ACOI 2017

# Nephrology Cases

# Case 1

62 yo male who was dxed with metastatic NSCLC 6 months ago and was treated with conventional therapy and XRT. Because of disease progression, he was started on ipilimumab (Yervoy) for which he had received his 2nd cycle 10 days ago

PMH HTN

Meds amlodipine 10 daily and ASA 81 mg

# Case 1

72 hours prior to admission he started to have increased weakness with orthostasis. He has poor oral intake. He was taken to the hospital by EMS after an episode of syncope

On arrival he was lethargic and his BP was 65/  HR 120

Nothing else on exam except for decreased volume

# Case 1

He was immediately given 30 ml/kg and labs were drawn

Labs: BUN 70/Cre 8 Na 126/K 6.4/Cl 100/$HCO_3$ 8
Glucose 45 Ca, $PO_4$, Mg OK. CK normal
CBC WBC 18 Nl diff; H/H 14/40; PLT 420
UA 10 RBCs; 10-20 WBC; UAC 210 UPC 700
+granular casts
ECG, CXR, Chest CT, US kidneys/bladder all negative

# Case 1

- After the bolus his BP was 80/ and another 30 ml/kg of NSS given. He was placed on an infusion supplemented with Na acetate (Yes we had no $NaHCO_3$)
- A cortisol was drawn and he was given hydrocortisone 100 IV q8
- Hemodynamically he was stabilized but he made < 500 ml urine over the 1$^{st}$ 24hrs

# Case 1

On day 2, he felt better but was still making little urine. MAP > 65 without pressors

Labs: BUN 90/Cre 9.5/Na 128/K 6/Cl100/$HCO_3$ 9

Cortisol 3. ACTH, TSH and prolactin sent

Because of oliguria and refractory acidosis, hemodialysis was started via IJ catheter

# Case 1

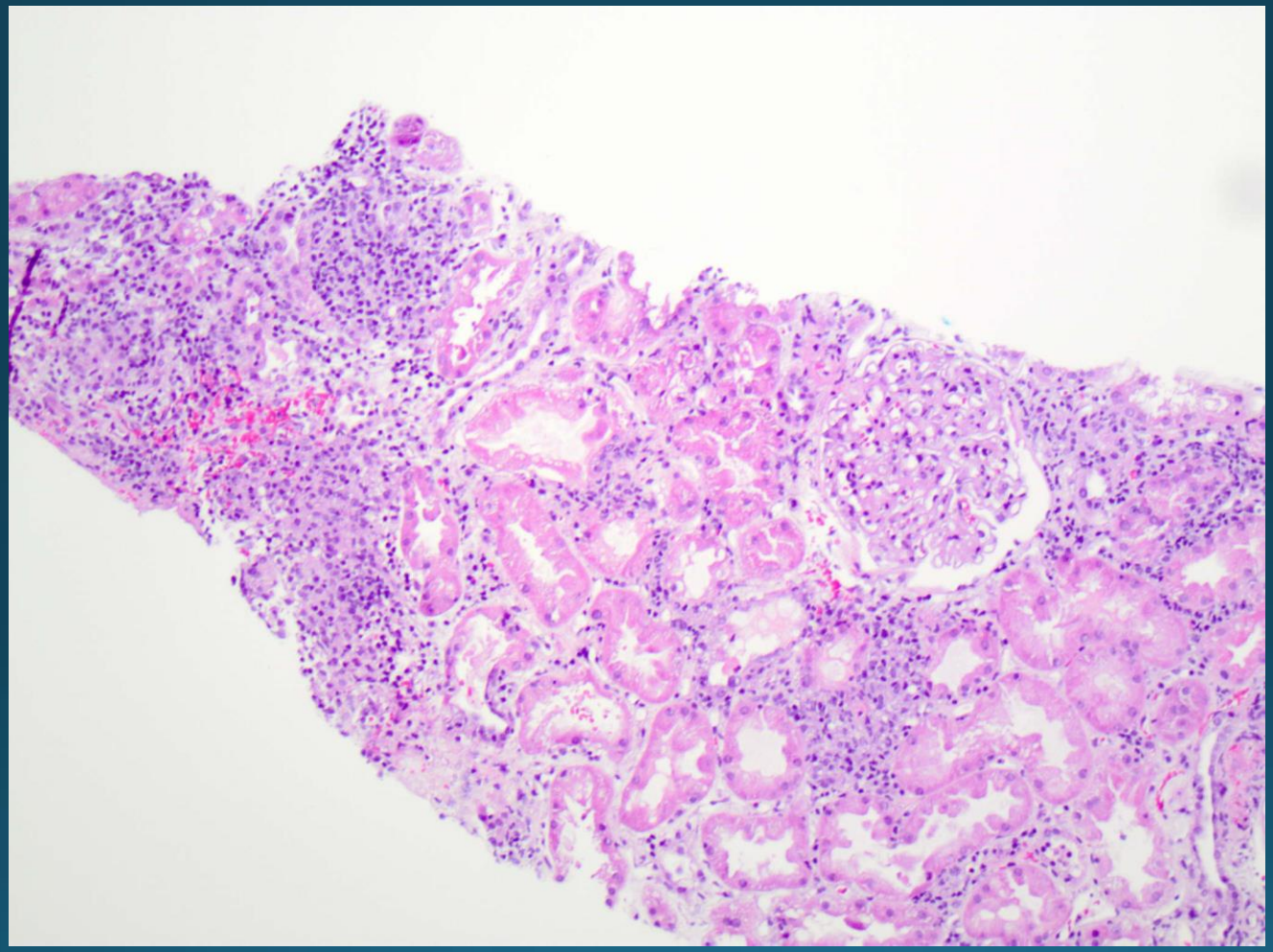
He had persistent oliguria and tolerated dialysis

TSH, ACTH and prolactin levels all low – confirming panhypopituitarism and hydrocortisone was tapered

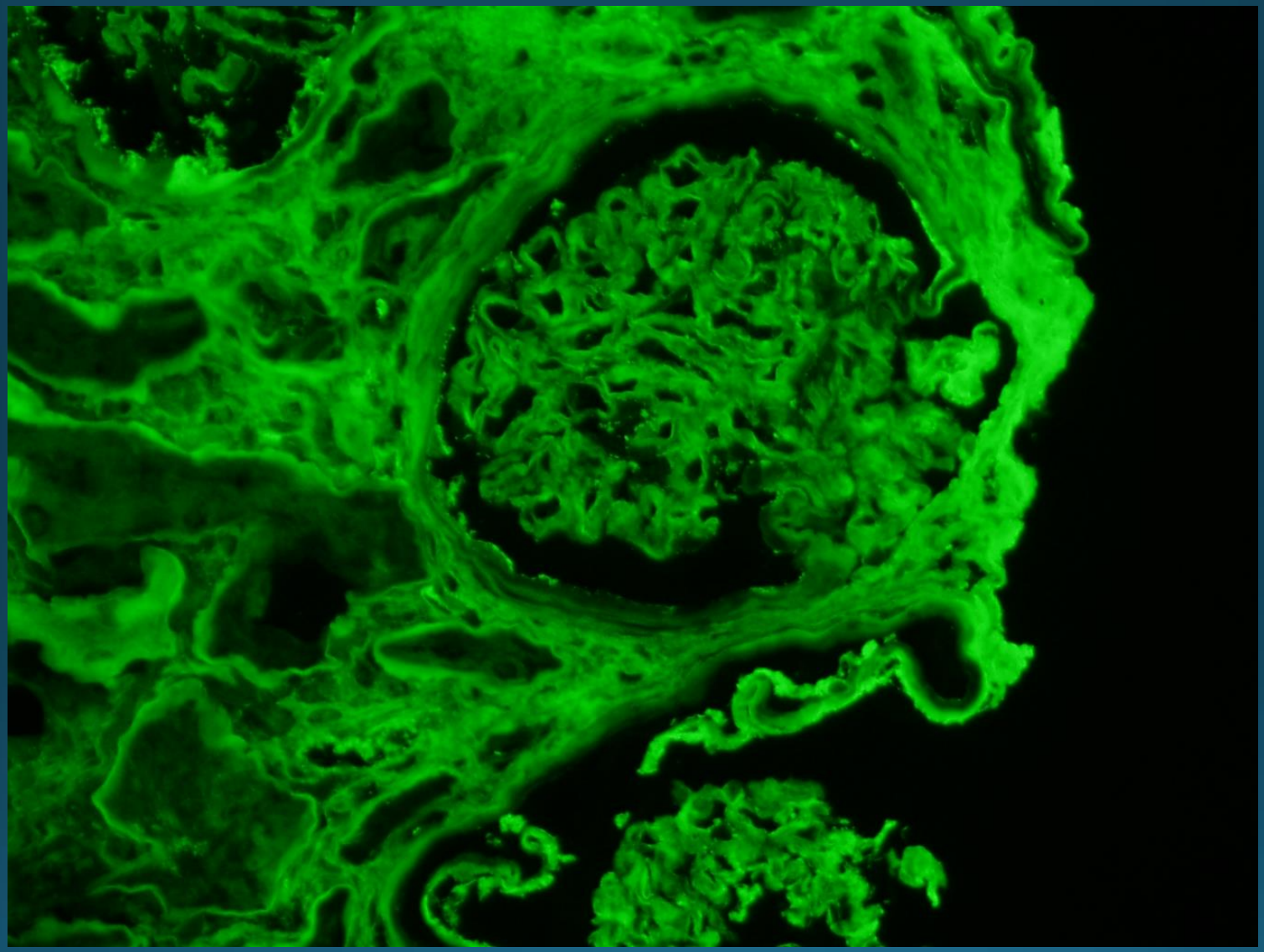
1 week into his course he was still oliguric.

Repeat UA – 10-15 RBCs, 20 WBCs, UAC 250, UPC 725, still with granular casts

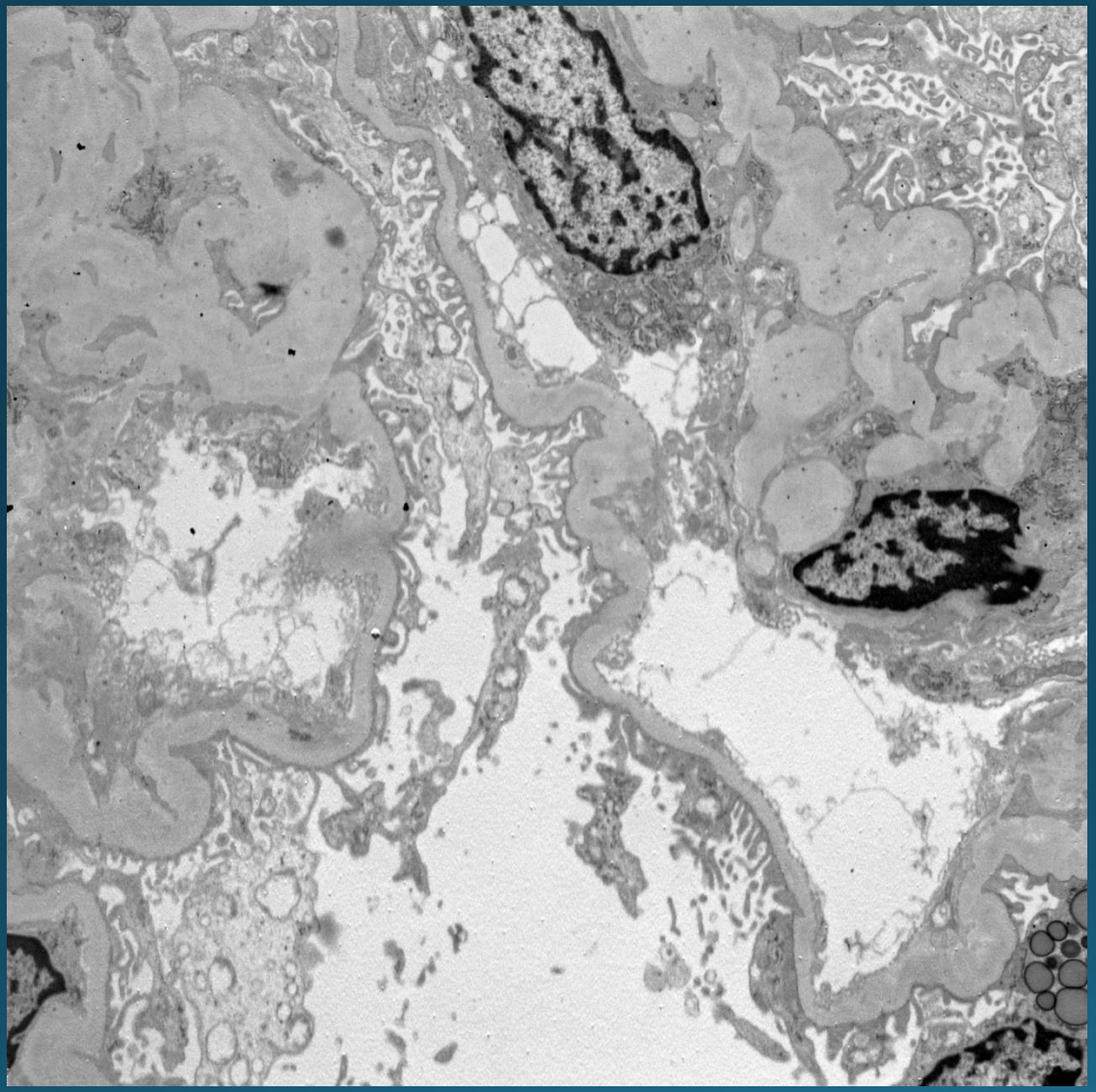
Renal biopsy performed



Interstitial nephritis and ATN



IgG no specific staining



No immune complex deposits seen.

# Checkpoint Inhibitors

- CTLA-4 Inhibitor
  - Ipilimumab (Yervoy)
- PD-1 Inhibitor
  - Pembrolizumab (Keytruda)
  - Nivolumab (Opdivo)
- PD-L1` Inhibitor
  - Durvalumab (Imfinzi)
  - Atezolizumab (Tecentriq)

# CPI Immune related Adverse Reactions

- Skin – rash
- CV – myocarditis
- Endocrine – thyroiditis, pancreatitis, panhypopituitarism
- Neurologic – myasthenia gravis
- Lungs –pneumonitis
- GI – colitis, hepatitis
- Kidney – nephritis, hypoNa

# CPI Kidney Pathophysiology

- Classic AIN – CPI as hapten
- Unmasking of tolerance to drug leading to AIN
- Immune mediated adverse reaction (autoimmunity)

# Adverse Renal Effects of Immune Checkpoint Inhibitors: A Narrative Review

Wanchoo et al. Am J Nephrol 2017;45:160-169
(DOI:10.1159/000455014)

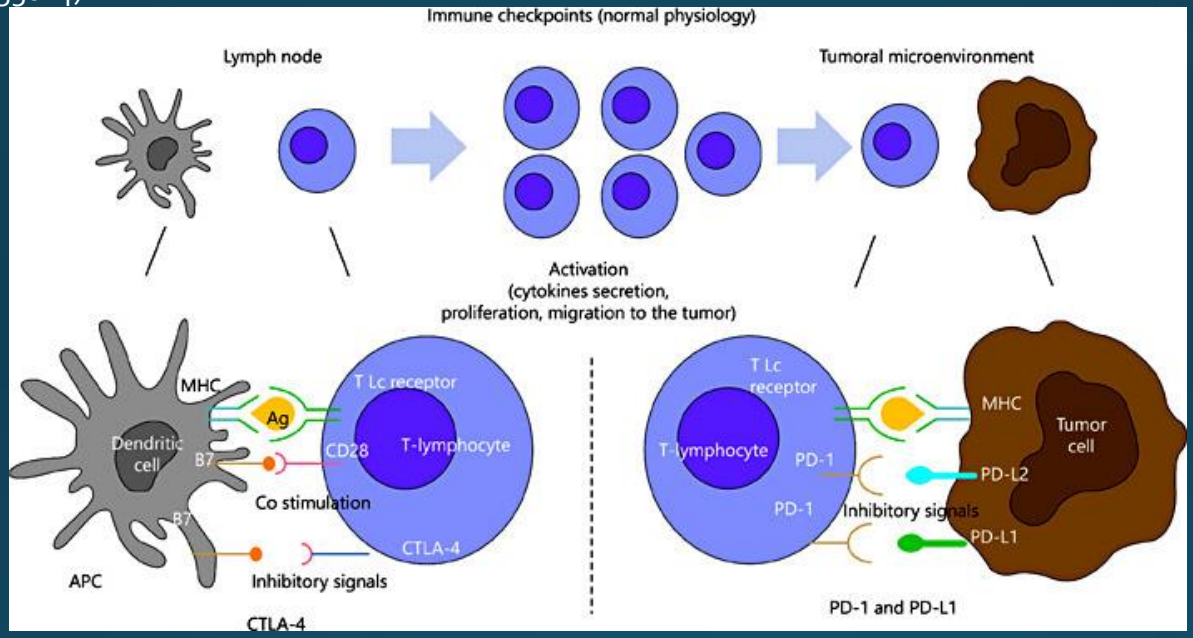



Fig. 1. CTLA-4 and PD-1 signaling networks at homeostasis. Integration of both positive and negative costimulatory signals during and after the initial T-cell activation will determine the fate and intensity of the alloimmune response. The first step in antigen (Ag) recognition is the binding of the antigen to major histocompatibility complex (MHC) molecules on the antigen presenting cell (APC) and creating a complex with the T cell receptor (TCR) located on the T cell. This is followed by the interaction of the CD28 molecule with B7 (CD 80/86) initiating a co-stimulatory signal leading to further T-cell stimulation (this is in addition to other co-stimulatory molecules not depicted here). As a negative feedback process to prevent overstimulation, T-cell activation leads to the upregulation of the CTLA-4 molecule, which competes with the B7-CD28 ligand and in turn leads to T-cell arrest, thus providing brakes to the immune system. Similarly, binding of the PD-1 molecule with PD-L1 and PD-L2 leads to an inhibitory signal with decreased effector T-cell function, suppressing immune surveillance and permitting neoplastic growth. It has to be noted that the majority of data supports the role of increased PD-L1 expression in human tumors and serves as the biomarker to consider PD-1 inhibitors for treatment. The role of PD-L2 in specific tumor immunology in humans is not well defined.

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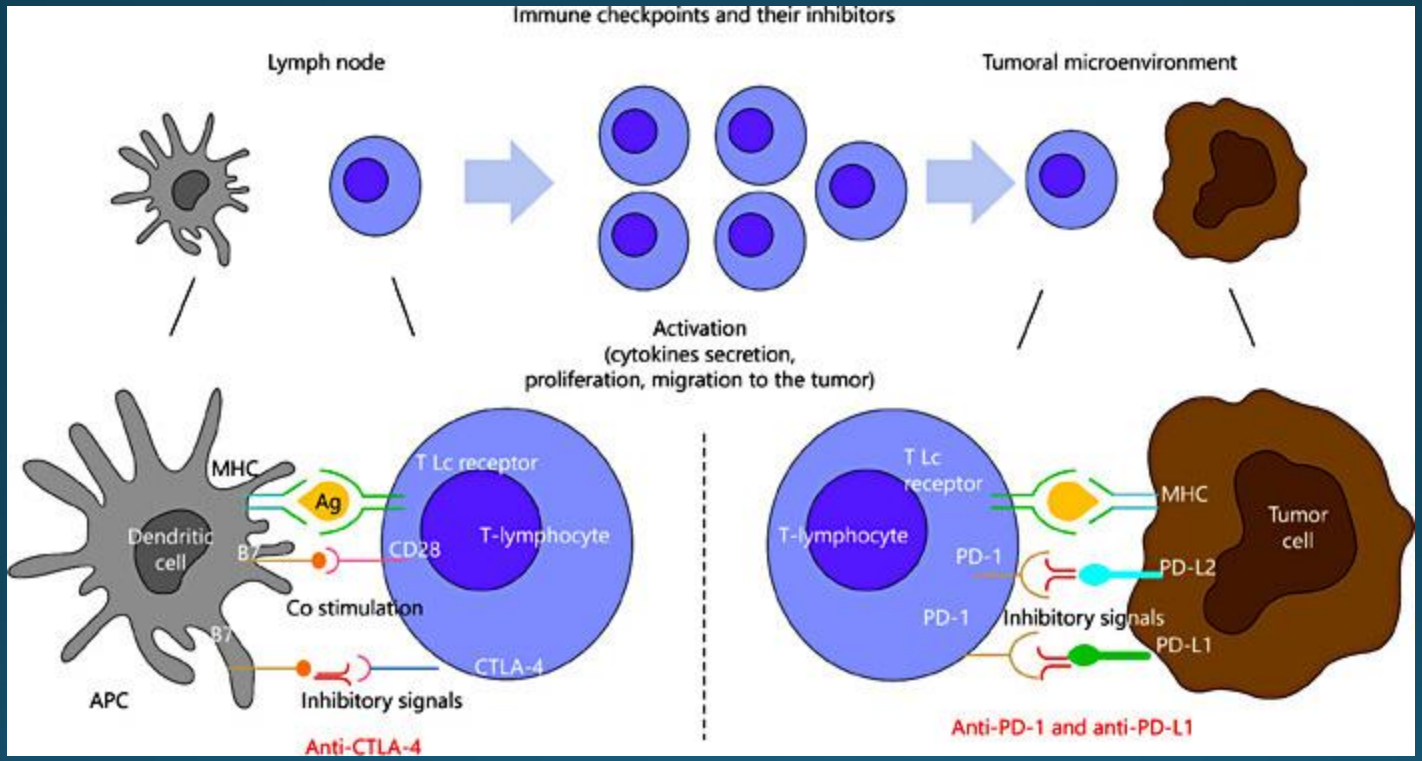


Fig. 2. Ipilimumab or CTLA-4 antagonist binds to the CTLA-4 molecule and prevents it from binding to B7, leading to the sustained activation of the T cell (lifting the foot off the brakes). PD- 1 inhibitors bind to the PD-1 molecule preventing its interaction with PD-L1/L2, thus leading to continued T-cell stimulation (pressing on the accelerator). It has to be noted that the majority of data supports the role of increased PD-L1 expression in human tumors and serves as the biomarker to consider PD-1 inhibitors for treatment. The role of PD-L2 in specific tumor immunology in humans is not well defined.

# Adverse Renal Effects of Immune Checkpoint Inhibitors: A Narrative Review

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| Drug name | Renal impairment* | Hypokalemia | Hyponatremia | Hypomagnesemia | Hyperkalemia | Hypophosphatemia | Hypernatremia | Grand total |
|---|---|---|---|---|---|---|---|---|
| Ipilimumab | **220** | 64 | 159 | 8 | 19 | 13 | 0 | 483 |
| Nivolumab | **20** | 5 | 14 | 2 | 4 | 1 | 0 | 44 |
| Pembrolizumab | 16 | 3 | **19** | 0 | 1 | 0 | 0 | 39 |

The numbers in the cell represent the total number of events of each category for the 3 immune check point inhibitors.
* Renal impairment comprises proteinuria, renal failure acute, acute kidney injury, elevated creatinine, hypercreatinemia, and nephritis.
** Bolded numbers represents most common reported reaction.
*** The search terms used for the FAERS database were "renal impairment, proteinuria, renal failure acute, acute kidney injury, elevated creatinine, hypercreatinemia nephritis, hyponatremia, hypokalemia, hypernatremia, hyperkalemia, hypophosphatemia, hypocalcemia, hypercalcemia, hypomagnesemia, and hypertension." There are important limitations with the FAERS database. The events are reported by providers and/or patients and there could be a reporting bias. In addition, not all demographic and comorbidity information is available to help identify if other nephrotoxic risk factors are present.

Table 1. Common reported renal adverse events to the FDA adverse reporting database (FAERS) from 2011 3rd quarter to 1st quarter of 2015

# Adverse Renal Effects of Immune Checkpoint Inhibitors: A Narrative Review

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| Agents | CTLA-4 antagonists (ipilimumab) | PD-1 inhibitors (nivolumab and pembrolizumab) |
|---|---|---|
| Mechanistic differences | 1. Limits T-cell response early in the immune response in lymphoid tissues<br>2. Expressed by T cells<br>3. CTLA-4 ligands expressed by antigen-presenting cells | 1. Limits T-cell response later in the immune response, primarily in peripheral tissues<br>2. Expressed by T cells and other immune cells<br>3. PD-1 ligands expressed by antigen-presenting cells and other immune cells and can be inducibly expressed in non-immune cells including tumor cells |
| Cancer | Metastatic melanoma**, lung cancer*, renal cell cancer*, prostate cancer*, cervical cancer*, colorectal cancer*, pancreatic cancer*, ovarian cancer*, urothelial cancer* | Metastatic melanoma**, non small cell lung cancer **, gastric cancer*, head and neck cancer*, urothelial cancer*, colorectal cancer*, gliobastoma*, pancreatic cancer*, hematologic malignancies* |
| Onset of AIN | AIN appears 6–12 weeks after initiation of therapy, with longest duration being 26 weeks. Late onset associated with more severe AKI requiring renal replacement therapy | AIN appears 3–12 months after initiation of therapy |
| Glomerular findings | Podocytopathy (membranous nephropathy and minimal change disease) and thrombotic microangiopathy reported | No cases of podocytopathy reported |
| Gender | No gender preferences | No gender preferences |
| Electrolyte disorders | Hyponatremia cases related to hypophysitis (secondary adrenal insufficiency) | Hyponatremia is rare |
| Transplant | In renal transplant patients, 2 cases reported no rejection when given as a solo agent | When given– patients had rejection especially following use with CTLA-4 inhibitors (4 cases reported), likely due to loss of tolerance |

AIN, acute interstitial nephritis.
** FDA approved, * in phase 2 or 3 clinical trials.

Table 2. Renal effects of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antagonists and the programmed death-1 (PD-1) inhibitors

**Table 2 | Clinical features of CPI-induced AKI**

| Pt | Urine sediment[a] | Proteinuria (dipstick/UPCR) | Day of AKI[b] | Days since last dose of CPI | Eos | HTN[c] | Oliguria[d] | Kidney size (cm) | Peak SCr (mg/dl) | Requirement for RRT | IRAEs |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 5–10 WBCs[e]<br>2 RBCs | 1+/0.6 | 54 | 54 | No | No | No | R 12.8<br>L 13.8 | 6.2 | No | Hypophysitis |
| 2 | 2–3 WBCs<br>3–5 RBCs | Trace/NA | 91 | 49 | No | No | No | R 12.2<br>L 13.2 | 4.1 | No | Thyroiditis; ileitis |
| 3 | 5–10 WBCs<br>0 RBCs<br>0–2 WBC casts | Trace/NA | 69 | 14 | No | No | No | R 11.6<br>L 12.6 | 9.7 | 3 HD treatments starting on day 130 | Hepatitis |
| 4 | 16–34 WBCs | NA/NA | 70 | 28 | NA | No | No | R 13.0<br>L 13.0 | 3.6 | No | None |
| 5 | 5 WBCs[e]<br>1 RBC | Neg/0.26 | 245 | 63 | No | No | No | R 13.2<br>L 13.0 | 2.9 | No | Hypophysitis; thyroiditis |
| 6 | 0 WBC<br>0 RBC | Neg/0.74 | 183 | 36 | No | Yes | Yes | R 10.9<br>L 13.5 | 11.7 | HD-dependent starting on day 183 | Hypophysitis;[f] colitis |
| 7 | 0 WBC[e]<br>0 RBC | Neg/NA | 224 | 14 | No | No | No | R 11.8<br>L 12.2 | 3.8 | No | Sicca syndrome with sialadenitis on lip biopsy; colitis |
| 8 | 6–9 WBCs<br>0–3 RBCs | 1+/0.98 | 154 | 7 | No | No | Yes | R 12.8<br>L 11.8 | 5.6 | HD-dependent starting on day 210 | None |
| 9 | 9 WBCs[e]<br>8 RBCs<br>WBC casts | 2+/0.12 | 42 | 21 | No | Yes | No | R 12.4<br>L 13.0 | 7.3 | No | Rash; colitis |
| 10 | 3 WBCs[e]<br>3 RBCs<br>WBC casts | 1+/0.73 | 120 | 57 | No | No | No | R 8.0<br>L 10.0 | 2.9 | No | None |
| 11 | 50–100 WBCs<br>0–2 RBCs | 1+/0.18 | 60 | 18 | 14.7% | No | No | R 10.2<br>L 10.0 | 4.5 | No | None |
| 12 | 20–50 WBCs<br>0-2 RBCs | 1+/NA | 21 | 21 | No | No | No | NA | 13.3 | 3 HD treatments starting on day 21 | None |
| 13 | 11–20 WBCs<br>0 RBCs | Neg/0.36 | 231 | 21 | No | No | No | R 10.7<br>L 11.9 | 2.5 | No | Iritis; colitis |
| Median<br>IQR | | 0.48<br>0.24–0.73 | 91<br>60–183 | 21<br>18–49 | | | | R 12.0, L 12.8<br>R 10.9–12.8<br>L 11.9-13.1 | 4.5<br>3.6–7.3 | | |

# CPI Nephropathy

- Timing is variable – 1- 9 months
- Incidence – 10-30% ??
- Severity usually severe – Stage 3 AKI
- More common with CTLA-4 and PD-1 combination. Associated with other IRAEs
- Responds to steroids
- May lead to transplant rejection
- Permanent discontinuation of PDI

# Case 1

- He was treated with prednisone 1 mg/kg for 1 month and then tapered over the next 3 months
- Dialysis was stopped after 3 weeks
- He has not been re-challenged with CPI

# Case 2

75 yo woman with a > 10 year hx of DM II and HTN who is admitted for AKI (normal eGFR 6 months ago)

3 months of constitutional symptoms – weakness, lethargy and more recently anorexia and nausea. + myoclonic jerks. + cough

ROS negative except above

Meds: metformin ASA and lisinopril

# Case 2

Labs: BUN 90/Cre 9/Na 138/K 6/Cl 110/$HCO_3$ 14

UA – + dysmorphic RBCs, few WBCs, few RTEs, no cellular casts UAC 2300 UPC 3500

US kidneys, CXR bilateral infiltrates

Serologic workup ordered

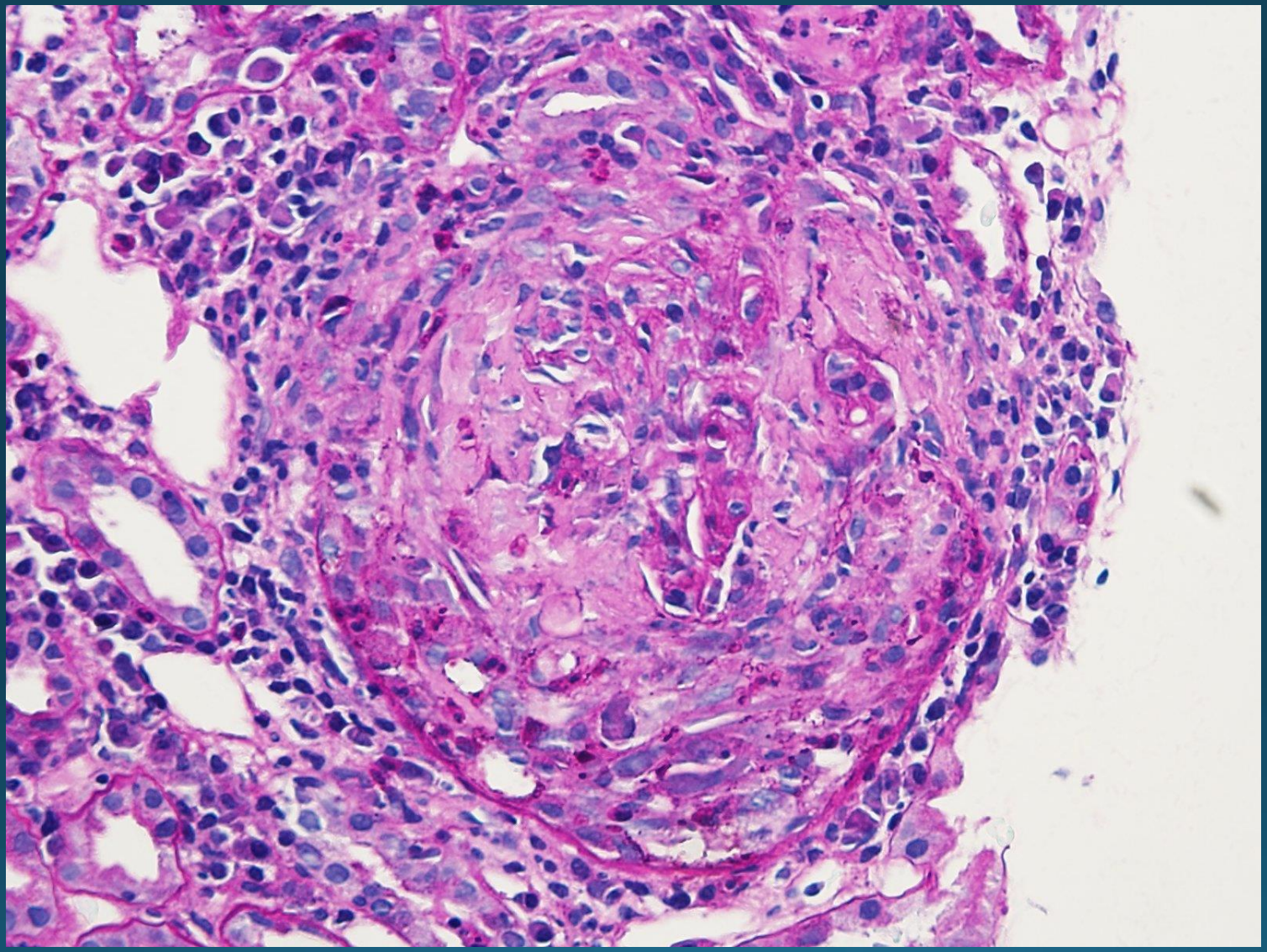
Placed on dialysis after no improvement for 48 hrs

# Case 2

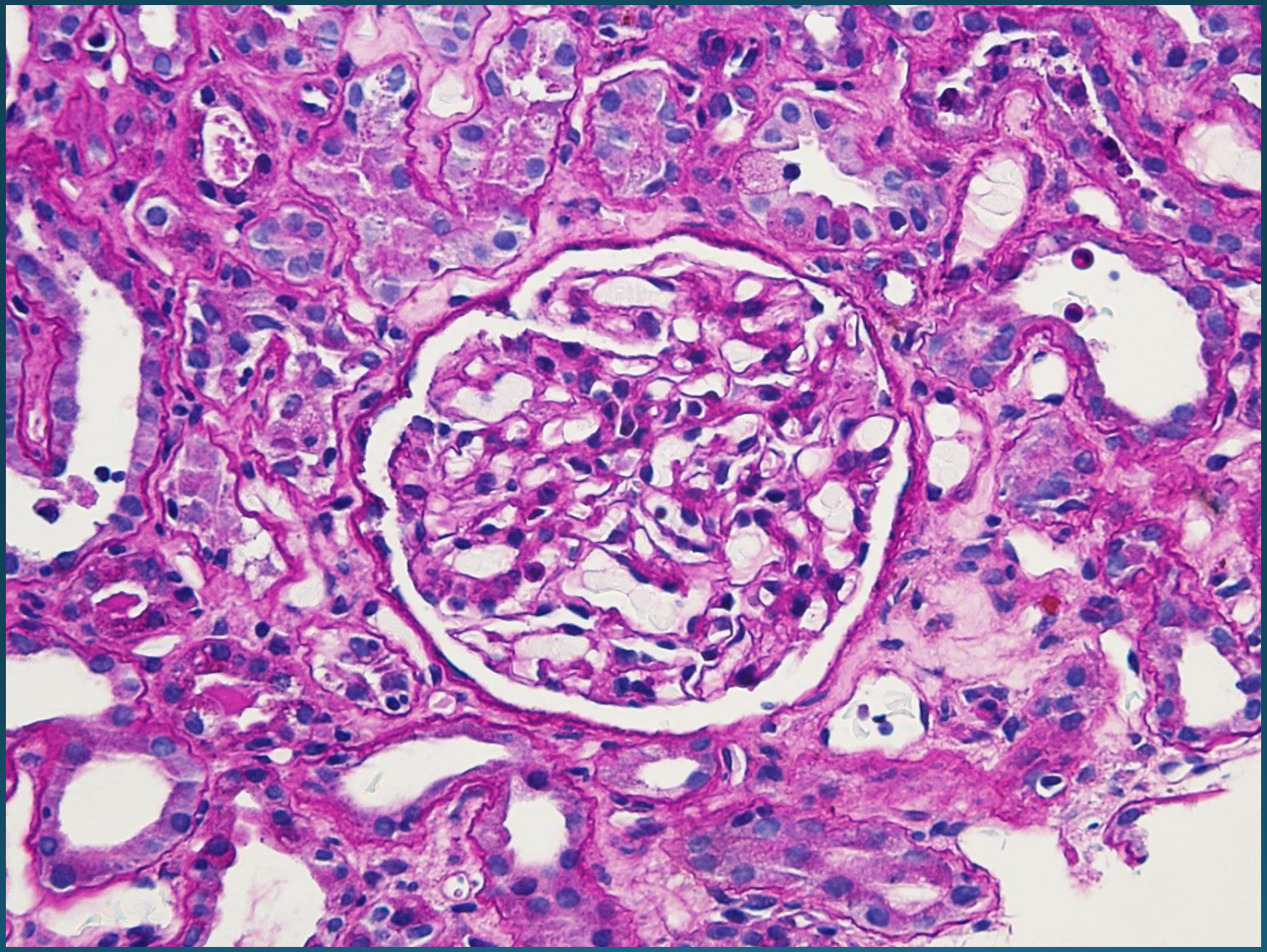
Complements normal

+ anti MPO in high titer. All of the rest of the serologic workup including anti GBM negative

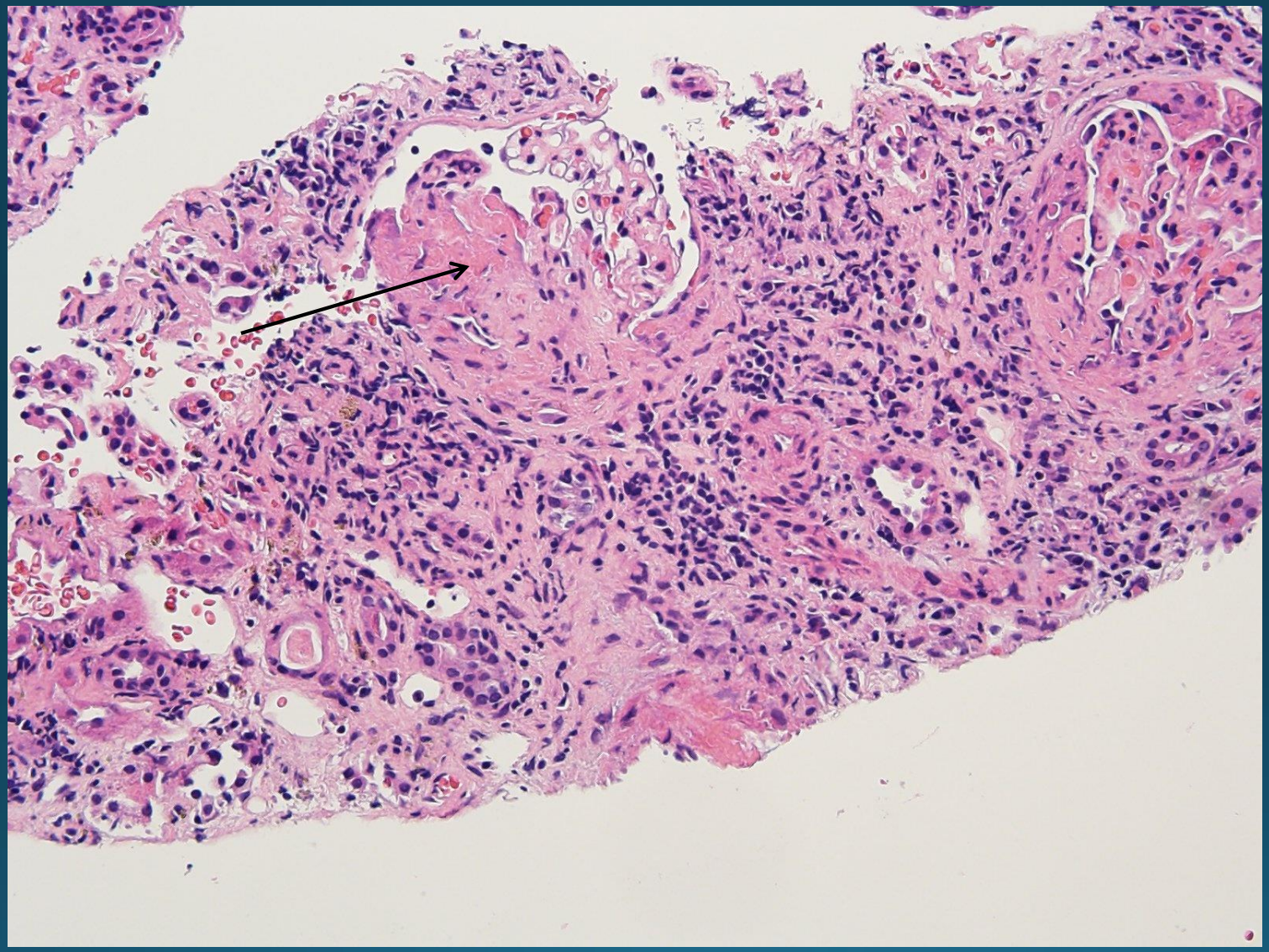
Renal biopsy performed



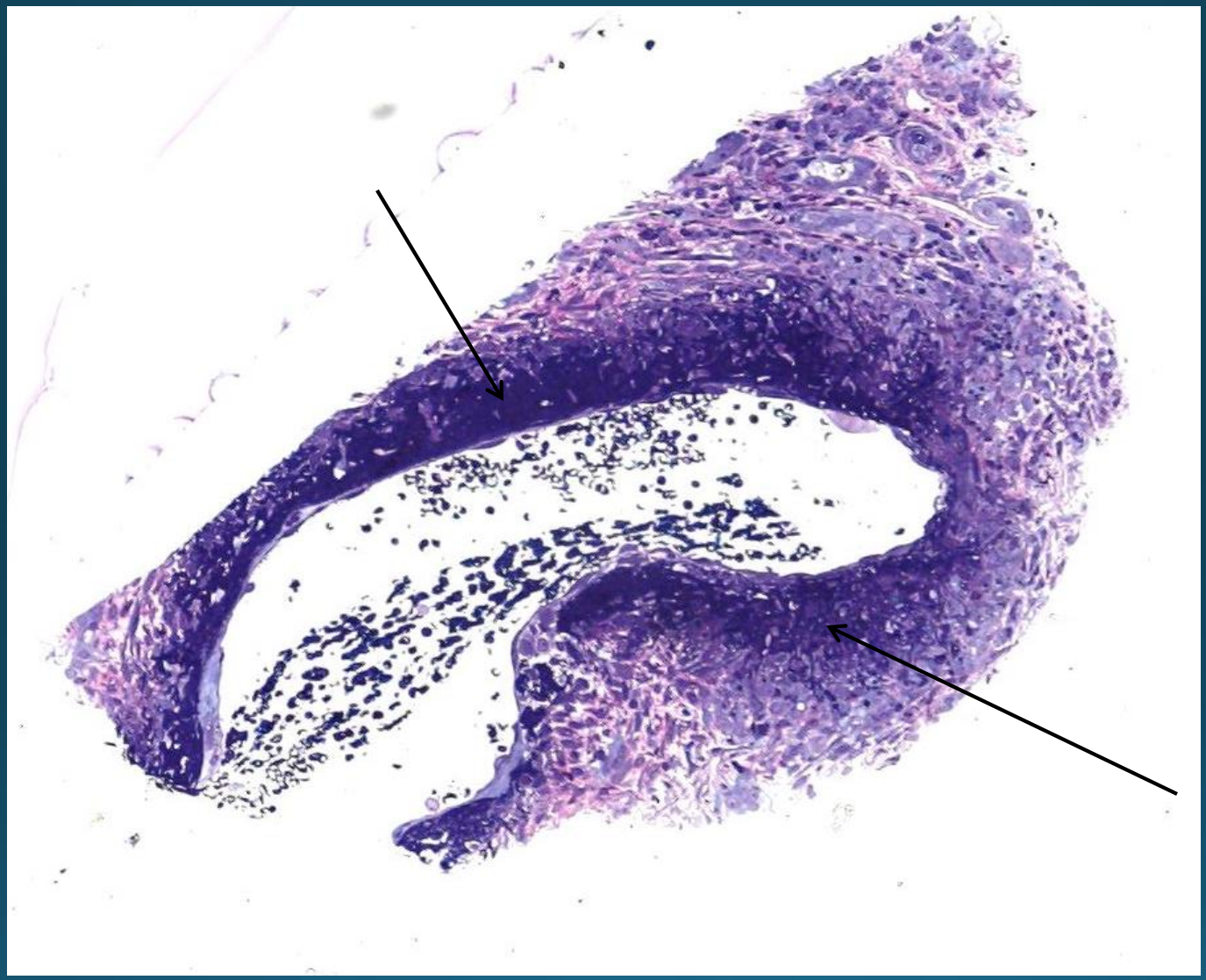
A big cellular crescent. PAS



A well preserved glomerulus. PAS



Interstitial inflammation, segmental glomerular necrosis (arrow). H&E



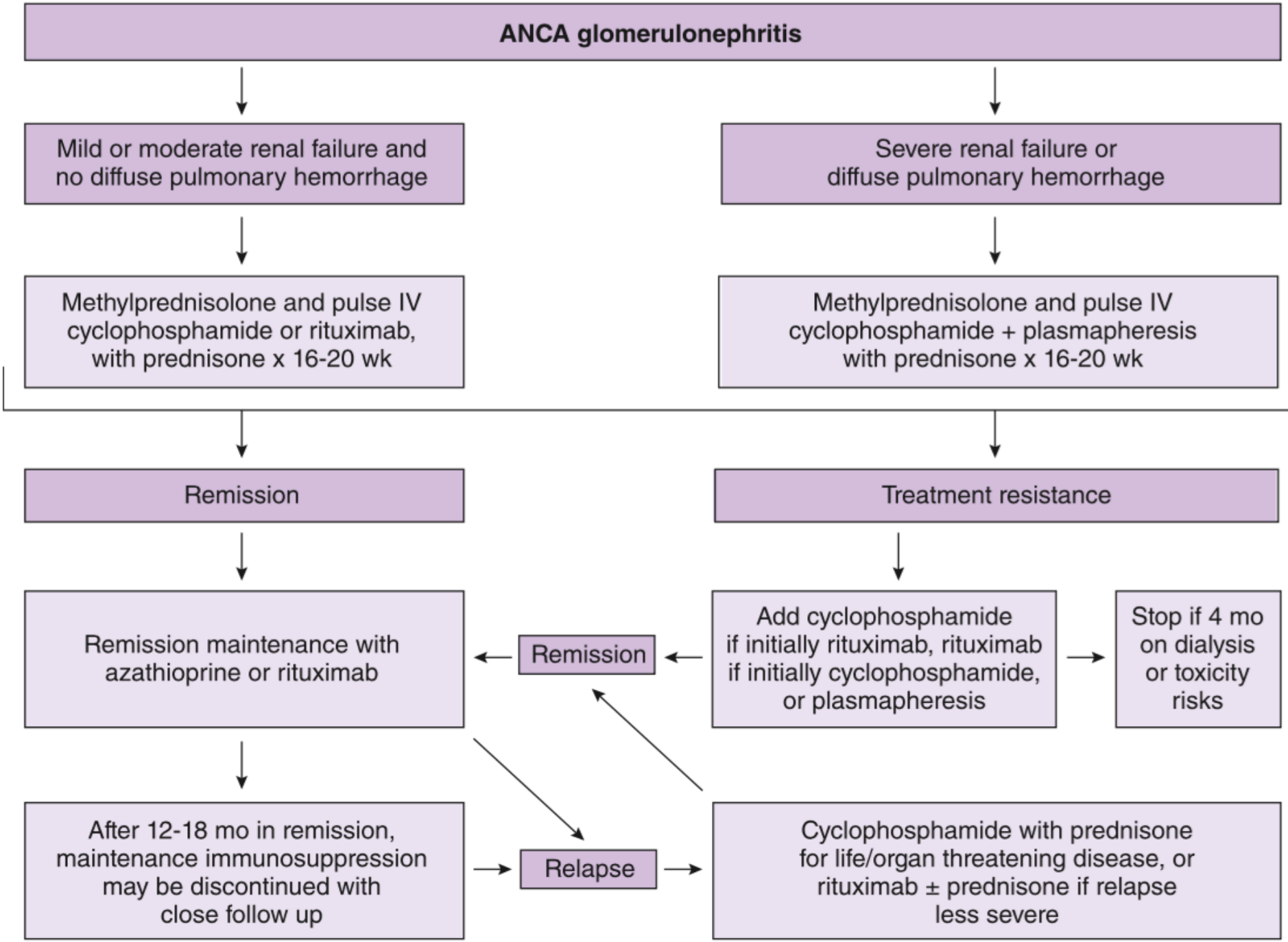
Vasculitis with fibrinoid necrosis of the arterial wall (arrows). Methylene blue basic fuchsin stained semithin sections cut from the tissue submitted for electron microscopy.

# Case 2

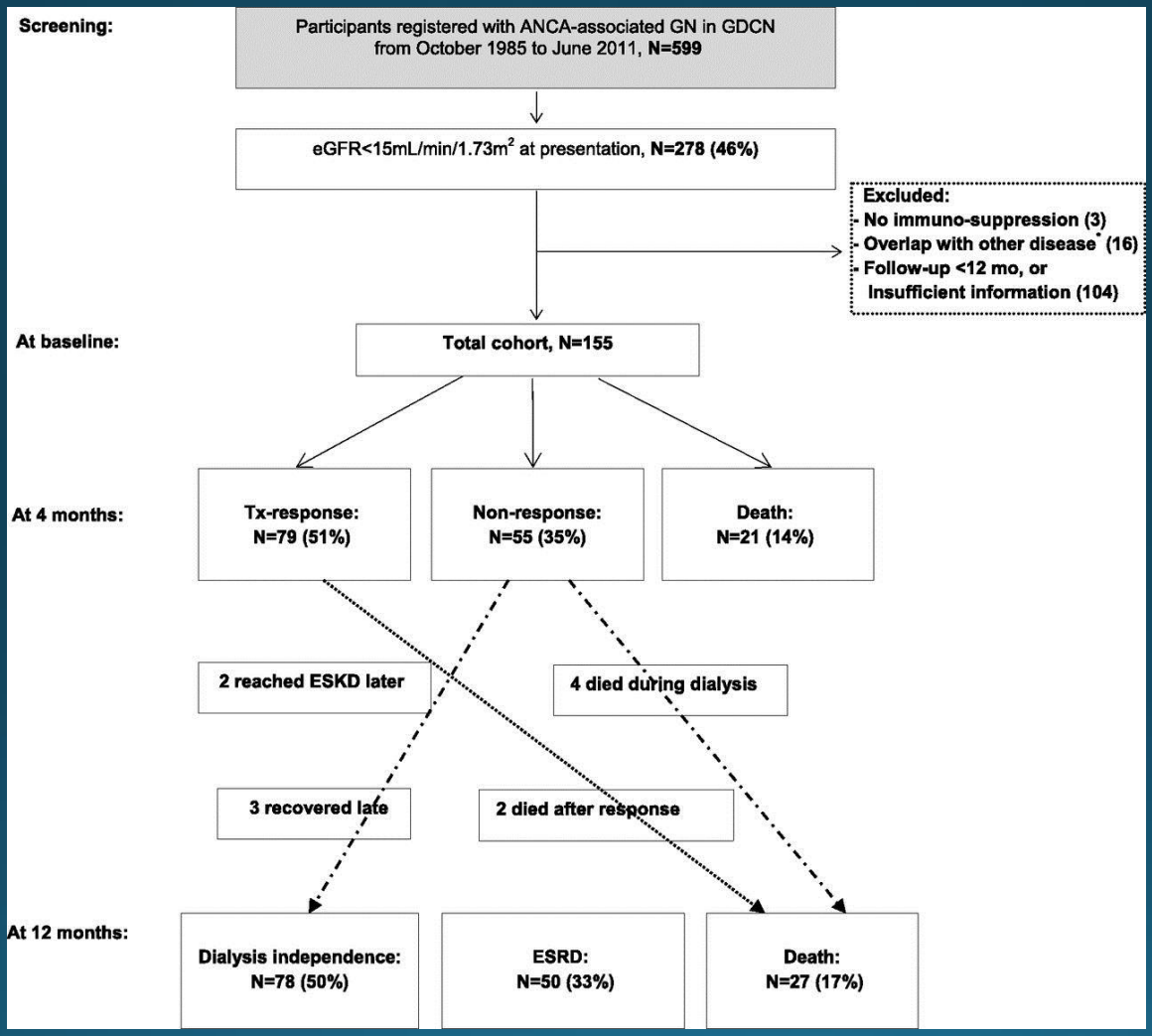
She was treated with high dose solumedrol

A discussion with patient regarding options and we decided on :

- Prednisone 60 with taper after 1 month
- IV cyclophosphamide 15 mg/kg IV q2-3 weeks
- Plasmapheresis 60 ml/kg for 7 exchanges
- DS TMP/SMX prophylaxis 3X weekly

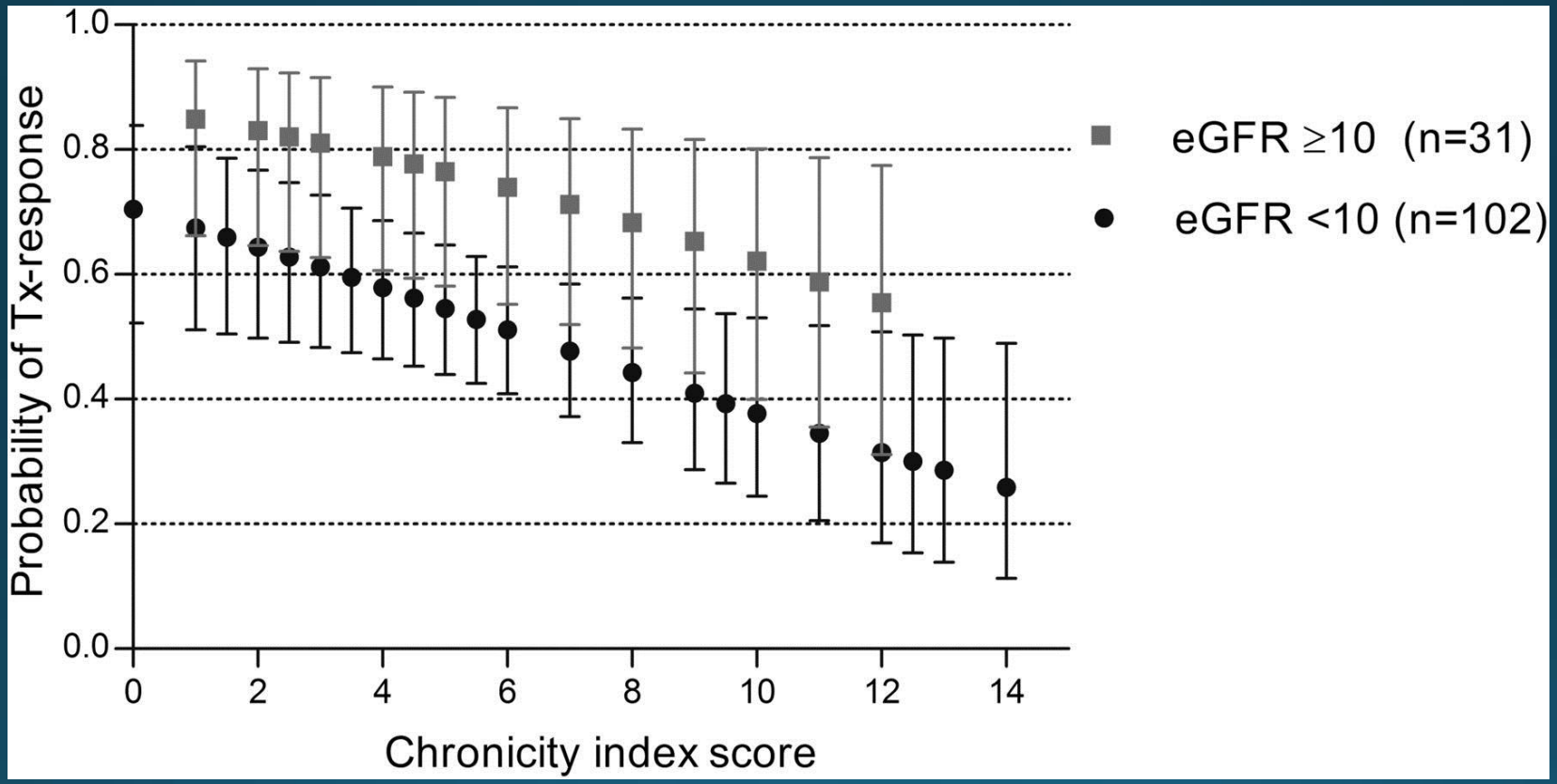

ANCA glomerulonephritis
Mild or moderate renal failure and no diffuse pulmonary hemorrhage
Severe renal failure or diffuse pulmonary hemorrhage
Methylprednisolone and pulse IV cyclophosphamide or rituximab, with prednisone x 16-20 wk
Methylprednisolone and pulse IV cyclophosphamide + plasmapheresis with prednisone x 16-20 wk
Remission
Treatment resistance
Remission maintenance with azathioprine or rituximab
Remission
Add cyclophosphamide if initially rituximab, rituximab if initially cyclophosphamide, or plasmapheresis
Stop if 4 mo on dialysis or toxicity risks
After 12-18 mo in remission, maintenance immunosuppression may be discontinued with close follow up
Relapse
Cyclophosphamide with prednisone for life/organ threatening disease, or rituximab ± prednisone if relapse less severe

# Clinical outcomes: the treatment response beyond 4 months after biopsy is uncommon.




Taewoo Lee et al. CJASN 2014;9:905-913

**Among cyclophosphamide-treated patients, the likelihood of treatment response was >14% (lowest confidence limit) even with highest chronicity index score and eGFR<10 ml/min per 1.73 m2.**

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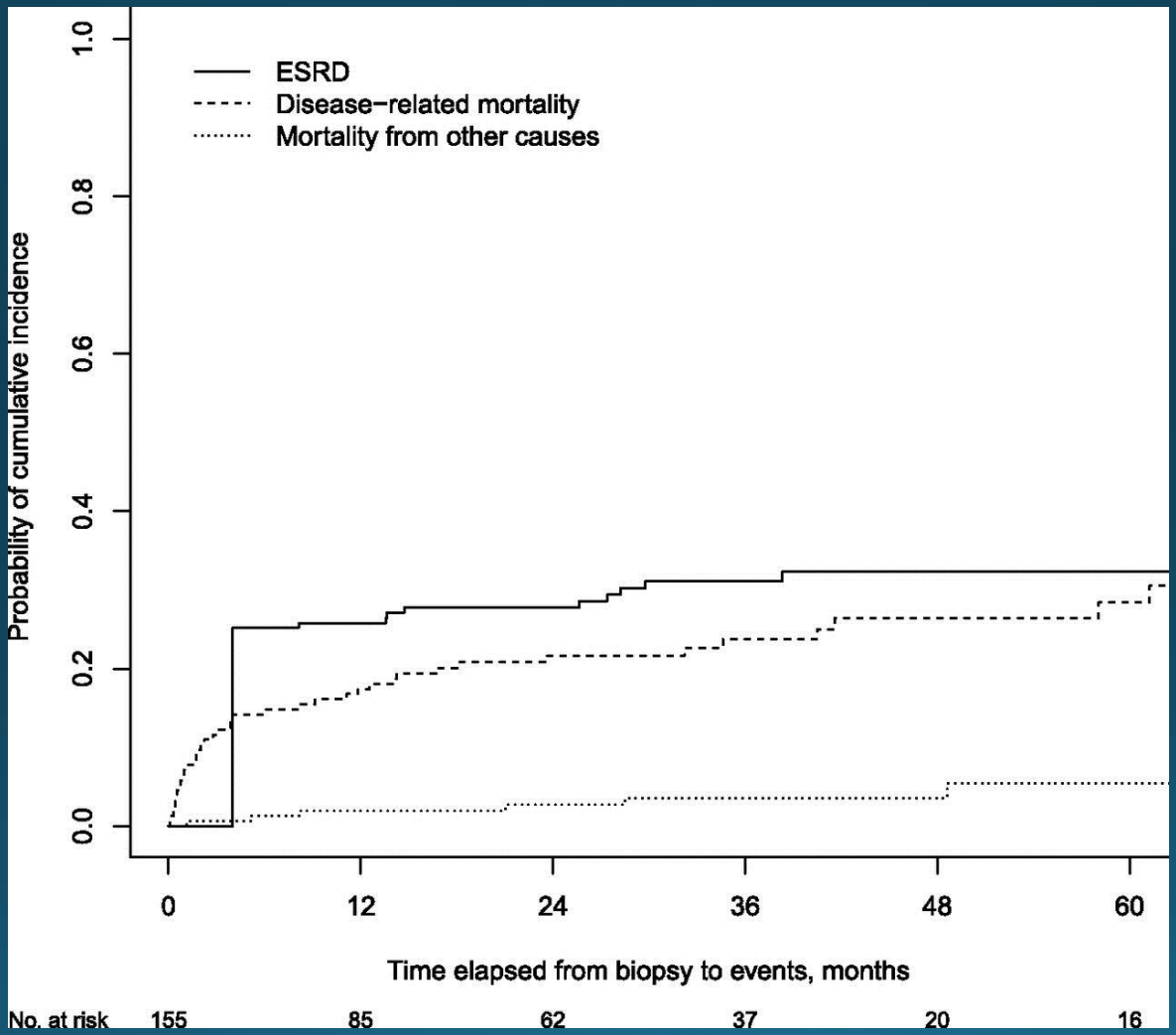
**Probability of cumulative incidence of ESRD, disease-related death, or death from other cause for the entire cohort.**

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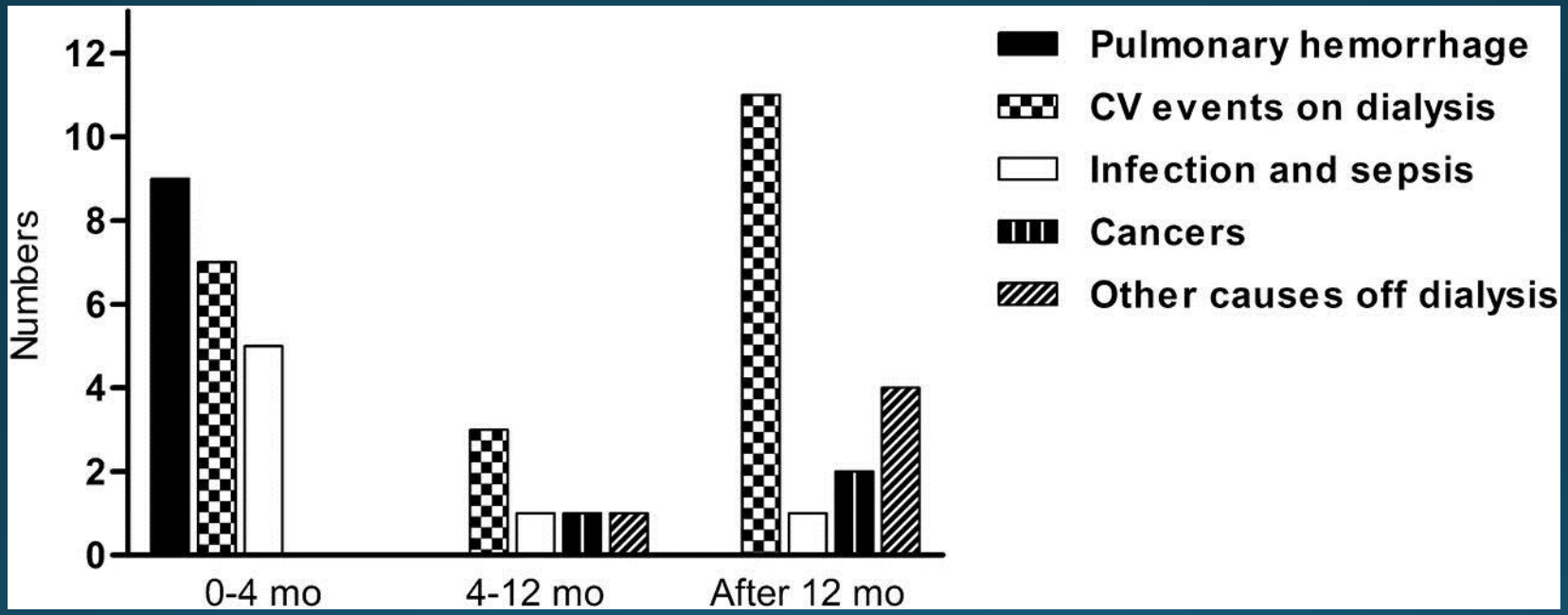
**Cause of death according to time periods after diagnosis.**




Taewoo Lee et al. CJASN 2014;9:905-913

# Summary

- Response rate even for severe renal failure txed with steroids and CYP 50%
- Mortality 15-20% and more likely if on dialysis
- If no response by 4 months < 5% responded
- Age, female sex, high chronicity index and eGFR < 10 predicted non-response

# Demographic and Clinical Characteristics of the Patients at Trial Entry

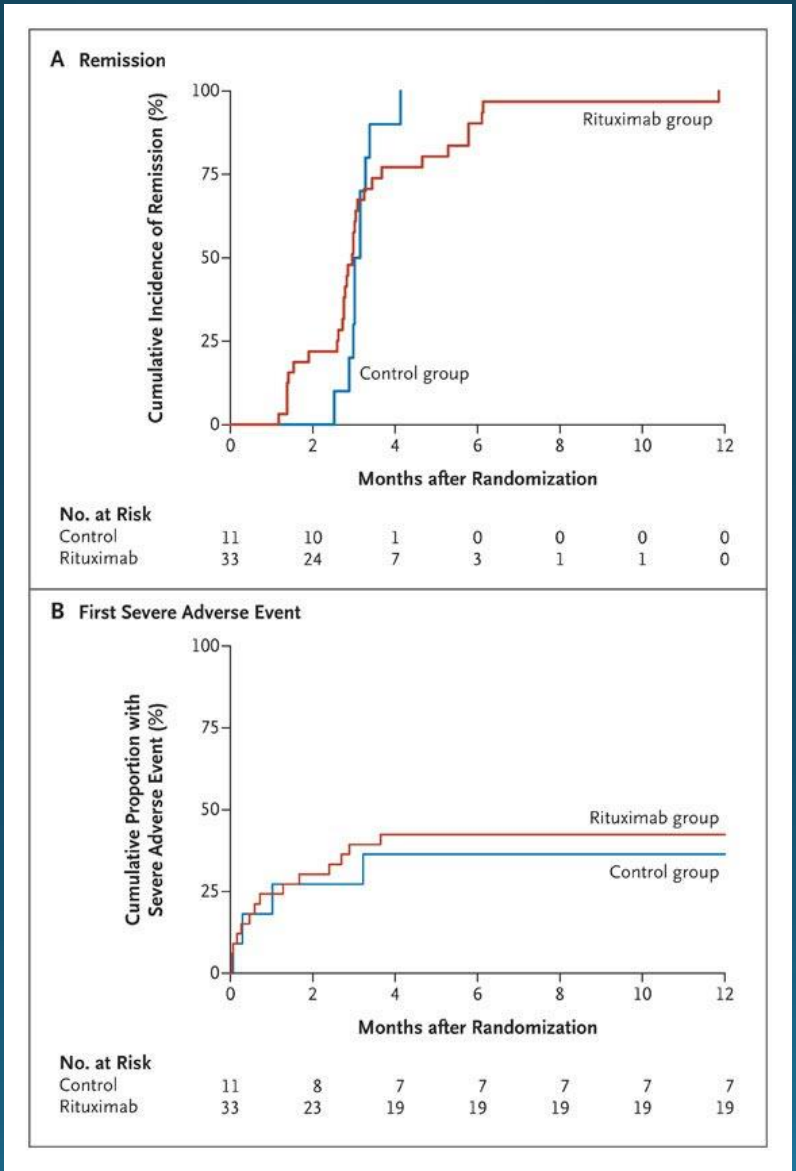
**Table 1. Demographic and Clinical Characteristics of the Patients at Trial Entry.***

| Variable | Rituximab Group (N=33) | Control Group (N=11) |
|---|---|---|
| Age — yr | | |
| Median | 68 | 67 |
| Interquartile range | 56–75 | 58–76 |
| Male sex — no. (%) | 17 (52) | 6 (55) |
| Diagnosis — no. (%) | | |
| Wegener's granulomatosis | 18 (55) | 4 (36) |
| Microscopic polyangiitis | 12 (36) | 4 (36) |
| Renal-limited vasculitis | 3 (9) | 3 (27) |
| Proteinase 3 and myeloperoxidase–ANCA binding — U/ml | | |
| Median | 53 | 79 |
| Interquartile range | 14–100 | 28–163 |
| ANCA-positive labeling pattern — no. (%) | | |
| Cytoplasmic | 20 (61) | 5 (45) |
| Perinuclear | 13 (39) | 6 (55) |
| Glomerular filtration rate — ml/min/1.73 $m^2$† | | |
| Median | 20 | 12 |
| Interquartile range | 5–44 | 9–33 |
| Organs involved — no. | | |
| Median | 3 | 2 |
| Interquartile range | 1–4 | 1–4 |
| Birmingham Vasculitis Activity Score | | |
| Median | 19 | 18 |
| Interquartile range | 14–24 | 12–25 |
| C-reactive protein — mg/dl | | |
| Median | 28 | 25 |
| Interquartile range | 12–87 | 7–87 |
| Erythrocyte sedimentation rate — mm/hr | | |
| Median | 52 | 64 |
| Interquartile range | 14–82 | 21–106 |
| Dialysis required at entry — no. (%) | 8 (24) | 1 (9) |
| Intravenous methylprednisolone — g | | |
| Median | 1 | 1 |
| Interquartile range | 1–1 | 1–1 |
| Use of plasma exchange — no. (%) | 8 (24) | 3 (27) |

* ANCA denotes antineutrophil cytoplasmic antibody.
† The glomerular filtration rate was 0 ml per minute among patients who underwent dialysis.

Jones RB et al. N Engl J Med 2010;363:211-220

# Cumulative Incidence of Remission and Cumulative Proportion of Patients with a Severe Adverse Event




Jones RB et al. N Engl J Med 2010;363:211-220

# RITUXIVAS Summary

- Response rate 76 and 82% (GFR 15-20)
- Death rate 16%
- Complication rate 40%
- Dialysis 9 patients – 5/9 came off dialysis

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

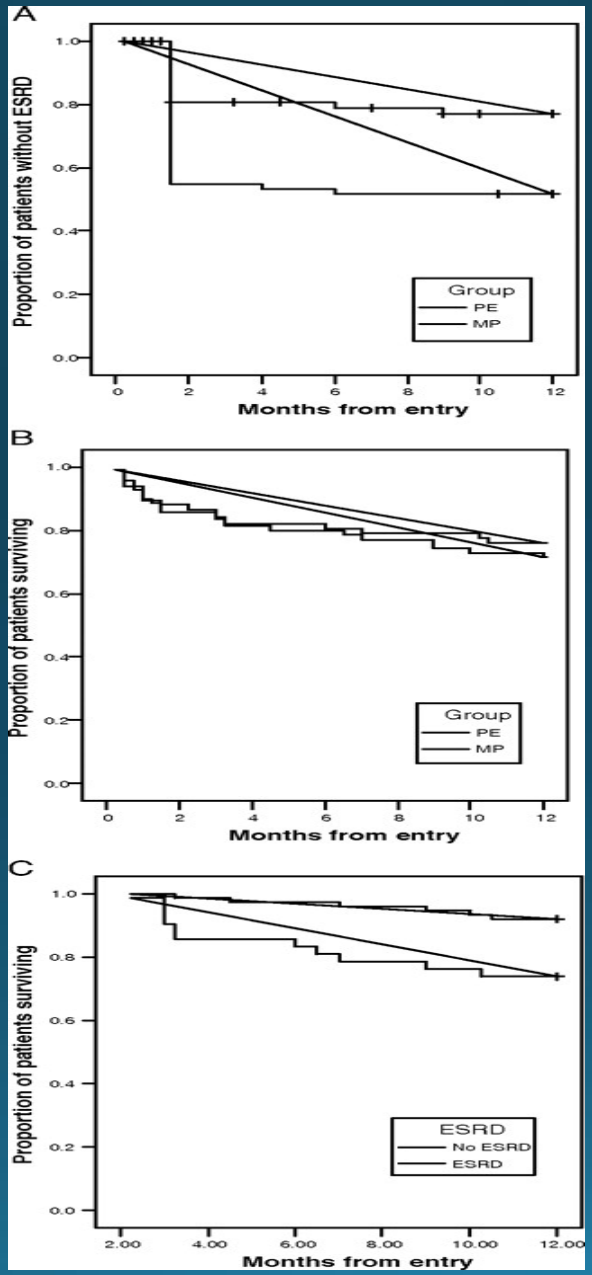
**Table 1.**

Baseline clinical and serologic characteristics of the patients with ANCA-associated systemic vasculitis and renal failure[a]

| 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 |

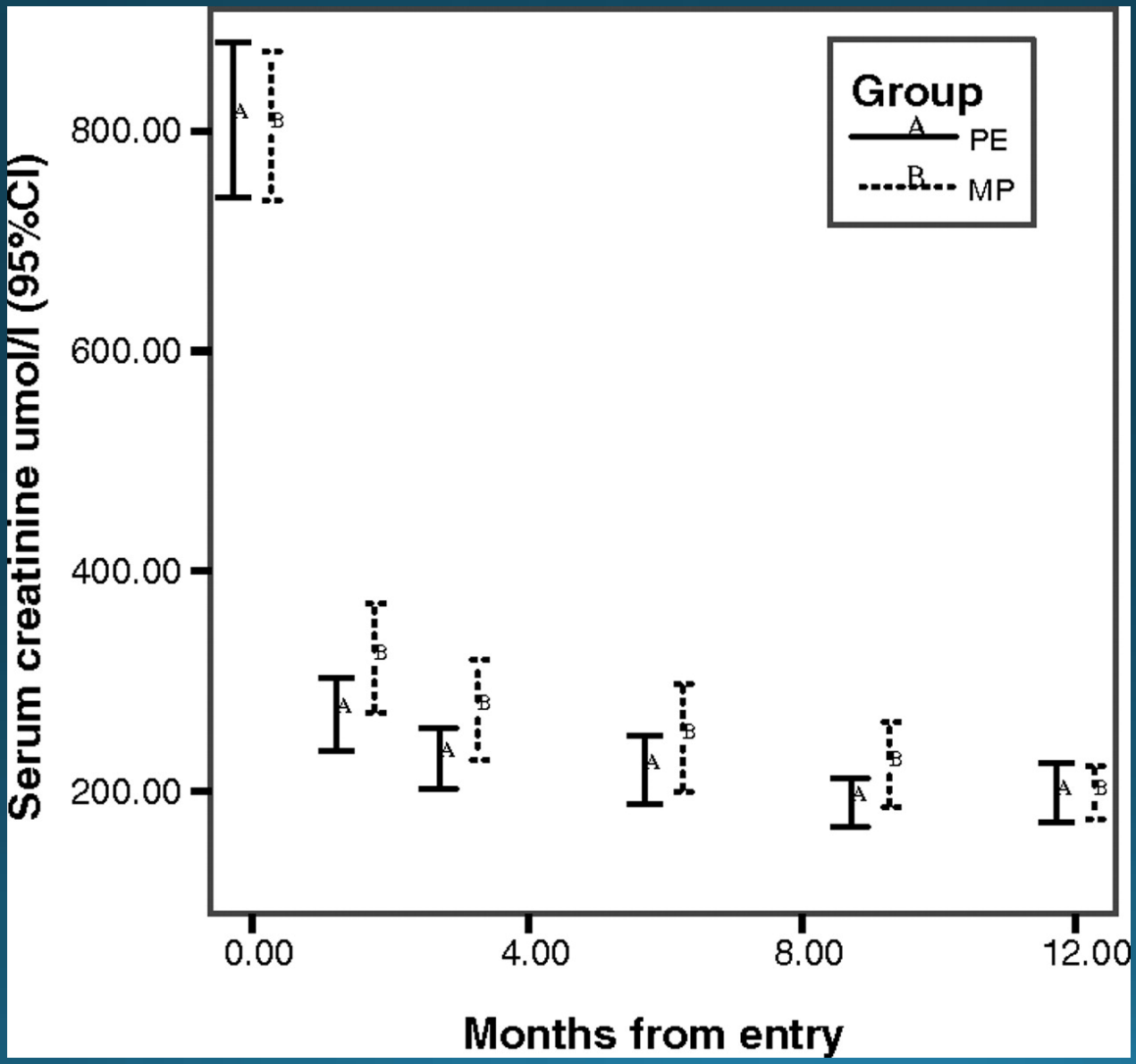
- [a] ANCA, autoantibodies to neutrophil cytoplasmic antigens; BVAS, Birmingham Vasculitis Activity Score; MPO, myeloperoxidase; PR3, proteinase 3.

# Proportion of patients in each group without progression to ESRD




David R.W. Jayne et al. JASN 2007;18:2180-2188

**Sequential serum creatinine (μmol/L) for those who recovered renal function (mean; 95% confidence interval [CI]).**




David R.W. Jayne et al. JASN 2007;18:2180-2188

# MPEX Summary

- Endpoint dialysis independence
- 49 VS 69% NNT 5
- ESRD 19 VS 43% NNT 4-5
- Patient survival (73%) and complication rates (50%) were the same

# Case 2

- Dialysis was continued via TVC
- She received CYP 15 mg/kg and she was discharged for outpatient pheresis 60 ml/kg for 7 TX
- She completed her plasmapheresis and her WBC nadir was > 5
- She was given her 2$^{nd}$ dose of CYP 3 weeks after the 1$^{st}$
- No signs of renal recovery thus far

# Case 2

- 2 weeks post her 2nd dose of CYP she developed fevers and weakness and went to ER
- CXR showed LLL infiltrate and patient admitted to ICU with qSOFA of 3
- She required IVF, mechanical ventilation, IV pressors and broad spectrum abx, Despite this she had refractory shock and died 36 hours into her hospitalization
- BC grew Cryptyococcus neoformans

**Table 3.** Adverse events according to type, severity (mild/moderate or severe/life threatening), and treatment group

| Adverse Event | Study Groups | | | | Total |
|---|---|---|---|---|---|
| | Intravenous Methylprednisolone | | Plasma Exchange | | |
| | Mild/ Moderate | Severe/Life Threatening | Mild/ Moderate | Severe/Life Threatening | |
| Leukopenia (at least 1 episode) | 35 | 7 | 35 | 8 | 85 |
| Recurrent leukopenia (>1 episode) | 13 | 2 | 11 | 4 | 30 |
| Infection | 13 | 17 | 11 | 20 | 61 |
| Thrombocytopenia | 2 | 0 | 3 | 5 | 10 |
| Allergy | 4 | 0 | 6 | 0 | 10 |
| Cardiovascular | 2 | 3 | 1 | 3 | 9 |
| Diabetes | 3 | 2 | 2 | 1 | 8 |
| Gastrointestinal | 0 | 1 | 3 | 2 | 6 |
| Bone fracture | 0 | 2 | 1 | 2 | 5 |
| Thrombosis | 1 | 0 | 1 | 3 | 5 |
| Hemorrhage | 0 | 1 | 1 | 1 | 3 |
| Alopecia | 0 | 0 | 2 | 0 | 2 |
| Vascular access complication | 0 | 1 | 0 | 1 | 2 |
| Other | 1 | 3 | 2 | 2 | 8 |
| Totals | 74 | 39 | 79 | 52 | 244 |
| No.(%) of patients with ≥1 event | 59 (87) | 32 (48) | 63 (91) | 35 (50) | 122 (89) |

# Severe Renal Involvement in AAV

- Patient with severe renal involvement have a higher mortality than rest of AAV patients likely due to disease
- ESRD population much higher risk population
- Death due to CV events on dialysis, dx complications and infection
- There is no degree of renal disease that treatment is no warranted