Monoclonal Gammopathies and Their Significance

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International Kidney and Monoclonal Gammopathy

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Membership on advisory boards or speakers' bureaus	**None**	
Funded grants or clinical trials	**None**	
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All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity	**None**	

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Case

- 66 year old male with stable IgM kappa MGUS (0.2g/dL) and history of hypertension, diabetes and CKD
- He presents to clinic with a subtle decline in kidney function

  - What are your next diagnostic steps?
  - What is your threshold to perform a kidney biopsy?

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Key questions

- In a population of patients with MGUS and chronic kidney disease, how prevalent is MGRS?
- How does a population of patients with MGRS differ from other patients with MGUS?
- Is renal biopsy being underutilized in the workup of possible MGRS?

Existing research

Research Paper

Monoclonal gammopathy of renal significance (MGRS) increases the risk for progression to multiple myeloma: an observational study of 2935 MGUS patients

- In a population of 2935 patients with MGUS, MGRS was diagnosed in 44 (1.5%)
- MGRS patients had significantly more progression to MM compared to other MGUS patients (18% vs. 3%, $p < 0.001$)

Steiner et al, Oncotarget, 2017

Study design

- Identified all patients with *both* MGUS and CKD seen at Tufts Medical Center between 2000-2017
    - Searched inpatient and outpatient EMR using ICD-9 and ICD-10 codes corresponding to each diagnosis

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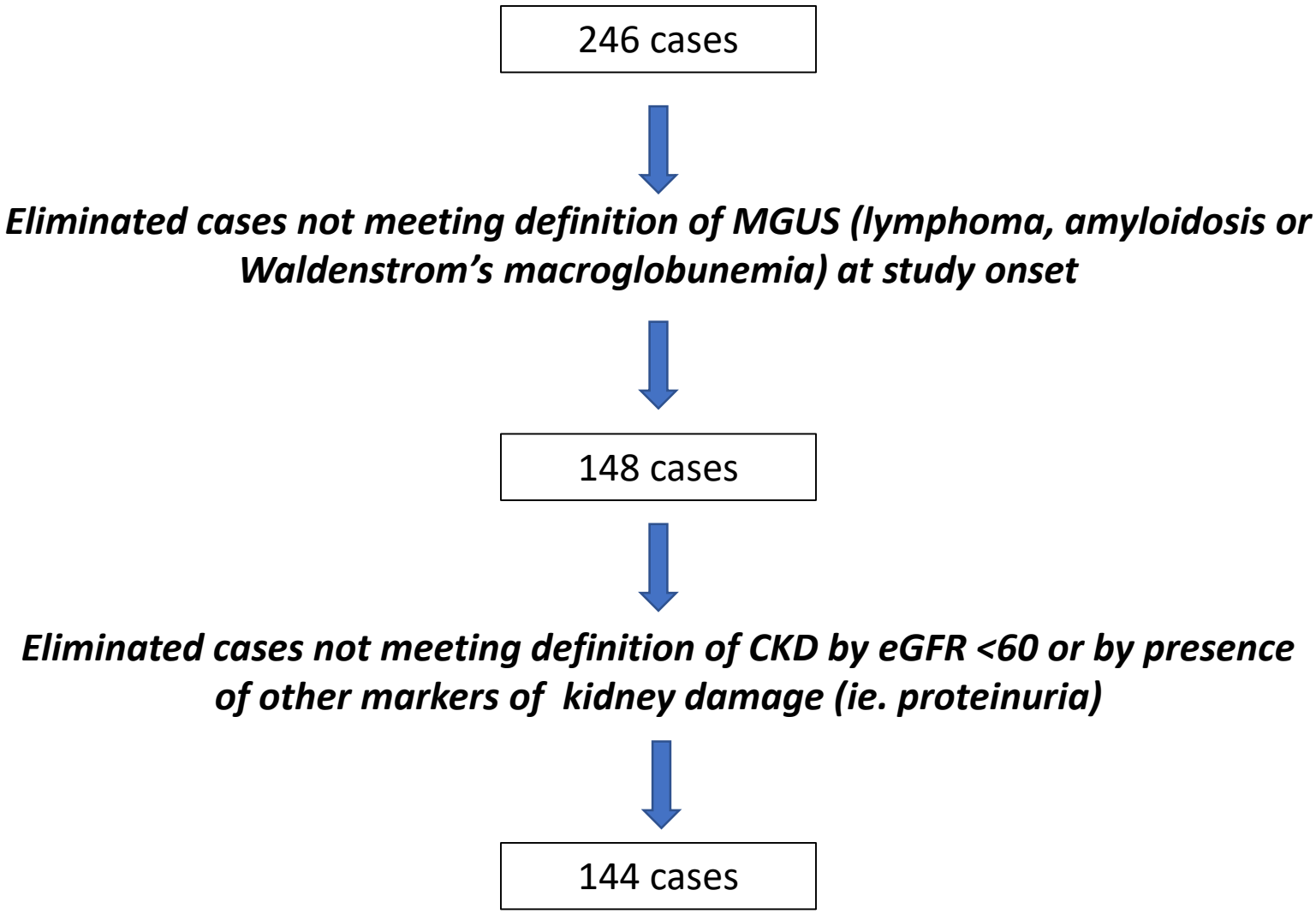
246 cases
Eliminated cases not meeting definition of MGUS (lymphoma, amyloidosis or Waldenstrom's macroglobunemia) at study onset
148 cases
Eliminated cases not meeting definition of CKD by eGFR <60 or by presence of other markers of kidney damage (ie. proteinuria)
144 cases

Baseline characteristics

Characteristic at Onset	MGUS + CKD population (n =144)
Age (median, years)	78
Gender (n, %) Male Female	 85 (59%) 59 (41%)
Race (n, %) White Black Asian Other	 96 (66.7%) 21 (14.6%) 22 (15.3%) 5 (3.5%)
Co-morbidities (n, %) Hypertension Coronary Artery Disease Diabetes Mellitus	 113 (78.5%) 44 (30.6%) 50 (34.2%)
M-spike* (median, g/dL)	0.54
κ/λ in kappa gammopathies (median)	1.83
κ/λ in lambda gammopathies (median)	0.82
eGFR (median, mL/min/1.73m2)	48
Creatinine (median, mg/dL)	1.4
Protein/creatinine* (median, mg/g)	39
Albumin creatinine* (median, mg/g)	90
Bone marrow biopsy performed (n, %)	53 (36.8%)
Kidney biopsy performed (n, %)	19 (13.2%)

Results

- In 3/144 (2.1%) patients, MGRS was confirmed by kidney biopsy
  - 2/3 were treated with chemotherapy
    - Negative SPEP/IFE, UPEP/IFE, bone marrow biopsy in 1 patient
  - 1/3 not treated due to active infection

- MGRS was **considered** as cause of kidney dysfunction in 20/144 patients (13.9%)
  - **Only 6 were further worked with kidney biopsy**

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Results

Possible MGRS cases	Absolute number	Percent of study population
MGRS confirmed by biopsy, treated with chemotherapy	2	1.4%
MGRS confirmed by biopsy, not treated with chemotherapy	1	0.7%
MGUS thought to be only cause of kidney disease, unknown if biopsy performed, presumably not treated with chemotherapy	1	0.7%
Other abnormal kidney biopsy without formal diagnosis of MGRS	2	1.4%
MGRS considered as one of possible causes of kidney disease	14	9.7%

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CKD stage

	Total study population (n = 144)	Population with suspected or confirmed MGRS (n=20)
1	2 (1.4%)	0 (0%)
2	33 (22.9%)	3 (15.0%)
3A	27 (18.8%)	4 (20.0%)
3B	33 (22.9%)	3 (15.0%)
4	25 (17.4%)	6 (30.0%)
5	22 (15.3%)	4 (20.0%)
Unknown	2 (1.4%)	0 (0%)

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Features of kidney disease

	Total study population (n = 144)	Population with suspected or confirmed MGRS (n = 20)
Hypertension	40 (27.8%)	13 (65.0%)
Diabetes	20 (13.9%)	5 (25%)
Cast nephropathy**	4 (2.8%)	0 (0%)
AKI, excluding cardiorenal	21 (14.6%)	3 (15.0%)
Cardiorenal/heart failure, valvular disease	10 (6.9%)	0 (0%)
Liver disease	1 (0.7%)	1 (5.0%)
Glomerulonephritis	5 (3.5%)	1 (5.0%)
Other glomerular disorder (membranous nephropathy, focal segmental glomerulosclerosis, IgA nephropathy, nephrotic syndrome)	5 (3.5%)	1 (5.0%)
Renal artery stenosis	5 (3.5%)	0 (0%)
Drug toxicity (tenofovir, cyclosporine, tacrolimus, levofloxacin causing acute interstitial nephritis)	6 (4.2%)	0 (0%)
Polycystic kidney disease	1 (0.7%)	0 (0%)
Other anatomic issues (single kidney, resection of kidney for mass, atrophic kidney)	6 (4.2%)	1 (5.0%)
Unknown/not specified	51 (35.4%)	0 (0%)

Biopsies!

- Bone marrow
  - 53/144 total patients (36.8%) had bone marrow biopsy
  - 12/20 patients (60%) in whom MGRS was considered had **bone marrow biopsy**
- Kidney
  - 19/144 total patients (13.1%) had kidney biopsies
  - **6/20** patients (30%) in whom MGRS was considered had kidney biopsy

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Disease progression

- Out of total study population (n= 144):
  - 8 (5.6%) progressed to smoldering or symptomatic multiple myeloma
  - 1 (0.7%) progressed to Waldenstrom's macroglobulinemia
  - 1 (0.7%) progressed to multiple myeloma + amyloid
- MGRS considered or confirmed (n =20)
  - 1 (5%) progressed to multiple myeloma

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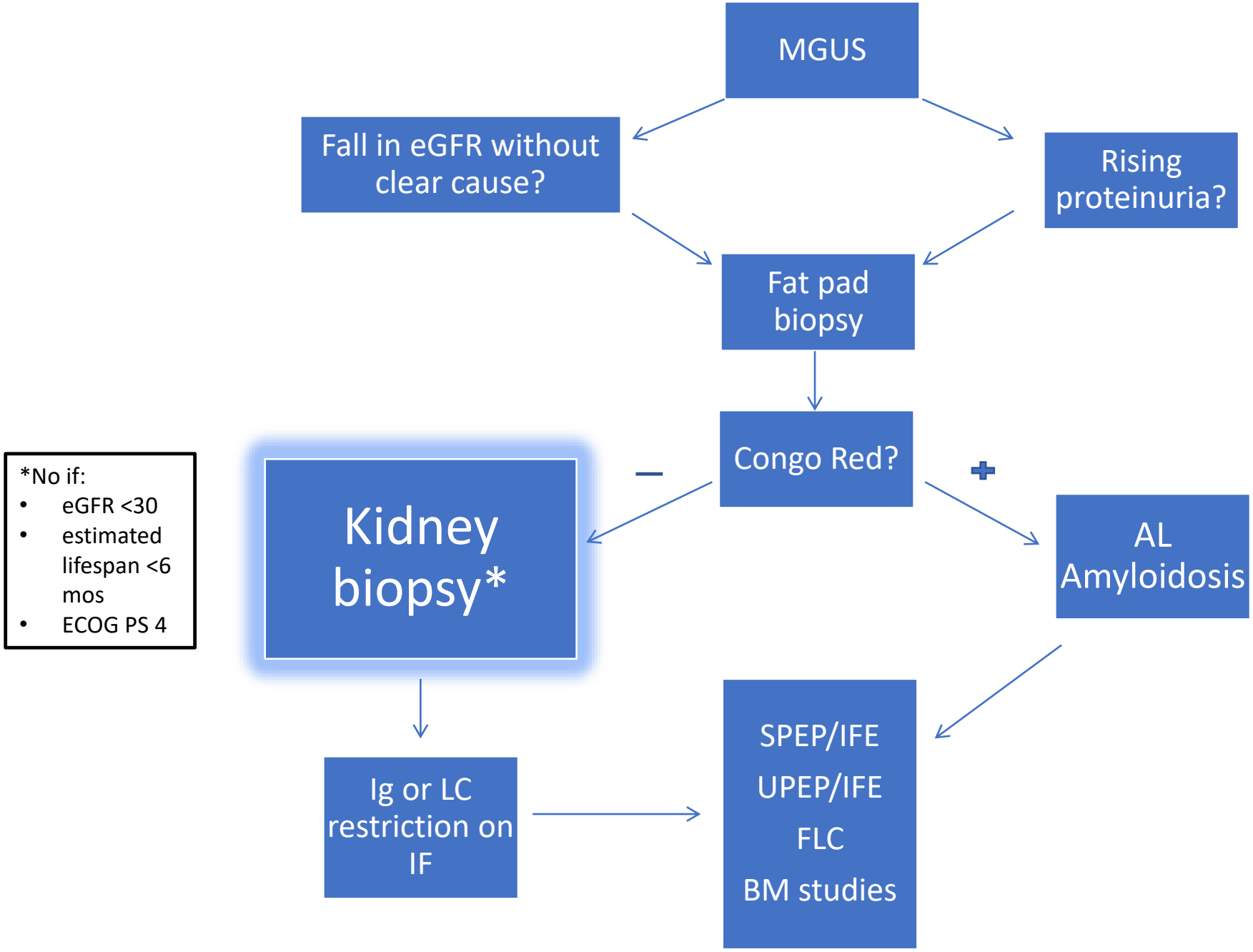
MGUS
Fall in eGFR without clear cause?
Rising proteinuria?
Fat pad biopsy
Congo Red?
–
+
Kidney biopsy*
AL Amyloidosis
*No if:
• eGFR <30
• estimated lifespan <6 mos
• ECOG PS 4
Ig or LC restriction on IF
SPEP/IFE
UPEP/IFE
FLC
BM studies

Back to the case!

- Patient underwent kidney biopsy, that found: **monoclonal immunoglobulin deposition disease (MIDD)** and diabetic glomerulopathy
- Treated with Rituxan
  - Treatment ultimately discontinued given worsening M-spike and kidney function

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Early detection is key!

- Organ failure occurs **silently** and can be **irreversible**
- Early treatment of these small clones can lead to superior survival compared to patients with multiple myeloma
- In individuals with MGUS and kidney disease, consider renal biopsy to evaluate for MGRS

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