Pulmonary Renal Syndromes

A Rheumatologic Emergency

Farhan Tahir MD

Agenda

- Pulmonary Renal Syndrome
  - A Rheumatologic Emergency
  - Classification
  - Characteristic Profile of Diseases
  - Mortality and Prognosis
- Interesting Cases and Differential Diagnosis
- Review of Clinical Management
- Summary

A Rheumatologic Emergency

- The term Pulmonary Renal Syndrome refers to the combination of diffuse alveolar hemorrhage and rapidly progressive glomerulonephritis
- There is a broad list of etiologies which can cause this syndrome and significant number of patients will present with rapid clinical deterioration and require admission to the intensive care unit
- Presentation is variable and could be related to exacerbation of the disease activity or to infectious complications secondary to severe immunosuppressive treatment
- Pulmonary–renal syndromes represent a major challenge since the outcome is based on early and accurate diagnosis and aggressive treatment and mortality can reach 25–50%

Presentation and Diagnostic Workup

- Fever, cough and dyspnea, often acute or sub acute(<1wk)
- Hemoptysis may be absent in 1/3 of patients
- When hemoptysis is present, one must exclude infection, left heart failure, severe mitral stenosis, pulmonary embolism and drug exposure (PTU and Cocaine) as possible etiologies so thorough history is extremely important
- CXR and Chest CT show diffuse bilateral infiltrates often impossible to differentiate form infection or acute pulmonary edema
- Early bronchoscopy is most helpful and serves two purpose, document hemorrhage and exclude airway lesions as source of bleeding and BAL fluid cultures exclude infection

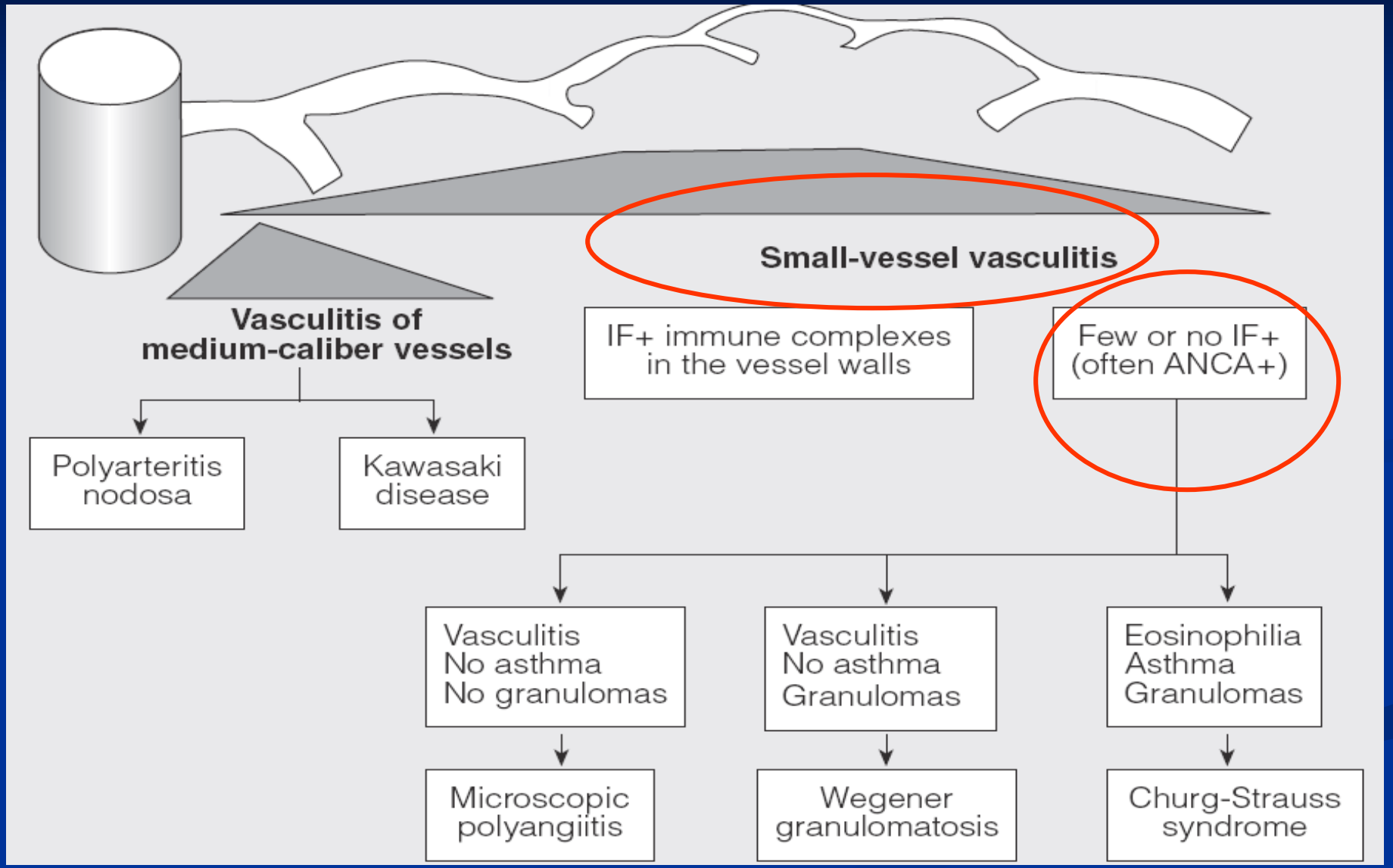
DLCO, Exhaled Nitric oxide and Biopsy

- TBBX specimen is small and unlikely to help establish diagnosis
- VATS or open lung biopsy although invasive is more definitive
- PFT testing particularly DLCO is helpful but impractical modalities for sick patients
- Increased intra alveolar hemoglobin binds NO and levels of NO are decreased in exhaled breath. Decreased exhaled Nitric oxide is a promising bedside test but not widely available
- Patients presenting with pulmonary renal syndrome, renal biopsy with IF has higher yield in identifying underlying cause

Basis of Classification

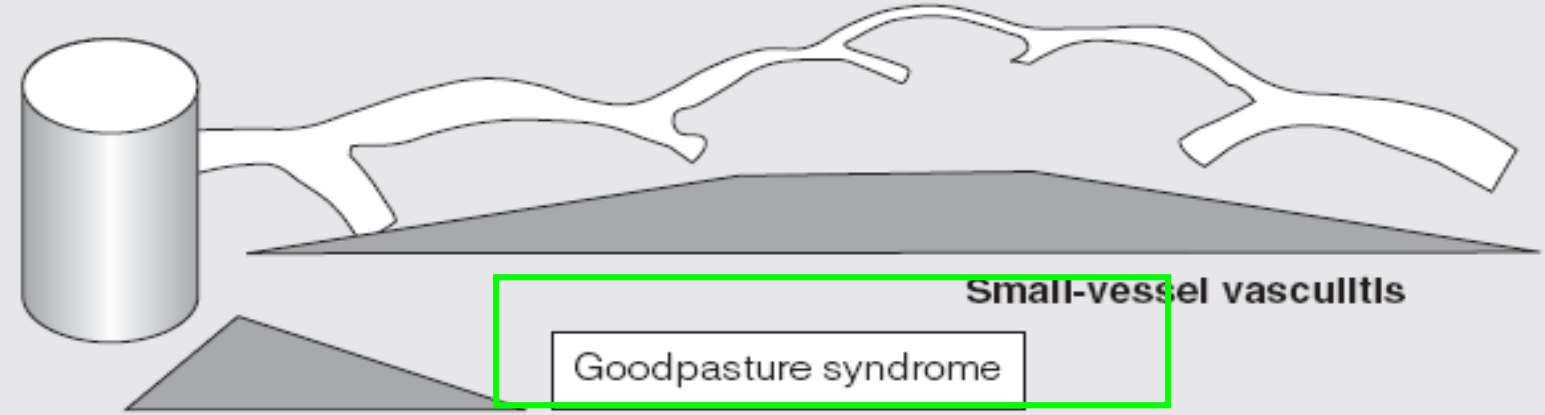
- A variety of mechanisms are implicated in the pathogenesis of this syndrome i.e. antibody mediated diseases, immune complex mediated and others i.e. drugs
- Underlying pulmonary pathology is small-vessel vasculitis involving arterioles, venules and, frequently, alveolar capillaries
- Underlying renal pathology is a form of focal proliferative glomerulonephritis
- Immunofluorescence helps to distinguish between antibody mediated and immune complex mediated diseases

Classification Based On Vessels Size



Arch Bronconeumol. 2008;44(8):428-36

Immune Complex Deposition



Goodpasture syndrome

IF+ immune complexes in the vessel walls

Little or no IF+ (often ANCA+)

Cryoglobulins in the blood or vessel walls	IgA immune deposits in the vessel walls	Systemic lupus erythematosus	Other sources of immune complexes
Cryoglobulinemic vasculitis	Henoch-Schönlein purpura	Lupus/rheumatoid vasculitis	Other vasculitis due to immune complexes

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Pattern of Immunofluorescence

Histologic and Immunofluorescence Data That Facilitate Diagnosis

Mechanism	Immunofluorescence Pattern	Terminology
Anti-GBM antibodies	Linear	Goodpasture syndromea
Immune complexes	Granular	Systemic lupus erythematosusa and other connective tissue diseases[a] Henoch-Schönlein purpura. Immunoglobulin A nephropathy. Idiopathic necrotizing glomerulonephritis with immune complexes
ANCA	Negative or pauciimmune	Wegener granulomatosisa Microscopic polyangiitis[a]. Churg-Strauss syndrome[a]. Idiopathic necrotizing glomerulonephritis without immune complexes
Unknown	Negative or pauciimmune	Idiopathic pulmonary hemorrhage[a]

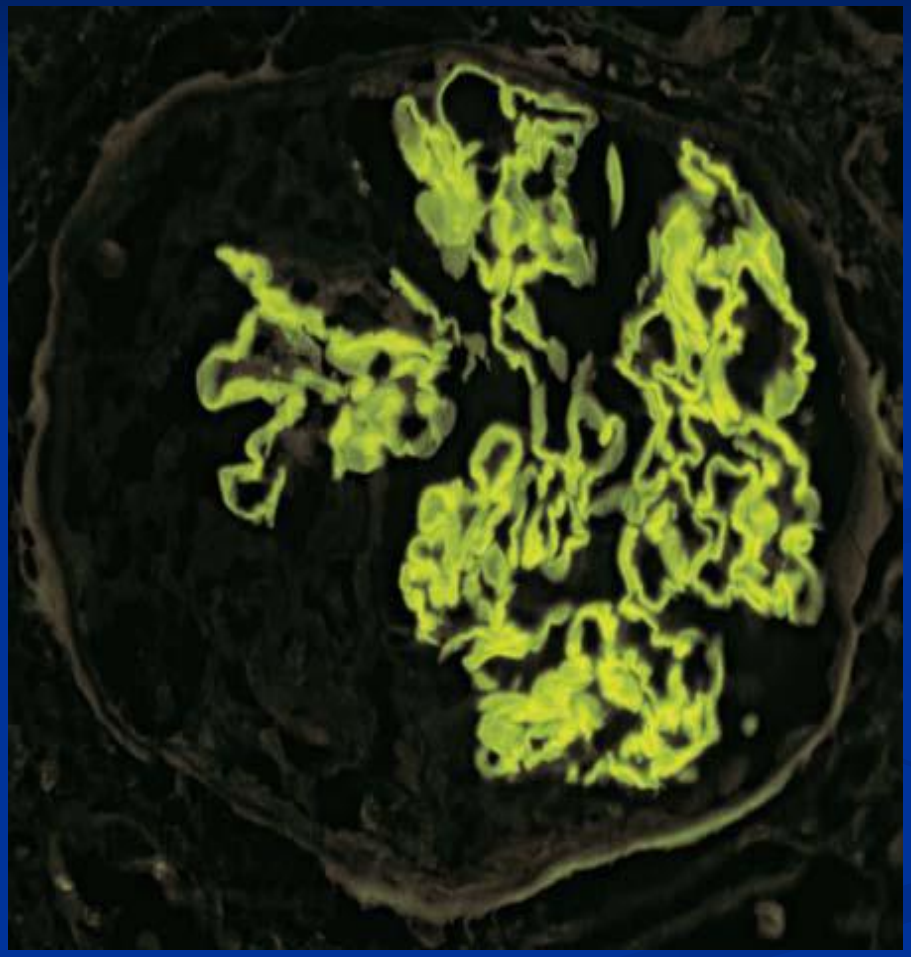
Arch Bronconeumol. 2008;44(8):428-36

Antibody mediated Vs Immune Complex Disease

SPECIFIC CAUSE	FREQUENCY	SUGGESTIVE DIAGNOSTIC FEATURES	SUGGESTIVE SEROLOGIC FEATURES
Goodpasture syndrome	20%–100% of patients develop alveolar hemorrhage (more likely in smokers and in men)	Smoking, hydrocarbon exposure, pulmonary-renal syndrome	Antiglomerular basement membrane antibody positivity Linear immunoglobulin G glomerular membrane deposits
Systemic lupus erythematosus	Up to 11% of patients have diffuse alveolar hemorrhage at onset (more commonly than any other connective tissue disorder)	Fever, arthralgia, rash	ANA positivity Anti-dsDNA antibodies Decreased C3 and C4

Arch Bronconeumol. 2008;44(8):428-36

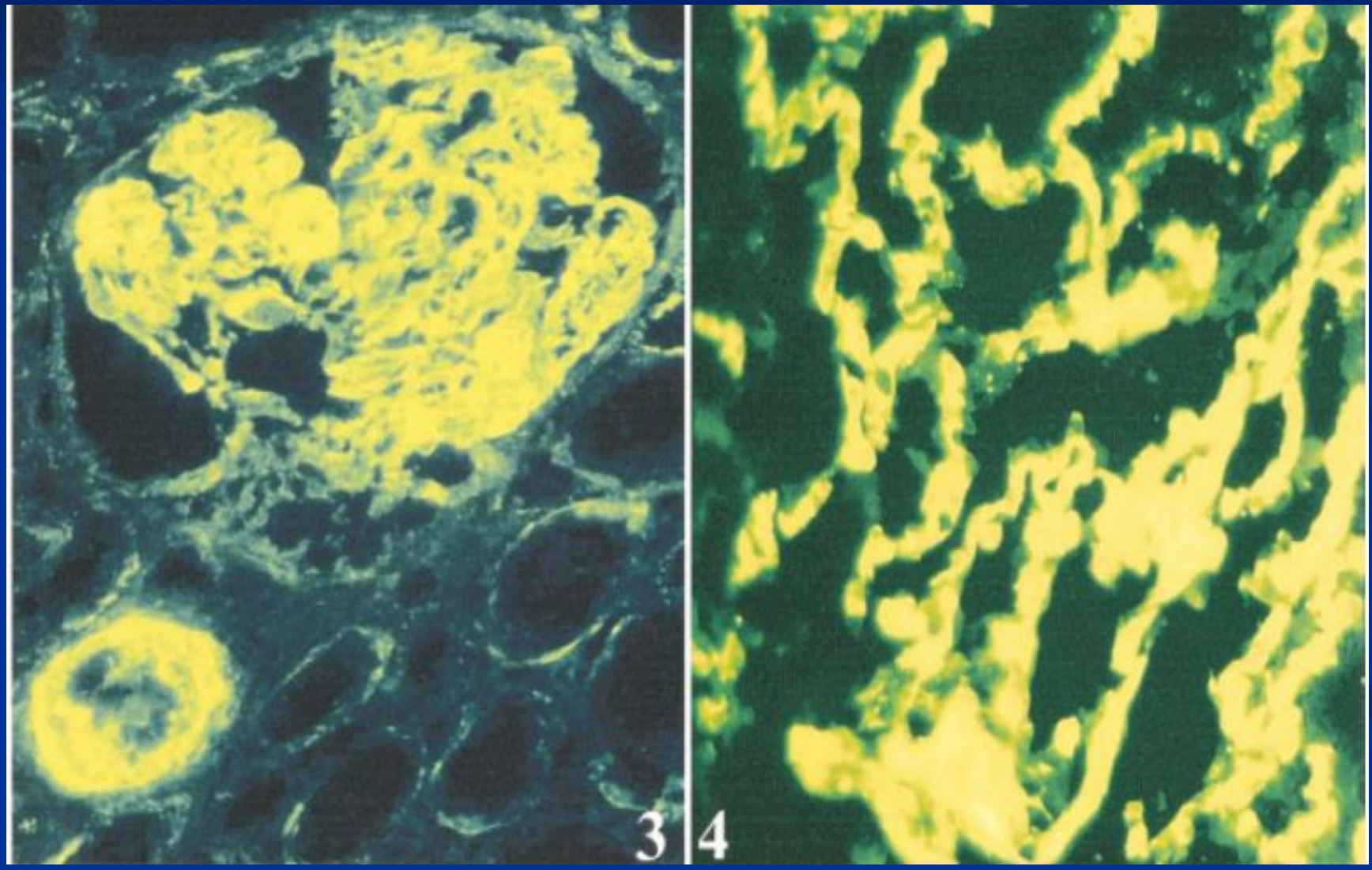
Renal Glomerulus with anti-GBM Disease



Linear staining of the GBM by direct immunofluorescence microscopy using an antibody specific for immunoglobulin G (Ig G)

Granular Immunofluorescence in SLE

Renal and Lung Immunofluorescence microscopy



Arch Pathol Lab Med—Vol 125, April 2001

Pauci-immune Vasculitis

SPECIFIC CAUSE	FREQUENCY	SUGGESTIVE DIAGNOSTIC FEATURES	SUGGESTIVE SEROLOGIC FEATURES
Wegener granulomatosis	Capillaritis in about one-third of patients	Glomerulonephritis, sinusitis, multiple cavitary pulmonary infiltrates, granulomata	c-ANCA positivity
Churg-Strauss syndrome	27%–77% of patients have radiographic abnormalities, but diffuse alveolar hemorrhage is very rare	Asthma, peripheral eosinophilia, cutaneous lesions, mononeuropathy or polyneuropathy, granulomata, tissue eosinophilia	p-ANCA positivity
Microscopic polyangiitis	Half of patients with pulmonary involvement present with diffuse alveolar hemorrhage	Systematic manifestations (glomerulonephritis, fever, myalgia, arthralgia) are more common than pulmonary disease (found in 40% of cases); necrotizing vasculitis	p-ANCA positivity

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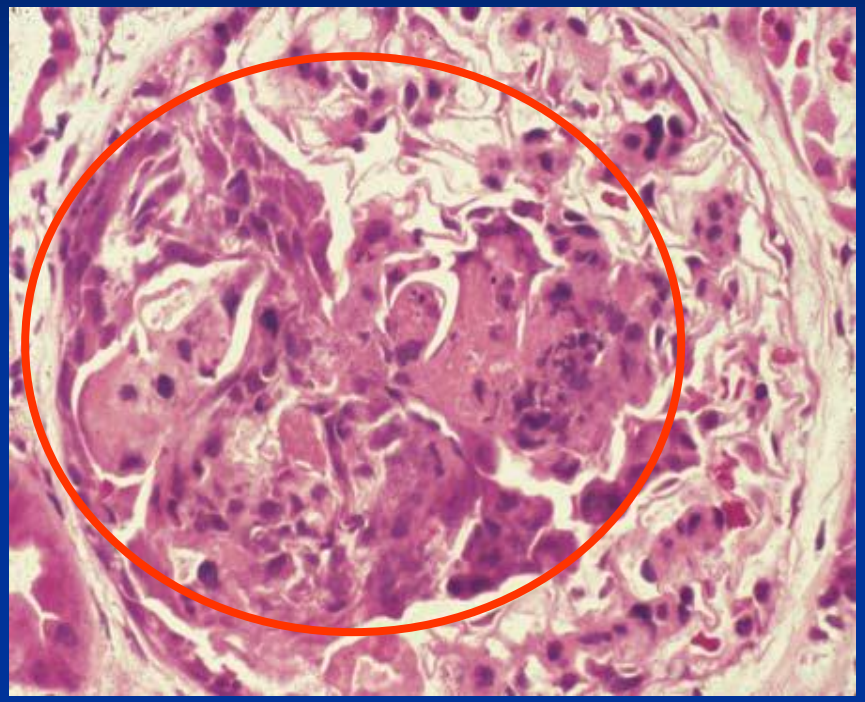
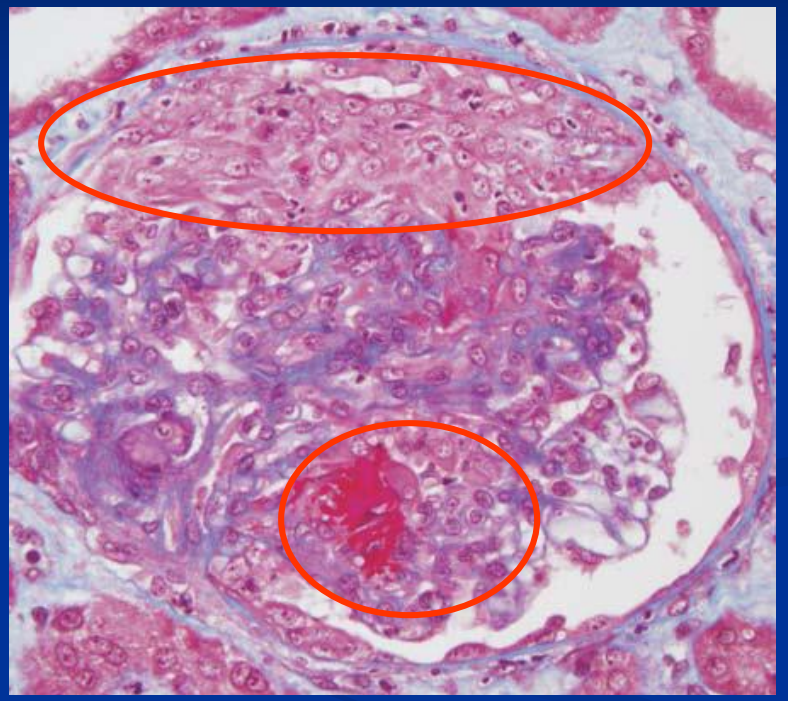
Crescentic Glomerulonephritis in Pauci immune Vasculitis

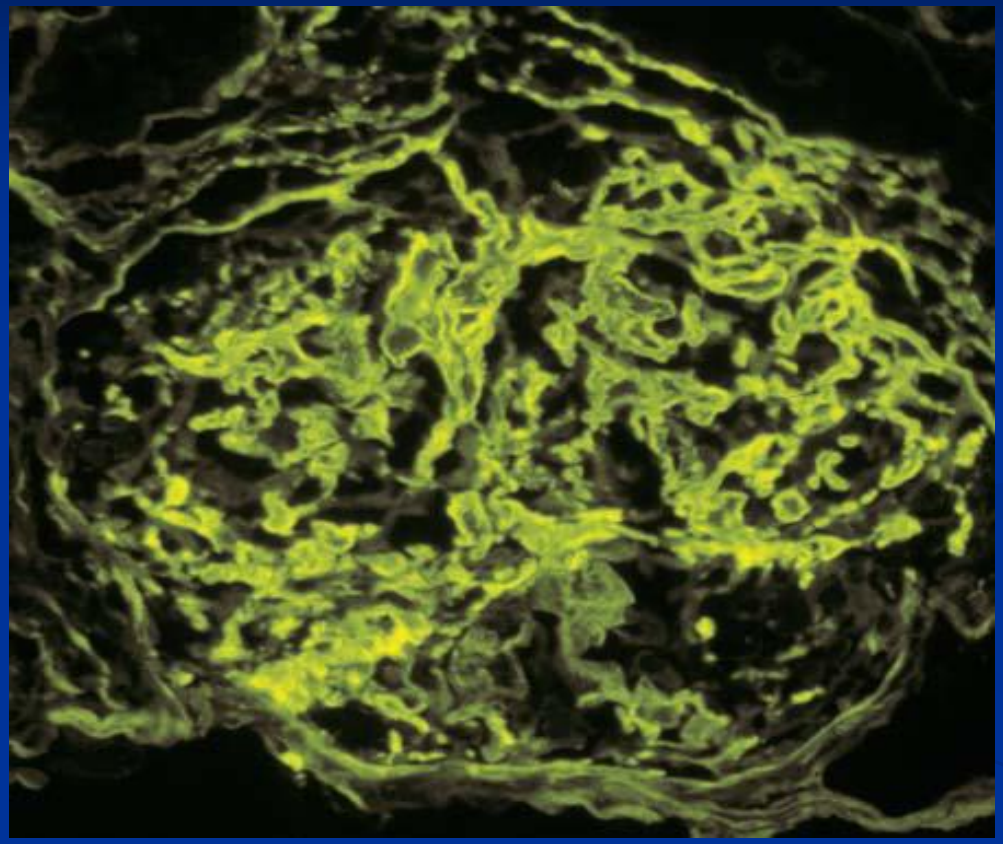


WG segmental fibrinoid necrosis and cellular crescent



MPA: cellular crescent at the top of the image and a small irregular (red) focus of fibrinoid necrosis

Direct immunofluorescence of ANCA Crescentic GN



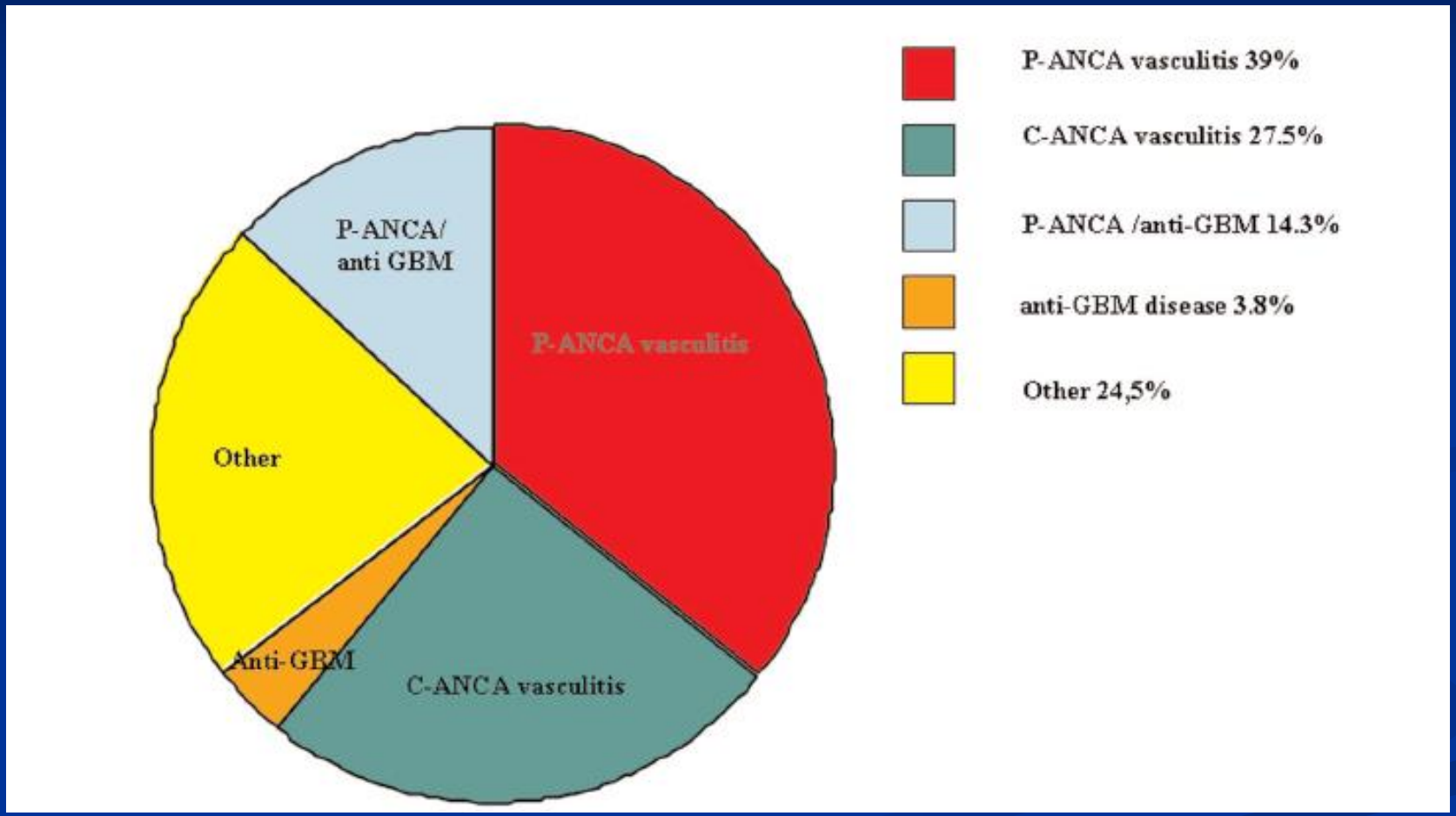
Irregular staining of a large crescent by IF microscopy using an antibody specific for fibrin

Pulmonary Renal Syndromes

- Pulmonary–renal syndrome in drug-associated ANCA-positive vasculitis
  - Propylthiouracil
  - D-Penicillamine
  - Hydralazine
  - Allopurinol
  - Sulfasalazine
- Pulmonary–renal syndrome in anti-GBM-postive and ANCA-positive patients
- Pulmonary–renal syndrome in autoimmune rheumatic diseases (immune complexes and/or ANCA mediated)
  - Systemic lupus erythematosus
  - Scleroderma (ANCA?)
  - Polymyositis
  - Rheumatoid arthritis
  - Mixed collagen vascular disease
- Pulmonary–renal syndrome in thrombotic microangiopathy
  - Antiphospholipid syndrome
  - Thrombotic thrombocytopenic purpura
  - Infections
  - Neoplasms
- Diffuse alveolar haemorrhage complicating idiopathic pauci-immune glomerulonephritis

Critical Care Vol 11 No 3 Papiris *et al.*

Relative Frequencies of Vasculitis



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Profiles of selected conditions that cause diffuse alveolar hemorrhage

	WEGENER GRANULOMATOSIS	MICROSCOPIC POLYANGIITIS	CHURG-STRAUSS SYNDROME	GOODPASTURE SYNDROME	SYSTEMIC LUPUS ERYTHEMATOSUS	IDIOPATHIC PULMONARY HEMOSIDEROSIS
Incidence (millions per year)[12–19]	8.5–10.3	6.8–8.9	0.5–3.7	3.0–4.0	60–350	0.2–1.2
Laboratory findings[20–24]						
Anti-GBM	No	No	No	Yes	No	No
c-ANCA	Yes	Possible	Possible	No	No	No
p-ANCA	Possible	Yes	Possible	No	No	No
ANA	No	No	No	No	Yes (99%)	No
Eosinophilia	Rare, mild	Rare, mild	Often, severe	Rare, mild	Possible	Possible
Organ involvement[20–24]						
Lungs	55%–90%[25–29]	25%–50%[36,37]	40%[42]	60%–94%[19,38,44]	50%–70%[45–49]	Always[52,53]
Diffuse hemorrhage	17%–50%[25,30,31]	10%–50%[38–40]	Rare[42,43]	80%–94%[19,38,43]	4%–20%[48,50]	Always[52,53]
Diffuse infiltrates	>15%[32]	>50%[32]	30%–70%[42,43]	80%–94%[19,38,43]	50%–70%[51]	Possible[52,53]
Kidney	70%–85%[26–29,33–35]	80%–90%[41]	25%	41%–71%[19,38]	Often	No
Other organs	Often	Often	Yes	No	Possible	No
Asthma[20]	Rare	Rare	Often	No	No	No
Prognosis[40,48,54–62]						
2-year survival	35%–37%	25%	20%–50%	33%–50%	50%–90%	25%
5-year survival	50%	35%–40%	20%–30%	80%	80%	5%–15%

Reaching Diagnosis in Challenging Cases

Hemoptysis and renal failure is not equivalent to pulmonary renal syndrome

Evaluating PAH and Hematuria

Are you dealing with a systemic vasculitis	Y/N
Is there evidence of oral and nasal inflammation	Y/N
Any history of Asthma, eosinophila or paranasal sinus disease	Y/N
Is there palpable purpra, arthritis or/and abdominal pain	Y/N
Does patient has bilateral pulmonary infiltrates + bronchoscopy with hemorrhagic BAL	Y/N
Oral and genital ulceration, uveitis and skin lesions	Y/N
Is there history of D-penicillamine or PTU use or BMT	Y/N
Risk factors for pneumonia with renal failure, in an immunosuppressed host (bacterial/viral or PCP)	Y/N
Is there new congestive heart failure with prior hx renal disease	Y/N

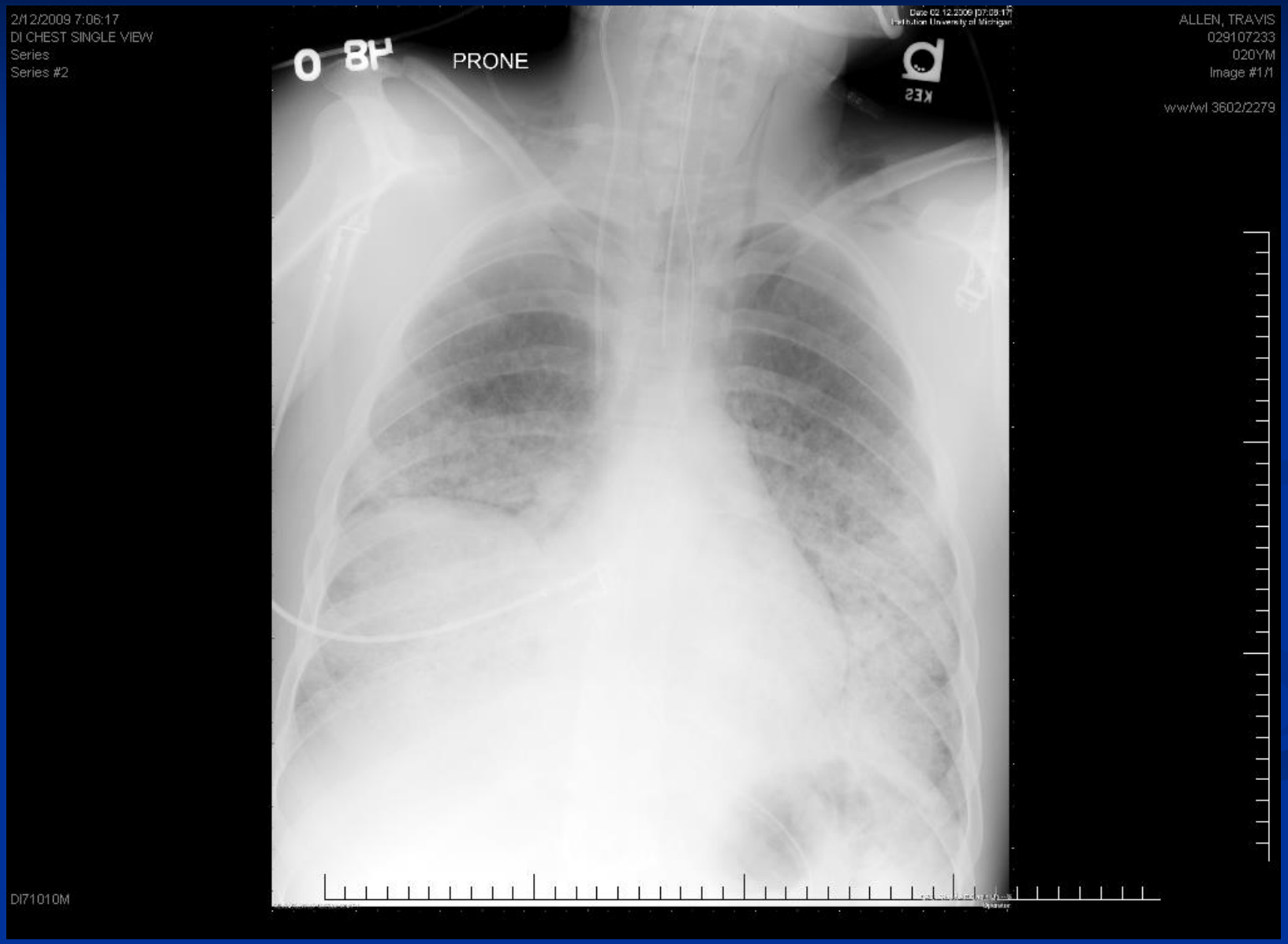
Evaluating PAH and Hematuria

Any evidence of MAHA (HUS/TTP): HPT, LDH, DAT, Peripheral smear, Low PLT	Y/N
Possibility of a bleeding diathesis: DIC , Coags, coumadin	Y/N
Is there nephrotic proteinuria → Pulmonary Embolism	Y/N
Serologies Lupus: ANA, ENA, DsDNA, C3,C4 Pauci-Immune: ANCA, Pr3, MPO, AGBM Immune complex Vasculitis: Cryo, RF, viral hepatitis Antiphospholipid syndrome: DRVVT,CAB, B2GP1	Y/N
Tissue biopsy showing necrosis, vasculitis, granulomatous inflammation	

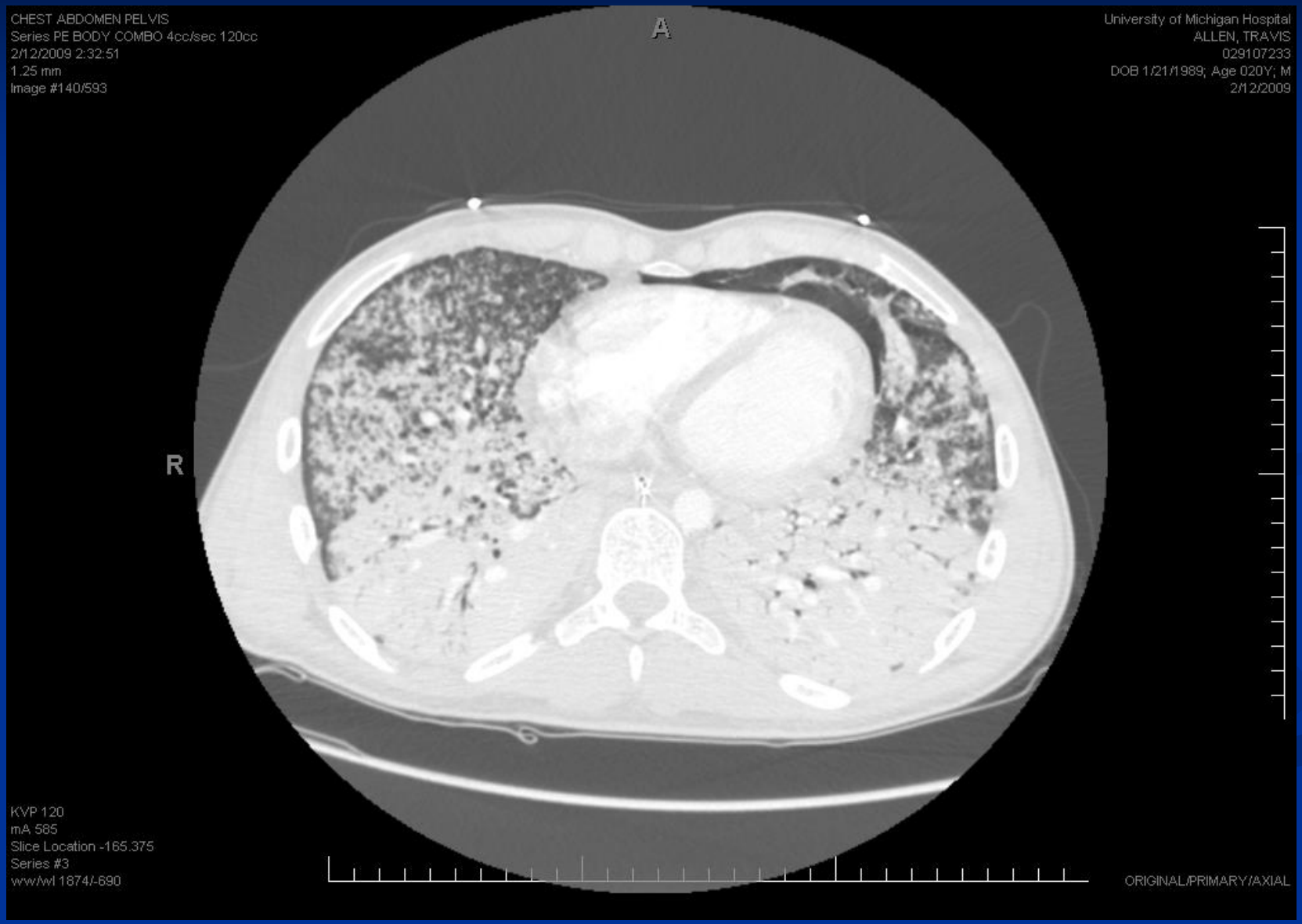
Case-1

Age/Sex	20 Male
Prior Hx	Neurofibromatosis
Presentation	Fevers, Respiratory distress, Hemoptysis
Laboratory	Wbc 15, hb 8, plt 395, creat 0.8, Ur: rbc5, no cast, pr30mg
COAGS	Normal ptt, inr, hpt, ldh
Chest X-ray	Pulmonary edema, pneumonia, pl eff
Chest CT	Bilateral opacities multilobar infection, ARDS. No PE
BAL/Bronch	sub segmental blood clots, no fresh blood
Microbiology	Legionalla and mycoplasma (neg), BAL : GS, Tb and fungal negative
ECHO	Not done
Immunology	Negative NAB, NCAB,CAB. Positive AGBM
Biopsy	Not done

DAH in a 20 year old male



DAH in a 20 year old male



Developing Differential Diagnosis

• necrotizing nasal or oral inflammation with granulomatous vasculitis? (Y or N)	N
• systemic vasculitis? (Y or N)	Y
• asthma, eosinophilia, and paranasal sinus diseas? (Y or N)	N
• palpable purpura, arthritis, and abdominal pain with acute GI hemorrhage? (Y or N)	N
• microangiopathic hemolytic disease? (Y or N)	N
• oral and genital aphthous ulcers, uveitis and skin lesions? (Y or N)	N
• recent history of D-penicillamine therapy? (Y or N)	N
• history of renal disease with signs of congestive heart failure? (Y or N)	N
• pneumonia with renal failure? (Y or N)	Y
• nephrotic level proteinuria? (Y or N)	N
• antibodies to glomerular basement membrane (anti-GBM)? (Y or N)	Y
• p-ANCA? (Y or N)	N
• c-ANCA? (Y or N)	N
• cryoglobulins? (Y or N)	N
• high titer of Rheumatoid factor (RF)? (Y or N)	N
• high titers of antinuclear antibodies (ANA)? (Y or N)	N

Differential Diagnosis and Treatment

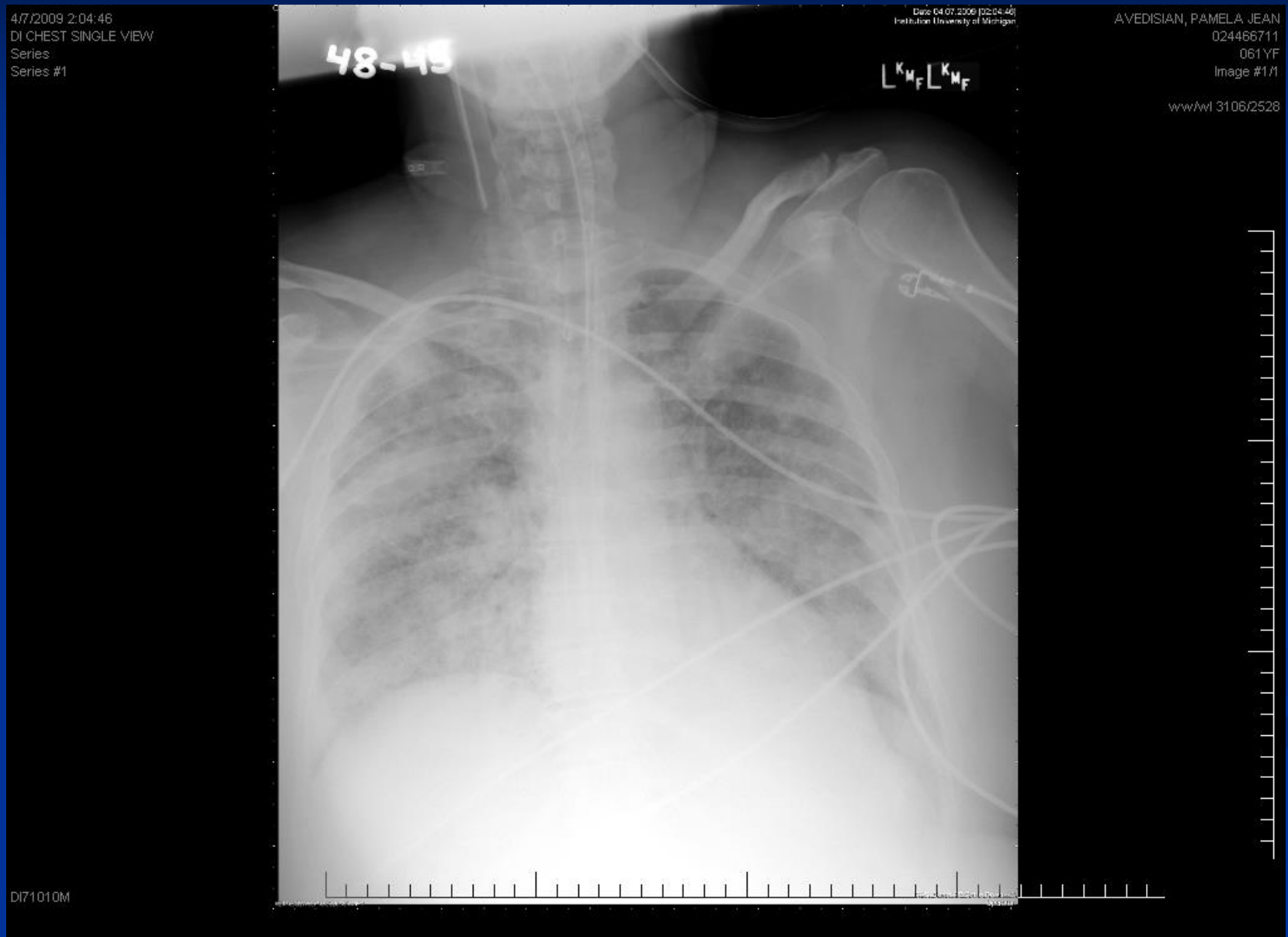
- Goodpastures's disease
- Infection

- Pulse dose steroids x3
- Plasmapheresis
- IV Cytoxan
- Broad spectrum antibiotics pending cultures
- IVIG for hypogammaglobulinemia
- Resulted in favorable outcome

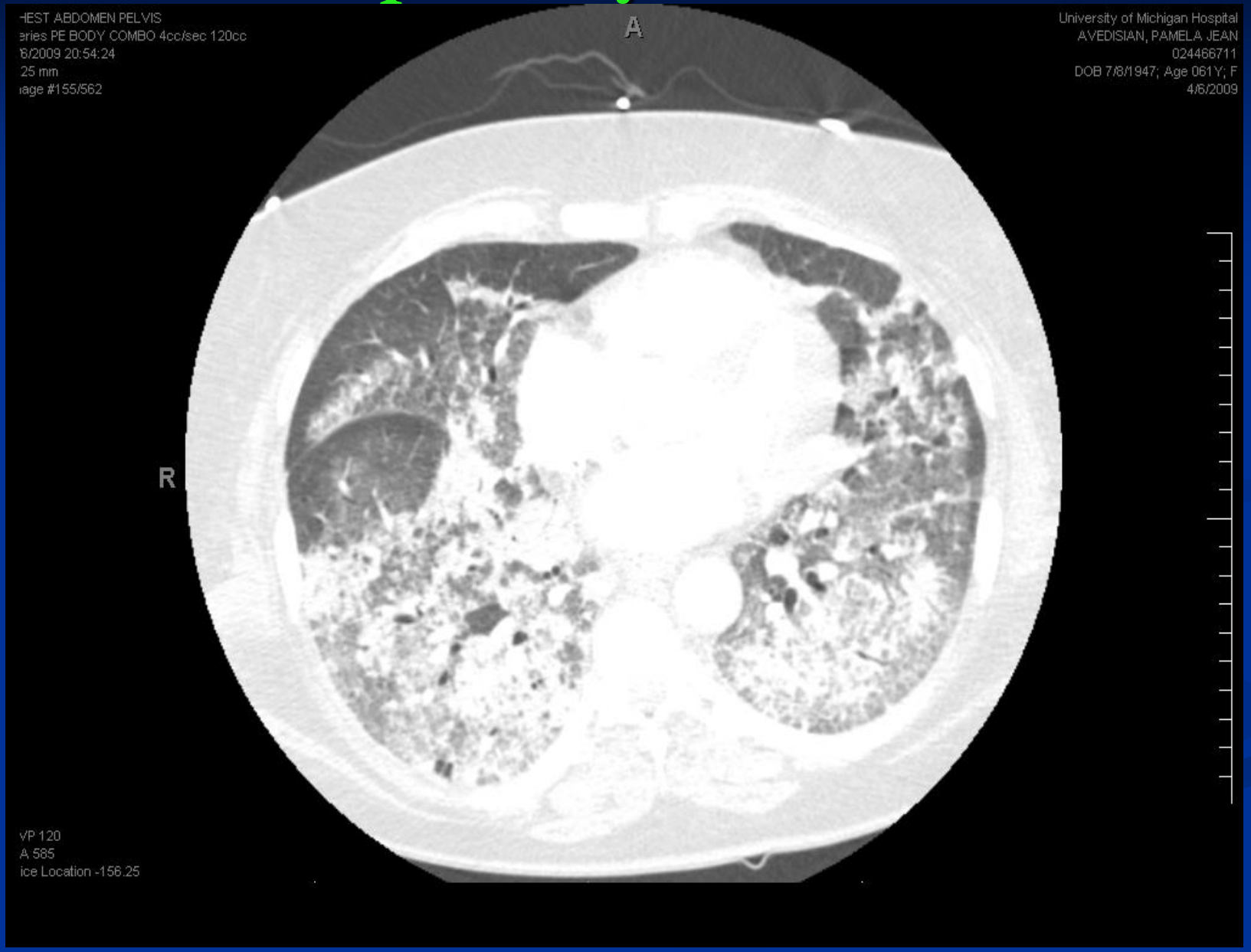
Case-2

Age/Sex	61 F recent travel to Mexico
Prior Hx	Hypertension, Dyslipedemia, Bronchitis
Presentation	Acute dyspnea, Fatigue and dry cough
Laboratory	Wbc 8.1, hb 9, plt 212, creat 0.9, Ur: rbc 100, no cast, pr
COAGS	Normal ptt, inr. (Hpt, LDH, DAT not done)
Chest X-ray	Pulm edema/ARDS and/or multifocal pneumonia
Chest CT	B/L consolidations and ground glass opacities, No PE
BAL/Bronch	Moderate amount of blood
Microbiology	Legionnella (neg), BAL : G.S,Tb and fungal negative
Echo	LVH, EF 60%
Immunology	Pos: P-anca, +MPO, Negative NAB,CAB,AGBM
Biopsy	Renal: Moderate to severe arteriolosclerosis; diffuse tubular injury/focal tubular necrosis

Acute Respiratory Distress in 61 F



Acute Respiratory Distress in 61 F



Developing Differential Diagnosis

• necrotizing nasal or oral inflammation with granulomatous vasculitis? (Y or N)	N
• systemic vasculitis? (Y or N)	Y
• asthma, eosinophilia, and paranasal sinus diseas? (Y or N)	Y
• palpable purpura, arthritis, and abdominal pain with acute GI hemorrhage? (Y or N)	N
• microangiopathic hemolytic disease? (Y or N)	N
• oral and genital aphthous ulcers, uveitis and skin lesions? (Y or N)	N
• recent history of D-penicillamine therapy? (Y or N)	N
• history of renal disease with signs of congestive heart failure? (Y or N)	N
• pneumonia with renal failure? (Y or N)	Y
• nephrotic level proteinuria? (Y or N)	N
• antibodies to glomerular basement membrane (anti-GBM)? (Y or N)	N
• p-ANCA? (Y or N)	Y
• c-ANCA? (Y or N)	Y
• cryoglobulins? (Y or N)	N
• high titer of Rheumatoid factor (RF)? (Y or N)	N
• high titers of antinuclear antibodies (ANA)? (Y or N)	N

Differential Diagnosis and Treatment

- Microscopic polyangitis
- Churg-Strauss Syndrome
- Pneumonia

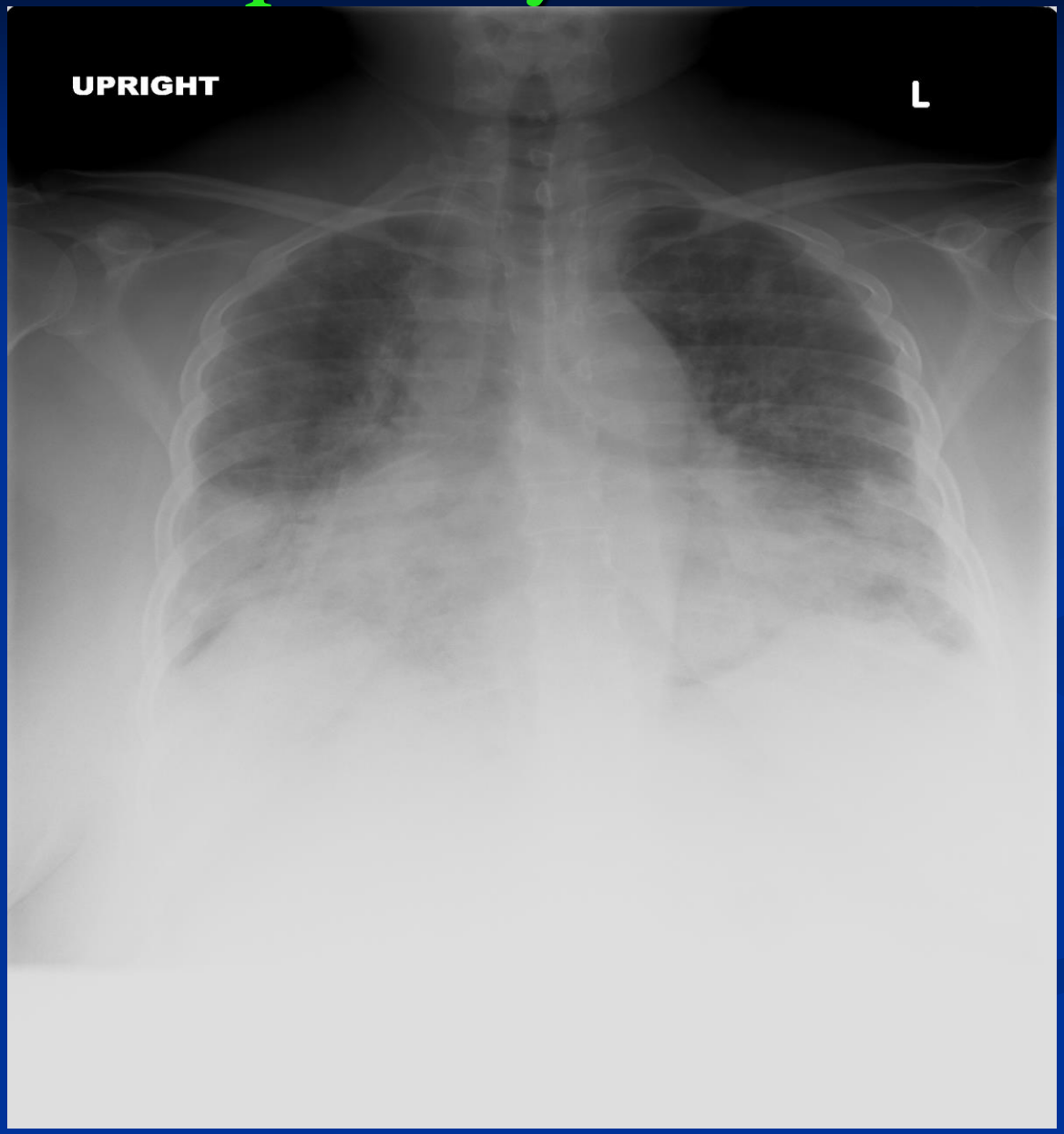
  Legionalla or PCP, Nosocomial infection

- Pulse dose steroids x3
- Plasmapheresis
- Hold Cytoxan concern for infection-pending cultures
- Broad spectrum antibiotics
- IV Cytoxan started after Renal biopsy
- Resulted in favorable outcome

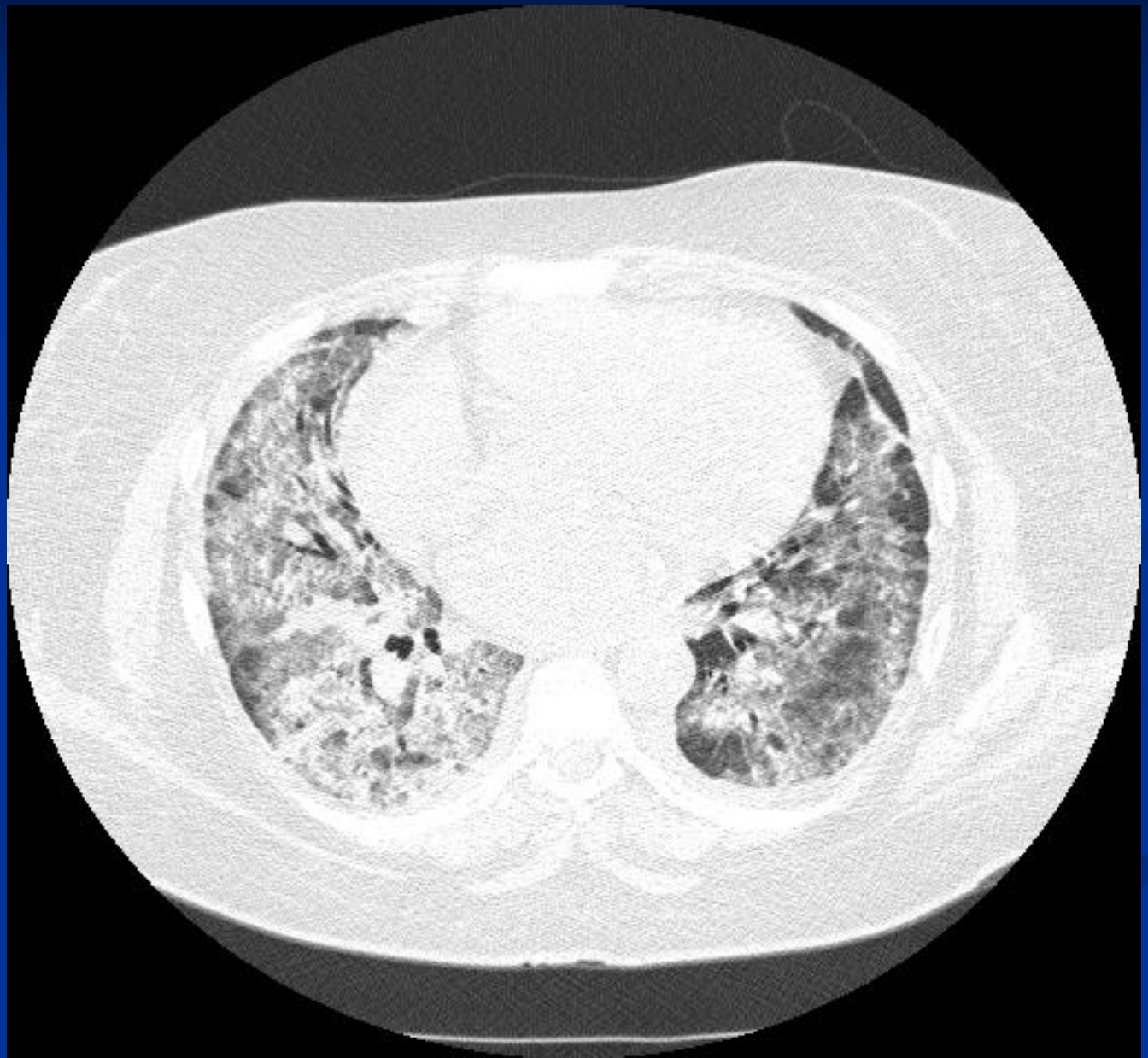
Case-3

Age/Sex	38/F
Prior Hx	Lupus
Presentation	SOB, cough with streaks of blood, not frank hemoptysis
Laboratory	Wbc 15, Hb 8->6.5 , Plt 155->85, Creat 1.5->2.6, Pr/cr : 12 g, Ur: 10rbc , smear 1-3 schitiocytes
COAGS	Normal PTT , INR, HPT 3, LDH 1415, DAT neg
Chest X-ray	Airspace opacities bilaterally, pulmonary edema, pneumonia and pulmonary hemorrhage
Chest CT	Pulmonary hemorrhage or pneumonitis
BAL/Bronch	RBC 147,000, WBC 1197
Microbiology	BAL(9/9) NEG, BAL 9/20: + Staph; neg AFB, FNG
Echo	Globally hypokinetic left ventricle , LVEF 40%
Immunology	NAB, DsDNA, Low C3,C4. Neg PR3,MPO,AGBM
Biopsy	Membranous focal necrotizing and proliferative GN

Acute Respiratory Distress in 38 F



Acute Respiratory Distress in 38 F



Acute Respiratory Distress in 38 F

• necrotizing nasal or oral inflammation with granulomatous vasculitis? (Y or N)	N
• systemic vasculitis? (Y or N)	Y
• asthma, eosinophilia, and paranasal sinus diseas? (Y or N)	N
• palpable purpura, arthritis, and abdominal pain with acute GI hemorrhage? (Y or N)	Y
• microangiopathic hemolytic disease? (Y or N)	Y
• oral and genital aphthous ulcers, uveitis and skin lesions? (Y or N)	N
• recent history of D-penicillamine therapy? (Y or N)	N
• history of renal disease with signs of congestive heart failure? (Y or N)	Y
• pneumonia with renal failure? (Y or N)	Y
• nephrotic level proteinuria? (Y or N)	Y
• antibodies to glomerular basement membrane (anti-GBM)? (Y or N)	N
• p-ANCA? (Y or N)	N
• c-ANCA? (Y or N)	N
• cryoglobulins? (Y or N)	N
• high titer of Rheumatoid factor (RF)? (Y or N)	N
• high titers of antinuclear antibodies (ANA)? (Y or N)	Y

Differential Diagnosis and Treatment

- Lupus nephritis flare with pulmonary hemorrhage
- TTP or HUS
- End-stage renal disease with congestive heart failure
- Legionalla pneumonia
- Nephrotic syndrome with hypercoagulable state causing a pulmonary embolus

- Pulse steroids
- Plasmapheresis
- Broad spectrum antibiotics
- IVIG
- Cytoxan
- Rituxan
- IVIG
- Cellcept

Alveolar Hemorrhage and Renal Microangiopathy in Systemic Lupus Erythematosus

Immune Complex Small Vascular Injury With Apoptosis

Michael D. Hughson, MD; Zhi He, MD; Jeffrey Henegar, PhD; Robert McMurray, MD

- 6 lupus, 2 with alveolar hemorrhage and 1 with diffuse alveolar damage (ARDS), 6/6 active lupus nephritis
- 2/3 lung pathology showed bland alveolar wall changes and immune complex deposits
- Patient with diffuse alveolar damage had invasive aspergillosis
- All 3/6 with pulmonary complications died, 2/6 received pulse steroids and 1 received cytoxan, No one received plasma exchange

Alveolar and Renal Microangiopathy

Lupus Patients With and Without Alveolar Hemorrhage: Summary of Clinical and Pathological Findings

Patient No.	Age, y/ Sex	Diagnosis	Cause of Death	Pulmonary Pathology	Renal Pathology†
1	28/F	SLE	Alveolar hemorrhage	Alveolar hemorrhage, bland alveolar wall changes, IgG, IgM, IgA, and EM alveolar wall deposits	Class IVb lupus nephritis (with segmental necrotizing lesions), lupus microangiopathy
2	22/F	SLE	Alveolar hemorrhage	Alveolar hemorrhage, bland alveolar wall changes, EM alveolar wall EM deposits	Class IVc lupus nephritis (with segmental necrotizing and sclerosing lesions), lupus microangiopathy
3	34/F	SLE	Mesenteric artery thrombosis, small intestinal infarction, septicemia	Pulmonary congestion, edema; no EM of IF alveolar wall deposits	Class IIb lupus nephritis (mesangial hypercellularity), arteriolosclerosis
4	19/M	Overlap syndrome, SLE-scleroderma	Colonic perforation, peritonitis, septicemia	Bronchopneumonia; no EM alveolar wall deposits	Class Va lupus nephritis (pure membranous nephropathy)
5	49/M	SLE	Diffuse alveolar damage, aspergillosis	Hyaline membranes, invasive aspergillosis; no EM of IF alveolar wall deposits	Class IVa lupus nephritis (mesangiocapillary proliferation without segmental lesions), arteriolosclerosis
6	21/M	SLE	Herpes simplex pneumonia	Herpes simplex pneumonia; no EM or IF alveolar wall deposits; pulmonary fibrosis, interstitial and alveolar; pleural fibrosis	Class Vc lupus nephritis (membranous glomerulonephritis associated with focal and segmental endocapillary hypercellularity, crescents, and sclerosis), uncomplicated IgG, IgM, C3, and C1q arteriolar deposits

Diffuse Alveolar Hemorrhage in SLE

- 510 lupus patients - 19 admissions for DAH (15 patients)
- 14/15 - lupus nephritis, 7/15 on monthly Cytoxan and prednisone >20mg
- Most episodes treated with pulse dose steroids, 10/19 IV Cytoxan and 12/19 received plasmapheresis
- 53 % overall mortality (concurrent infection 78%, no infection 20%, prior Cytoxan use 70%, poor prognostic factors Mech. ventilation and infection
- 6/19 - Primary lung infection (HSV and Legionalla, CMV, staph)
- Patients on Cytoxan, 4/6 (had primary infection versus only 2 patients among 8 who were not on Cytoxan)
- 3/19 episodes were associated with nosocomial infection (Ecoli, MRSA and Candida)

Medicine Issue: Volume 76(3), May 1997, pp 192-202 , ZAMORA, MARTIN R. etal

Review of Treatment

- Use of Immunosuppression and Plasma Exchange in PRS - 13 case series and 1 RCT
  - Goodpastures's Syndrome
  - Small Vessel Vasculitis
  - SLE
  - Antiphospholipid Syndrome
- Non Immunosuppressive Treatment Modalities in DAH

Long-Term Outcome of Anti–Glomerular Basement Membrane Antibody Disease Treated with Plasma Exchange and Immunosuppression

Jeremy B. Levy, MA, PhD, MRCP; A. Neil Turner, PhD, FRCP; Andrew J. Rees, MSc, FRCP, FMedSci; and Charles D. Pusey, MSc, FRCP, FRCPath

- 71 patients with positive anti GBM antibody disease presented who with pulmonary hemorrhage and rapidly progressive GN
- Followed in three categories based on renal function at presentation
  - Creatinine <5.6mg/dl (<500mgUmol/l), n=19
  - Creatinine >5.6mg/dl(>500mgUmol/l) but no dialysis dependent, n=13
  - Dialysis dependent with in 72 hours, n=39
- All treated with IS including oral prednisone 1mg/kg(or 60mg max), Cytoxan (2-3mg/kg/day) for 2-3 months, No Pulse steroids
- Plasma exchange (50ml/kg or 4L)daily for at least 14days

Ann Intern Med. 2001;134:1033-1042.

Survival at 1 Year

Renal Function at Presentation	Patients	Median Creatinine Concentration	Median Proportion of Crescents (Range)	1-Year Patient Survival
	n	*μmol/L*	%	←
Creatinine concentration < 500 μmol/L	19	207 (53–475)	28 (0–87)	19 (100)
Creatinine concentration ≥ 500 μmol/L	13	700 (505–955)	55 (38–100)	11 (83)
Dialysis dependent	39	NA	100 (62–100)	26 (65)
Total	71	317 (53–955)	41 (0–100)	55 (77)

Long-Term Survival

Renal Function at Presentation	Patients	Median Follow-Up	5-Year Patient Survival*	Current Survival	Median Time to Death (Range)
	n	*mo*	*n (%)*		*mo*
Creatinine concentration < 500 μmol/L	19	120 (12–280)	16 (94)	16 (84)	267 (12–280)
Creatinine concentration ≥ 500 μmol/L	13	96 (1–265)	8 (80)	8 (62)	96 (1–120)
Dialysis dependent	39	22 (0.2–289)	16 (44)	14 (36)	5 (0.2–237)
Total	71	90 (0.2–289)	40 (63)	38 (54)	9 (0.2–280)

Renal Function at Presentation	Patients	Median Time to Death (Range)	Surviving Patients with Independent Renal Function	
			At 5 Years†	At Death or Last Follow-Up
	n	*mo*	*n (%)*	
Creatinine concentration < 500 μmol/L	19	267 (12–280)	15 (94)	14 (74)
Creatinine concentration ≥ 500 μmol/L	13	96 (1–120)	4 (50)	9 (69)
Dialysis dependent	39	5 (0.2–237)	2 (13)	2 (5)
Total	71	9 (0.2–280)	21 (53)	25 (35)

Plasmapheresis Therapy for Diffuse Alveolar Hemorrhage in Patients With Small-Vessel Vasculitis

Philip J. Klemmer, MD, W. Chalermskulrat, MD, Michael S. Reif, MD, Susan L. Hogan, PhD, David C. Henke, MD, and Ronald J. Falk, MD

- 20 pts with DAH and confirmed Pauci-immune SVV
- 17MPA, 2 WG,1 CSS at UNC
- Treated with pulse dose steroids x3 days, 18/20 received intravenous cytoxan (0.5g/m2) and plasmapheresis daily until DAH improved, Mean number of apheresis 6(range 4-9)
- Average time to admission and first exchange was 2 days
- DAH had 100% response rate
- 14/20 (70%) had abnormal renal function on admission
- Creatinine (4.5+/- 4.5)at baseline and on discharge 2.4=/- 0.8.

Clinical Parameters in SVV

Patient No.	Sex	Race	Admission Age (y)	Diagnosis	ANCA Pattern	Admission Hematocrit (units)	Admission Serum Creatinine (mg/dL)	Ventilator Required	Days on Ventilator	Apheresis Treatments	Lung Symptom Outcome
1	F	C	61	MPA	C	24.0	0.8	Yes	5	6	Resolved
2	M	C	49	MPA	C	24.0	16.6	No	NA	4	Resolved
3	M	C	72	MPA	C	25.0	0.7	No	NA	8	Resolved
4	F	AA	92	MPA	P	19.0	3.9	Yes	2	5	Resolved
5	F	C	75	MPA	P	19.0	7.8	Yes	6	6	Resolved
6	F	C	72	WG	P	23.0	1.2	Yes	10	7	Resolved*
7	M	C	50	CS	C	34.0	0.9	No	NA	6	Resolved
8	M	C	65	MPA	P	20.0	7.0	No	NA	6	Resolved
9	F	C	68	MPA	P	22.6	4.6	Yes	7	6	Resolved
10	F	AA	71	MPA	Negative	23.0	10.5	Yes	12	7	Resolved
11	M	AA	70	MPA	P	18.6	9.7	Yes	3	9	Resolved
12	M	H	43	MPA	C	28.0	1.0	No	NA	4	Resolved
13	F	C	60	MPA	P	17.0	2.5	No	NA	5	Resolved
14	M	C	70	MPA	P	20.0	7.2	No	NA	4	Resolved
15	M	C	60	MPA	P	18.9	3.4	Yes	6	6	Resolved
16	F	C	58	MPA	P	19.7	1.8	Yes	26	9	Resolved
17	F	C	77	MPA	P	24.0	5.8	No	NA	6	Resolved
18	M	AA	41	WG	C	45.0	1.6	No	NA	6	Resolved
19	F	C	59	MPA	P	30.9	0.8	No	NA	6	Resolved
20	M	C	78	MPA	P	24.0	9.7	No	NA	7	Resolved
Total	10 F,	15 C,	63 ± 11	1 CS,	6 C,	24.0 ± 6.5	4.7 ± 4.0	9/20	8.5 ± 7.2;	6.15 ± 1.42	100%

American Journal of Kidney Diseases, Vol 42, No 6 (December), 2003

RCT: Plasmapheresis and Pulse Steroids

CLINICAL RESEARCH www.jasn.org

Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis

David R.W. Jayne,* Gill Gaskin,† Niels Rasmussen,‡ Daniel Abramowicz,§ Franco Ferrario,‖ Loic Guillevin,¶ Eduardo Mirapeix,** Caroline O.S. Savage,†† Renato A. Sinico,‖ Coen A. Stegeman,‡‡ Kerstin W. Westman,§§ Fokko J. van der Woude,‖‖ Robert A.F. de Lind van Wijngaarden,¶¶ and Charles D. Pusey; on behalf of the European Vasculitis Study Group†

*Department of Medicine, Addenbrooke's, Hospital, Cambridge, United Kingdom; †Renal Section, Division of Medicine,

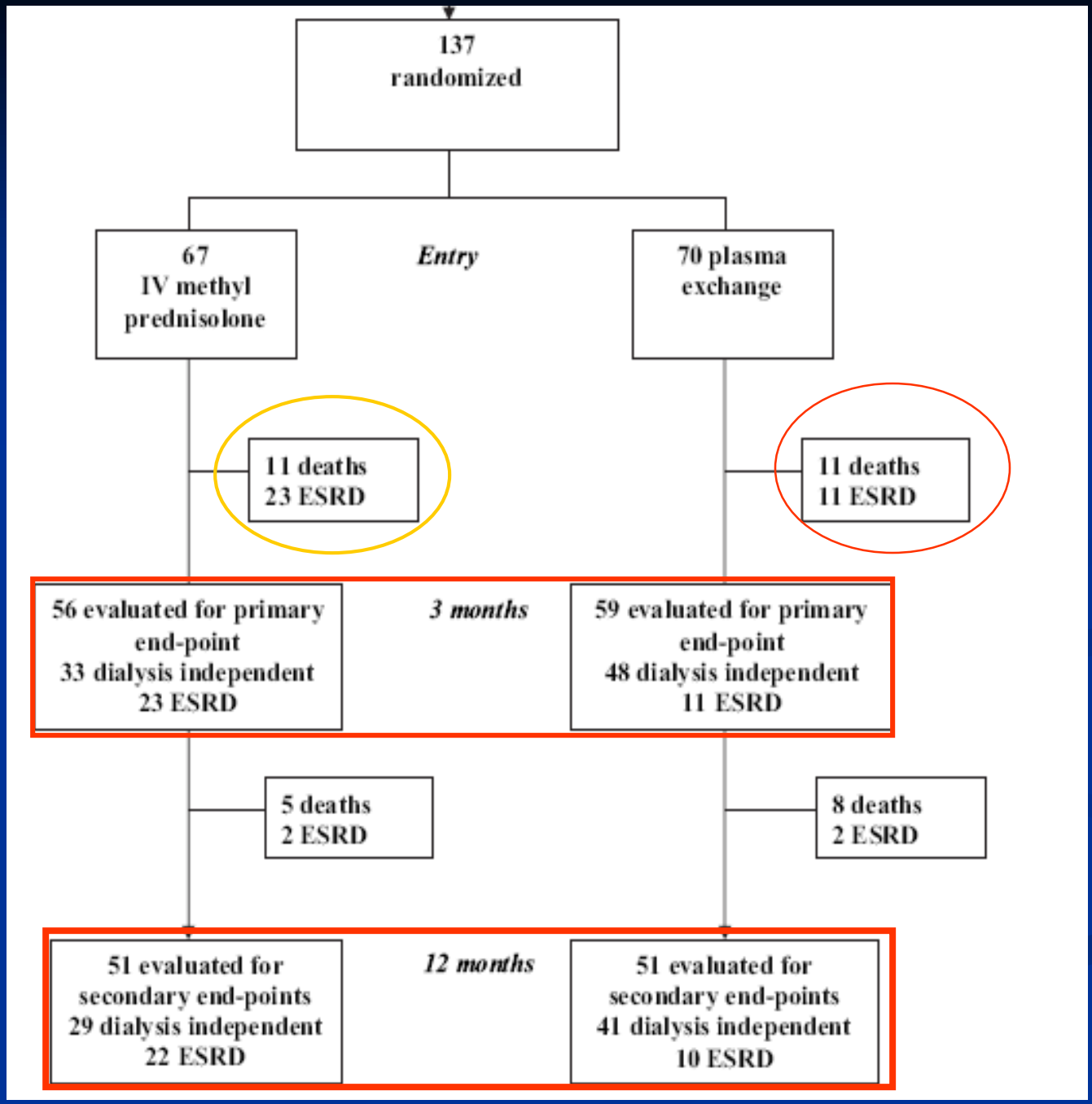
Study Design and Results

- 137 patients with ANCA-associated systemic vasculitis, biopsy confirmed and creatinine >5.8mg/dl were randomized
- One arm received seven plasma exchanges (n=70), second arm received Pulse steroids (total 3g)
- All received oral prednisone and Cyclophosphamide (details not clear)
- Renal survival follow up, HR for PE vs IVPS: 0.47(P+0.03)

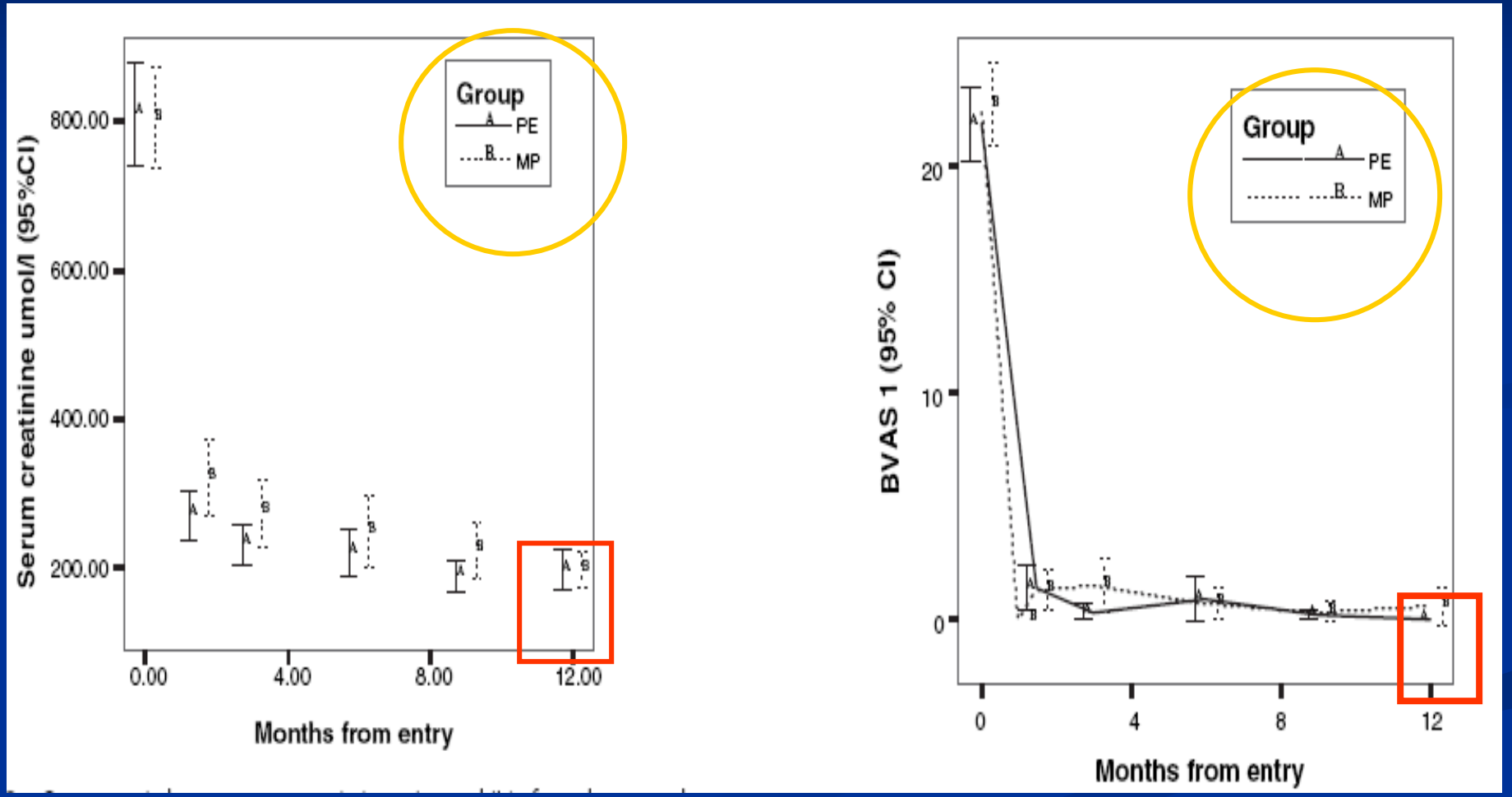
Duration	Pulse steroid	Apheresis	P value
3Month	49%	69%	0.02
12Month	43%	59%	0.008

Clinical and Serologic Characteristics

Clinical and Laboratory Features at Entry	Intravenous Methylprednisolone (*n* = 67)	Plasma Exchange (*n* = 70)	Total (*n* = 137)	*P*
Age (yr; median [range])	66 (27 to 81)	67 (28 to 79)	66 (27 to 81)	0.93
Female gender (*n* [%])	24 (36)	29 (41)	53 (38.7)	0.50
Wegener's granulomatosis/microscopic polyangiitis (*n* [%])	24/43 (35.8/64.2 8)	18/52 (25.7/74.3)	42/95 (30.7/69.3)	0.20
Nonoliguric/dialysis requiring (*n* [%])	19/48 (28.4/71.6)	23/47 (32.9/67.1)	42/95 (30.7/69.3)	0.57
PR3-ANCA (*n* [%])	31 (46.3)	26 (37.1)	57 (42.6)	0.35
MPO-ANCA (*n* [%])	31 (46.3)	40 (57.1)	71 (51.9)	
ANCA negative (*n* [%])	3 (4.5)	4 (5.7)	7 (5.3)	
BVAS	21 (12 to 41)	21 (12 to 39)	21 (12 to 41)	0.69
Vasculitis Damage Index (median [range])	0 (0 to 4)	0 (0 to 7)	0 (0 to 7)	0.86
Creatinine (μmol/L; median [range])	718 (498 to 1566)	754 (500 to 1669)	735 (498 to 1669)	0.96
C-reactive protein (mg/L; median [range])	108 (2 to 264)	76 (7 to 281)	93 (2 to 281)	0.23
Erythrocyte sedimentation rate (mm/h; median [range])	84 (2 to 150)	94 (20 to 140)	89 (2 to 150)	0.34


137
randomized
67
IV methyl
prednisolone
Entry
70 plasma
exchange
11 deaths
23 ESRD
11 deaths
11 ESRD
56 evaluated for primary
end-point
33 dialysis independent
23 ESRD
3 months
59 evaluated for primary
end-point
48 dialysis independent
11 ESRD
5 deaths
2 ESRD
8 deaths
2 ESRD
51 evaluated for
secondary end-points
29 dialysis independent
22 ESRD
12 months
51 evaluated for
secondary end-points
41 dialysis independent
10 ESRD

Renal Function and Vasculitis Activity



Adverse Effect Profile in Each Group were comparable

Clinical Nephrology, Vol. 54 – No. 4/2000 (282-288)

Diffuse alveolar hemorrhage in lupus nephritis

J.G. Lee[1], K.W. Joo[2], W.K. Chung[2], Y.C. Jung[3], S.H. Zheung[2], H.J. Yoon[2], Y.S. Kim[2], C. Ahn[2], J.S. Han[2], S. Kim[2], J.S. Lee[2]

[1]Department of Internal Medicine, Eulji University School of Medicine, [2]Department of Internal Medicine, College of Medicine, Seoul National University, Seoul, and [3]Department of Internal Medicine, Boondang Jaesaeng Hospital, Sungnam, Korea

- 7 lupus nephritis - 9 episodes DAH
- Serologic evidence of flare and lung biopsy c/w IC deposits
- Treated pulse dose steroids and IV Cytoxan (3/9) and oral 1mg/kg Cytoxan in 6/9 with no plasma exchange
- Mortality 57%, higher mortality associated with infections PCP and actinobacter, severe anemia at presentation and longer duration of mechanical ventilation

Pulmonary Hemorrhage in Systemic Lupus Erythematosus

Humeira Badsha, Cheng Lay Teh, Kok Ooi Kong, Tsui Yee Lian, and Hiok Hee Chng

Semin Arthritis Rheum 33:414-421

- 22 active lupus pts (SLEDAIs mean 12) who p/w respiratory distress and hemoptysis and all in the early course of lupus
- Preceding month of presentation there was rise in SLEDAI and DLCO
- 19 received pulse steroids and cytoxan(500mg/m2), 11/22 received plasmapheresis(2-6 times) but no added benefit from plasmapheresis
- 4/22 had concurrent infection
- Mortality 36%

Treatment of Hemorrhagic Lupus Pneumonitis With Plasmapheresis

R.W. Erickson, W.A. Franklin, and W. Emlen

Seminars in Arthritis andRheurnatism, Vo124, No 2 (October), 1994

- Three patients with biopsy proven acute alveolar capillaritis
- All patient received pulse dose steroids and IV cytoxan and plasma exchange and 2/3 improved with first treatments
- One patient also received IVIG for recurrent hemorrhage
- Very favorable outcome with plasmapheresis but catious for infection and procedure related complications which are reported as high 67% and 12%

Antiphospholipid Antibodies as a Cause of Pulmonary Capillaritis and Diffuse Alveolar Hemorrhage: A Case Series and Literature Review

Kevin D. Deane, MD,* and Sterling G. West, MD†

- Primary APS can cause DAH and alveolar capillaritis through APL antibody mediated endothelia cell activation in the absence of thrombosis
- All 4 patients with DAH treated with pulse dose steroids and IV monthly cytoxan (0.5 -1 g) for three months, two responded well to treatment
- 2/4 had recurrent pulmonary hemorrhage on switching intravenous to oral cytoxan and initiated IVIG (400mg/kg x5 days)
- Author also suggested empiric antibiotic coverage for infection

CASE REPORT

Recombinant factor VIIa and intravenous immunoglobulin therapy for diffuse alveolar haemorrhage: A cautionary tale?

Karen K.K. Sheares*, Ravi Mahadeva

Respiratory Medicine Division, Department of Medicine, Addenbrooke's NHS Trust, Hills Road, Cambridge CB2 2QQ, UK

Received 26 April 2005; accepted 16 June 2005

- DAH of unclear etiology, negative auto antibodies and absence of systemic vasculitis or concurrent infection (?IPH)
- Recurrent hemorrhage non responsive to 10 daily treatments of plasmapheresis and pulse steroids x 3d and transient response to IV bolus of recombinant factor
- Responded to 4 day course of IVIG(2g/kg/d) and pulmonary hemorrhage
- 8 days later readmitted for pulmonary embolism, treated with heparin products without bleeding

Successful pulmonary administration of activated recombinant factor VII in diffuse alveolar hemorrhage

Lars Heslet[1], Jorn Dalsgaard Nielsen[2], Marcel Levi[3], Henrik Sengeløv[4] and Pär I Johansson[5]

[1]Department of Intensive Care ITA 4131, University Hospital of Copenhagen, Rigshospitalet, Blegdamsvej 9, DK 2100 Denmark

- 6 patients with DAH treated with intrapulmonary administration of 50ug rFVIIa via BAL
- DAH was attributed to sarcoidosis, WG, AIDs, AML and post stem cell transplant
- Complete and sustained hemostasis in 3/6 with single dose and rest required second doses
- Use of intravenous forms of rFVIIa is approved for hemophilia

Mortality Associated with Pulmonary Renal Syndrome

Mortality Associated with Pulmonary Vasculitis

Prognostic Factors for Hospital Mortality and ICU Admission in Patients With ANCA-Related Pulmonary Vasculitis

FERNANDO HOLGUIN, MD, MPH; BASSEL RAMADAN, MD; ANTHONY A. GAL, MD; JESSE ROMAN, MD

Poor Prognostic Factors

Variable	28-day Death (11 Pts) 17%	Survivors (54 Pts) 83%
Mean age (range)[a]	60 (39–81)	47 (10–83)
Gender (Female %)	27%	50%
BUN (95% CI)[a]	53 (23–85)	29 (22–37)
F_{IO_2} (%) (95% CI)[a]	54 (35–74)	31 (25–39)
HCT (95% CI)	28 (25–32)	32 (30–34)
Hemoglobin (95% CI)[b]	9.6 (9–11)	10.75 (10–12)
ICU length of stay (95% CI)[a]	16 (10–22)	4 (1–8)
PH (95% CI)	7.40 (7.3–7.45)	7.39 (3.8–7.41)
WBC (95% CI)[b]	15.4 (10–21)	11.8 (10–13)
MV length of use (95% CI)[a]	11.5 (6–17)	3.6 (1–7)
Hospital length of stay (95% CI)	21 (12–33)	14 (9–20)
Hemodialysis	5 (45%)	11 (20%)
Cytoxan	7 (63%)	44 (81%)
Alveolar hemorrhage	7 (64%)	32 (59%)
Capillarities on pathology	6 (54%)	32 (59%)
Necrotizing granuloma on path	6 (54%)	24 (44%)
P-ANCA	2 (18%)	10 (18%)
Systemic steroids	11 (100%)	53 (98%)
C-ANCA	8 (73%)	42 (78%)
Blood transfusion[a]	7 (63%)	7 (13%)
Mechanical ventilation[a]	9 (82%)	9 (17%)
Secondary infection[a]	5 (45%)	6 (11%)
Tobacco use	5 (45%)	16 (30%)

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES October 2008 Volume 336 Number 4

Poor Prognostic Factors

Variable	P value
Mean Age - 60y	<0.05
Mean BUN - 53	<0.05
Low Hemoglobin -9.8%	=0.05
Elevated WBC count -15.4	=0.05
Fio2 54%	<0.05
ICU length of stay – 16days	<0.05
Mech. Ventilator use	<0.0001
Need for Blood transfusion	<0.0002
Secondary infection	<0.005

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES October 2008 Volume 336 Number 4

Factors affecting the mortality of DAH in lupus nephritis.

Clinical Nephrology, Vol. 54 – No. 4/2000 (282-288)

Author (et al.)	Year	D/total No	D/RF	D/infection	D/mech. vent	D/HD
Eagen	1978	3/4	1/1	3/3	3/3	1/1
Carette	1984	3/8	1/3	2/3	3/5	1/3
Schwab	1993	2/8	0/1		1/4	0/1
Erickson	1994	1/3	1/3	1/1	1/3	0/2
Zamora	1997	8/19	5/12	7/9	8/13	
Lee	2000	4/9	4/4	2/3	3/3	3/3
Total		21/51	12/24	15/19	19/31	5/10
Relative risk			1.5	4.2	6.1	1.3
p value			0.27	< 0.0001	0.0004	0.72

Summary of Diagnostic Workup

- It is a life threatening condition which requires early intervention to prevent high mortality
- Concurrent infection, severe anemia and long mechanical dependence are poor prognostic markers
- Aim for an early bronchoscopy to document hemorrhage and exclude infection
- Biopsy (open lung or renal with IF) can be extremely helpful and reassuring

Summary of Treatment

- Common practice to use of Pulse dose steroids and Cytoxan in life threatening renal and pulmonary involvement
- There is good data early use of plasma exchange followed by IVIG in life threatening and treatment resistant cases
- Plasma exchange has been helpful in situations with concomitant need for anticoagulation