AKI Academy Challenging cases

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Case 1 :Background

45 year old man

Presented to GP with arthralgia, breathlessness, cough and rash

Prescribed diclofenac for arthralgia

Subsequently, haemoptysis, epistaxis and weight loss of approximately 3 Kg- presented to A/E

Investigations :

Urea 17.7 mmol/L, creatinine 345 umol/L

Deterioration in clinical and biochemical findings at local hospital

Case 1 Local hospital- deterioration

Admitted to Intensive Care Unit

- Hb 9, WCC 18.5, Platelets 386.
- Urea 28.2, creatinine 563, Na+ 127, K+ 5.7
- Bicarbonate 18 mmol/l
- CRP 464
- Hypoalbuminaemic- 25
- Bilirubin 9, ALP 80, ALT 23, GGT 41.
- Calcium 2.54, Phosphate 3.09

Case 1 Intensive Care Unit

Haemofiltration commenced

Further Investigations

- PR3 ANCA 700 (NR 0-25)

Diagnosis suspected

- ANCA associated vasculitis

Initial treatment

- Methlyprednisolone 500mg daily for 3 days
- Cyclophosphamide 700mg.

Case 1-Transferred to renal unit

Bloods

- Hb 11 (after transfusion), WCC 15.4, Platelets 414
- Urea 39.5, creatinine 432
- Albumin 19
- CRP 119
- Complement- elevated C3 1.78, normal C4 0.43
- Serology- GBM neg, MPO neg, C-ANCA positive
- PR3-ANCA 358.

Urinanalysis

- Red blood cells and proteinuria

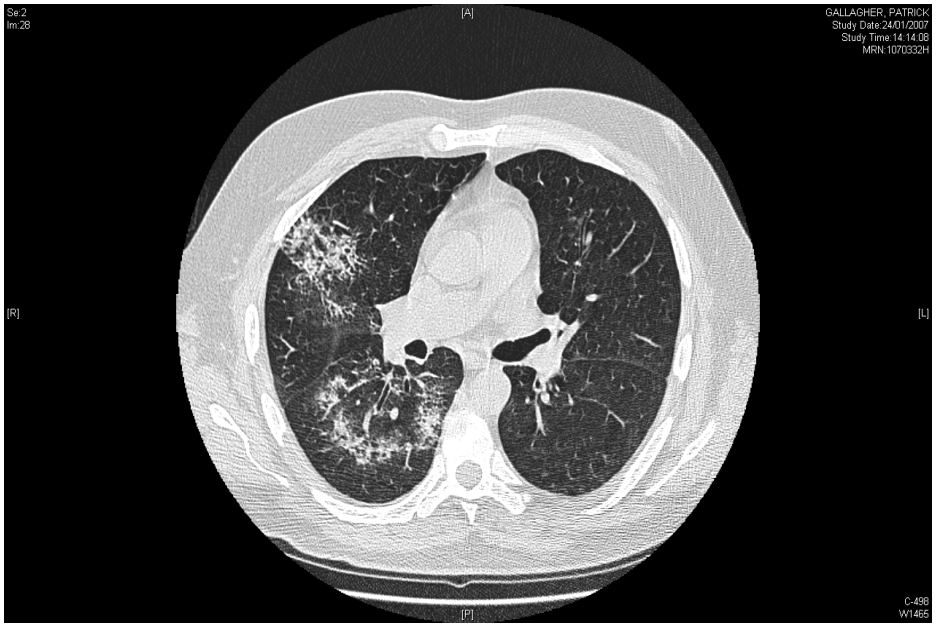
Case 1- Further Investigations

CT chest and sinuses

- patchy consolidation within anterior and posterior segment of right upper lobe.

  Patchy airspace changes left lingula

- Right maxillary sinus- mucosal thickening.



Renal Biopsy performed

Case 1-Management

Plasma Exchange

- Exchanged against 4 litres FFP.
- Total 11 exchanges over the following 16 days.

Corticosteriods

- Commenced prednisolone 60mg.

Cyclophosphamide

- Dose dependant upon GFR
- <10mls: 7.5mg/kg, 10-30: 11.25mg/kg, >30mls: 15mg/kg
- 10 pulses: 1-3 every 2 weeks, 4-10 every 3 weeks.

Case 1 – Follow up

Required 1 further haemodialysis treatment

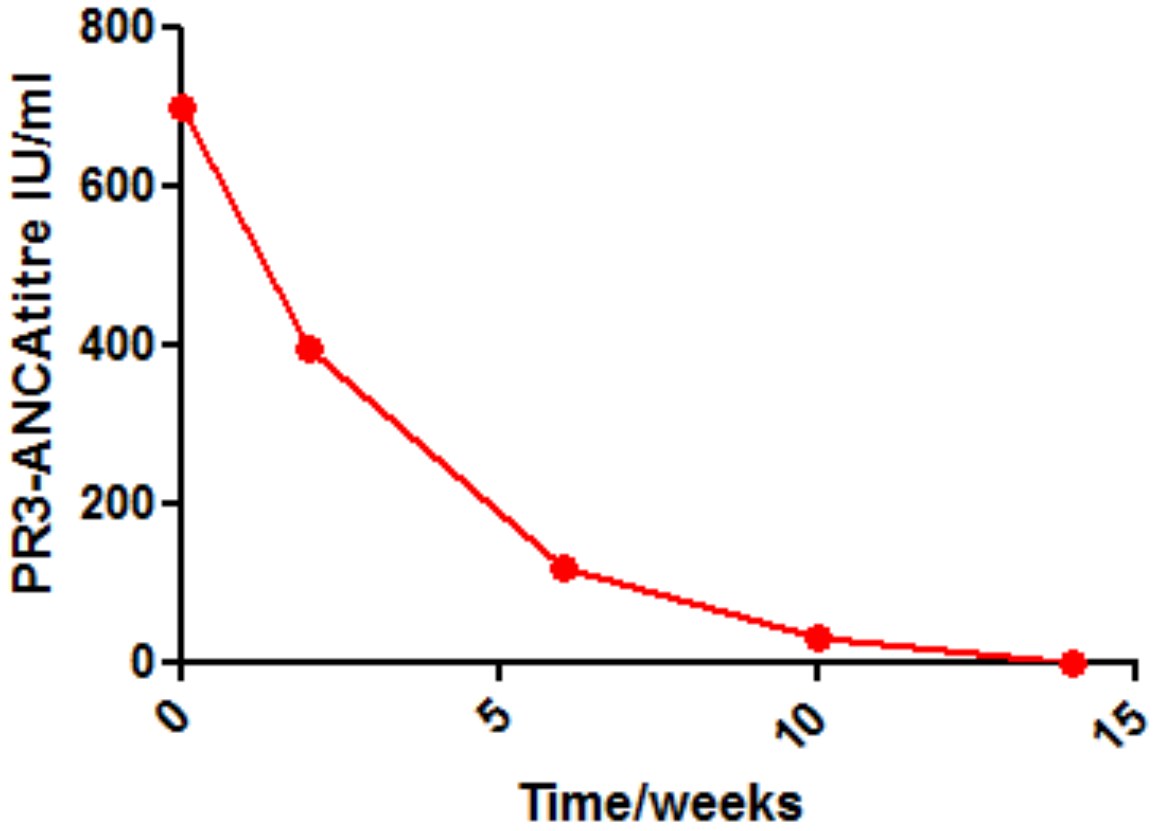
Improvement in renal function

- Day 10 creatinine 327
- Day 20 creatinine 232- discharged

Followed up in out-patient clinic

- Regular IV cyclophosphamide treatment
- Reached baseline creatinine 170-180
- At 5 months following presentation , cyclophosphamide switched to azathioprine 150mg/day
- Maintained prednisolone 10mg/day

Case 1- ANCA titre



Case 1-follow up

At 5 ½ months, re-presents to A/E

- 2 day Hx rigors
- No obvious source of infection
- No symptoms of active vasculitis
- Maintenance immunosuppression- Pred 10mg, aza 150mg

- On examination- peripherally cool, hypotensive 80/40mmHg
- Examination essentially normal.

- Urinanalysis- blood and protein present.

Case 1-further investigations

Blood tests

- Urea 15.8mmol/l, creatinine 279 μmol/l (147 three days earlier)
- CRP 202.
- Hb 10.6, WCC 11 (neutrophils 9.4, lymphocytes 1.0, eosinophils 0.6), platelets 177

Renal USS

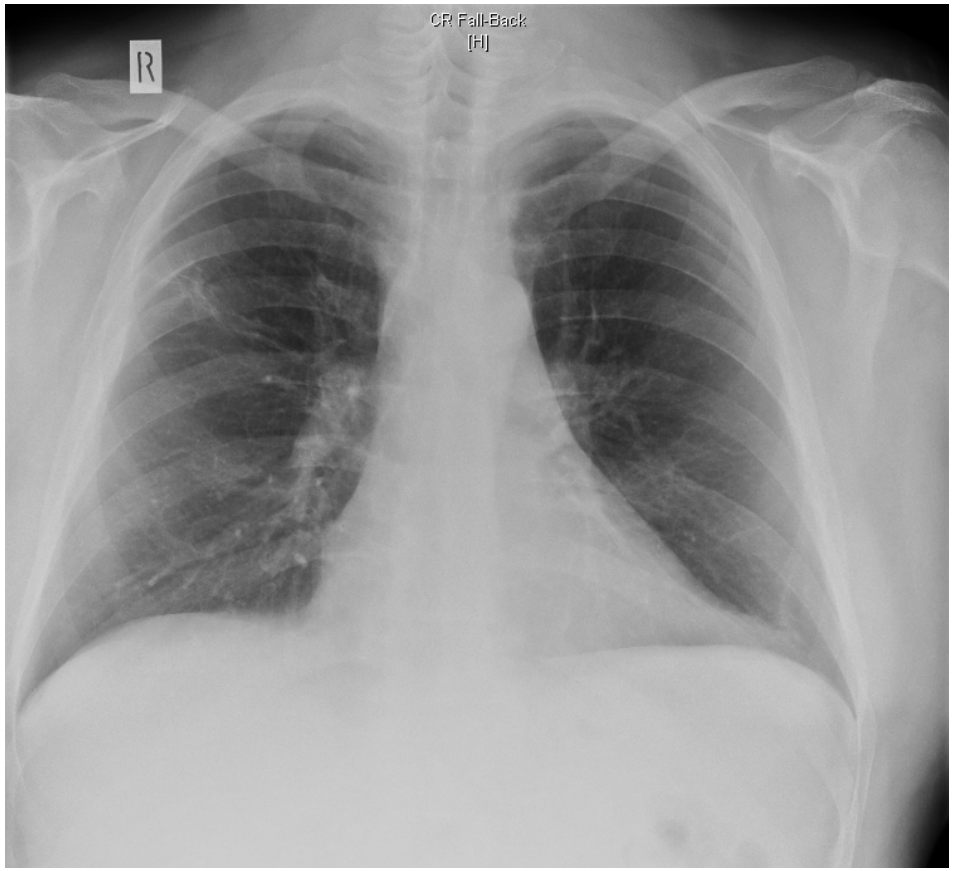
- Normal, no hydronephrosis

  12.7cm, 13.2cm.

Lung function

- Kco within normal range 1.69 (1.09-2.21) 102% predicted.

Case 1 -Chest radiograph



Case 1 – further management

Remained anaemic with relative hypotension

CXR

- Clear, not compatible with alveolar haemorrhage.

ANCA

- PR3-ANCA initially within normal range 14IU/ml (0-25) but then increased to 49 IU/ml after a week

Treated with IV fluids and broad-spectrum antibiotics

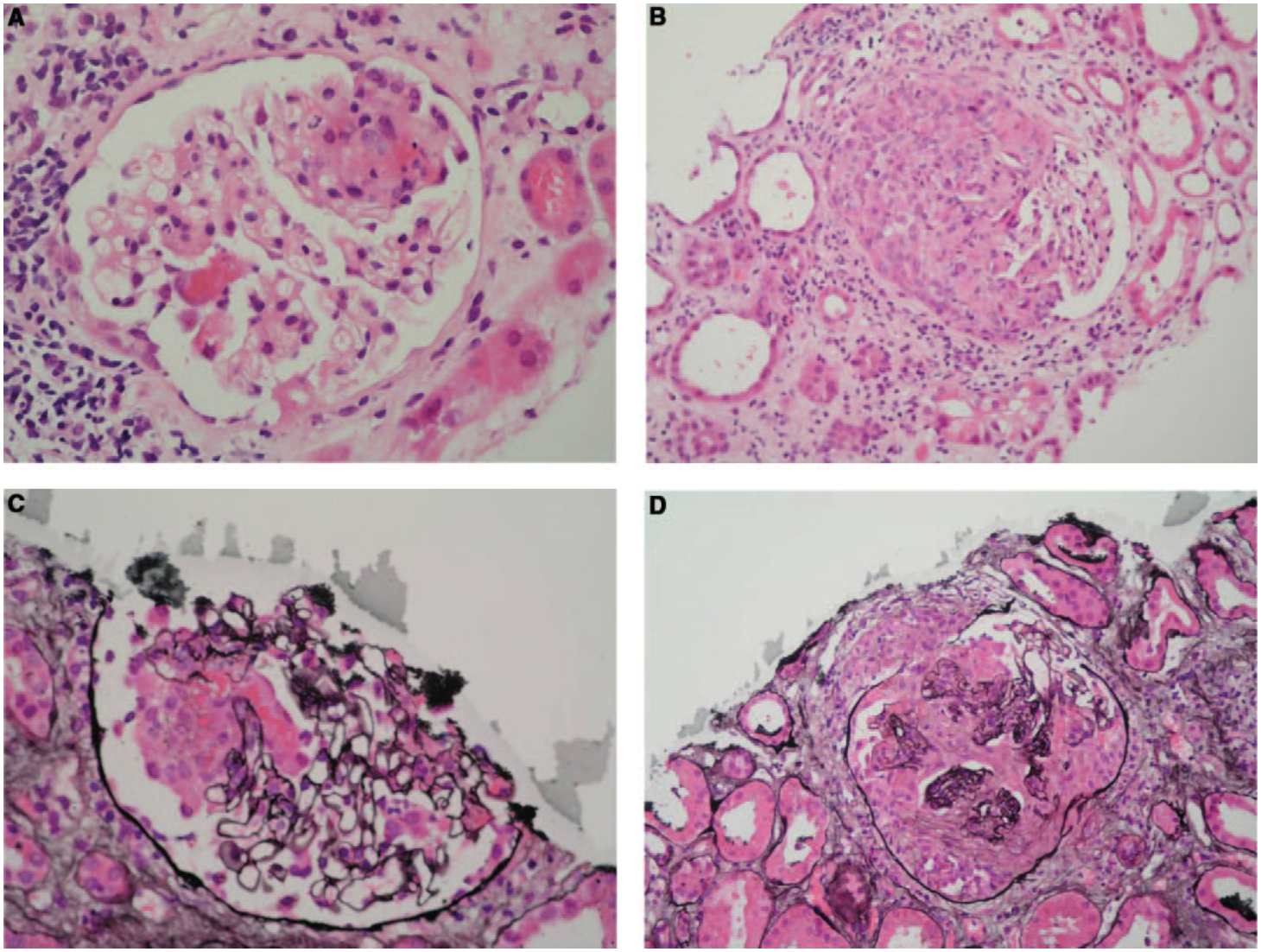
- Vancomycin and tazocin

Case 1- Differential Diagnosis

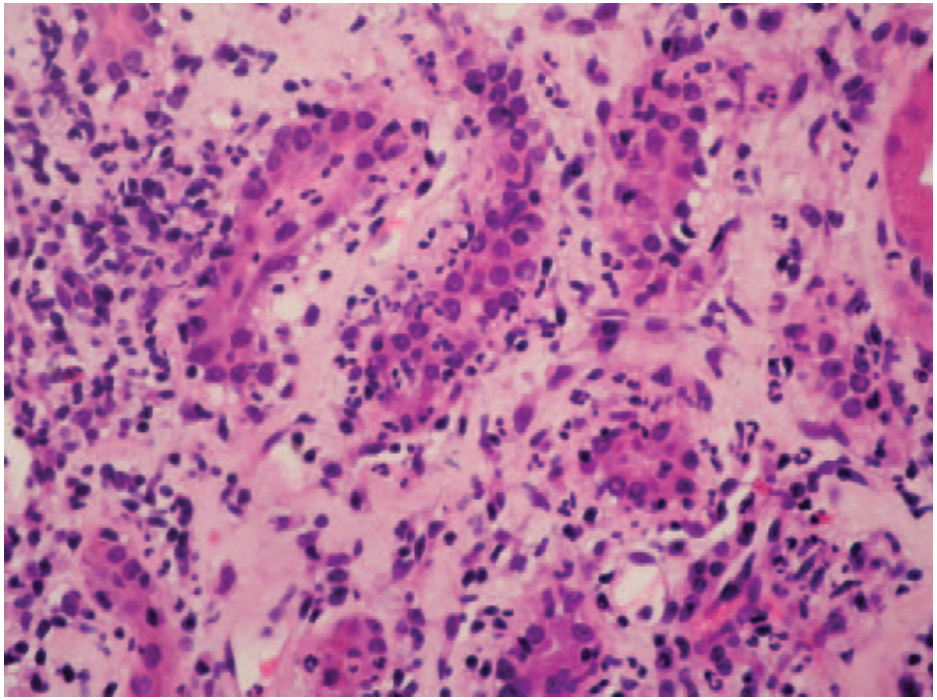
1. Anaemia and hypotension — Pulmonary haemorrhage
   Septic.
2. Active urinary sediment — Disease relapse
3. Fevers, hypotensive — Hypovolaemia

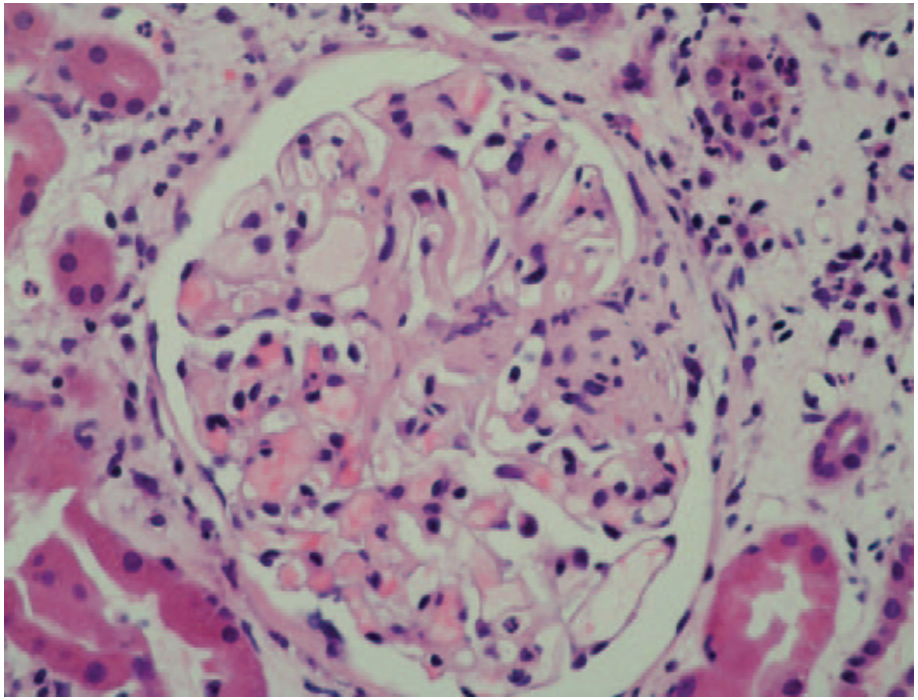
A renal biopsy was performed.

Case 1- Pathology at presentation



Case 1- Pathology at follow up





Case1- Final Diagnosis

Azathioprine induced interstital nephritis;

No evidence of recurrent focal necrotising glomerulonephritis or vasculitis

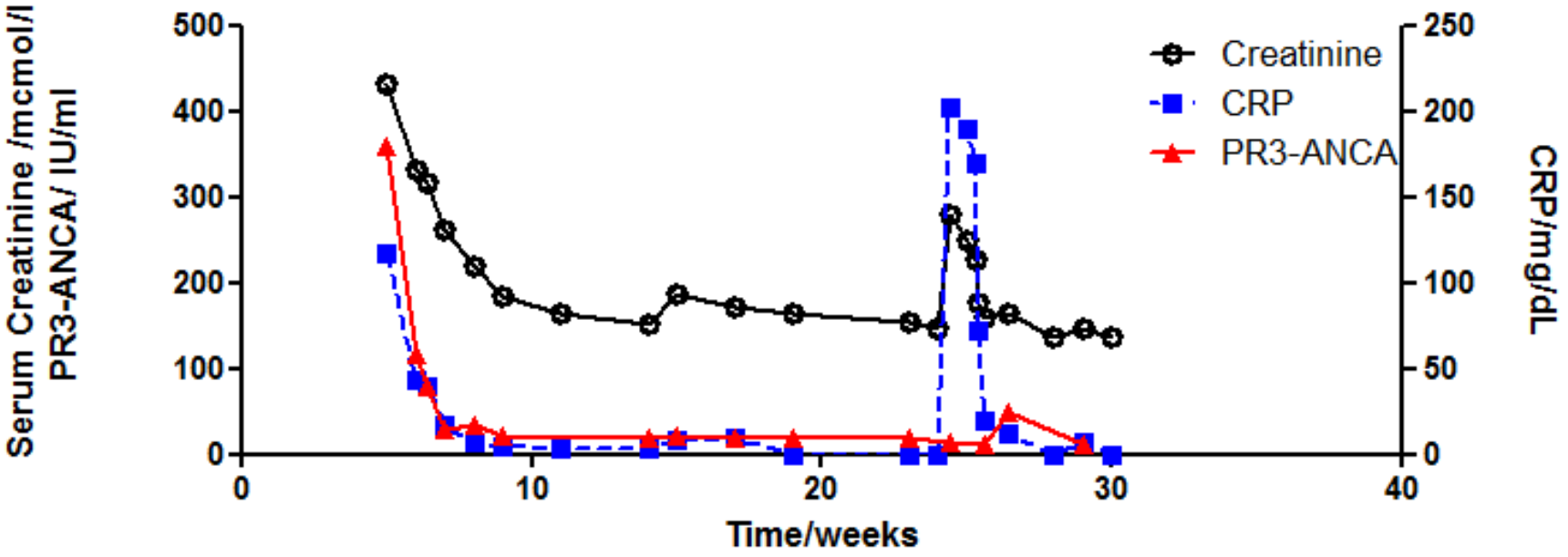
Treatment

- High dose steroids
- Azathioprine stopped
- MMF started as maintenance immunosuppression

Creatinine subsequently decreased rapidly to 176

1 month after stopping Aza- creatinine 137 and Hb 12.7 g/dL

Graph of results



Azathioprine

- Azathioprine metabolised in the liver to become an active drug, through its conversion to 6-mercaptopurine.
- It inhibits *de novo* purine synthesis and hence DNA and RNA synthesis.
- Its metabolites are excreted via the kidneys but in an inactive form.
- Toxicity commonly bone marrow suppression, megaloblastic anaemia and hepatic dysfunction. The risk of marrow suppression is increased in patients with low thiopurine methyltransferase (TPMT) activity.
- Survey of >500 pts with RA , none had renal impairment

Azathioprine Interstitial nephritis

- Rare
- Reported in association with GPA, classical polyarteritis, and RA.
- Allergic symptoms(rash, fever, arthralgias) also reported in cryoglobulinaemia, leucocytoclastic vasculitis anti-GBM disease, as well as other forms of ANCA associated vasculitis
- Symptoms develop 1 week to 1 year after treatment started.
- Resolution rapid and re-exposure results in more rapid relapse.
- No obvious patient susceptibility identified, although most have renal impairment at start of azathioprine therapy

Azathioprine Interstitial nephritis

- 1 patient with GPA (Reinhold-Keller et al. 2001)
- Systemic symptoms (fever, headache, myalgia, arthralgia) 10 days after azathioprine commenced
- Acute phase response, acute decline in renal function and elevated liver function tests (AST, γGT), stable cANCA; Sterile cultures.
- Treated as disease relapse with further cyclophosphamide and high dose steroids and resolution of symptoms/signs within two weeks
- Cyclophosphamide converted back to aza and symptoms relapsed within hours.
- Renal biopsy revealed extensive interstitial oedema and neutrophil rich interstitial nephritis with no active GN
- Subsequently maintained in remission with methotrexate

Azathioprine Interstitial nephritis

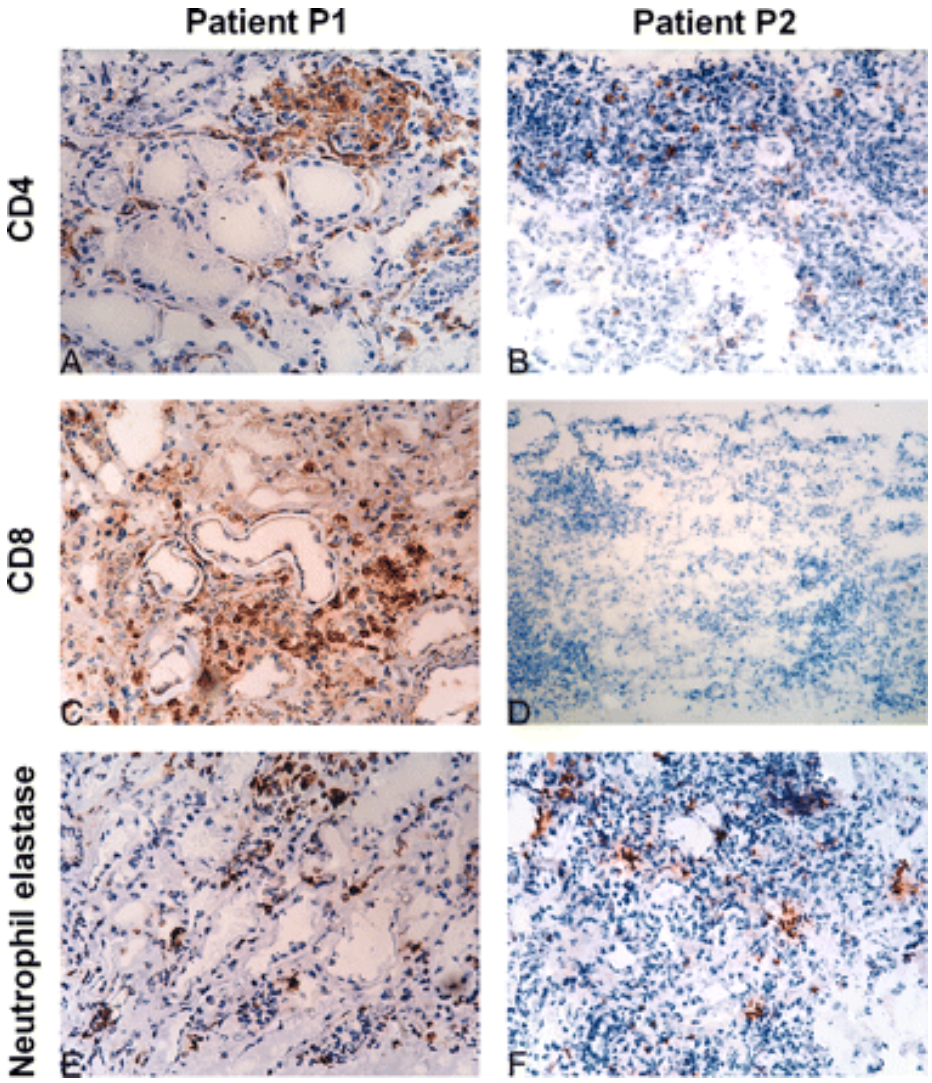
- 5 patients with azathioprine hypersensitivity, 2 with WG, 1 PAN, 2 transplant recipients (Parnham et al.1996)
- 4 with biopsy proven TIN, 1 granulomas
- 3 vasculitis patients in remission, mimicked disease reactivation
- All had renal impairment (Scr 160-270 μmol/l)
- All systemic symptoms fever, arthralgias and sudden decline in renal function
- Occurred 1-2 weeks after starting azathioprine
- Re-challenge in two resulted in relapse on same day

Azathioprine Interstitial nephritis

- Characterised by neutrophil rich infiltrate, with some eosinophils

- Unusual feature in drug induce TIN, although reported in some cases in which drug-specific T cells also made high levels of neutrophil chemoattractant CXCL8(IL-8)

- Neutrophil numbers in glomeruli in ANCA disease and non-ANCA GN have been correlated to expression of IL-8
- IL-8 can also be demonstrated in tubules and interstitium
- Tubular epithelial cell monolayer exposed to IFNγ or TNF can synthesise IL-8 and IL-6 and allow PMN to transmigrate across them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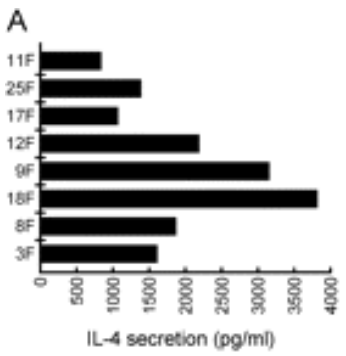
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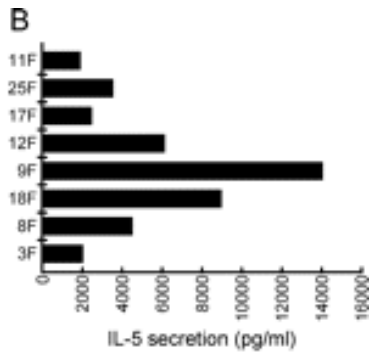
IL-4 secretion (pg/ml)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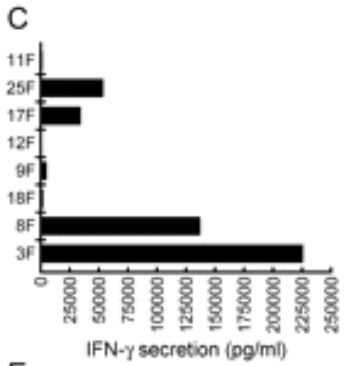
IL-5 secretion (pg/ml)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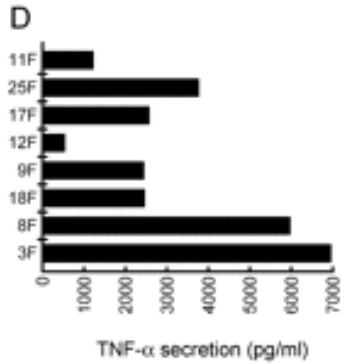
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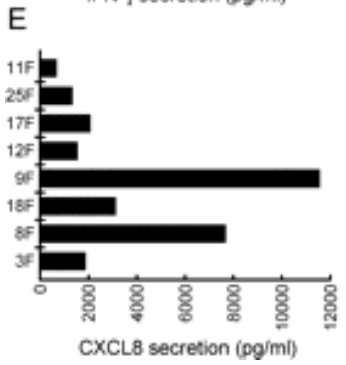
TNF-α secretion (pg/ml)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CXCL8 secretion (pg/ml)

Case 1-conclusion

- Biopsy important
- Many causes of AKI
- Lack of disease features compelling

Case 2- Presentation

- 35 Afro-Caribbean male
- Sudden onset R flank pain radiating to R groin and thigh following straining to pass stool, associated with fresh PR bleeding
- No urinary symptoms
- Presented to A/E at local hospital and admitted

Case 2- Background

- Similar episode 10 months earlier
- Attended A/E
- Investigations
  - Urinalysis blood +++ , protein +
  - CT KUB no calculi
  - Creatinine 146 μmol/l
- Diagnosed with renal colic; treated with analgesics

Case 2-PMH

- Asthma
- Epilepsy as a child
- Sickle Cell Trait
- Saggital Sinus Thrombosis 1998
  - warfarinised for 2 years

Case 2-Investigations

	A/E	Day 1	Day 2
Hb	16.4	13.6	13.2
Wcc	9.3	17.5	18.3
Plt	**142**	**100**	**101**
MCV	77		
Neut	6.6		
INR	1.1		
Fibrinogen	427		
ESR			25
Na	143		
K	3.6		
Urea	5.4		**10.4**
Creatinine	**159**		**332**
Amylase	122		
CRP	**4**		**279**
ALT			**215**
ALP			**55**
CK			**546**

Case 2-Initial Investigations

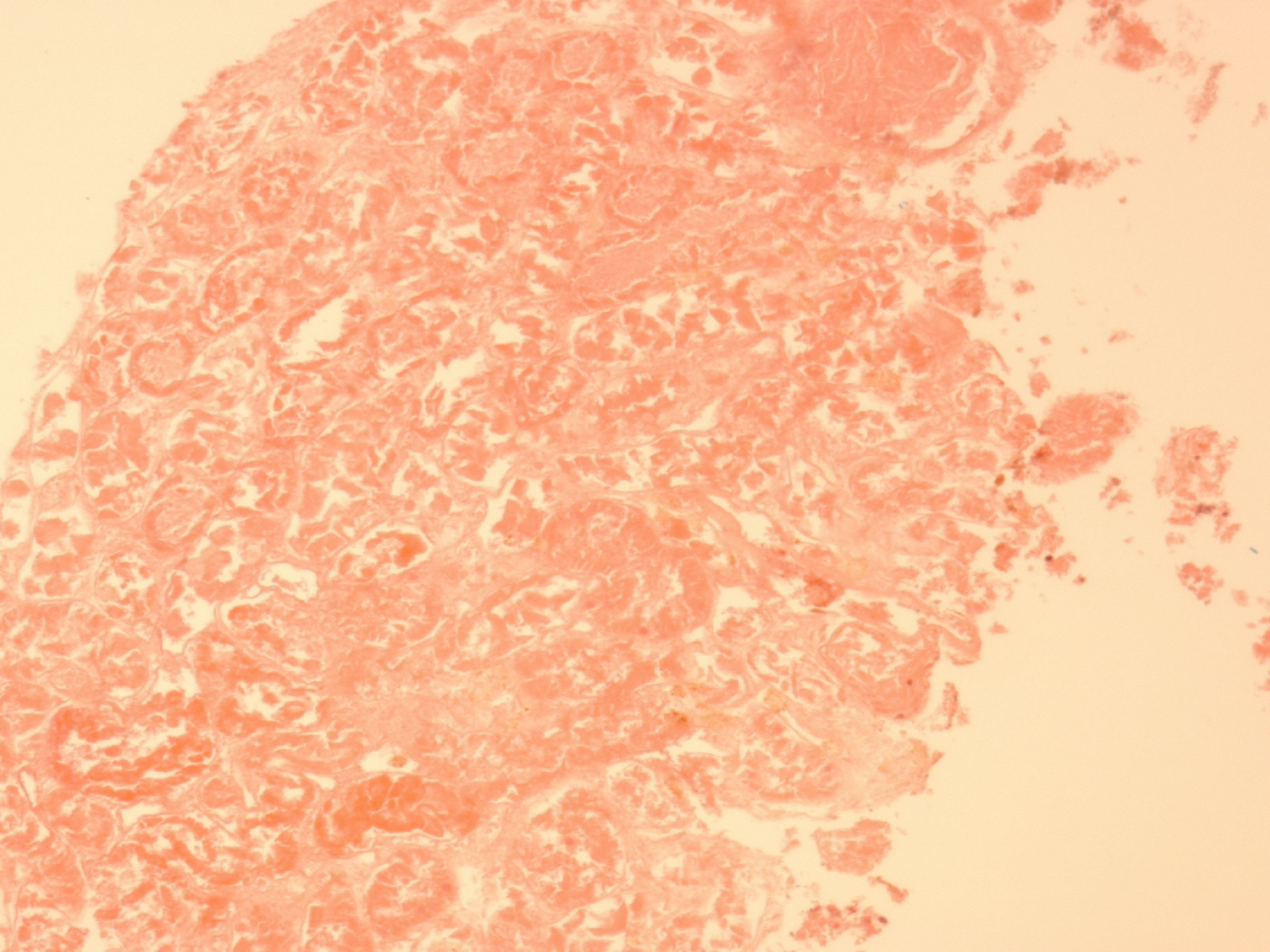
- CXR/AXR: Unremarkable
- CT KUB: No calculi, normal appearance of kidneys and bladder
- USS abdo with renal doppler: R kidney 10.8cm, L kidney 12cm, normal size and shape, no hydronephrosis, no collections.
- Other organs normal
- Urinalysis: nil growth, scanty epithelial and WCC

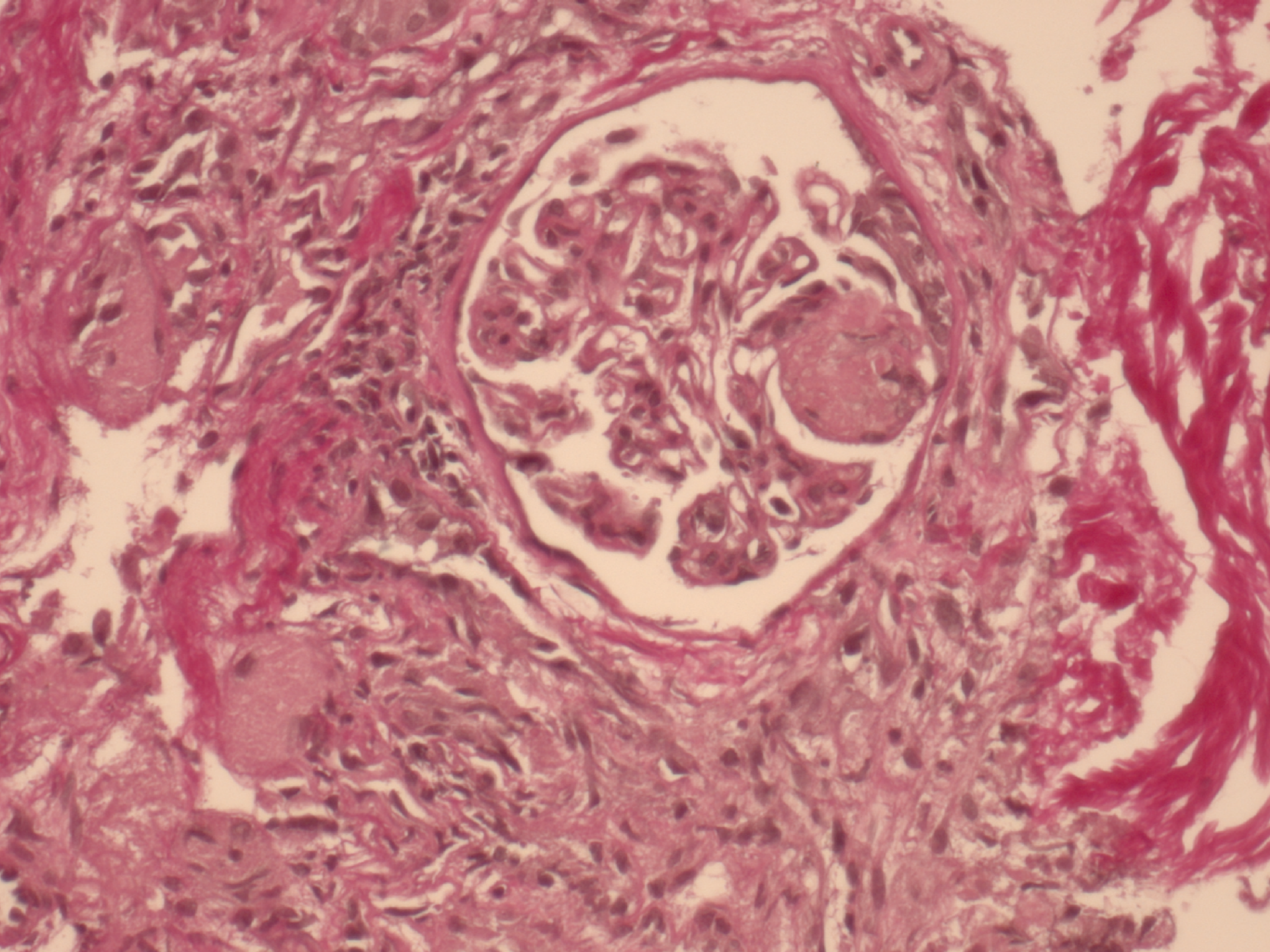
Case2-Progress

- Low grade pyrexia
- Persistent abdominal pain
- Further history:
- Abdo pain intermittent over previous 10 months;
- Decreasing exercise tolerance to 100m with myalgia affecting calves and thighs
- Episodes of discomfort and discolouration of fingers

Case 2- Additional history

- Lives with wife
- Currently unemployed
- Ex smoker: quit 6/12 ago
- Occasional alcohol
- Cocaine use 15 years ago
- Regularly attending gym
- Recent travel to Crete, nil elsewhere





Echo

- Normal LV/RV with normal systolic function
- LVEF >55%
- No evidence of thrombus/ masses
- No evidence of emboli

Bloods

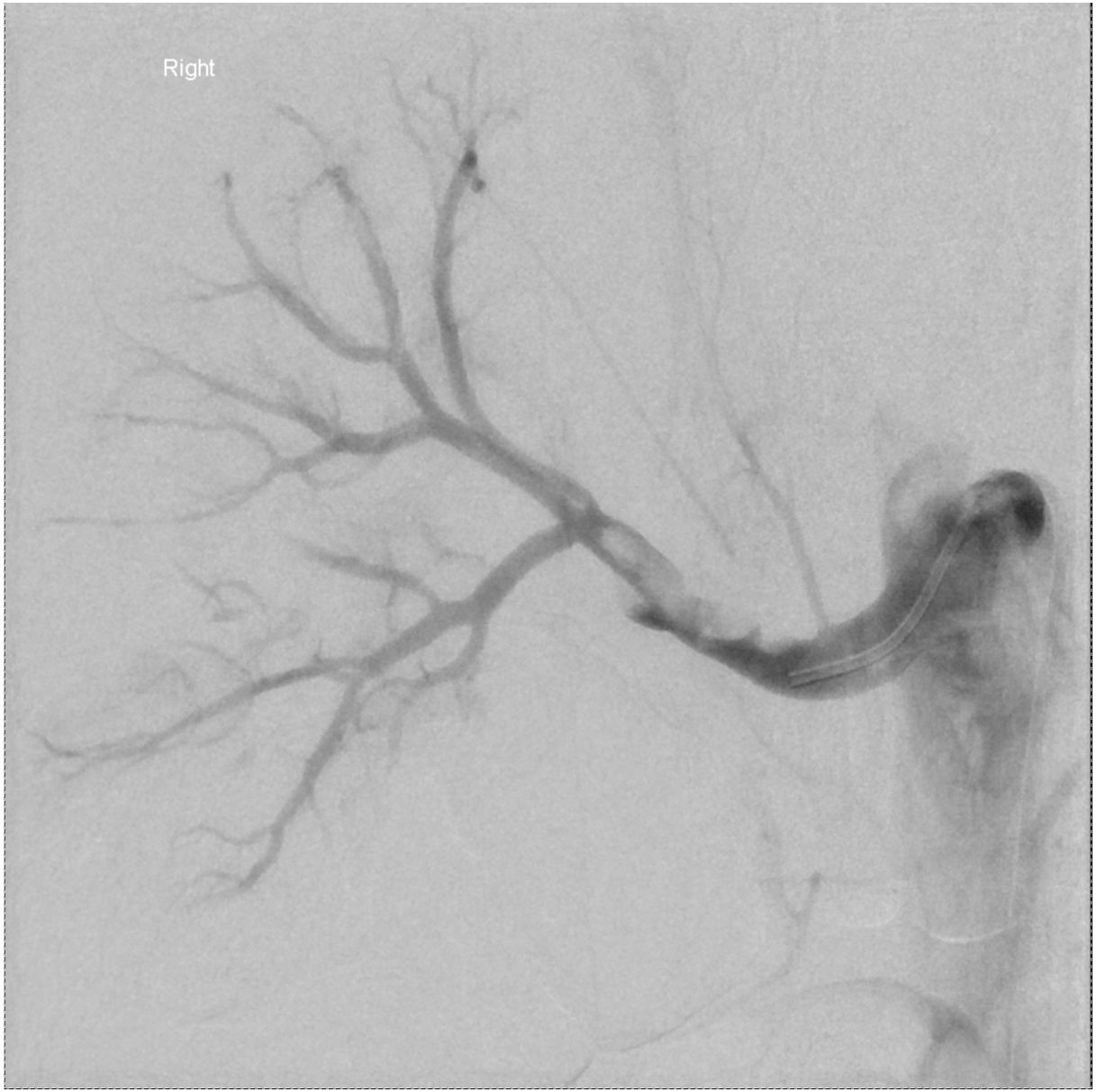
ANA	NEG	HIV	NEG	Fibrinogen	9.4g/L
ANCA	NEG	HBV	NEG	Homocysteine	8.9umol/L
ENA	NEG	HCV	NEG		
dsDNA	5iu/mL	Lupus Anticoag			
C3	155mg/dL	Factor VIII:c bioassay	640iu/dL		
C4	50mg/dL	Free Protein S	131iu/dL		
anti GBM	<1EU	Protein C:AC	119iu/dL		
IgG	9.5g/L	Antithrombin III	115iu/dL		
IgM	0.7g/L	Prothrombin 3	Normal variant		
IgA	1.9g/L	Factor V leiden genotype	normal		

From 1998

- Extensive thrombophilia screen –ve
  - plasma viscosity,
  - syphilis serology,
  - factor V leiden,
  - protein C and S and
  - anti-thrombin 3,
  - lupus anti-coag screen and auto-immune screen – ve

CSF protein and glucose normal

- Creatinine 103
- Urea 3.7
- ?lost to follow up for life long warfarin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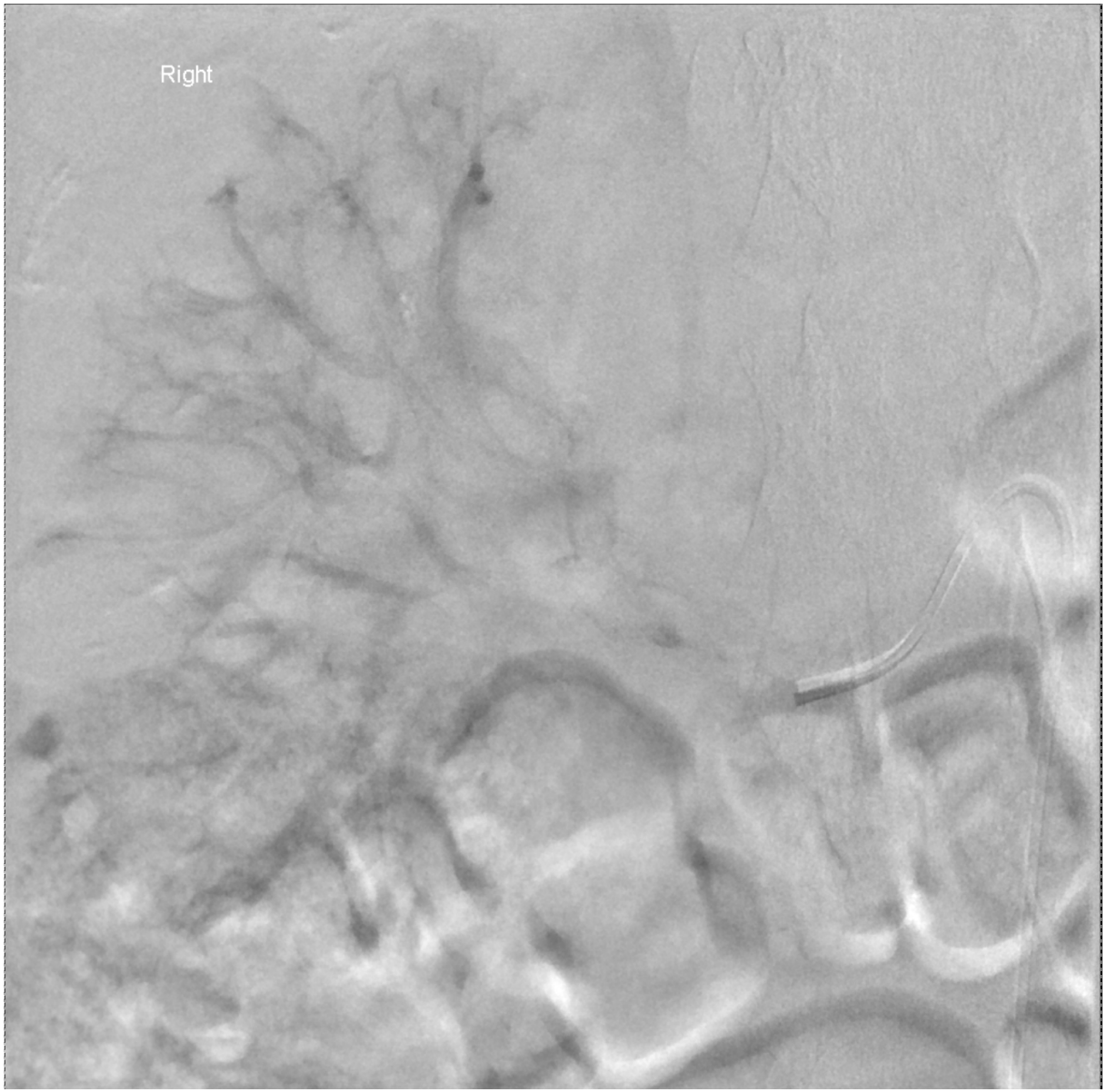
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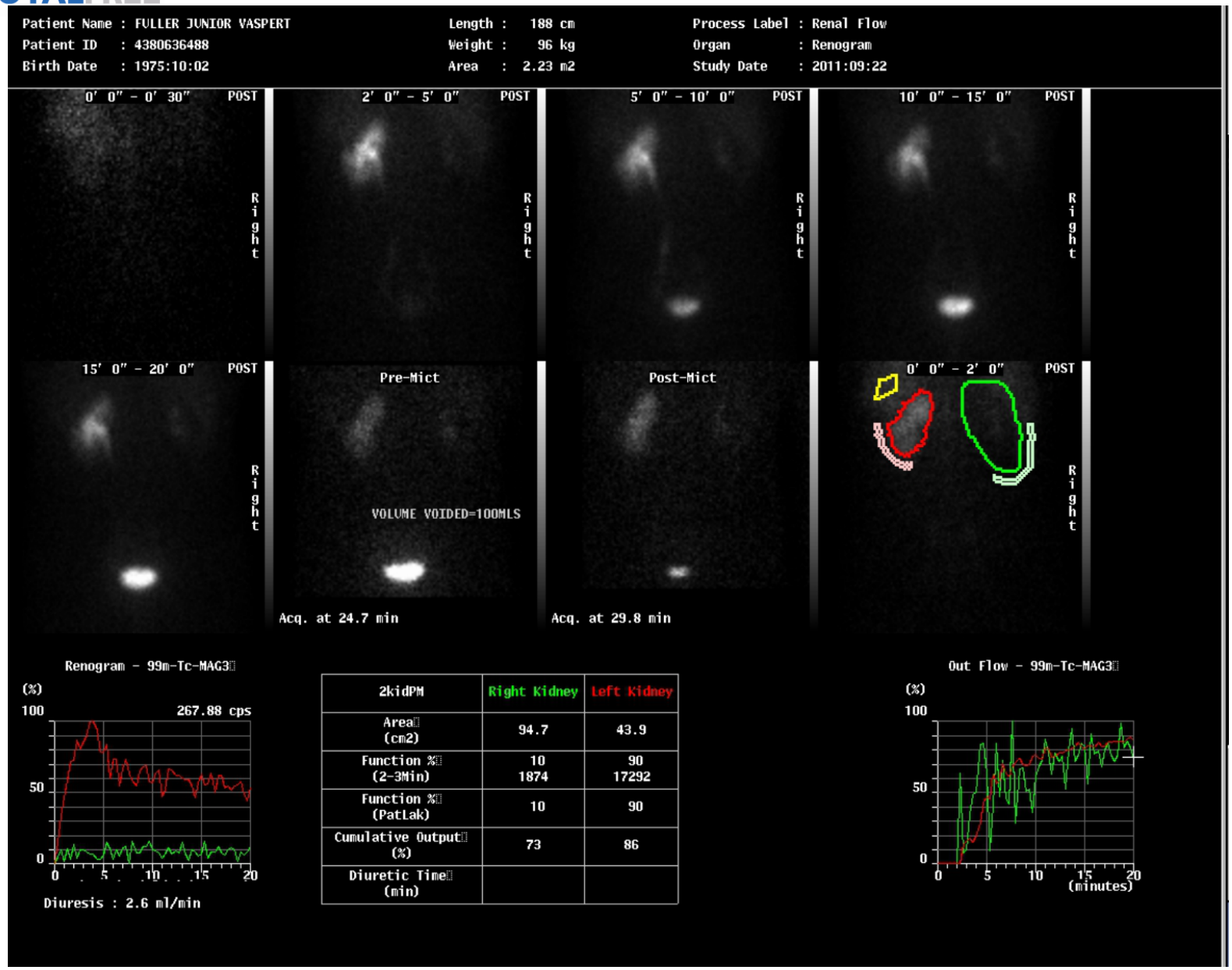
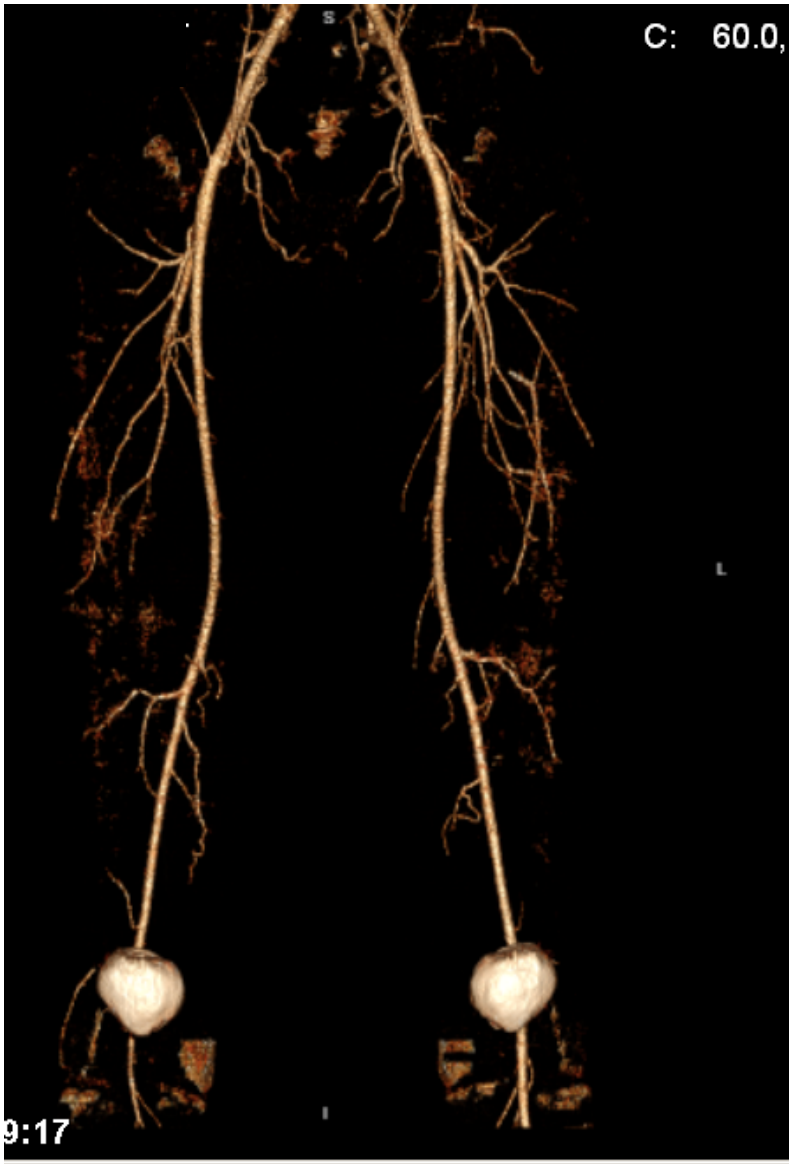


2kidPM	Right Kidney	Left Kidney
Area (cm2)	94.7	43.9
Function % (2-3Min)	10 1874	90 17292
Function % (PatLak)	10	90
Cumulative Output (%)	73	86
Diuretic Time (min)		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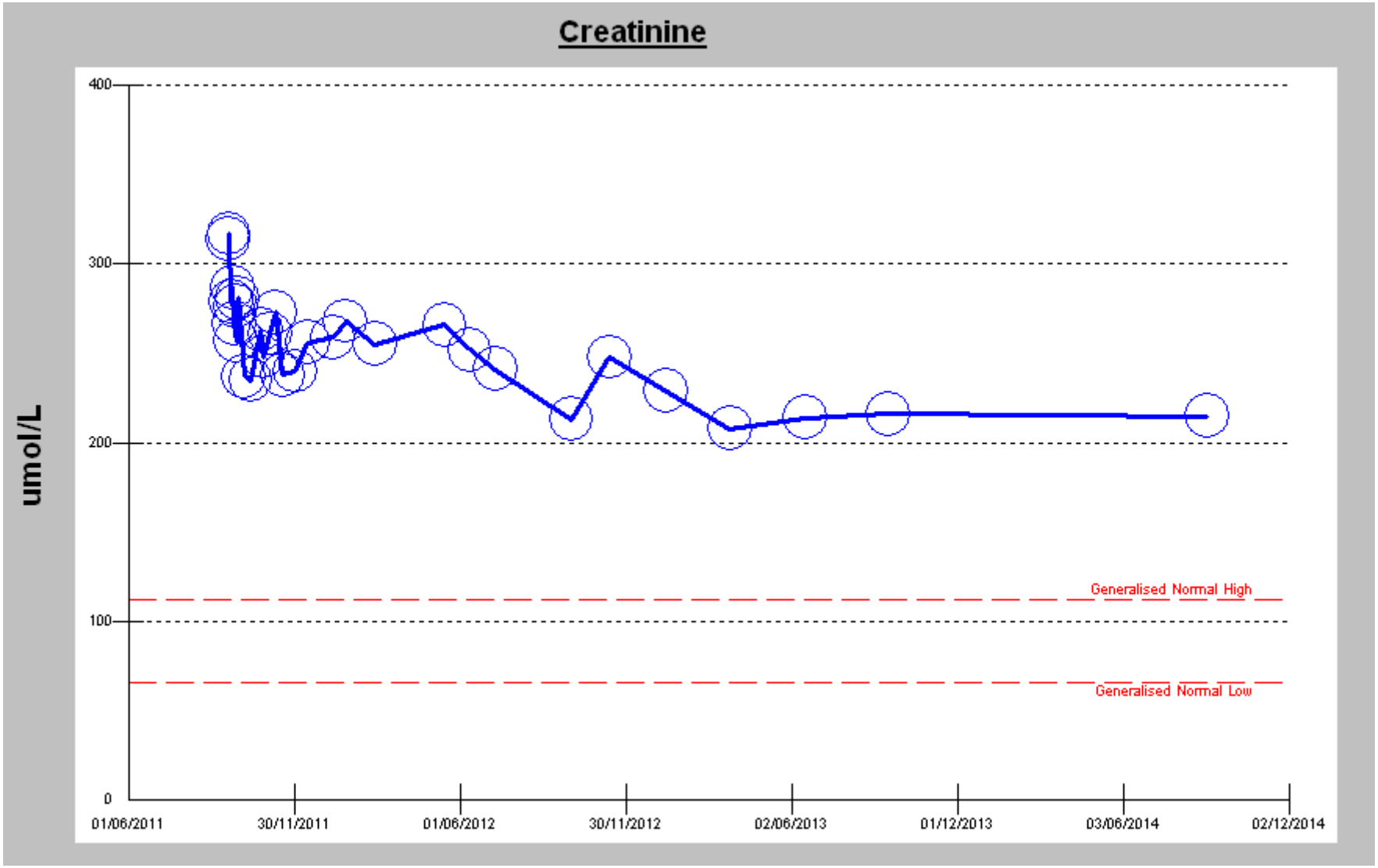
Case 2- Management

- Diagnosis: Polyarteritis nodosa (variant)
- Anti-coagulated
- Plasma exchanged, Immunosuppressed with 3 months of steroids and CYP following sperm banking
- Maintained stable renal function
- Some improvement in claudication symptoms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01/06/2011
30/11/2011
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30/11/2012
02/06/2013
01/12/2013
03/06/2014
02/12/2014

Polyarteritis Nodosa

FOCAL, PANMURAL, NECROTIZING vasculitis.

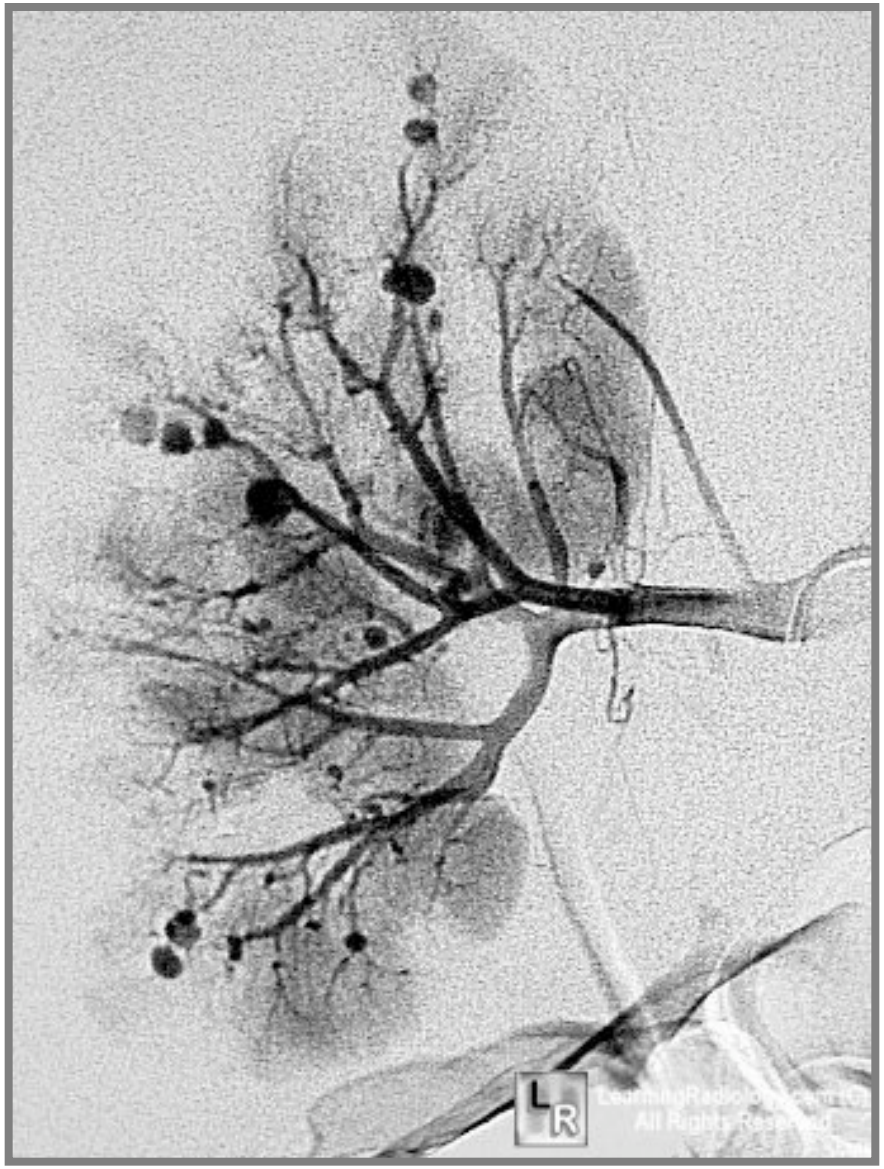
Blood vessels of **medium** caliber

Male **2 : 1** Female

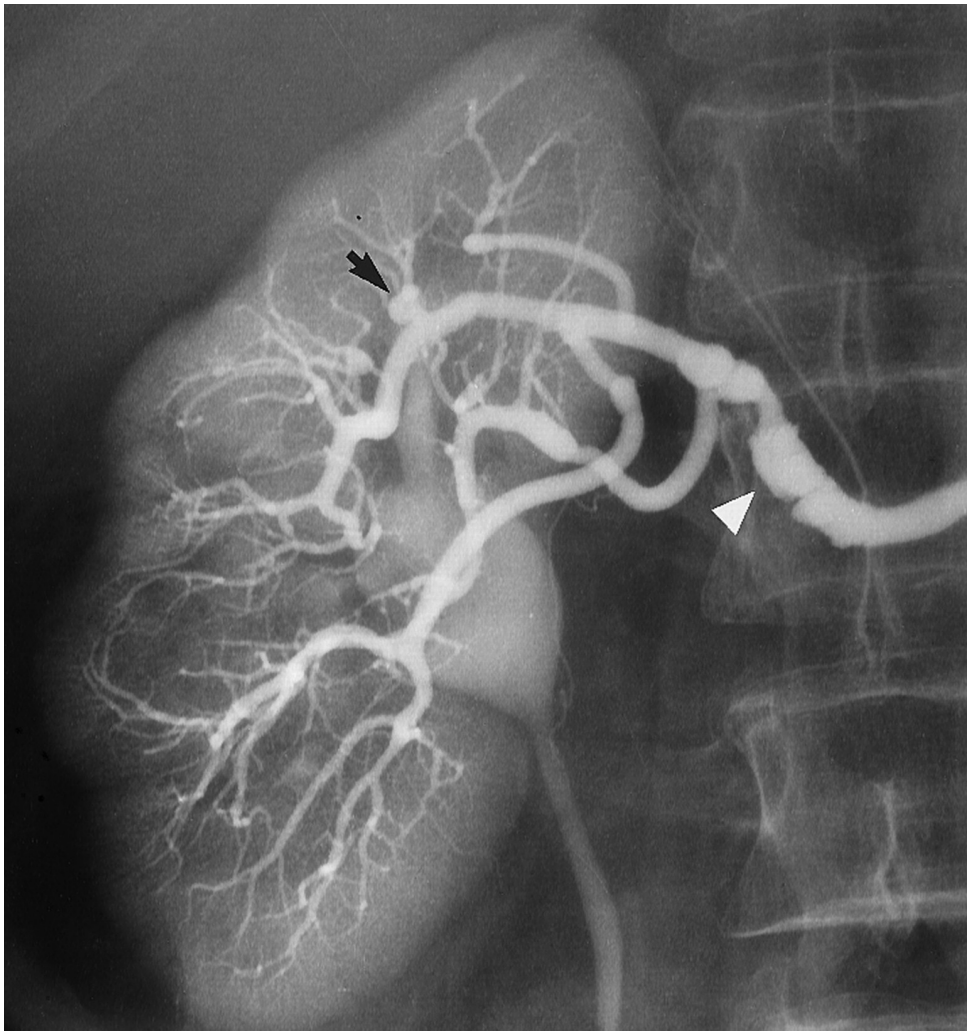
50- 70 yrs

2- 33: 1 000 000

Most patients have positive angiographic evidence

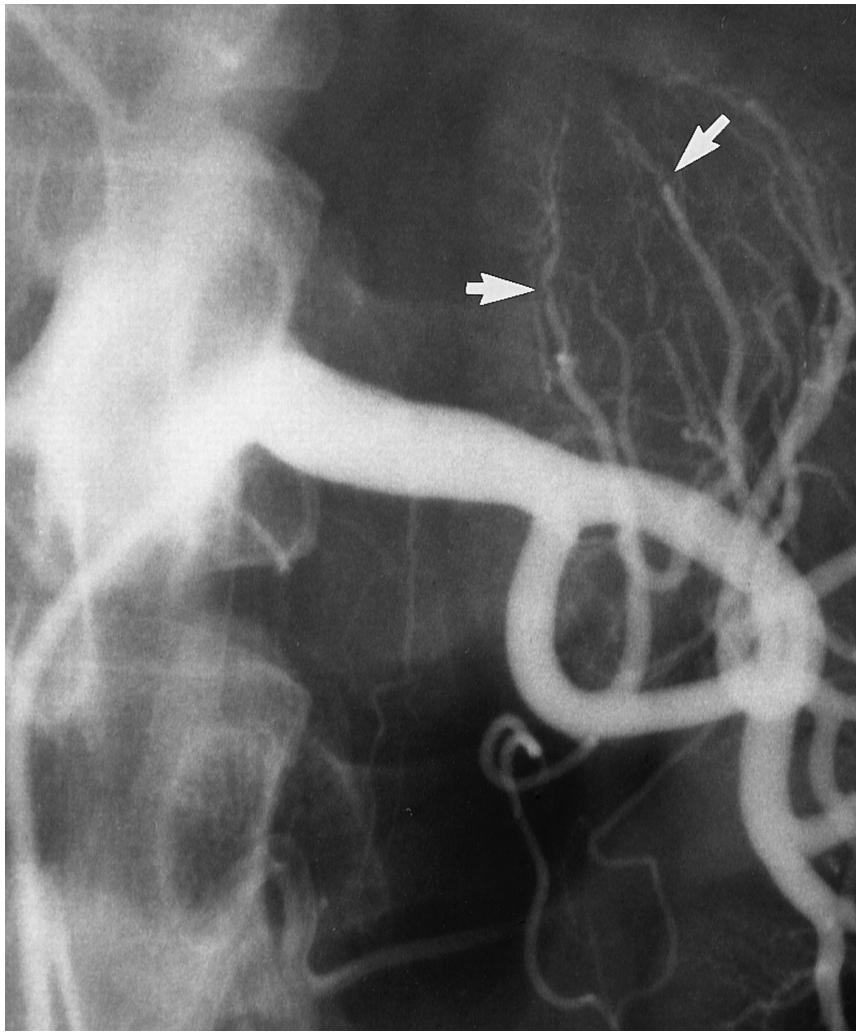


Right renal arteriogram - aneurysm and ectasia.

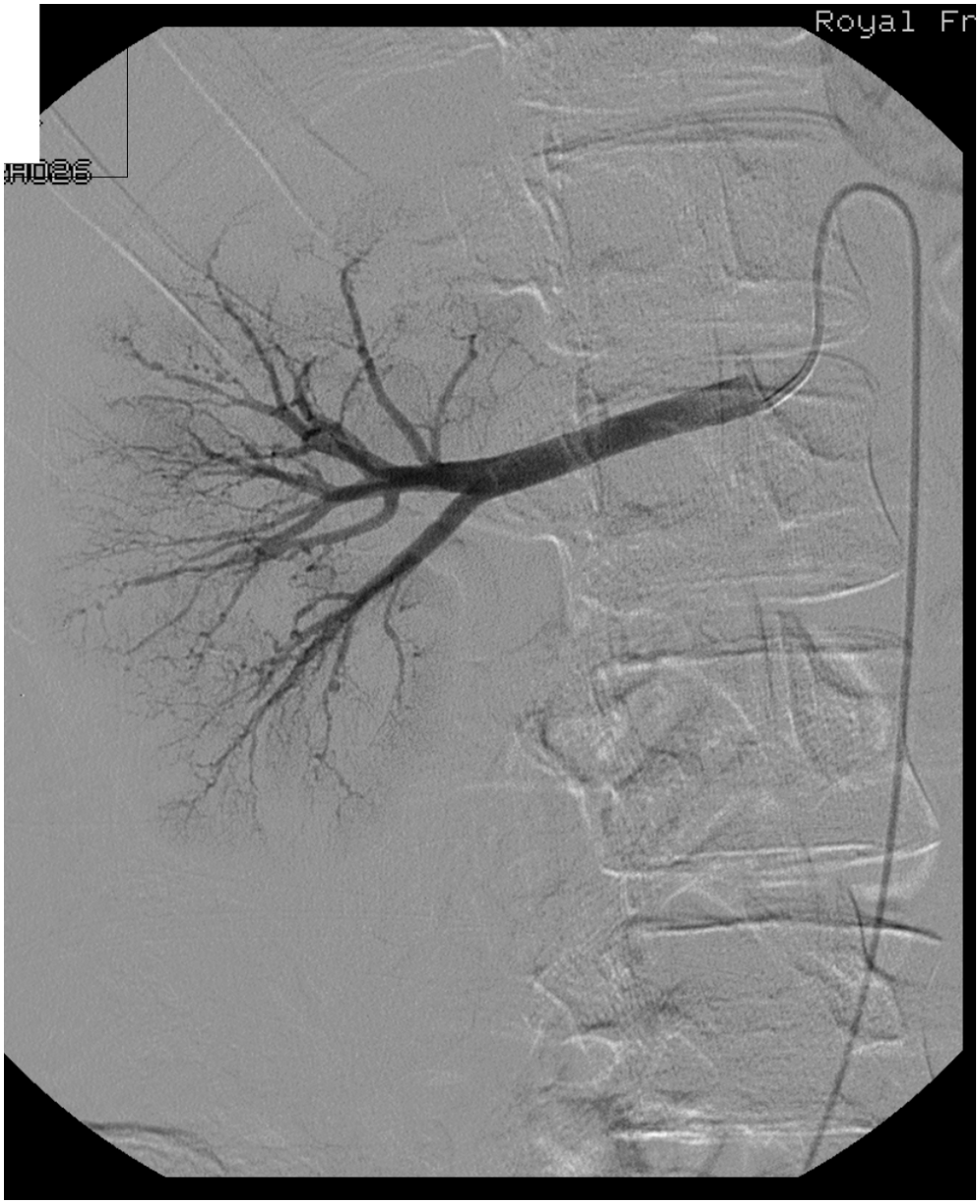


Stanson A W et al. Radiographics 2001;21:151-159

Occlusive lesion in a 24-year-old man with PAN.



Stanson A W et al. Radiographics 2001;21:151-159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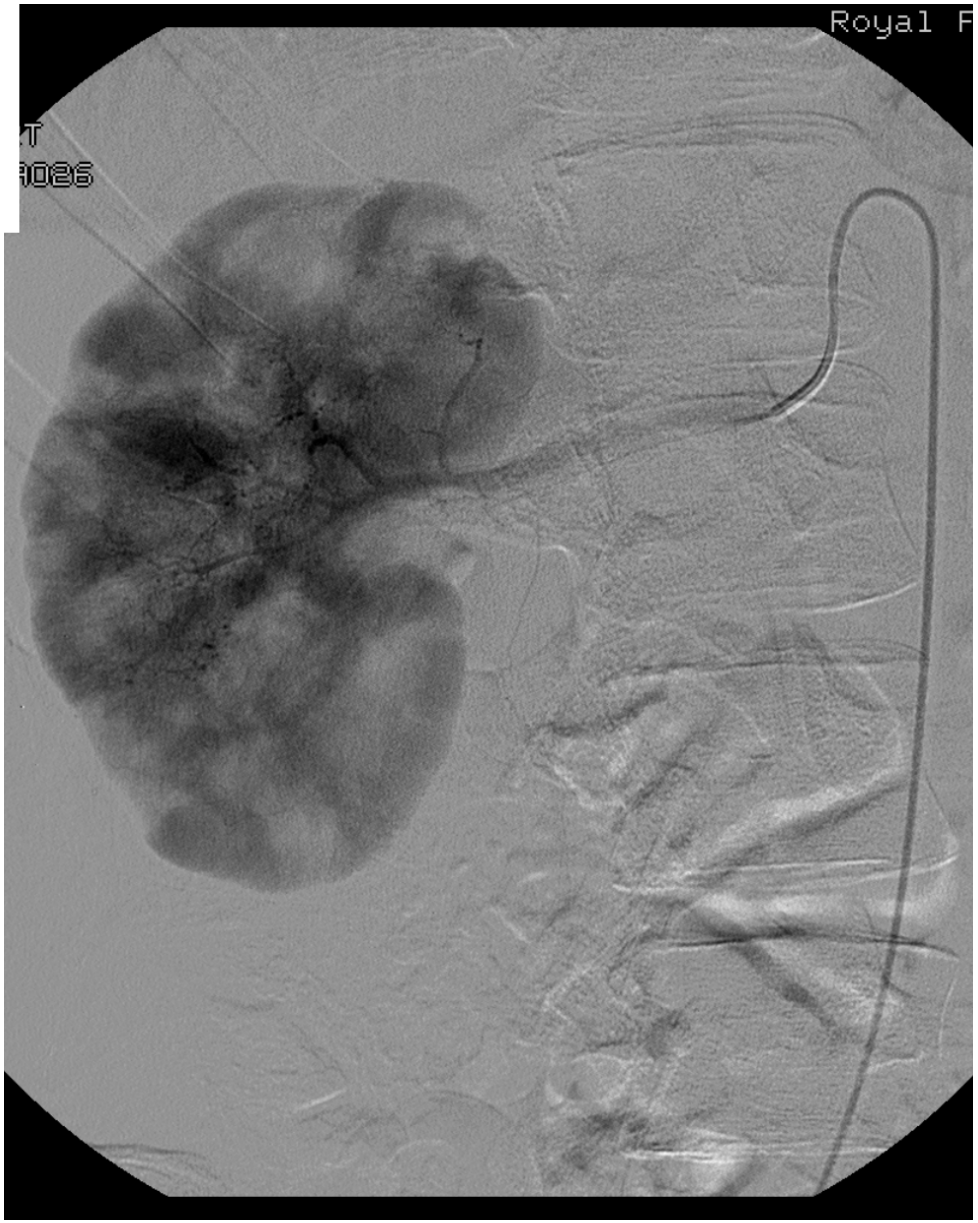
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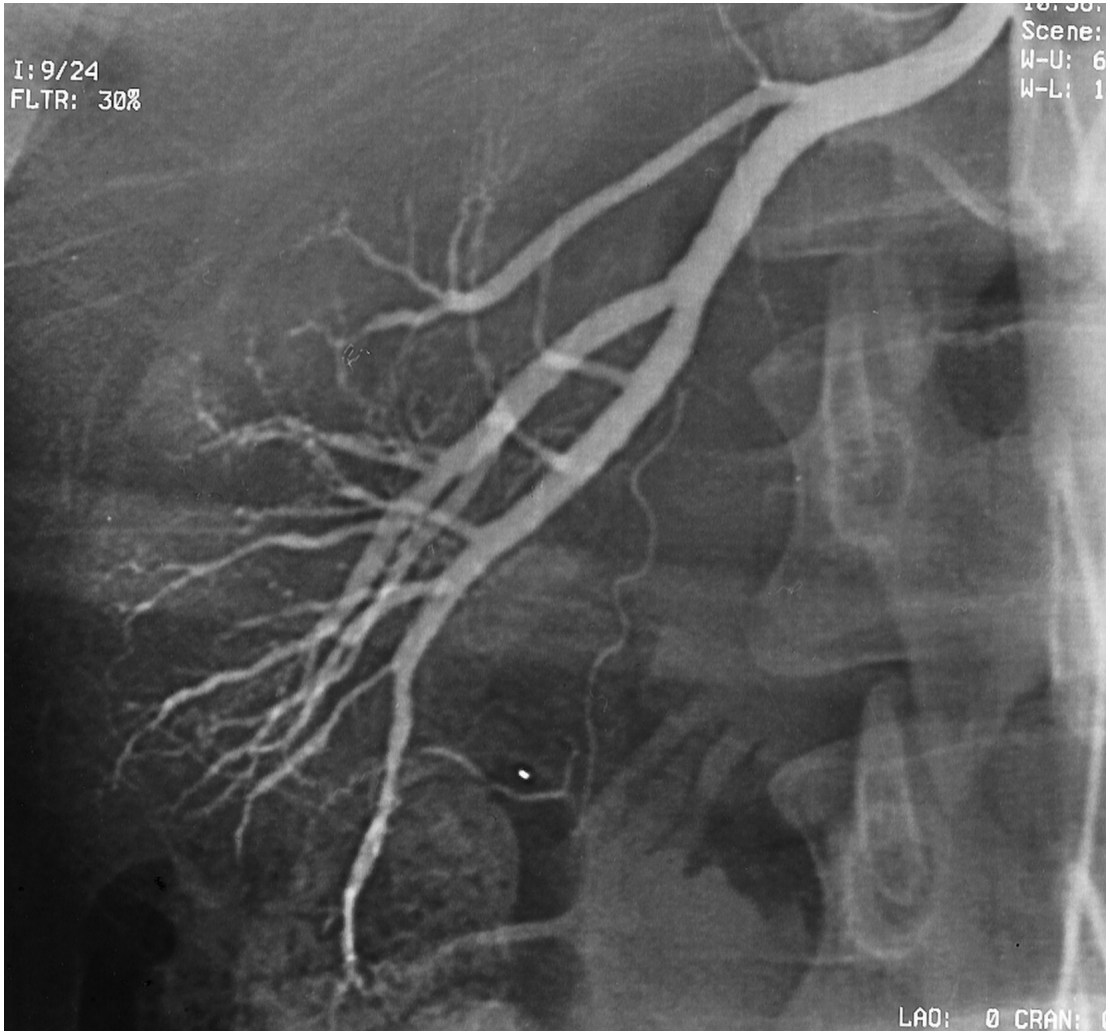
Occlusive disease in an 18-year-old woman with PAN.



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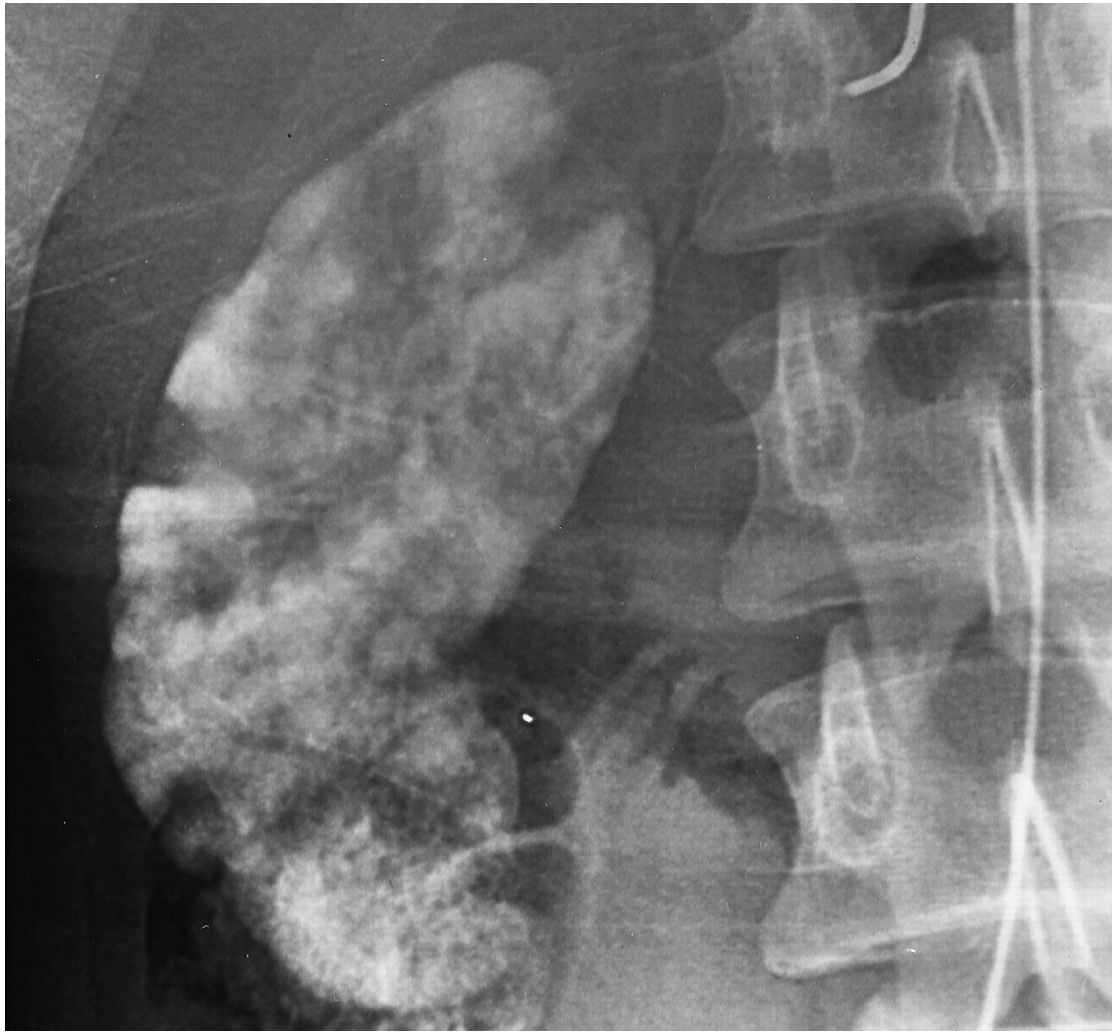
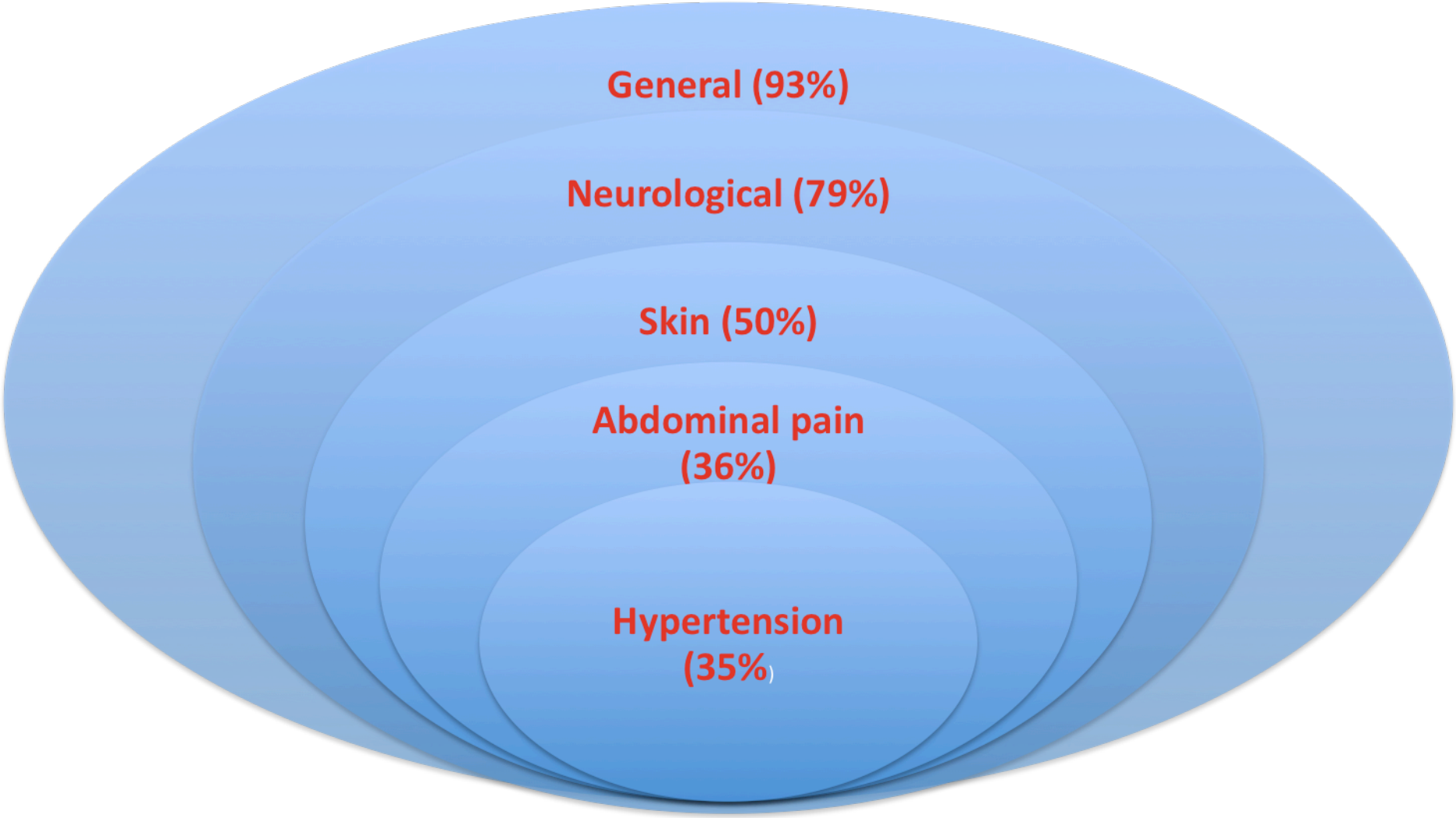


Stanson A W et al. Radiographics 2001;21:151-159

Clinical features



Pagnoux et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. Arthritis Rheum 2010 Feb;62(2):616-26.

Pathology

Idiopathic

Secondary

- Hepatitis B
- HIV
- Hepatitis C
- Hairy cell leukemia

Bardin T, Gaudouen C, Kuntz D, et al. Necrotizing vasculitis in human immunodeficiency virus infection (abstr). Arthritis Rheum 1987
Libman BS, Quismorio FP, Jr, Stimmler MM. Polyarteritis nodosa-like vasculitis in human immunodeficiency virus infection. J Rheumatol 1995;
Saadoun et al. Hepatitis C virus-associated polyarteritsi nodosa. Arthritis Care Res 2010

HBV related PAN

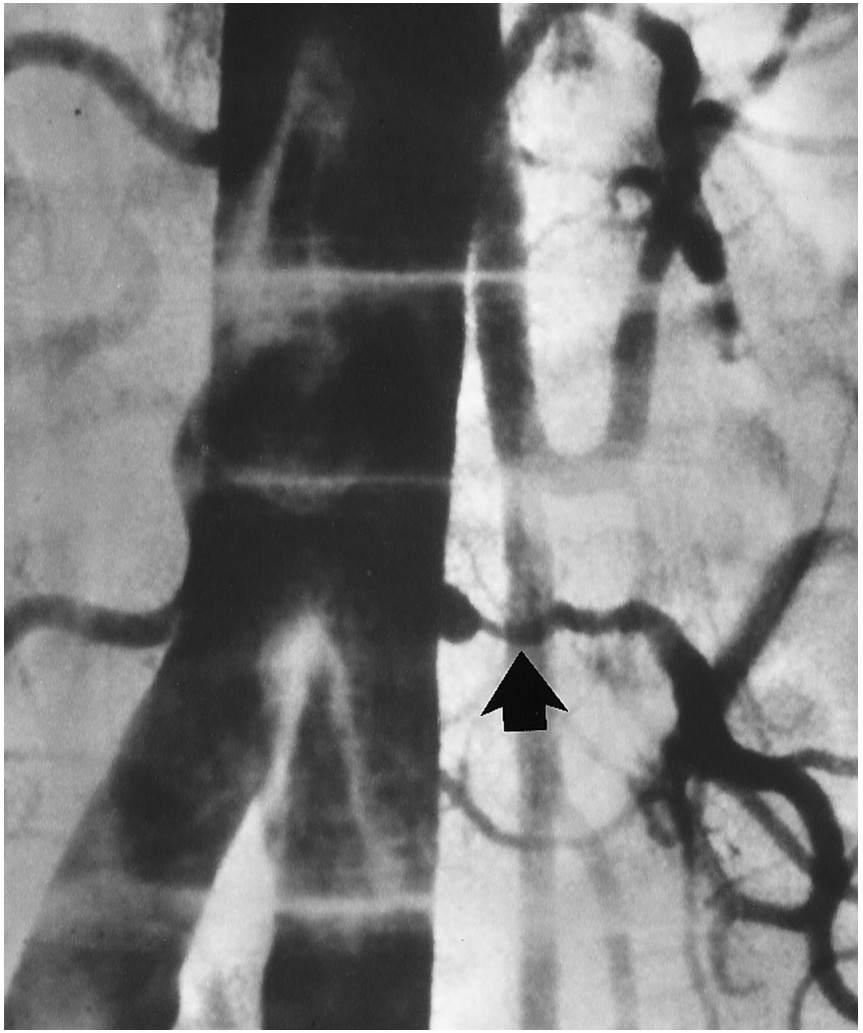
Pagnoux et al. Retrospective study of 348 patients with PAN

1/3 associated with HBV

- within 6 months of infection
- peripheral neuropathy
- abdominal pain
- cardiomyopathy
- ochitis
- hypertension

Less relapse (10.6% vs 21.8%)

Angiogram of a 61-year-old man with PAN demonstrates stenosis of the left lumbar artery (arrow).



Stanson A W et al. Radiographics 2001;21:151-159

Diagnosis

Symptomatology

- Febrile illness
- Weight loss
- Multiple organ involvement

Differentials

- ANCA
- Viral screen

Angiography

Tissue biopsy

ACR 1990 criteria for the classification of PAN

1. Weight loss > 4 kg
2. Livedo reticularis
3. Testicular pain/tenderness
4. **Myalgias, weakness or leg tenderness**

- Mono- or polyneuropathy
- Diastolic BP >90 mmHg
- **Elevated urea (>40) or creatinine (>115)**
- Hepatitis B virus
- **Arteriographic abnormality** - aneurysms or occlusions
- Biopsy of small or medium-sized artery containing polymorphonuclear cells

Treatment

Severity - adapted strategy

- Plasma Exchange
- High-dose glucocorticoids and cyclophosphamide
- Glucocorticoids alone
- HBV associated PAN
  - Lamivudine
  - Plasma Exchange
- Cutaneous PAN
  - NSAIDS / colchicine / dapsone

Clinical Course

Relapse occurs in **40%** of treated patients, with a median interval of **33 months**

The disease may be fulminant; if untreated, the 5-year survival is **< 15%.**

Survival increases to **80% with steroid** treatment, with or without cytotoxic drugs

Guillevin L, Jarrousse B, Lok C, et al. Long-term follow-up after treatment of PAN and Churg-Strauss angiitis with comparison of steroids, plasma exchange and cyclophosphamide to steroids and plasma exchange: a prospective randomized trial of 71 patients. J Rheumatol 1991; 18:567-574.
Guillevin L, Fain O, Lhote F, et al. Lack of superiority of steroids plus plasma exchange to steroids alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome. Arthritis Rheum 1992

Conclusions

Radiographic lesions

- occlusive lesions more frequent
- aneurysms increase specificity of diagnosis

BUT not a requirement

Hepatitis B

- decreasing incidence and not required for diagnosis
- different treatment