgA1
Anti glycan IgG or IgA1 bind Gd-IgA
Immune complexes IgA1-IgG, IgA1-IgA1, complement
Glomerular injury

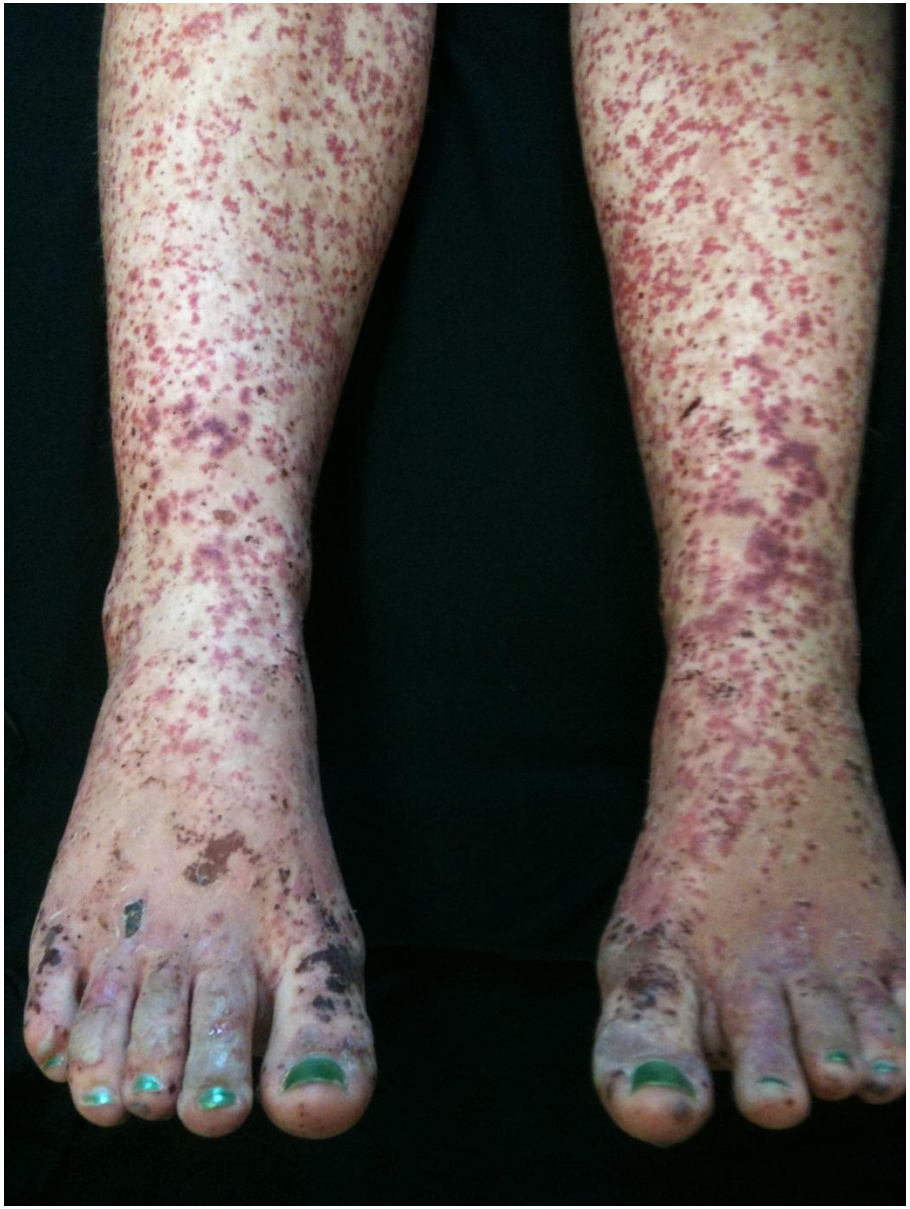
Main clinical features

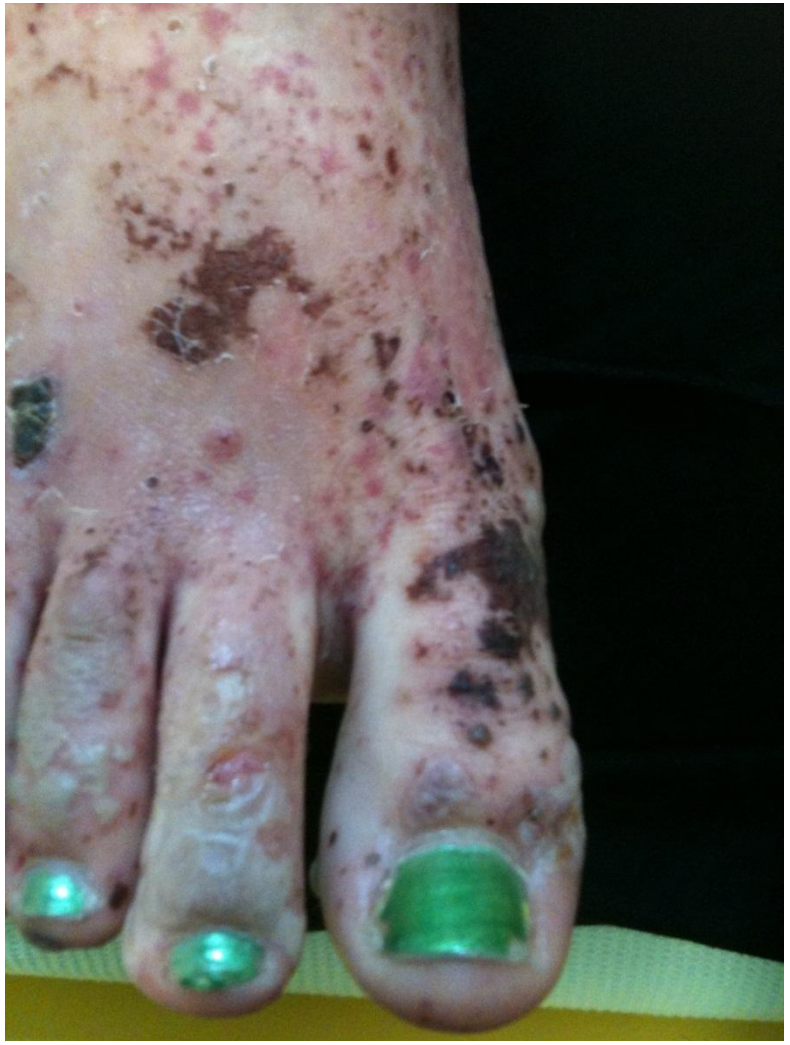
- Palpable purpura
- Arthritis or arthralgia
- Abdominal pain
- Gastrointestinal haemorrhage
- Glomerulonephritis

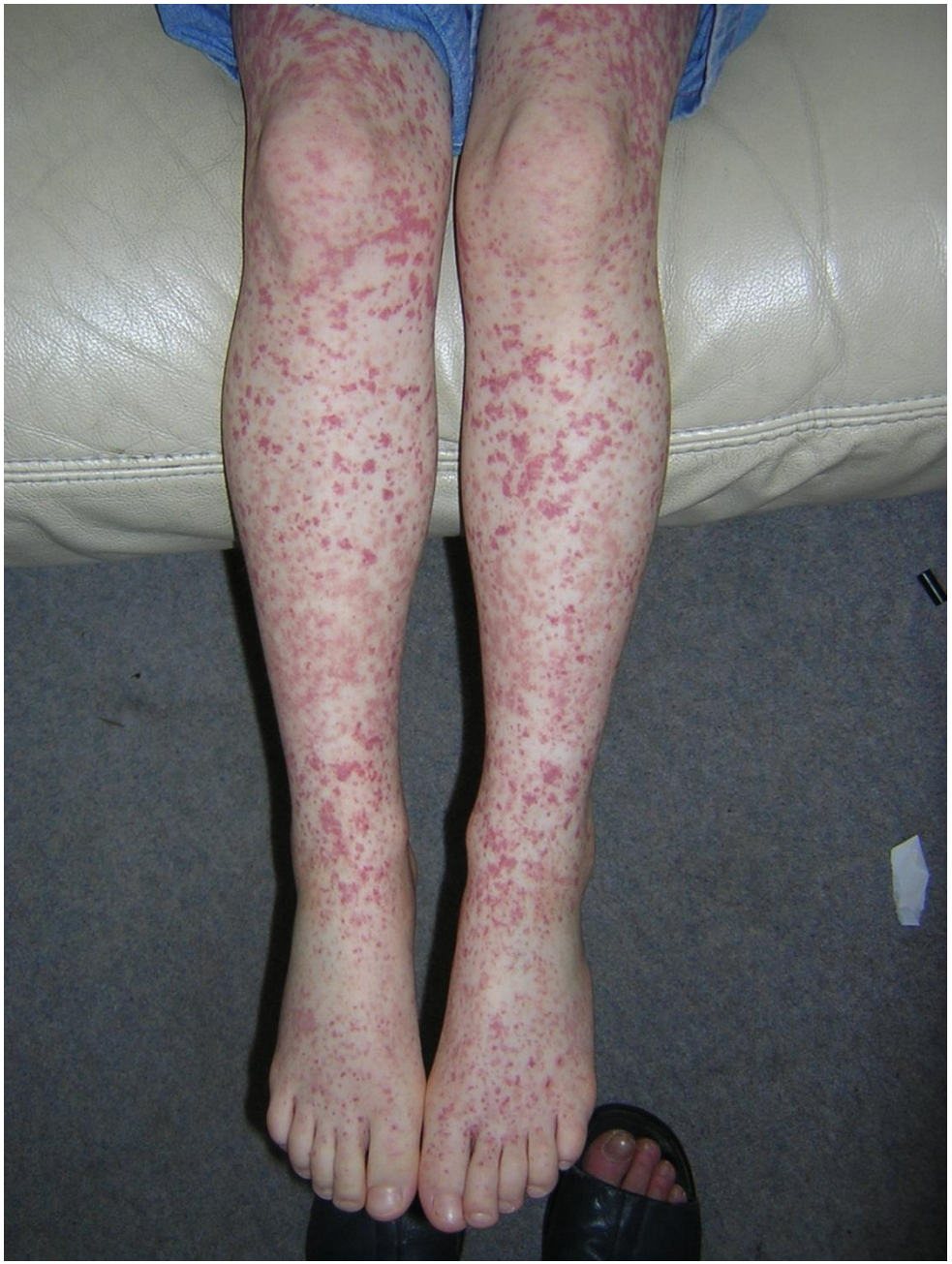
Other features

Intussusception
Pancreatitis
Pulmonary disease with haemorrhage
Orchitis
CNS involvement – fits and coma
Ureteric obstruction
Parotitis
Carditis
Guillain-Barre syndrome

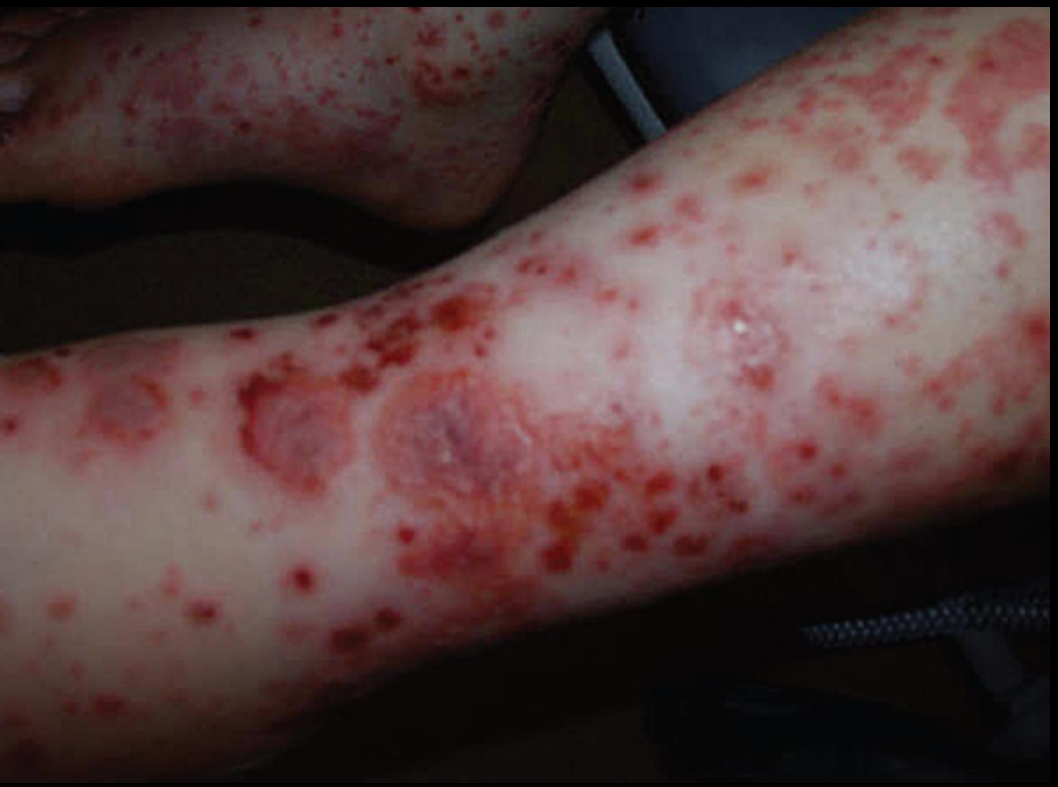


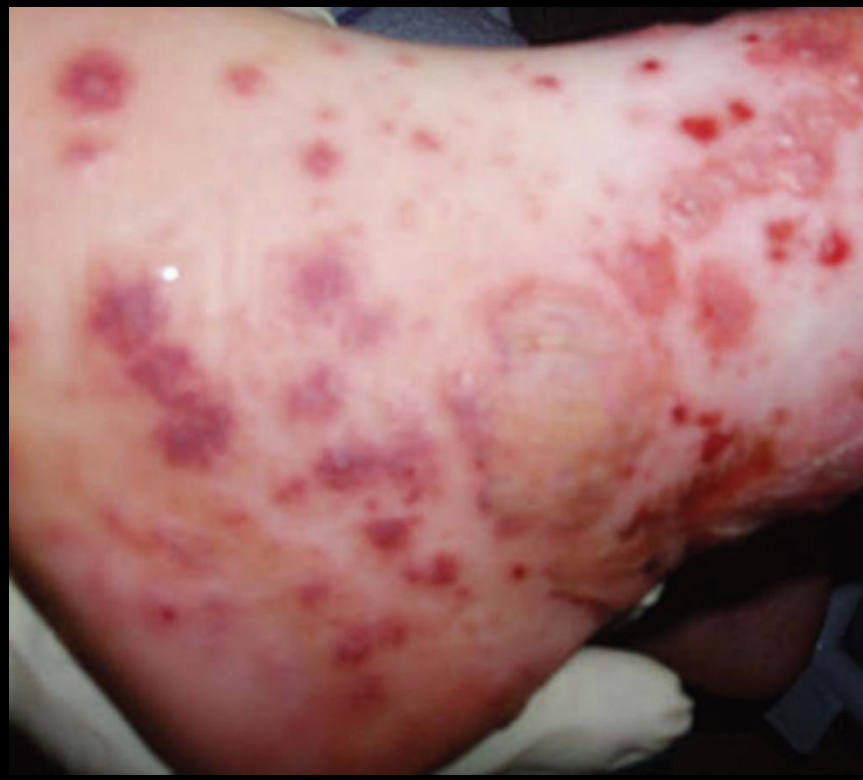




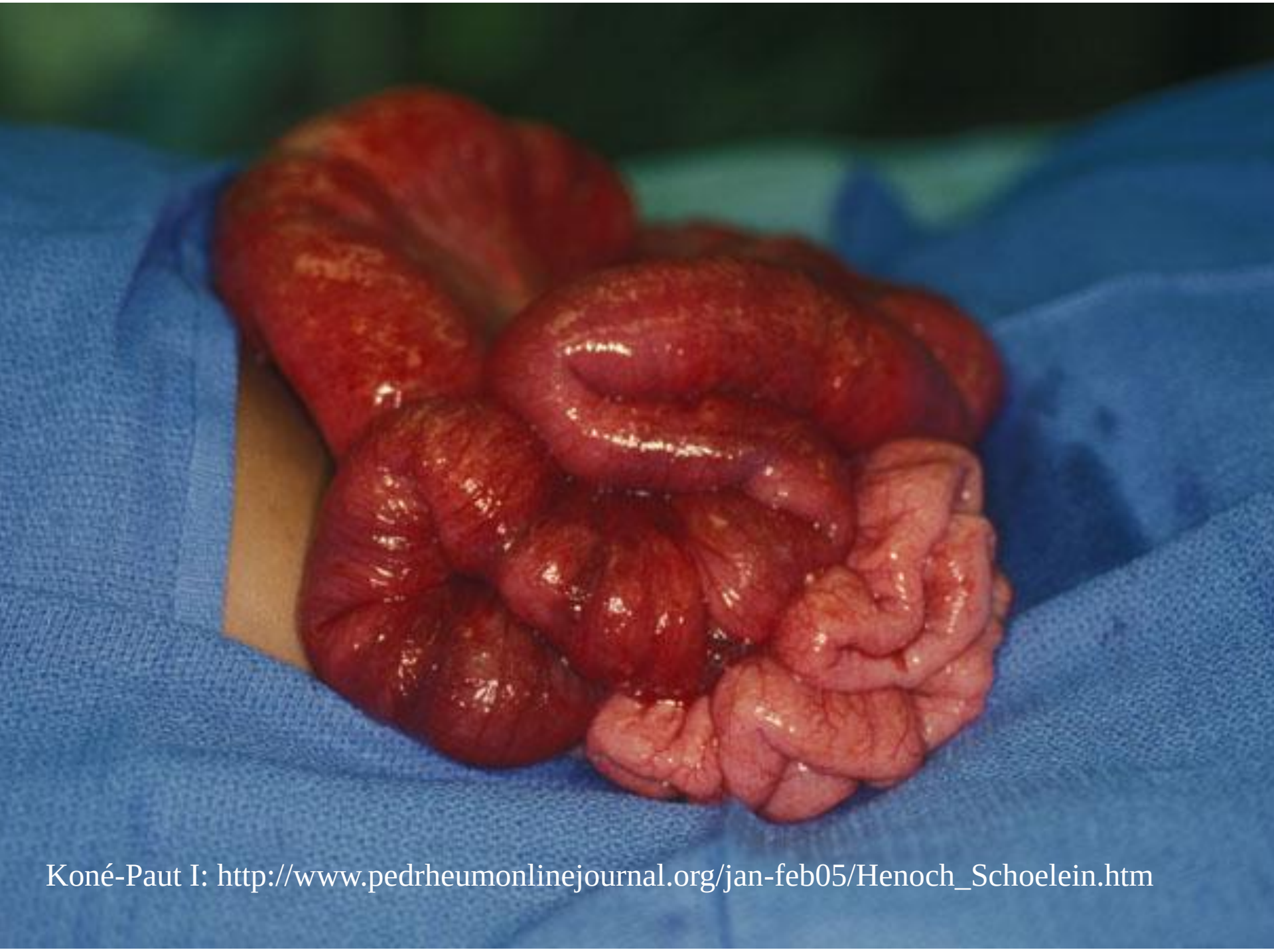


Bullous HSP



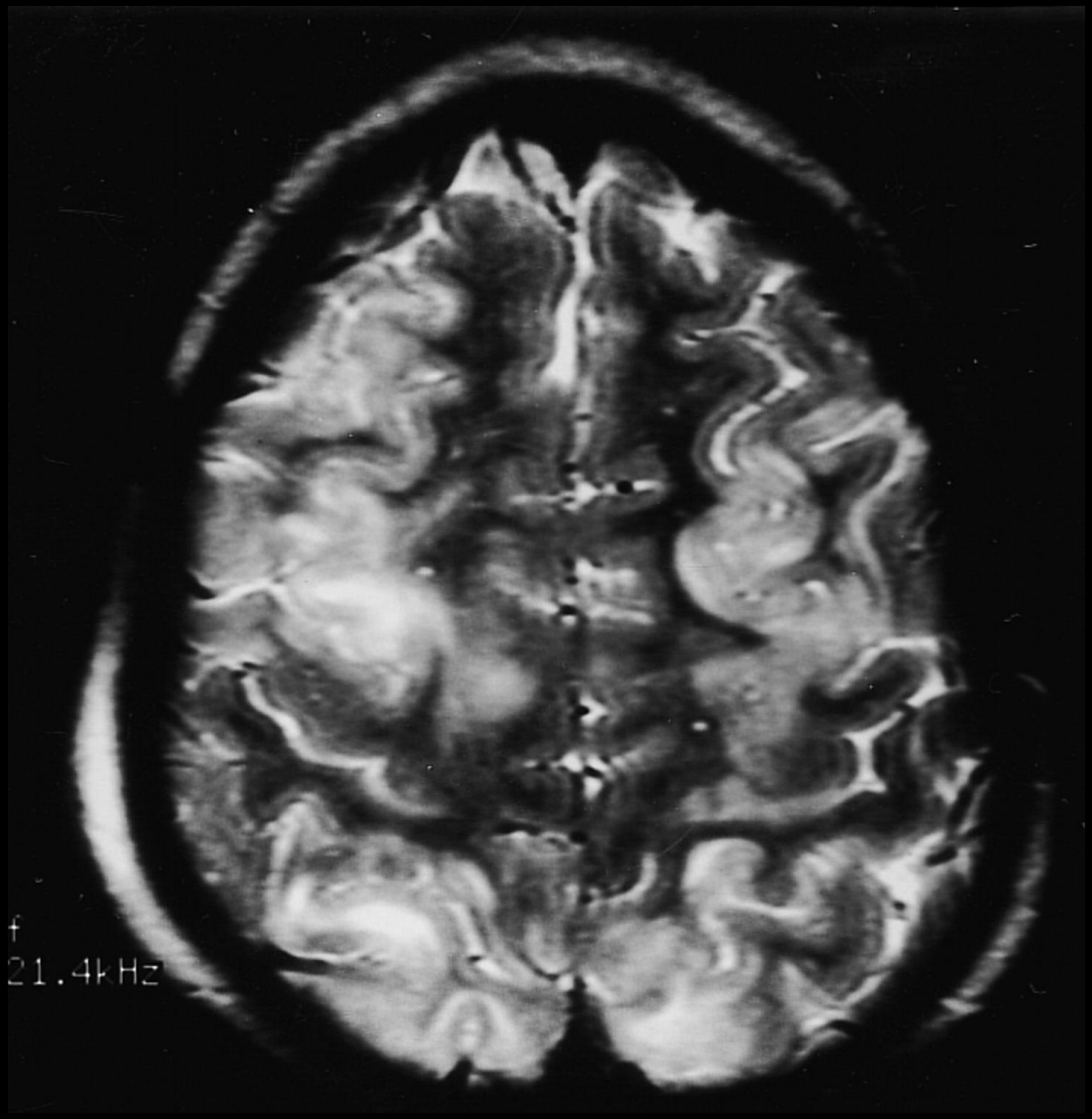


Kausar S et al Journal of Dermatological Treatment. 2009; 20:88–90

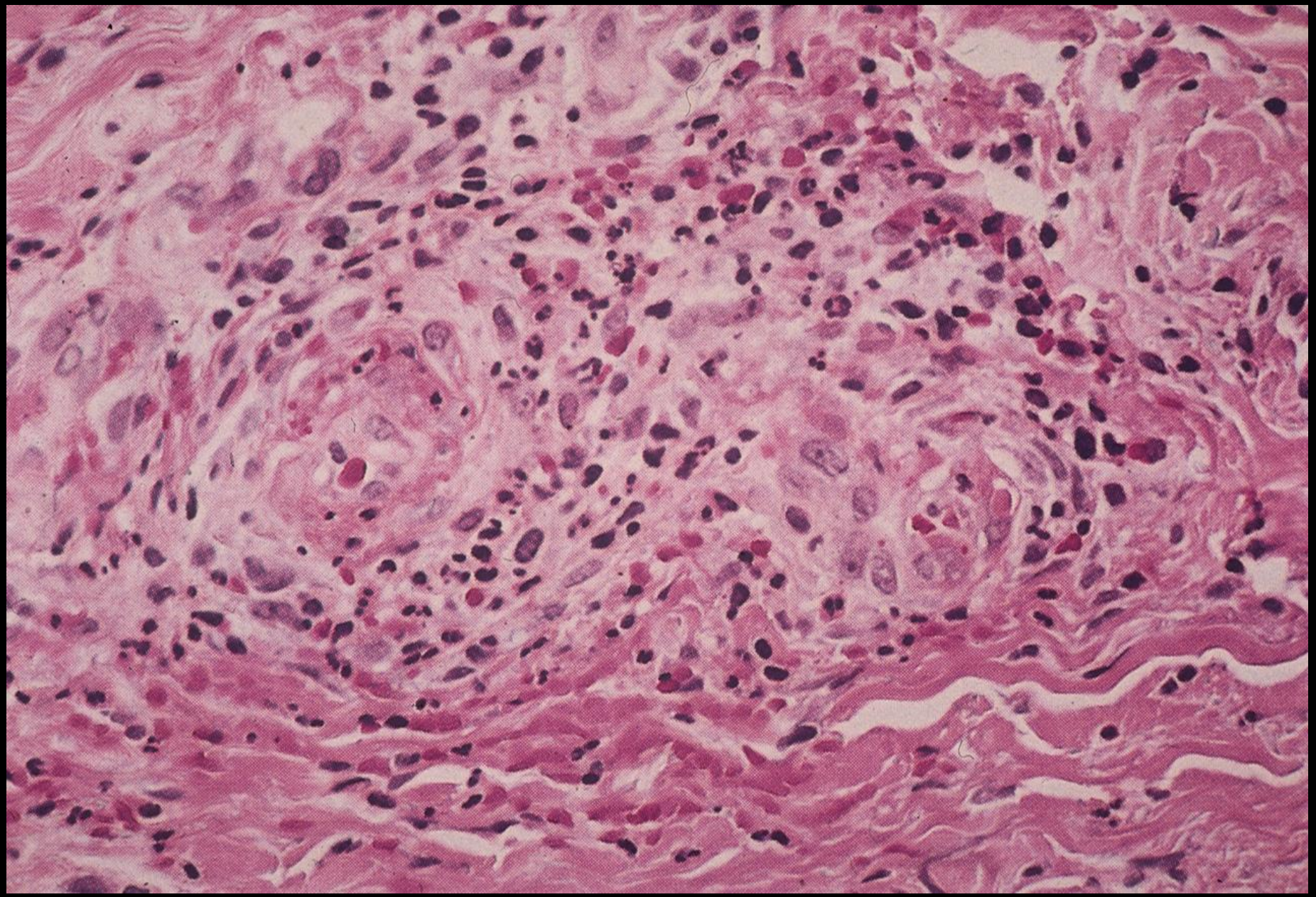


Koné-Paut I: http://www.pedrheumonlinejournal.org/jan-feb05/Henoch_Schoelein.htm

HSP: Cerebral vasculitis

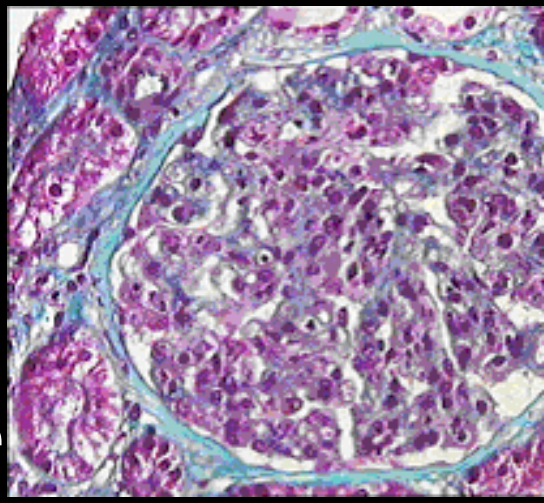


Bakkaloglu, S. A. et al. Nephrol. Dial. Transplant. 2000 15:246-248



Vascular deposition of IgA

HSP nephritis



- Focal and segmental proliferative glomerulonephritis
- 20-61% of HSP patients, depending on criteria for definition of nephritis
- Normally manifest between a few days and a few weeks after clinical presentation, but can occur up to 2 months or (rarely) more from presentation

Who needs a renal biopsy?

1. Nephritic/nephrotic presentation (urgent)
2. Raised creatinine, hypertension or oliguria (urgent)
3. Heavy proteinuria (Ua:Ucr persistently >100 mg/mmol) on an early morning urine sample at 4 weeks. Serum albumin not necessarily in the nephrotic range.
4. Persistent proteinuria (not declining) after 4 weeks?

HSP Treatment

- Supportive
- Steroids do not prevent nephritis
- For severe HSPN: lack of evidence base
  - Individualised: steroids, CYC, MMF, AZA, plasma exchange, others

Zaffanello M, Fanos V (2009) Treatment-based literature of Henoch-Schönlein purpura nephritis in childhood. Pediatr Nephrol. 24:1901–1911

HSPN: Rx based on severity

- RPGN: (>50% crescents) aggressive therapy with corticosteroid, cyclophosphamide and possibly plasma exchange
- Severe nephritis but not rapidly progressive (<50% crescents):
  - Corticosteroids alone or in combination with
  - CYC, AZA, MMF, others
- Persistent proteinuria: ACEI

Zaffanello M, Fanos V, 2009

Indication for steroid in non-renal HSP: personal practice

- Severe haemorrhagic oedema affecting the face or scrotum
- Severe bullous HSP
- Testicular involvement
- Severe gastrointestinal symptoms, particularly abdominal pain and gastrointestinal bleeding
- Other severe systemic manifestation:
  - pulmonary haemorrhage; cerebral vasculitis, pancreatitis etc

HSP outcome

- Benign

- But significant morbidity associated with cutaneous and gastrointestinal disease in short term

  and renal disease in the long term

Poorer renal prognosis

- Nephrotic syndrome
- Nephritic and nephrotic syndrome
  - 20% of patients with acute mixed nephritic and nephrotic syndrome progressed to end stage renal failure
  - 44 to 50% develop hypertension or chronic kidney disease
- Older children (>7 yrs) and adults

Duration of clinical features

- 1/3 of children have symptoms for less than 14 days
- 1/3 for 2-4 weeks
- 1/3 greater than 4 weeks
- Recurrence of symptoms occurs in around 1/3 of cases, generally within four months of resolution of the original symptoms.
  - Recurrences are more frequent in those with renal involvement.

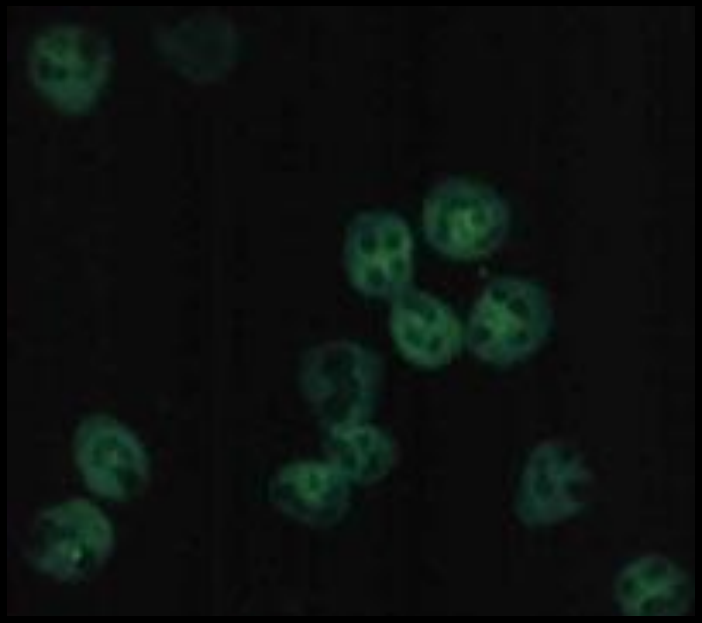
Long term renal involvement in HSP

- Narchi et al 2005. ADC, 90:916-920
  - 1133 children (12 studies)
  - Renal involvement 34%
    - 80% isolated haematuria/proteinuria
    - 20% nephritis or nephrotic syndrome
  - Renal involvement occurred by 4 weeks in 85%
  - Persistent renal involvement in 1.8%

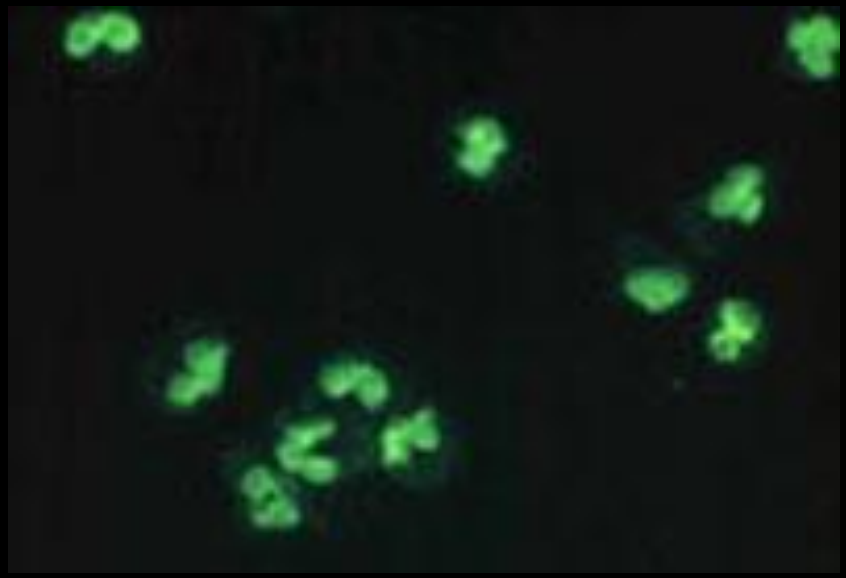
ANCA associated vasculitides

- Granulomatosis with polyangiitis (GPA) (formerly Wegener's granulomatosis)
- Microscopic polyangiitis (MPA)
- Eosinophilic Granulomatosis with polyangiitis (EGPA; formerly Churg Strauss Syndrome)

ANCA



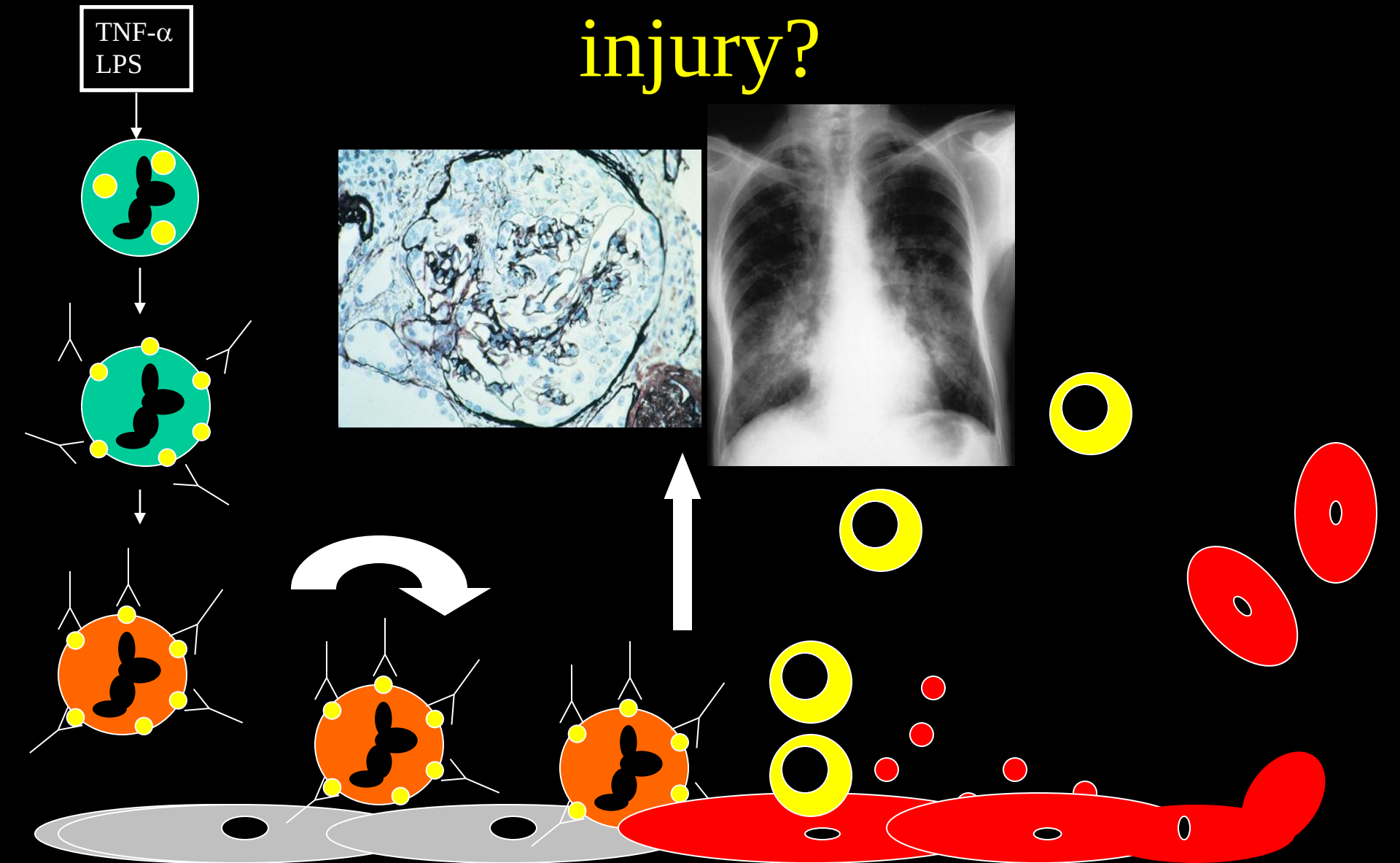
cANCA
PR3-ANCA



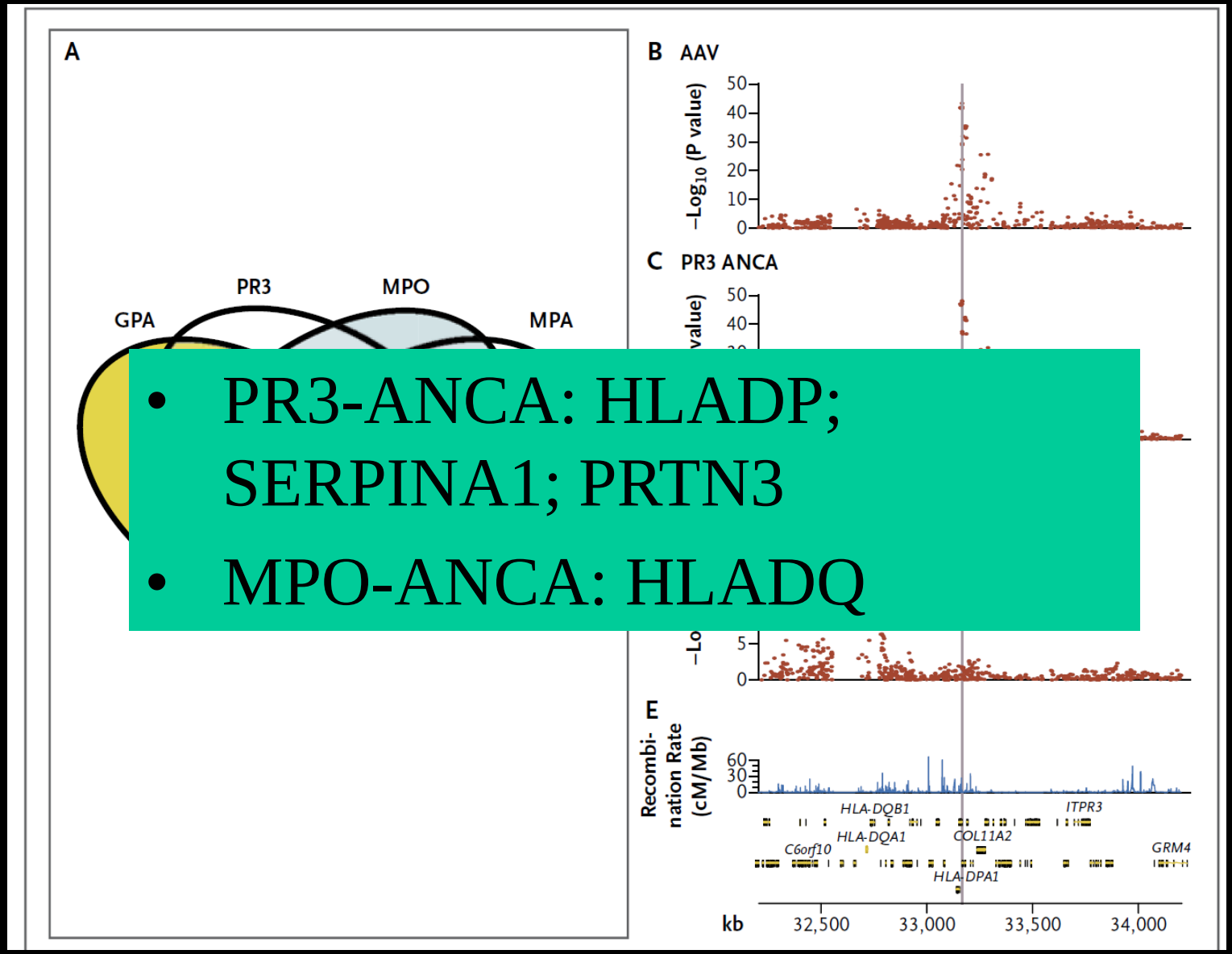
pANCA
MPO-ANCA

How do ANCA cause vasculitis?

How do ANCA cause vascular injury?



Why do patients develop ANCA? Nature and nurture…



- PR3-ANCA: HLADP; SERPINA1; PRTN3
- MPO-ANCA: HLADQ

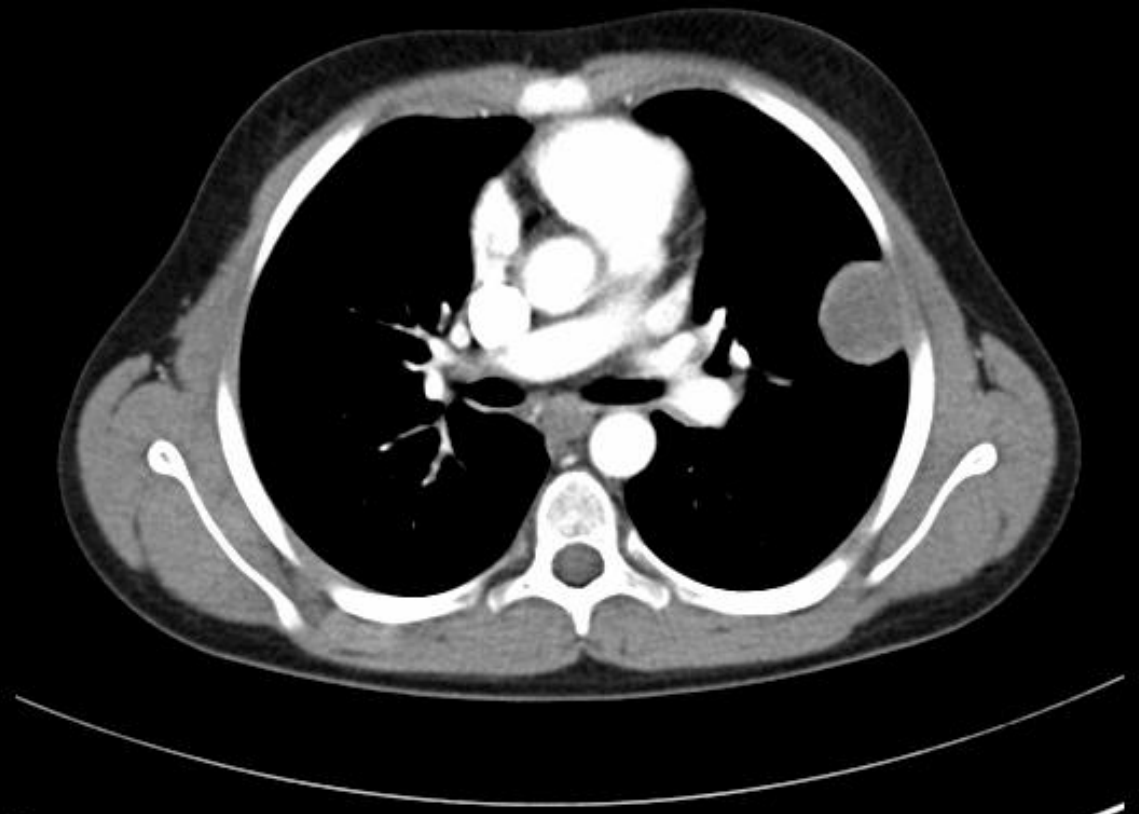
Granulomatosis with polyangiitis (Wegener's granulomatosis)

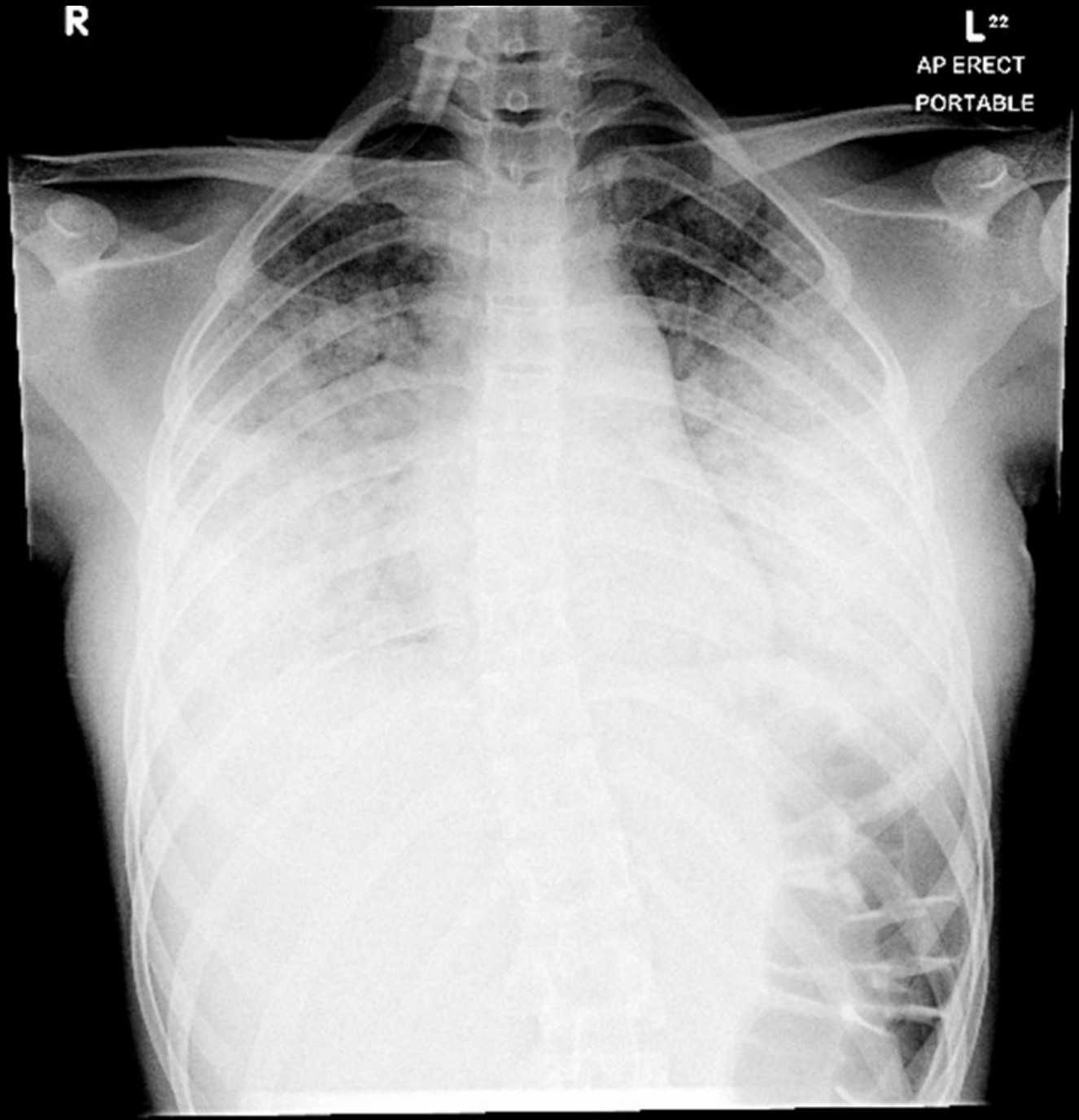
GPA (Wegener's granulomatosis)
[2010, Ozen S et al ARD]

At least 3 out of 6 of the following criteria:

1. histopathology
2. upper airway involvement
3. laryngo-tracheobronchial stenoses
4. pulmonary involvement
5. ANCA positivity
6. renal involvement

Sn 93.3% Sp 99.2%

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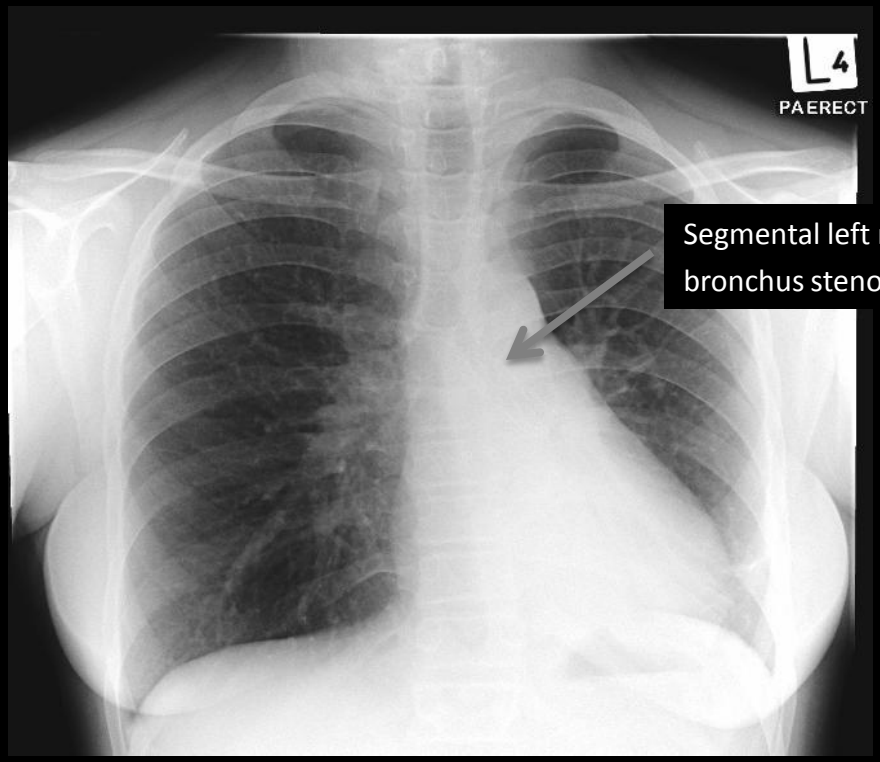

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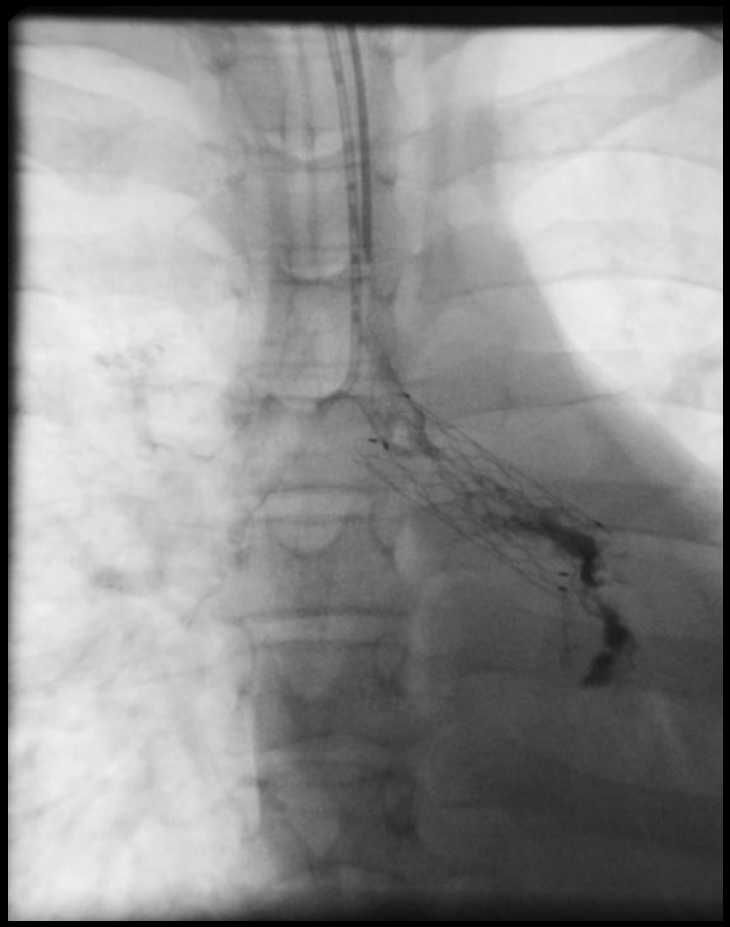

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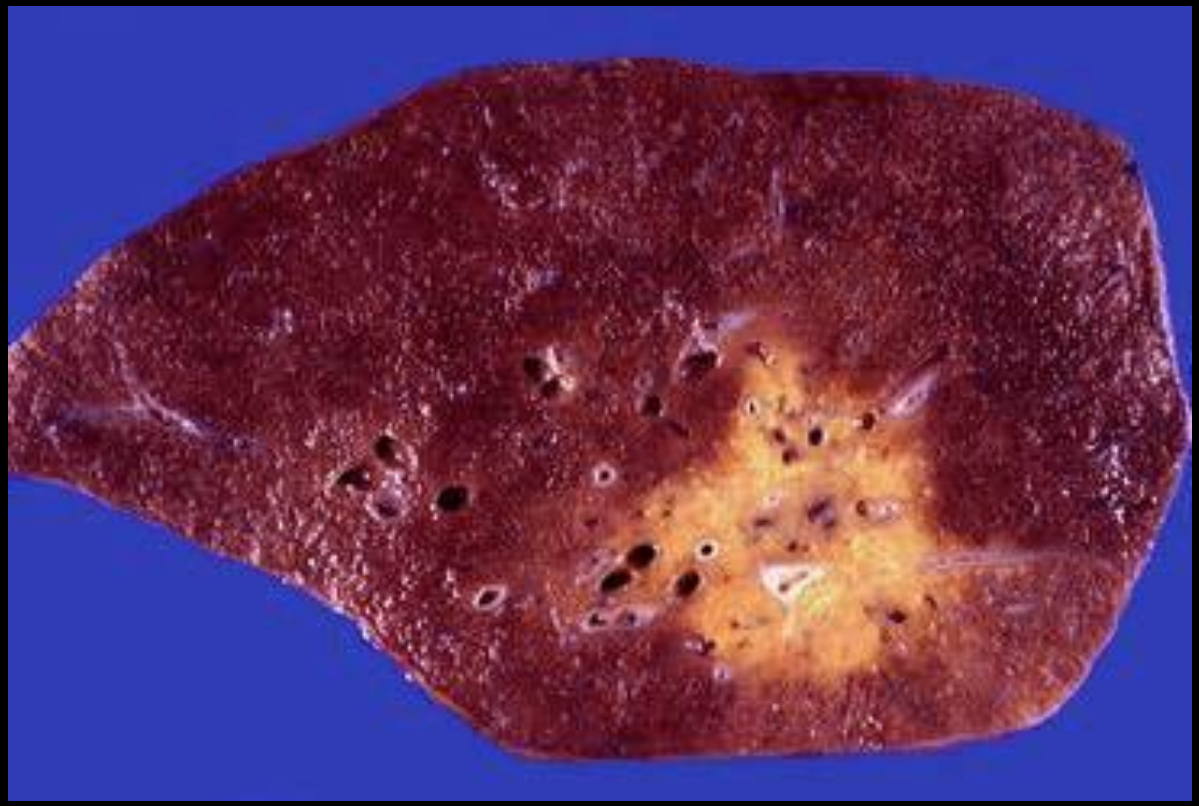
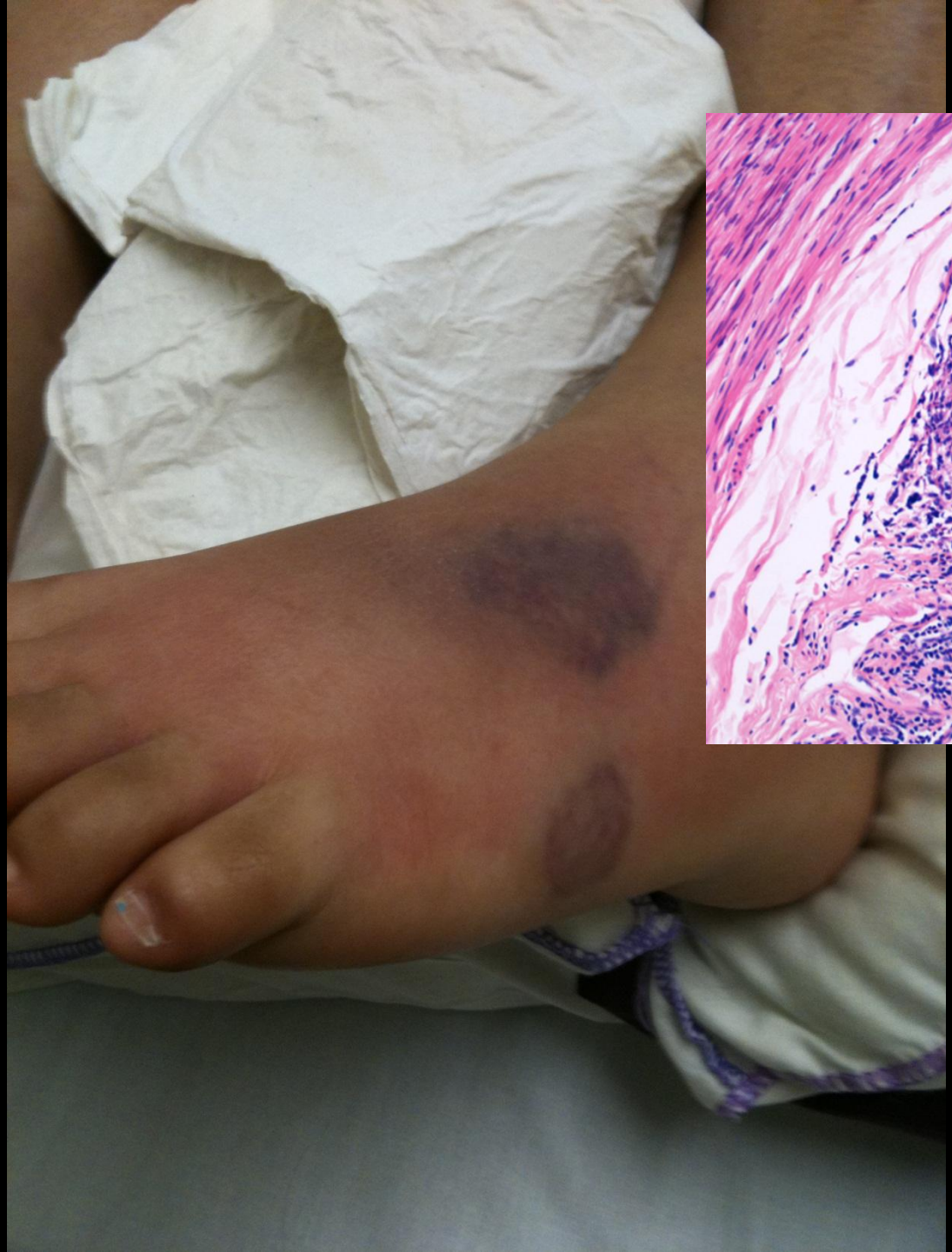
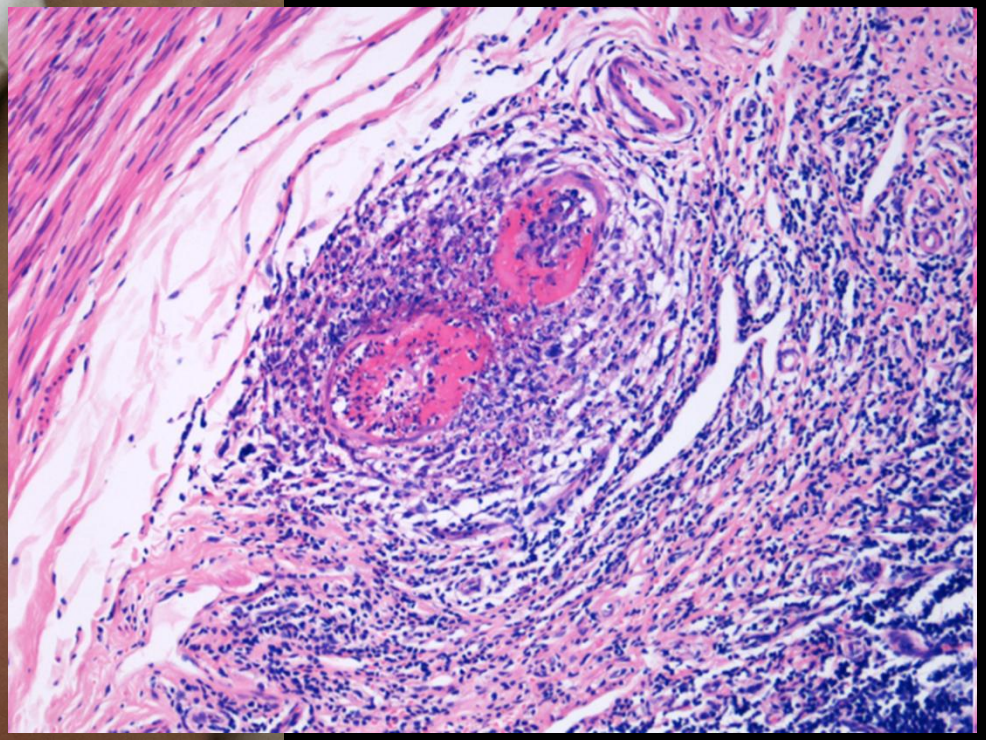
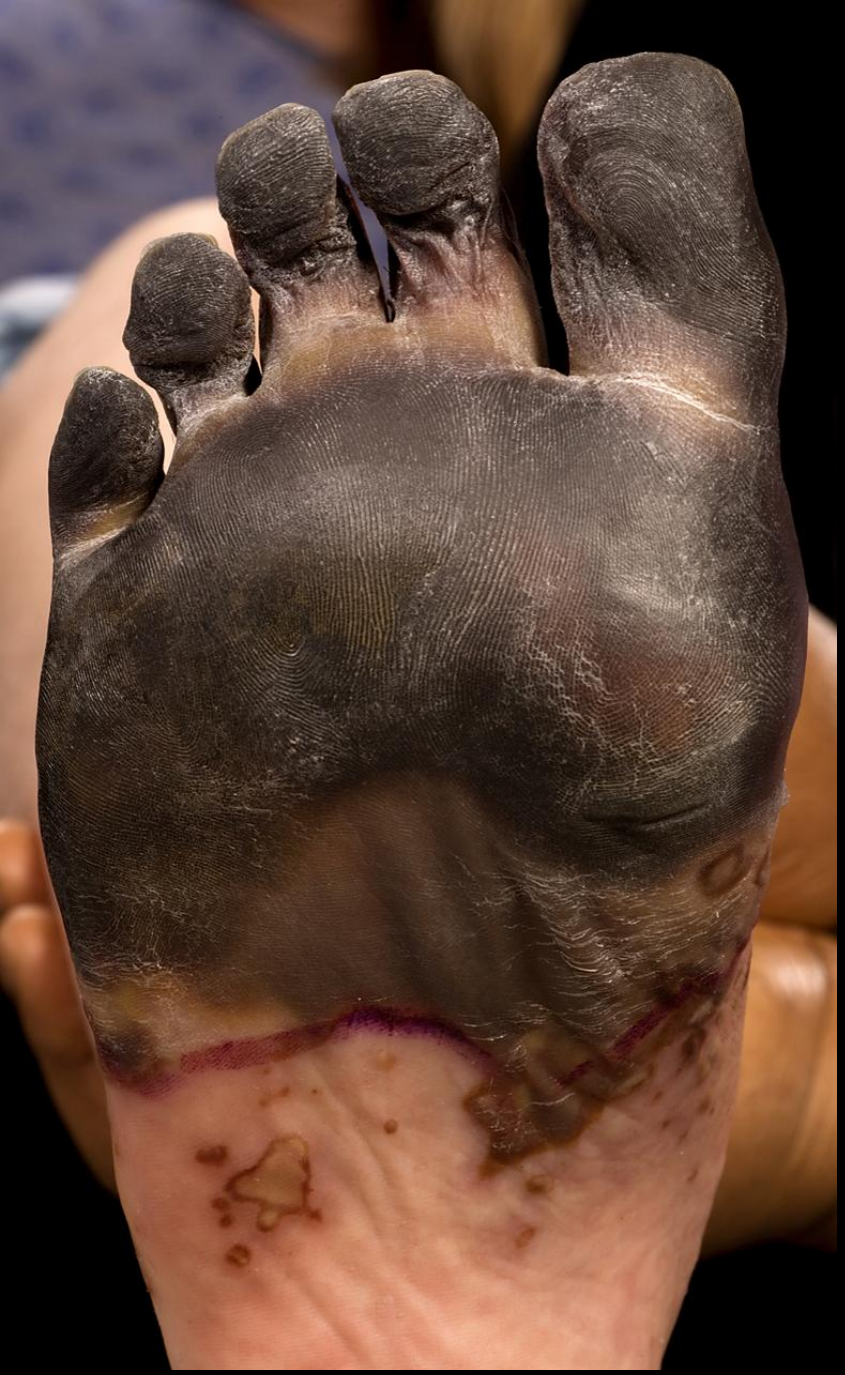
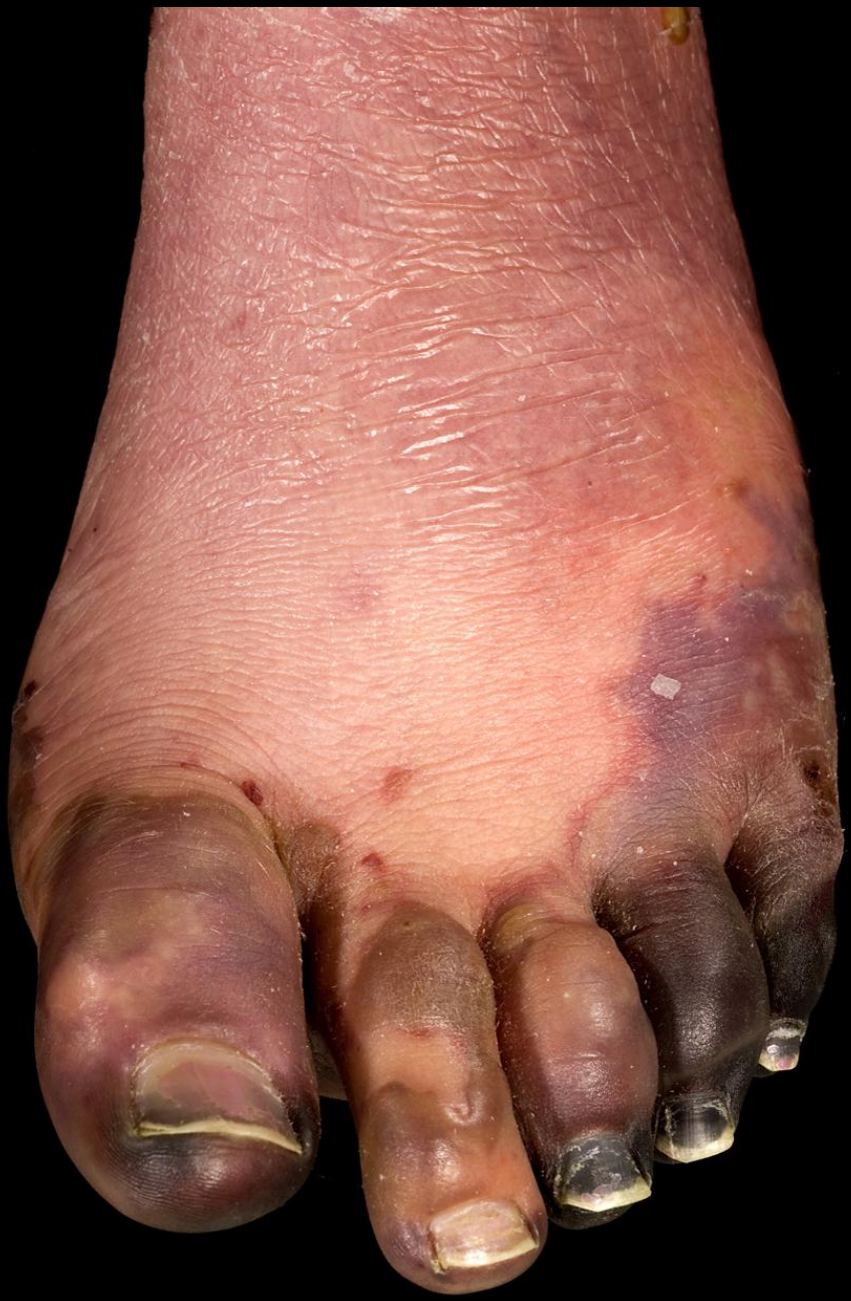
WG: lung

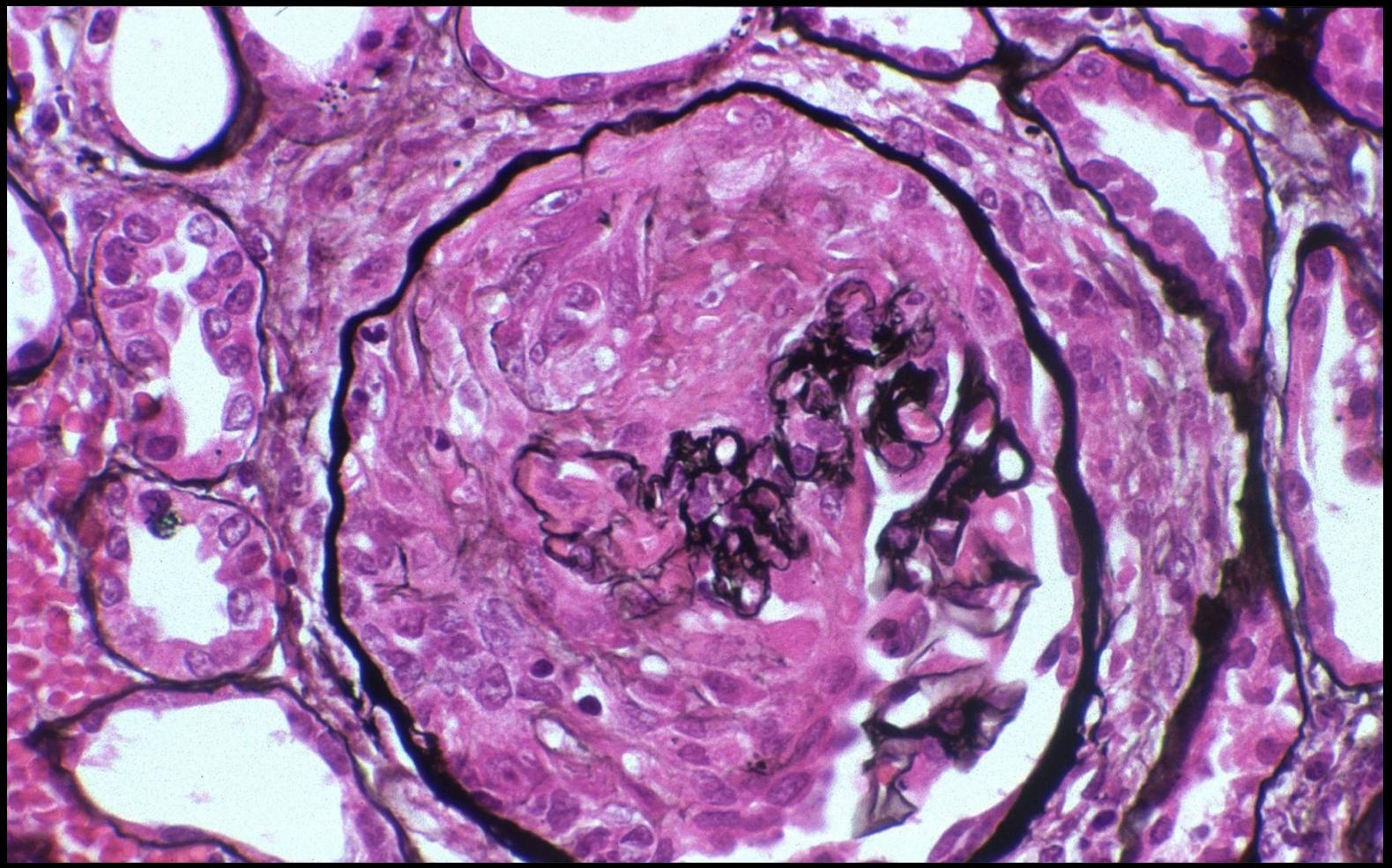










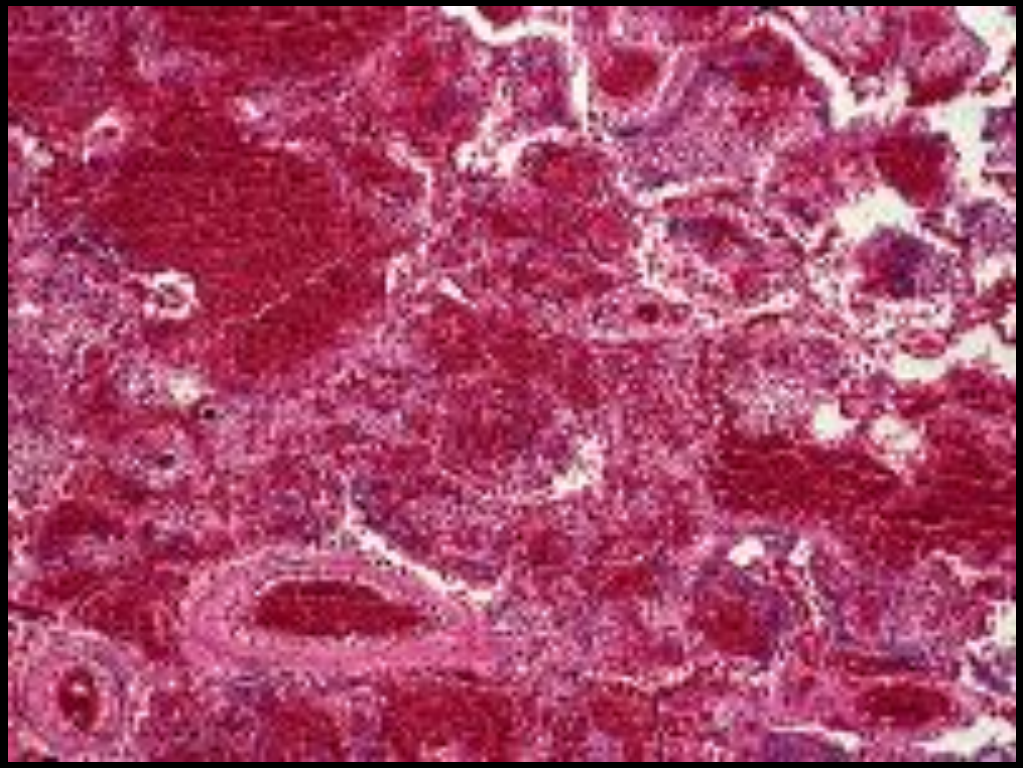


MPA

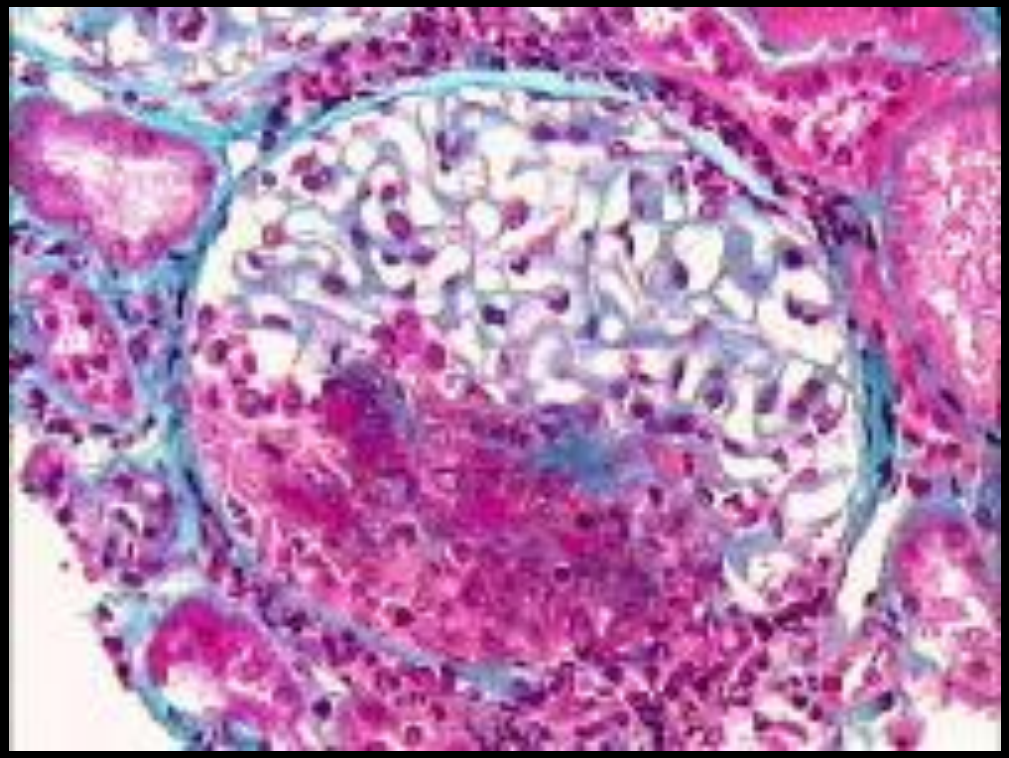
Microscopic polyangiitis

- Necrotizing SVV with few or no immune deposits
- Pulmonary capillaritis and glomerulonephritis (rapidly progressive renal failure)
  - But any organ can be affected
- pANCA; MPO-ANCA
- Renal Limited form (but watch out for other organ involvement)

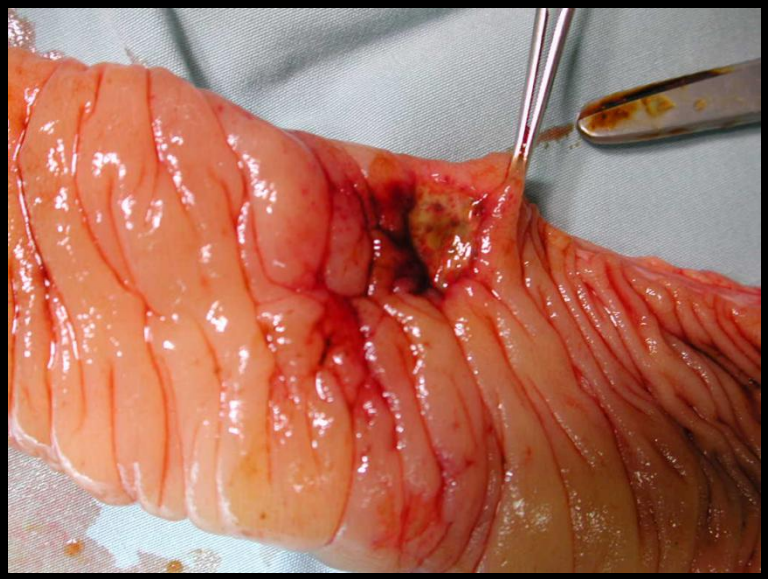
Microscopic polyangiitis: alveolar haemorrhage



MPA: glomerulus



Microscopic polyangiitis (MPO-ANCA)



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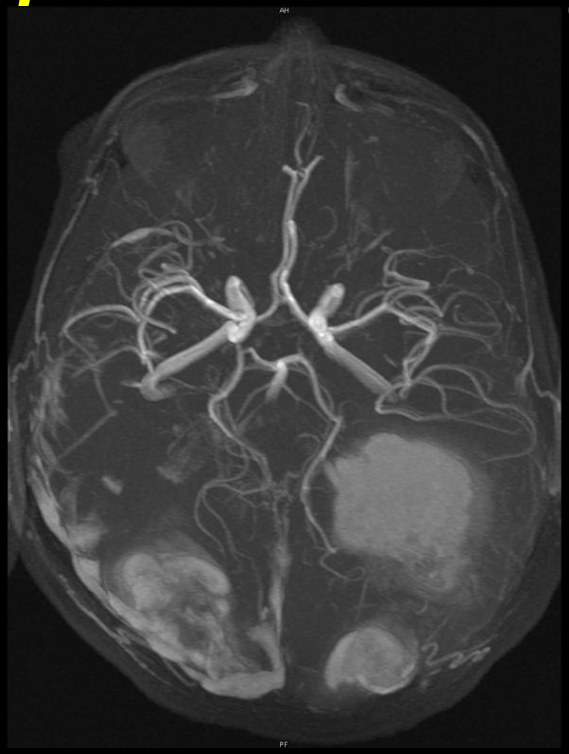


B

9A: Resected colon taken from a 13-year-old girl with microscopic polyangiitis (initially regarded clinically as renal limited vasculitis; MPO ANCA positive), and severe renal failure due to crescentic nephritis. Torrential gastrointestinal haemorrhage was the result of vasculitis affecting the colon, and a vasculitic ulcer is depicted.

9B: Magnetic resonance angiography (MRA) of the brain performed following acute visual loss in a 12 year old previously well female, with MPO ANCA positivity, but normal renal function. Multiple parieto-occipital haematomas are depicted. The intra and extra-cranial t large and medium-sized arteries were normal, and the final diagnosis was MPO ANCA positive small vessel vasculitis of the brain.

Churg Strauss Syndrome

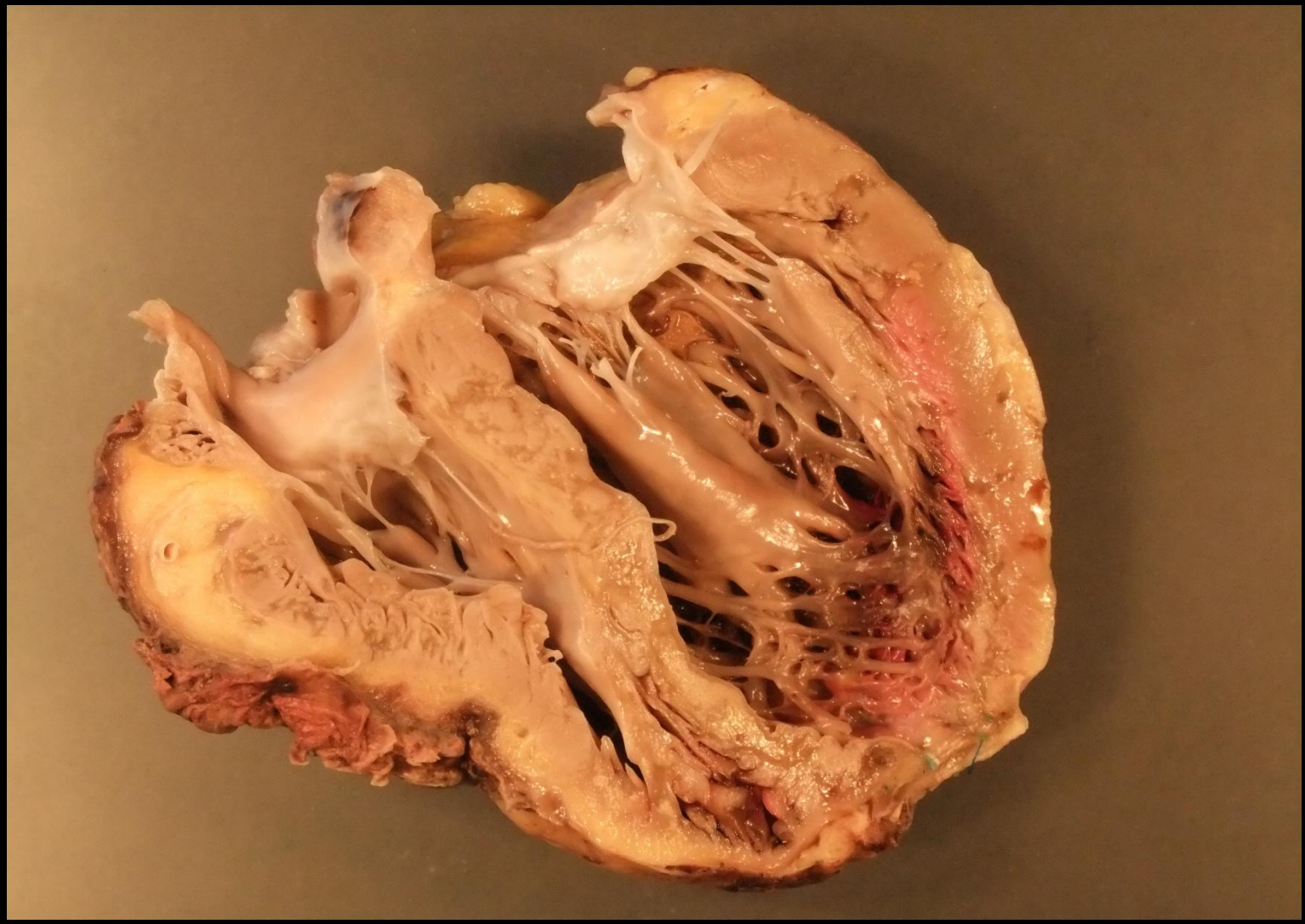
CSS

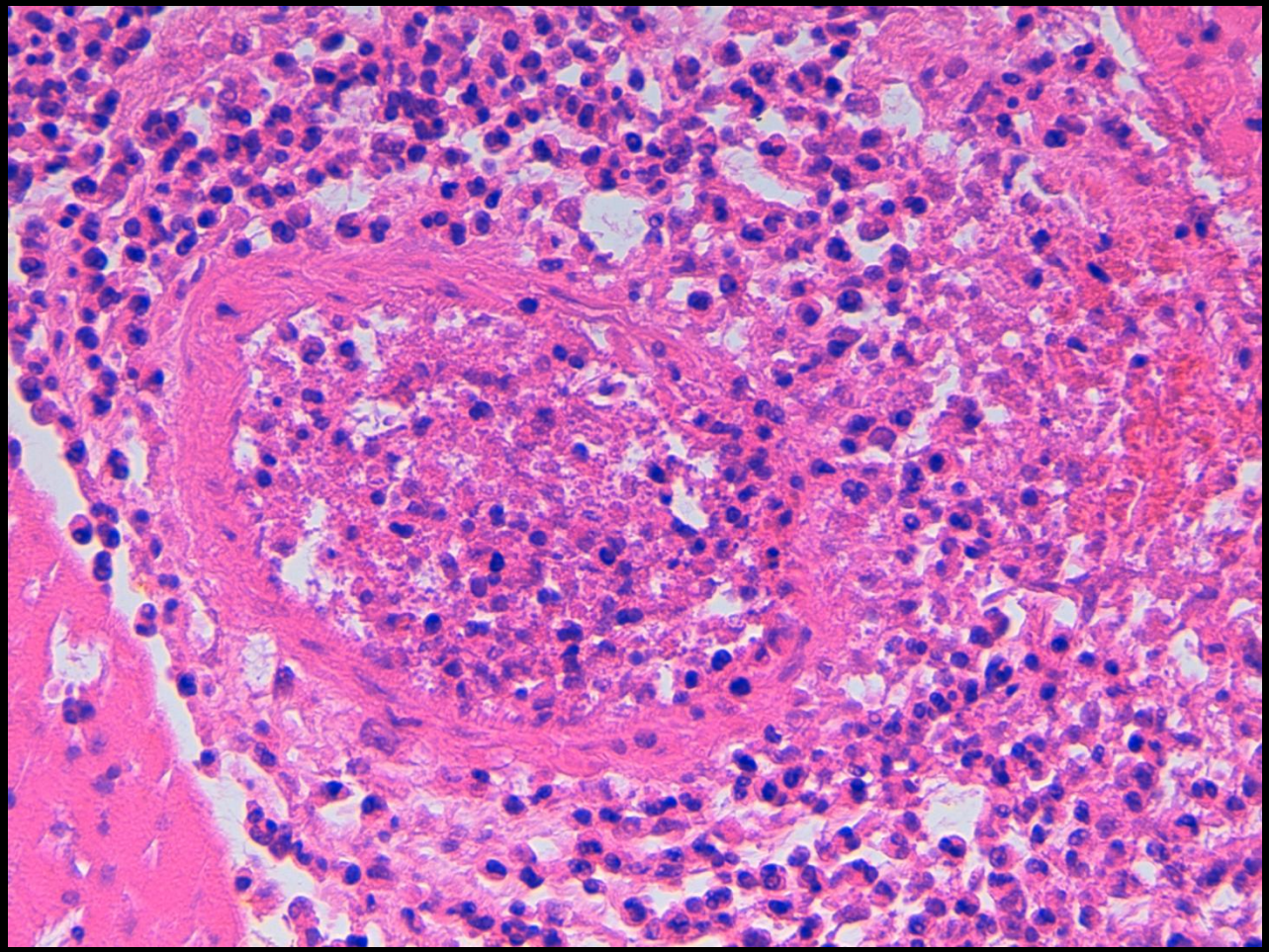
- Eosinophil rich and granulomatous inflammation, esp. of respiratory tract
- Necrotizing vasculitis of small and (possibly) medium vessels
- Associated with asthma and hypereosinophilia
- MPO-ANCA positivity

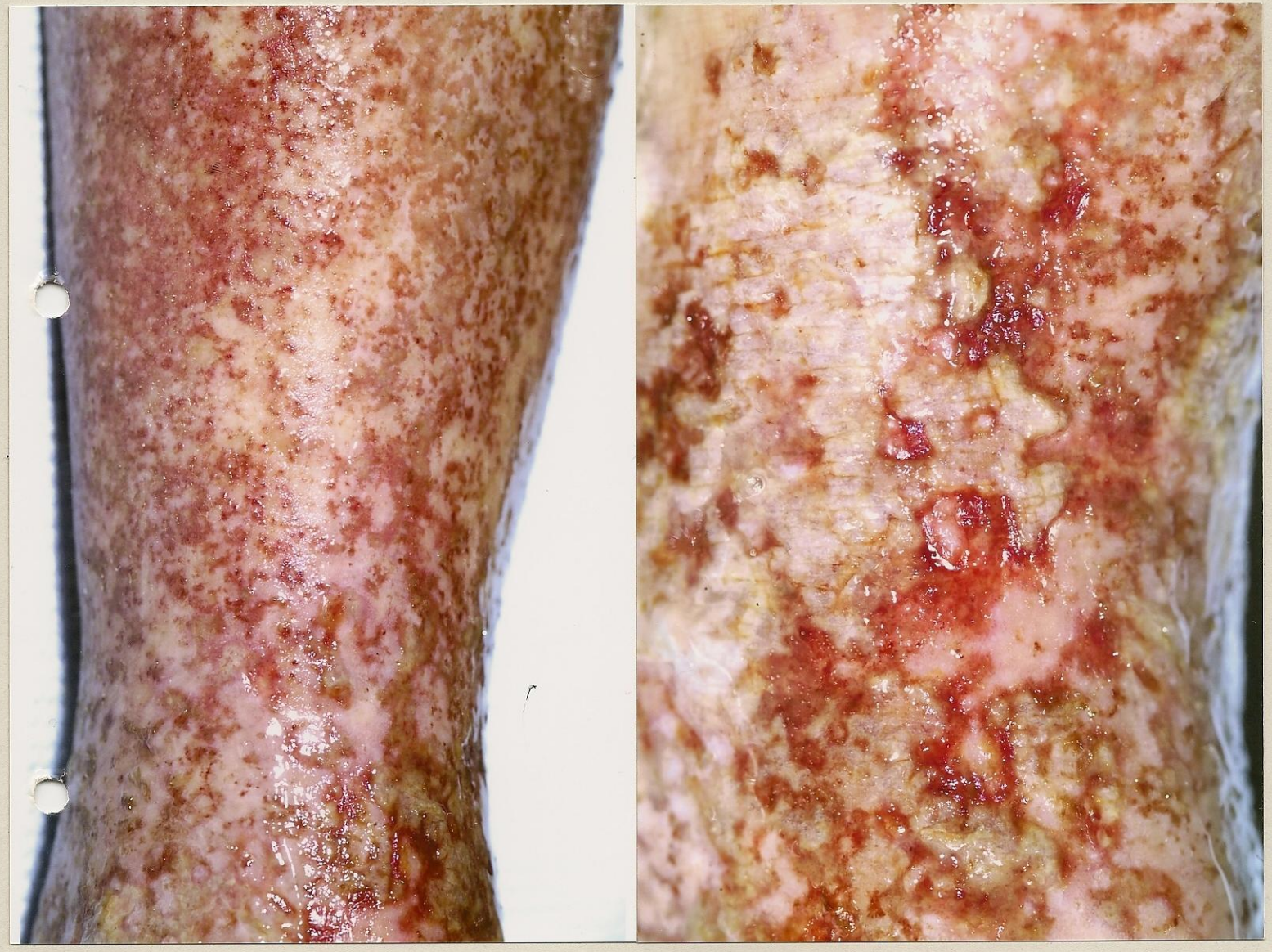
CSS in kids: n=32

Zwerina et al 2008

- All patients had significant eosinophilia and asthma
- Histological evidence of eosinophilia and/or vasculitis was present in virtually all patients
- ANCA were found in only 25%







ANCA to monitor disease activity and guide Rx?

Annals of Internal Medicine

Ann Intern Med. 2007;147:611-619.

ARTICLE

Antiproteinase 3 Antineutrophil Cytoplasmic Antibodies and Disease Activity in Wegener Granulomatosis

Javier D. Finkielman, MD; Peter A. Merkel, MD, MPH; Darrell Schroeder, MS; Gary S. Hoffman, MD; Robert Spiera, MD; E. William St. Clair, MD; John C. Davis Jr., MD, MPH; W. Joseph McCune, MD; Andrea K. Lears, BS; Steven R. Ytterberg, MD; Amber M. Hummel; Margaret A. Viss; Tobias Peikert, MD; John H. Stone, MD, MPH; and Ulrich Specks, MD, for the WGET Research Group

Treatment

Standard treatment of AAV in children: “induction/maintenance”

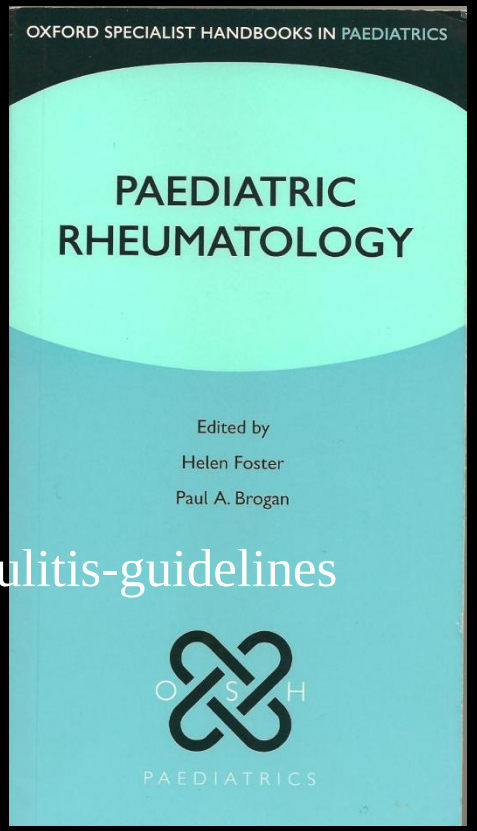
- Induction:
  - Corticosteroids PLUS CYC (+/-PE) PLUS Antiplatelet agent
- Maintenance:
  - Low dose corticosteroid; AZA, MMF, other
- Rituximab: induction and/or maintenance

AAV outcome in children

- GPA: 40% develop renal failure; 12% mortality
- MPA: mortality 0-14%
- EGPA: mortality 18%

SHARE guidelines
http://www.printo.it/SHARE

Oxford Handbook of Paediatric Rheumatology



http://www.vasculitis.org.uk/professionals/paediatric-vasculitis-guidelines