APPROACHES AND TREATMENT OF RARE PLASMA CELL DYSCRASIAS: MGCS, POEMS SYNDROME, CASTLEMAN DISEASE AND AMYLOIDOSIS

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DISCLOSURES

Company	Disclosure
Celgene, Takeda, Pfizer, Alnylam, Caelem, Janssen	Research dollars
Intellia, Caelem, Janssen HaemalogiX	Ad board

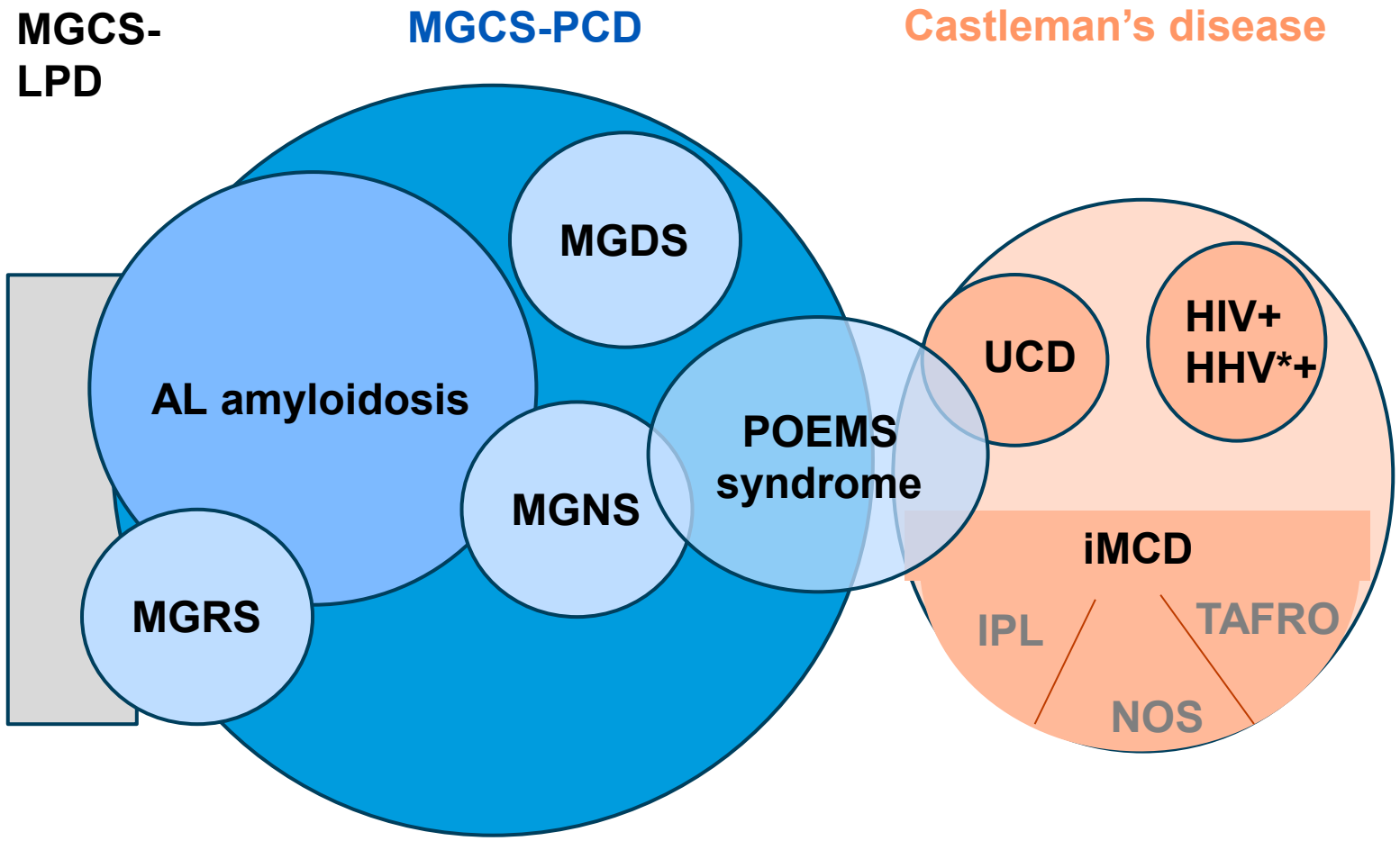
GOALS

1. Recognize these rare entities
   - MGCS – mostly plasma cell driven, occasionally LPD driven
   - Castleman's disease – occasionally associated with clonal plasma cell disorder, but more often not

2. Understand treatment options

3. Realize importance of systematic follow-up

OUR WORK FOR TODAY



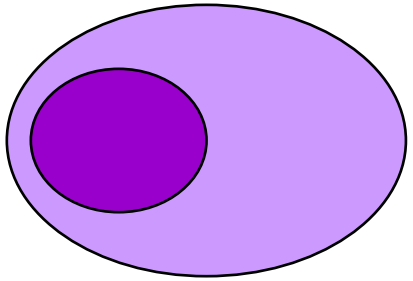
MGCS, monoclonal gammopathy of clinical significance; LPD, lymphoproliferative disorder; PCD, plasma cell disorder; MGRS, monoclonal gammopathy of renal significance; MGDS, monoclonal gammopathy of dermal significance; MGNS, monoclonal gammopathy of neural significance; UCD, unicentric Castleman's disease; iMCD, Idiopathic multicentric Castleman's disease; TAFRO, thrombocytopenia, anasarca, fever, fibrosis (marrow), renal dysfunction, organomegaly

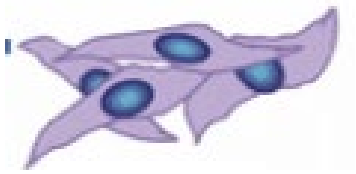
GENERAL COMMENTS

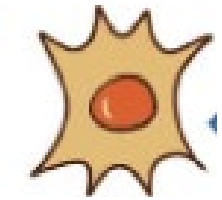
- Majority of the MGCS are deposition diseases
- Many of the MGCS are predominantly single organ
- Although considerable morbidity, mortality and rates of overt malignancy are rare for most conditions
- How much of these diseases relates to “an unlucky monoclonal protein” rather to a distinctly different plasma cell clone is unknown

DRIVERS OF MGCS?

Plasma cell (or lymphoid clone)

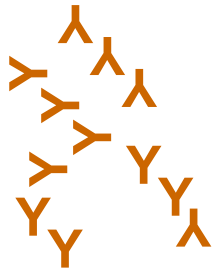




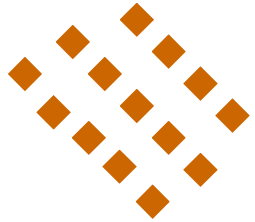


Plasma cell microenvironment

Humoral mediators

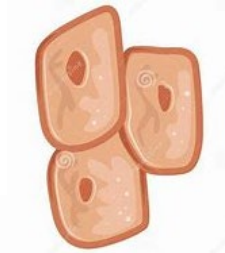


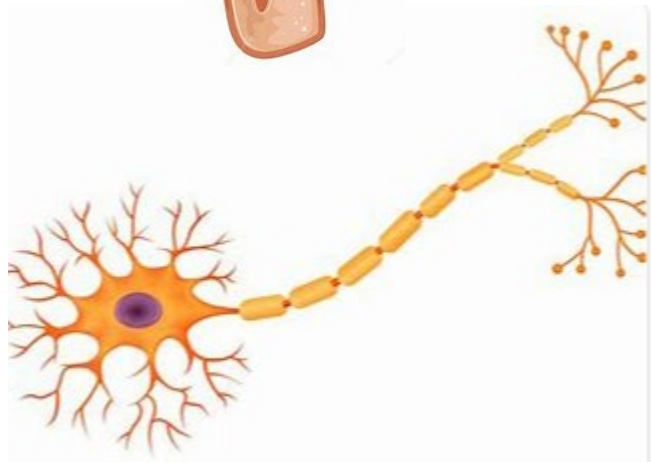
Antibodies



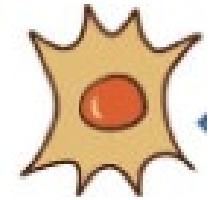
Cytokines or chemokines

Target tissue cells

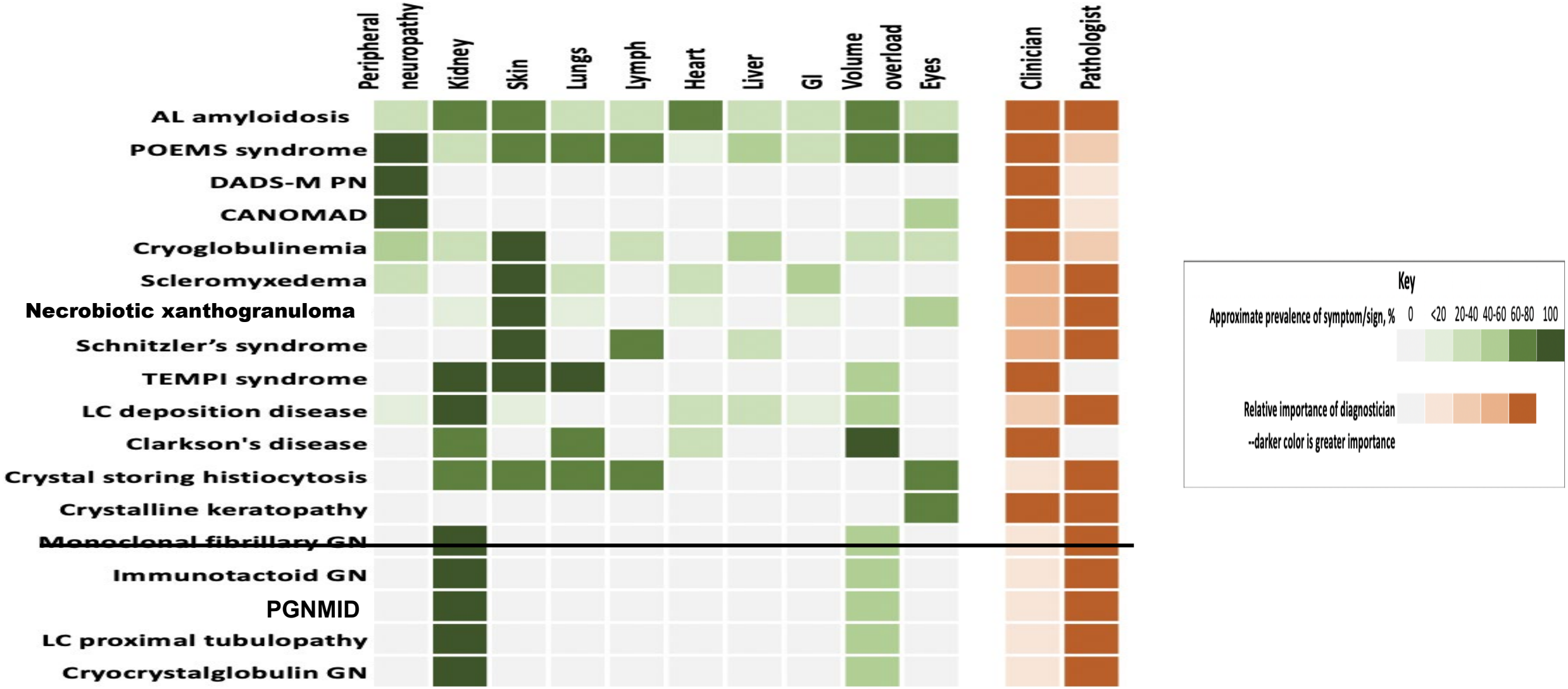




Target tissue microenvironment



Dispenzieri ASH education book 2020



DADS, distal acquired demyelinating symmetric neuropathy with M protein; CANOMAD, chronic ataxic neuropathy, ophthamoplegia, IgM, cold agglutinins, and disialosyl antibodies; PGNMID, proliferative glomerulonephritis with monoclonal immunoglobulin deposits

CASE 1: MR. AI

MR. AI, 67-YEAR-OLD

- Mid 2014: beginning of paresthesias and a 20 kg weight loss between 2014 and 1/2015.
- January - February 2015: Anorexia and nausea/vomiting—additional 10 kg weight loss.
  - Hb 12.8 Cr 1.4, TSH 4.9, AM cortisol 7.6 (borderline). CRP normal. Vitamin B12 1141.
  - SPEP w/o IFE was normal, lambda FLC 6.22; ratio of 0.3987
  - PET and CT chest/abdomen/pelvis: unremarkable.
  - EGD/colonoscopy: unremarkable. No amyloid

Month
-19

Month
-12

MR. AI, 67-YEAR-OLD

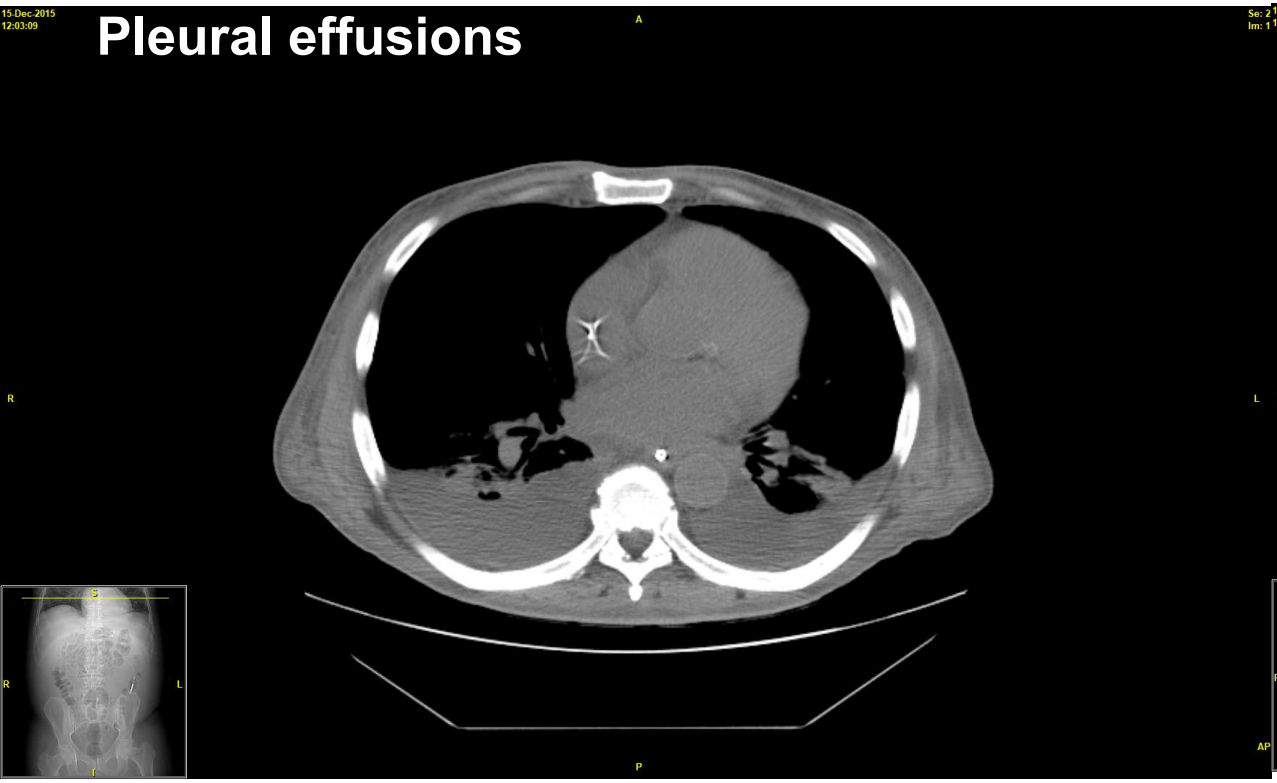
Month
-9

- April - November 2015: progressive muscle weakness, cachexia/weight loss, and demyelinating neuropathy.
  - Profound volume overload that was presumed to be related to AKI from AIN (ceftriaxone) with a creatinine up to 2.3. ”MGUS.“

MR. AI, 67-YEAR-OLD

Month
-1

- 12/10 -12/30/2015: hospitalized for severe malnutrition
  (>30 kg weight loss) with anasarca



MGCS – PERIPHERAL NERVE PRESENTATION

Modified from Dispenzieri ASH education book 2020

DADS, distal acquired demyelinating symmetric neuropathy with M protein; CANOMAD, chronic ataxic neuropathy, ophthamoplegia, IgM, cold agglutinins, and disialosyl antibodies

MR. AI, 67-YEAR-OLD

Month
-1

- Progressive demyelinating sensorimotor neuropathy, adrenal insufficiency, ascites, pleural effusions, IgA λ (536 mg/dL), lipodystrophy, estimated PA pressure 64/20, and VEGF 320 pg/mL

POEMS syndrome

Both 1 and 2 present

MAJOR CRITERIA	***1. Polyneuropathy***	★
	2.Monoclonal plasma cell dyscrasia (almost always λ)	★
	3. Sclerotic bone lesions 4. Castleman's disease 5. Vascular endothelial growth factor elevation ***At least one of 3-5 present***	★
MINOR CRITERIA ***At least 1 of 6-11 present***	6. Organomegaly (splenomegaly, hepatomegaly, or LA)	★
	7. Endocrinopathy	
	8. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails)	
	9. Papilledema	
	10. Extravascular volume overload (edema, pleural eff, or ascites)	★
	11. Thrombocytosis / polycythemia	

*** Polyneuropathy and monoclonal plasma cell disorder present in all patients; to make diagnosis *at least* one other major criterion and 1 minor criterion is required to make diagnosis**

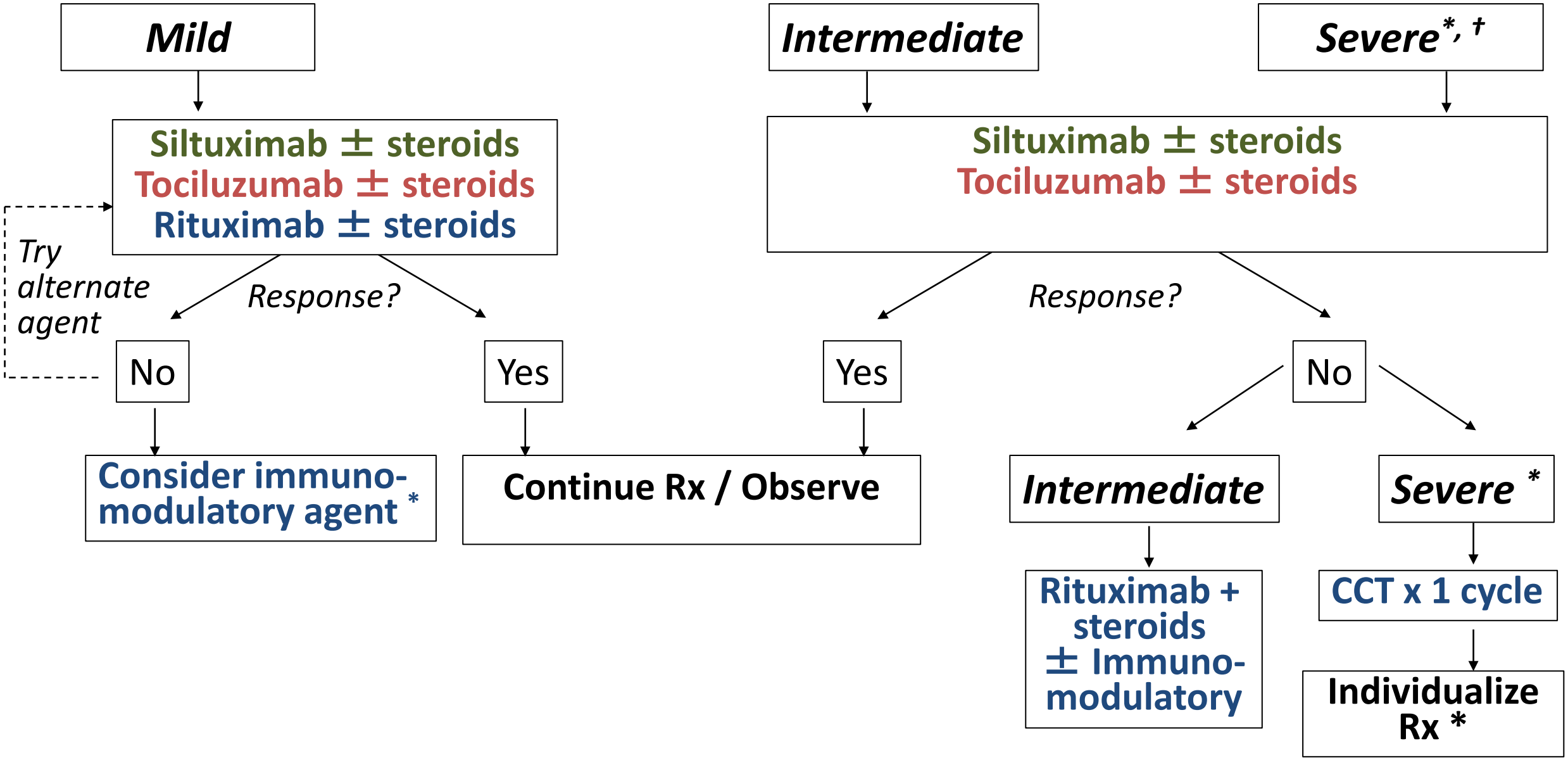
Dispenzieri, A., Blood Reviews, 2007. 21(6): p. 285-299.

THERAPY OF MGCS – NERVE *(MOSTLY ANECDOTAL)*

	1st line	2nd line	Other
AL amyloidosis	Dara-CyBorD +/- ASCT	Clone directed therapy	Supportive care
POEMS	Clone directed therapy	Clone directed therapy	Supportive care
Cryoglobulinemia	Treat underlying cause	Rituximab	
DADS-M	Intravenous gammaglobulin	Rituximab	
CANOMAD	Intravenous gammaglobulin	Clone directed therapy	3rd line: clone directed therapy
SLONM*	Intravenous gammaglobulin	Clone directed therapy	

DADS, distal acquired demyelinating symmetric neuropathy with M protein
CANOMAD, chronic ataxic neuropathy, ophthamoplegia, IgM, cold agglutinins, and disialosyl antibodies
SLONM, sporadic late onset nemaline myopathy; * not nerve, but muscle but presents motor

Management of iMCD



CASE 2: MS. VGL

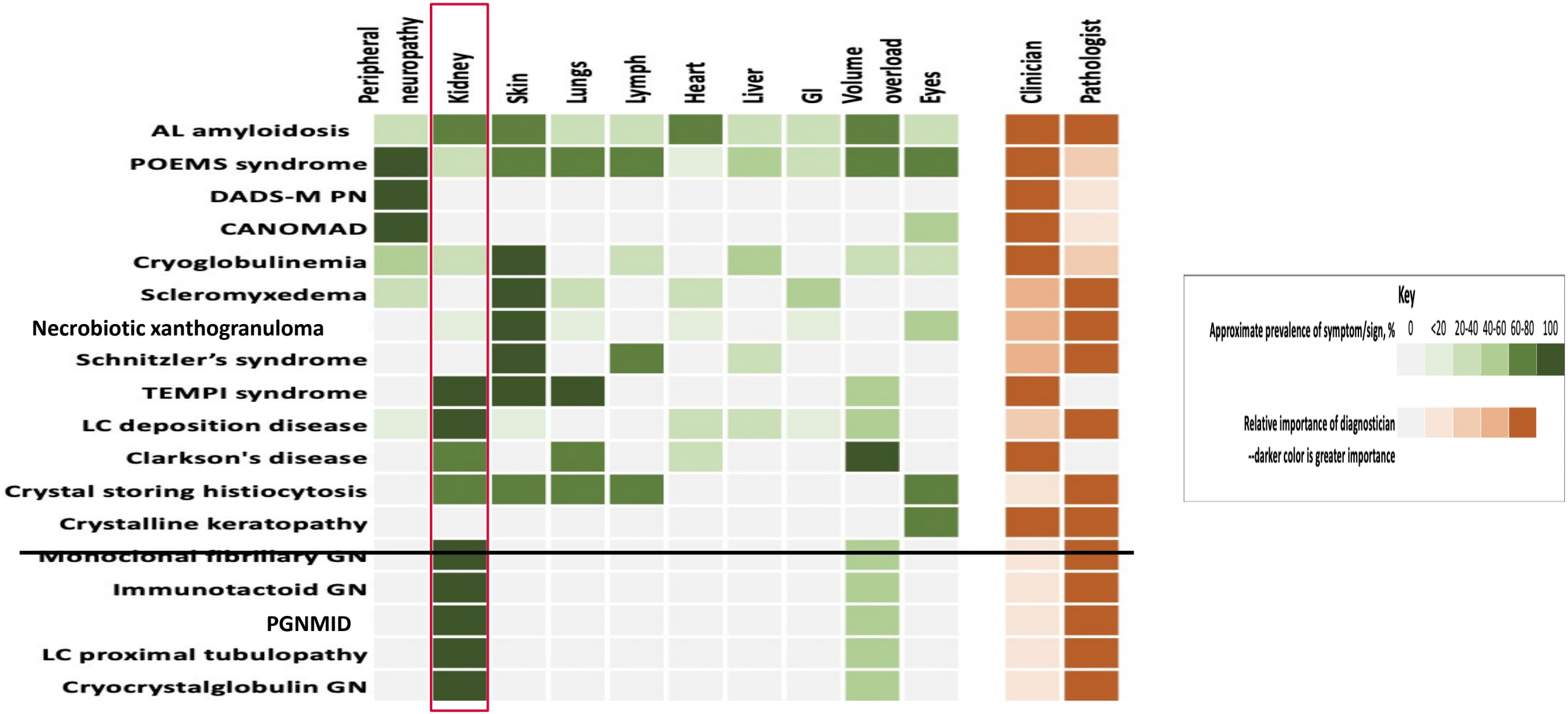
VGL: FEMALE MG AND RENAL ISSUES

- Age 31: Proteinuria 1700 mg/24 hr and IgG lambda 0.5 g/dL: August 1987

International Kidney & Monoclonal Gammopathy Research Group

http://www.ikmgresearchgroup.com

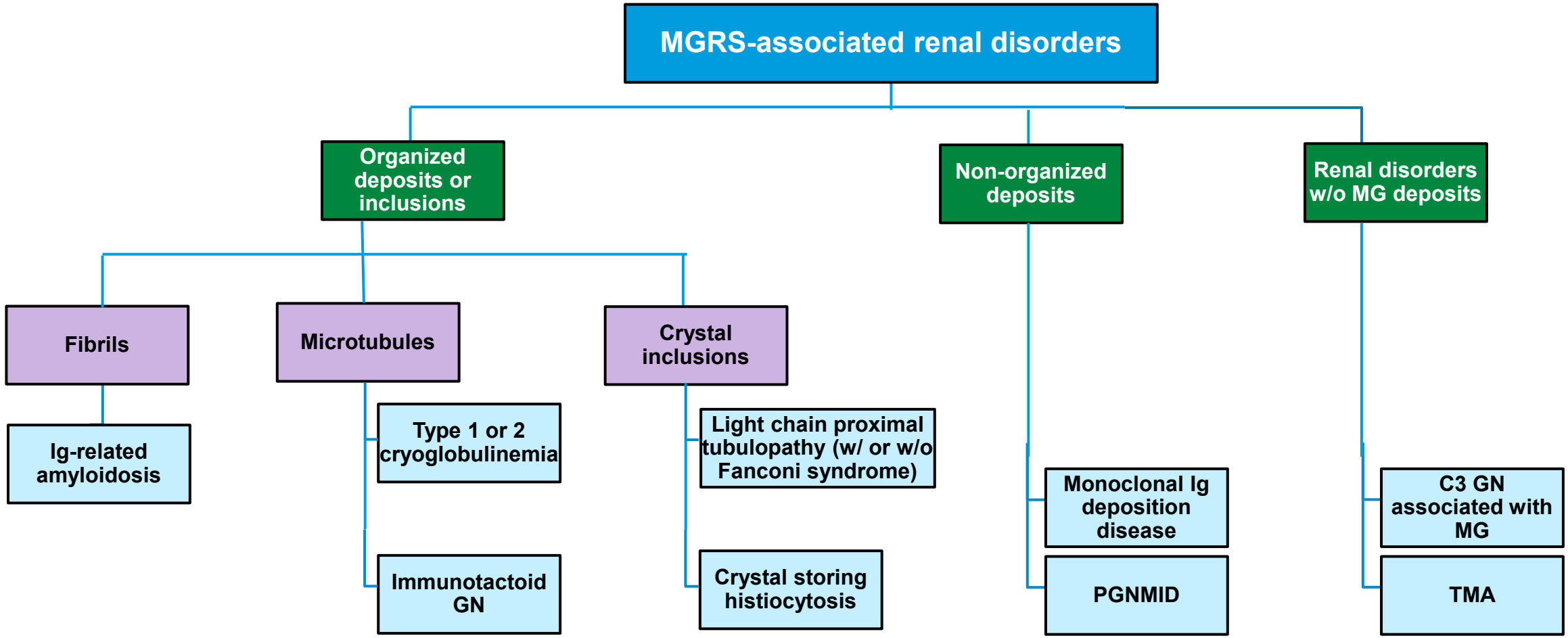
MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE



PGNMID, proliferative glomerulonephritis with monoclonal immunoglobulin deposits

Dispenzieri ASH education book 2020

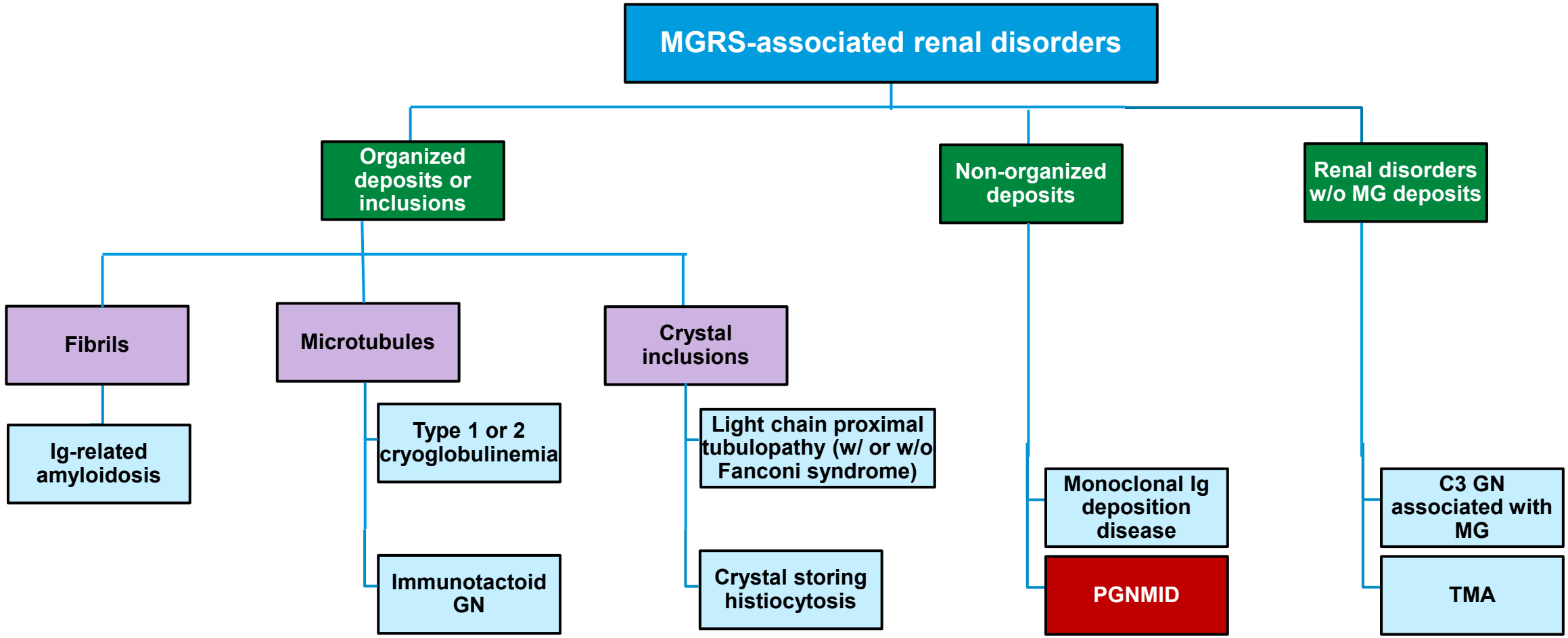
MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE (MGRS)



PGNMID, proliferative glomerulonephritis with monoclonal immunoglobulin deposits; LCPT, light chain proximal tubulopathy; MIDD, monoclonal immunoglobulin deposition disease

Modified from Bridoux F,. *Kidney Int*. 2015;87(4):698-711. Leung, N., *Nat Rev Nephrol* 15, 45–59 (2019).

MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE (MGRS)



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VGL: FEMALE MGRS: PGNMID

Date	Cr	24-hour urine TP	Ser M-spike/ FLC / BMPC	Intervention / Comment
9/1988	1.5	1700	0.5 g/dL	Biopsy MPGN; Observation
1/2002	4.0	7726	0.6 /-/-	**CTX / Pred** x 6 months
10/2002	4.0	1900	0.6 /-/-	Renal transplant
11/2002	2.5	3272	0.6/-/15%	Renal biopsy: recurrent disease; Pheresis/**Medrol→ pred**
7/2003	2.8	14000		Pheresis; S. Aureus infection→ 4 month dialysis
1/2005	2.5	1795	1.2 ; 173 mg/dl /20%	**ASCT** with plan to do second renal Tx
4/2005	1.7	760	0; 56 mg/dL; 5%	No need for second kidney ☺

THERAPY OF MGRS *(MOSTLY ANECDOTAL)*

	1st line	2nd line	Kidney Tx
AL amyloidosis	Dara-VCD	Clone directed Rx	Good outcomes
MIDD	Clone directed Rx [2]		Good outcomes
Cryoglobulinemia	Underlying dz; emergency PE, high-dose steroids	Rituximab	Good outcomes
LCPT	Clone directed Rx[3]		Mixed [6]
Immunotactoid GN	Clone directed Rx[4]		
C3GN with mIg	Clone directed Rx [5]		Mixed [5,6]
PGNMID	Clone directed or Rituximab [1]	Clone directed Rx [1]	Mixed [7]

http://www.ikmgresearchgroup.com/

PGMID, proliferative glomerulonephropathy with monoclonal immunoglobulin deposits; MIDD, monoclonal Ig deposition disease; C3GN with MIg, C3 glomerulonephritis with monoclonal gammopathy

[1] Nasr (2020) KI 97:589-601. *[2] Joly (2019) Blood 133:576-87.* [3] Vignon (2017) Leukemia 31:123-9. *[4] Javaugue* (2019) *Kidney Int* 96(1):94-103 [5] Chauvet (2017)Blood 129:1437-47. 6 Heybeli C (*2022*). *Am J Kidney Dis Feb; 79: 202-216.* [7] Buxea (2019) Transplantation 103:1477-85.

VGL: FEMALE MGRS: PGNMID

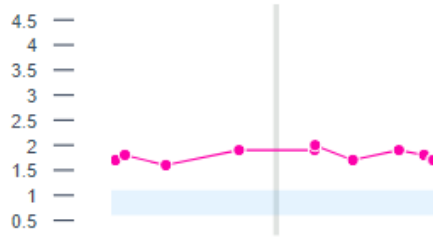
- 2005 to 2012, numbers stable (24 years into diagnosis)
- Starting 2012, there was a subtle rise in her serum lambda FLC, but steep rise in mid-2013.
- Also in 2013, she started noting DOE

Back to Grid

2012 2013

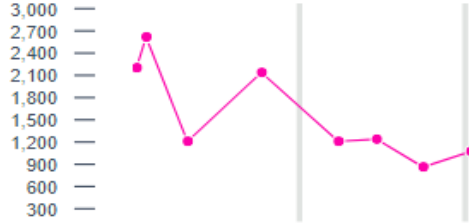
GEN CHEMISTRY

Creatinine



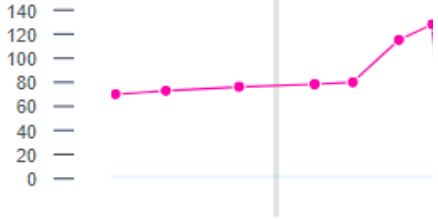
TIMED URINE STUDIES

Total Protein, 2...



IMMUNOGLOBULINS

Lambda Free Li...

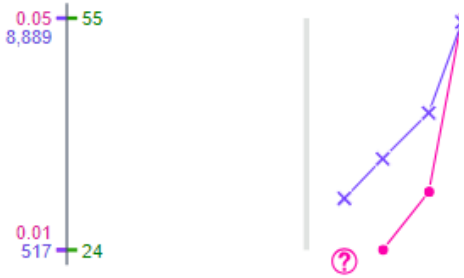


LIPIDS/CARDIAC RISK

Troponin T

Troponin T, 5th ...

NT-Pro BNP



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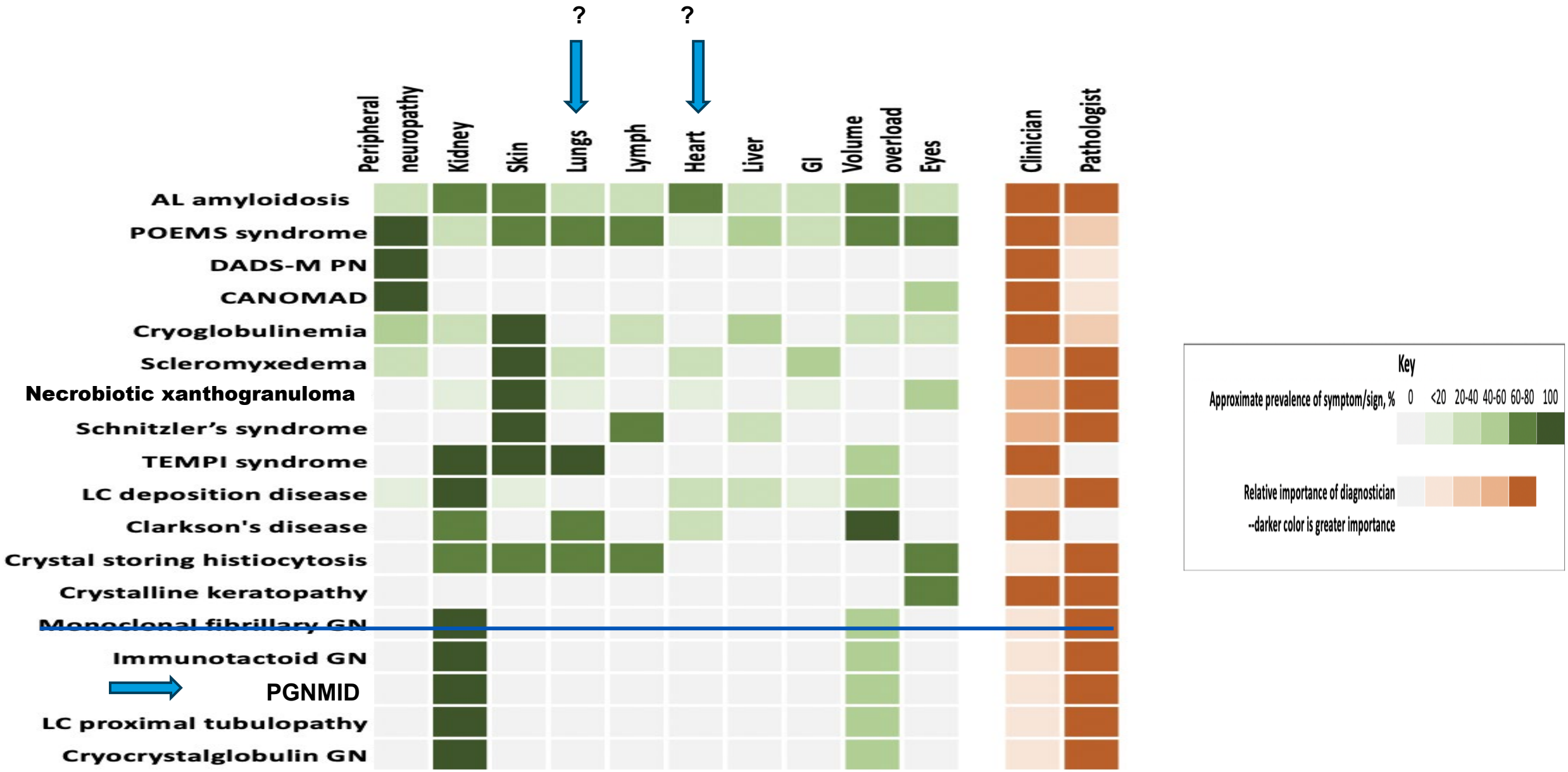

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VGL: FEMALE MGRS: MPGN

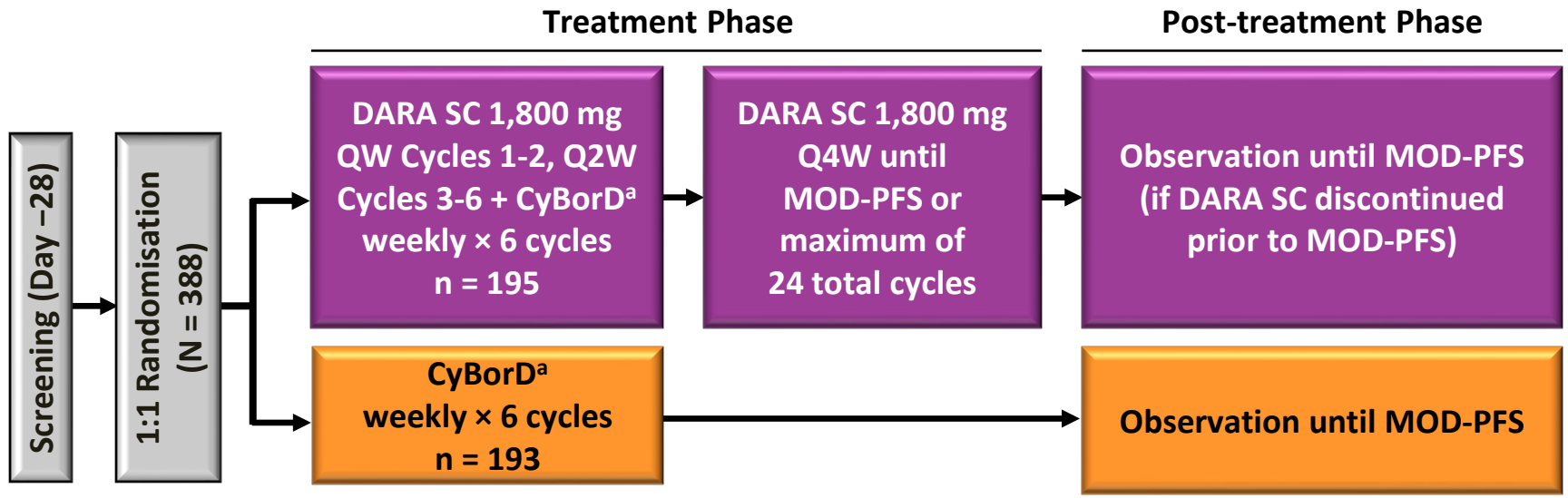
- The NT-proBNP in March 2013 had risen to 2376.
- Due to progression of her symptoms and her cardiac biomarkers, an endomyocardial biopsy was performed on 11/2013
- AL (lambda) amyloid was found


Back to Grid
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
GEN CHEMISTRY
Creatinine
4.5
4
3.5
3
2.5
2
1.5
1
0.5
TIMED URINE STUDIES
Total Protein, 2...
3,000
2,700
2,400
2,100
1,800
1,500
1,200
900
600
300
IMMUNOGLOBULINS
Lambda Free Li...
140
120
100
80
60
40
20
0
VCD x
8 m→
V x 5 m
DRd x 1 m→
Dd x 22 m
ASCT#2
Ixa
maint.
x 8 m
LIPIDS/CARDIAC RISK
Troponin T
Troponin T, 5th ...
NT-Pro BNP
0.05
8,889
0.01
517
55
24

ANDROMEDA is a randomized, open-label, active-controlled, phase 3 study of DARA SC plus CyBorD vs CyBorD alone in newly diagnosed AL amyloidosis

Key eligibility criteria:

- AL amyloidosis with ≥1 organ impacted
- No prior therapy for AL amyloidosis or MM
- Cardiac stage I-IIIA (Mayo 2004)
- eGFR ≥20 mL/min



Stratification criteria:

- Cardiac stage (I vs II vs IIIA)
- Transplant typically offered in local country (yes vs no)
- Creatinine clearance (≥60 mL/min vs <60 mL/min)

Primary endpoint: Overall haematologic CR rate

Secondary endpoints: MOD-PFS, organ response rate, time to haematologic response, overall survival, safety

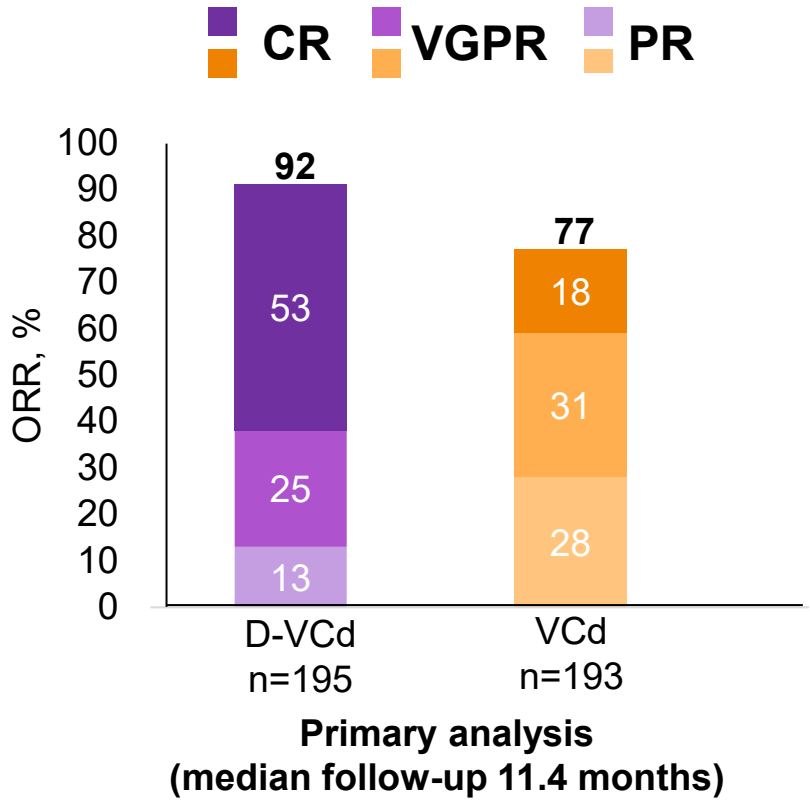
MM, multiple myeloma; eGFR, estimated glomerular filtration rate; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; MOD-PFS, major organ deterioration progression-free survival; CR, complete response; IV, intravenous; PO, oral. [a]Dexamethasone 40 mg IV or PO, followed by cyclophosphamide 300 mg/m^2 IV or PO, followed by bortezomib 1.3 mg/m^2 SC on Days 1, 8, 15, and 22 in every 28-day cycle for a maximum of 6 cycles. Patients will receive dexamethasone 20 mg on the day of DARA SC dosing and 20 mg on the day after DARA SC dosing.

Kastritis et al; EHA 2020

ANDROMEDA: HEMATOLOGIC OVERALL RESPONSE

Median time to ≥VGPR[a] was 0.56 months for D-VCd and 0.82 months for VCd

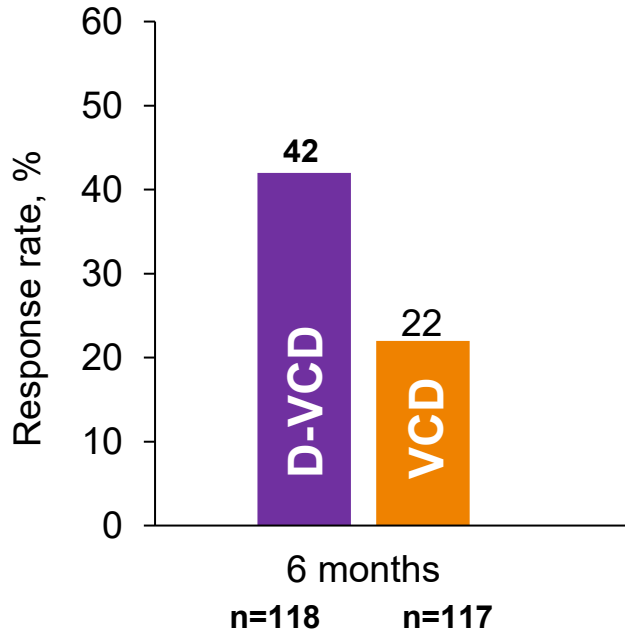
Hematologic



Primary analysis
(median follow-up 11.4 months)

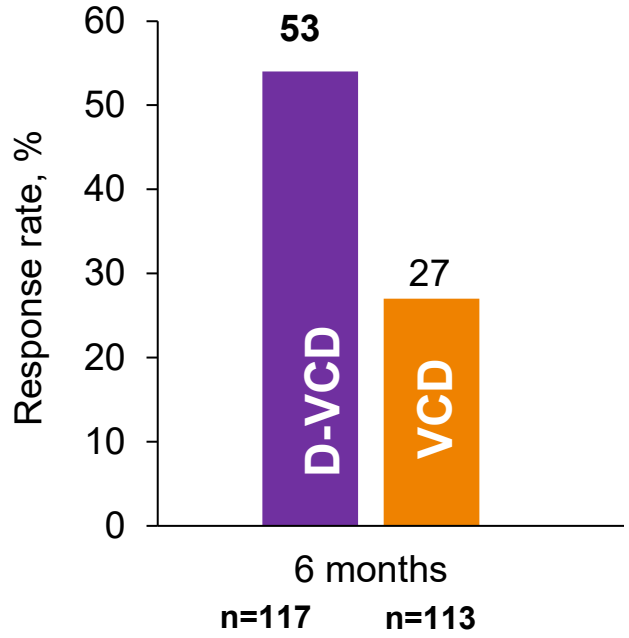
Cardiac at 6 mo

Odds ratio 2.4 (95% CI 1.4–4.4)
***P*=0.0029**



Renal at 6 mo

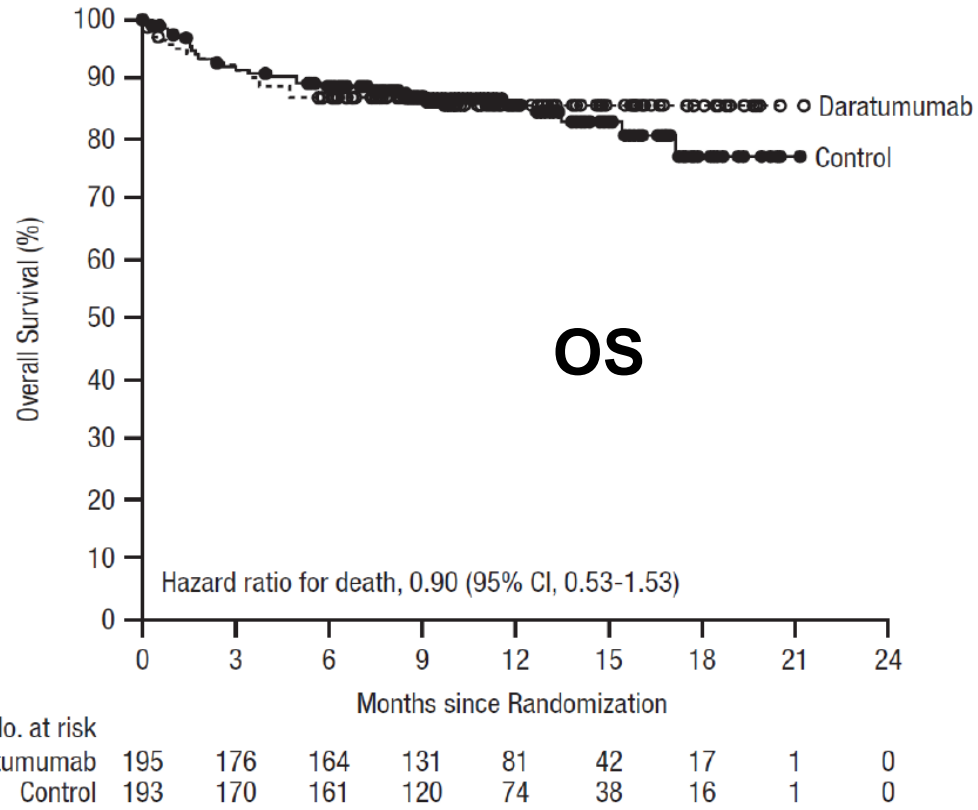
Odds ratio 3.3 (95% CI 1.9–5
***P*<0.0001**



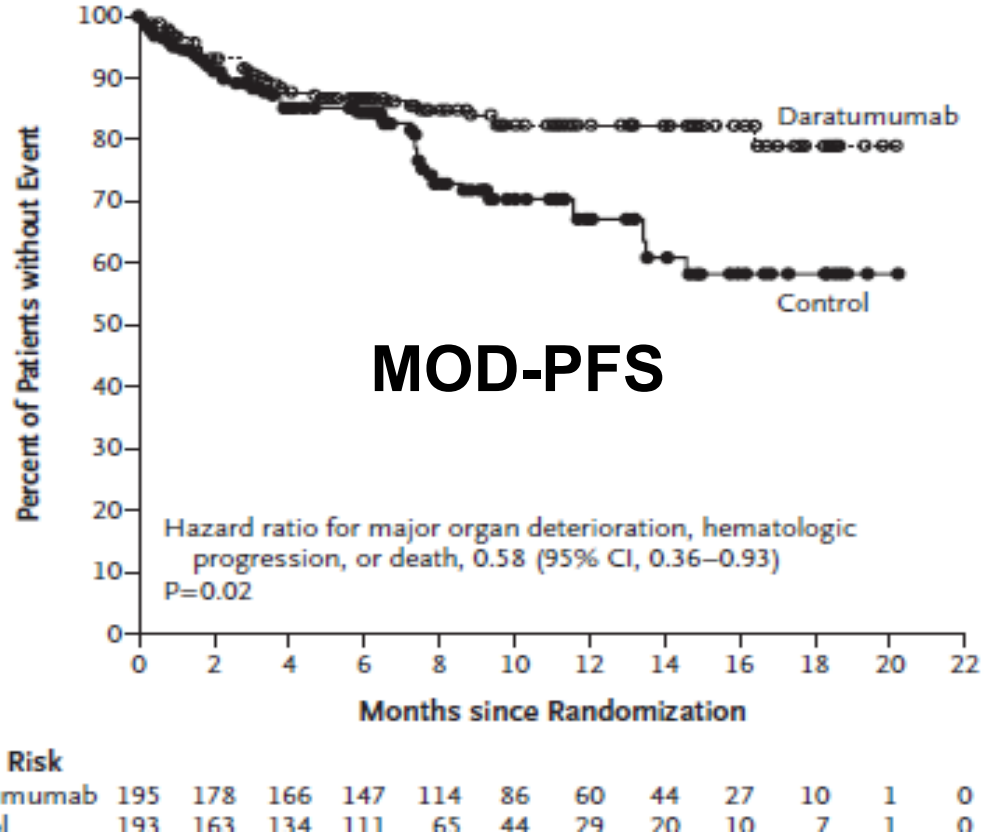
[a]Among ≥VGPR responders (D-VCd, n=154; VCd, n=97); [b]Numbers have been rounded.
CI, confidence interval; CR, complete response; D-VCd, daratumumab/bortezomib/cyclophosphamide/dexamethasone; ORR, overall response rate; PR, partial response; VGPR, very good partial response.

Kastritis E, et al. N Engl J Med. 2021 Jul 1;385(1):46-58.

ANDROMEDA: OS & PFS @ median FU of 11.4 months



OS

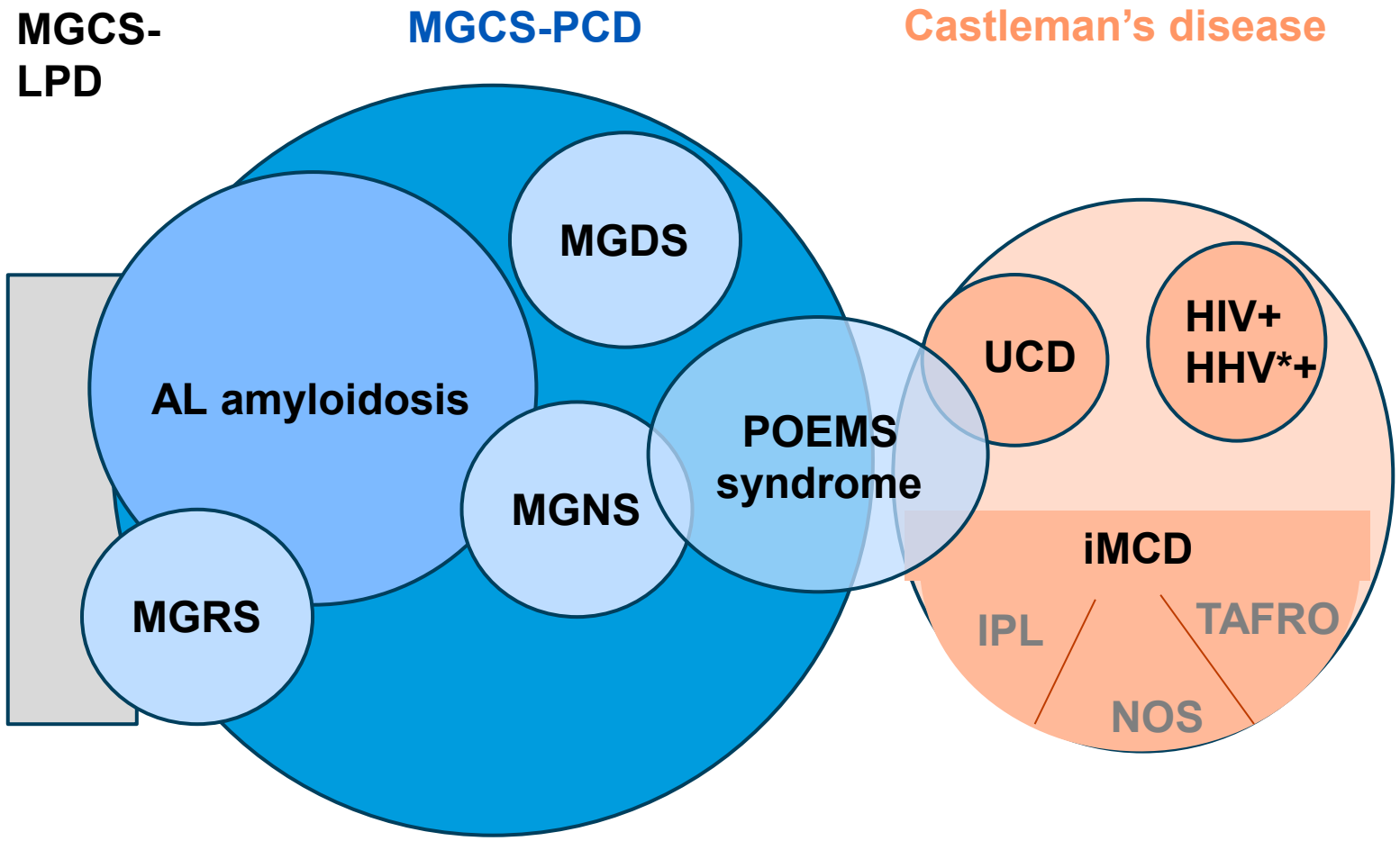


MOD-PFS

MOD PFS = hemPFS, dialysis or heart transplant

Kastritis N Engl J Med 2021;385:46-58.

OUR WORK FOR TODAY



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MONOCLONAL GAMMOPATHY OF CLINICAL SIGNIFICANCE

1. Some of the hardest monoclonal gammopathy consultations, especially if patient with other comorbidities
2. Good history and examination go a long way if you know your differential diagnosis
3. Treatment is anecdotal, but making a diagnosis is the first step (clone directed Rx and IVIG, most common)
4. Most of these patients have excellent survival, but diagnosis & treatment prevents and reverses morbidity

MYELOMA, AMYLOID, DYSPROTEINEMIA GROUP AT MAYO

Rochester

- Nadine Abdallah
- Moritz Binder
- Francis Buadi
- Joselle Cook
- David Dingli
- Angela Dispenzieri
- Amy Fonder
- Morie Gertz
- Ronald Go
- Martha Grogan
- Suzanne Hayman
- Miriam Hobbs
- Lisa Hwa
- Prashant Kapoor
- Tax Kourelis
- Shaji Kumar
- Robert Kyle
- Martha Lacy
- Yi Lin
- Nelson Leung
- Eli Muchtar
- Vincent Rajkumar
- Rahma Warsame

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- Rafael Fonseca
- Craig Reeder
- Julie Rosenthal

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- Ricardo Parrondo
- Vivek Roy
- Tamur Sher

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- **National Cancer Institute**
- **JABBS Foundation**
- **Predolin Foundation**
- **Andrew and Lillian A. Posey Foundation**

THANK YOU FOR YOUR ATTENTION.

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MGCS — DERMATOLOGIC PRESENTATIONS

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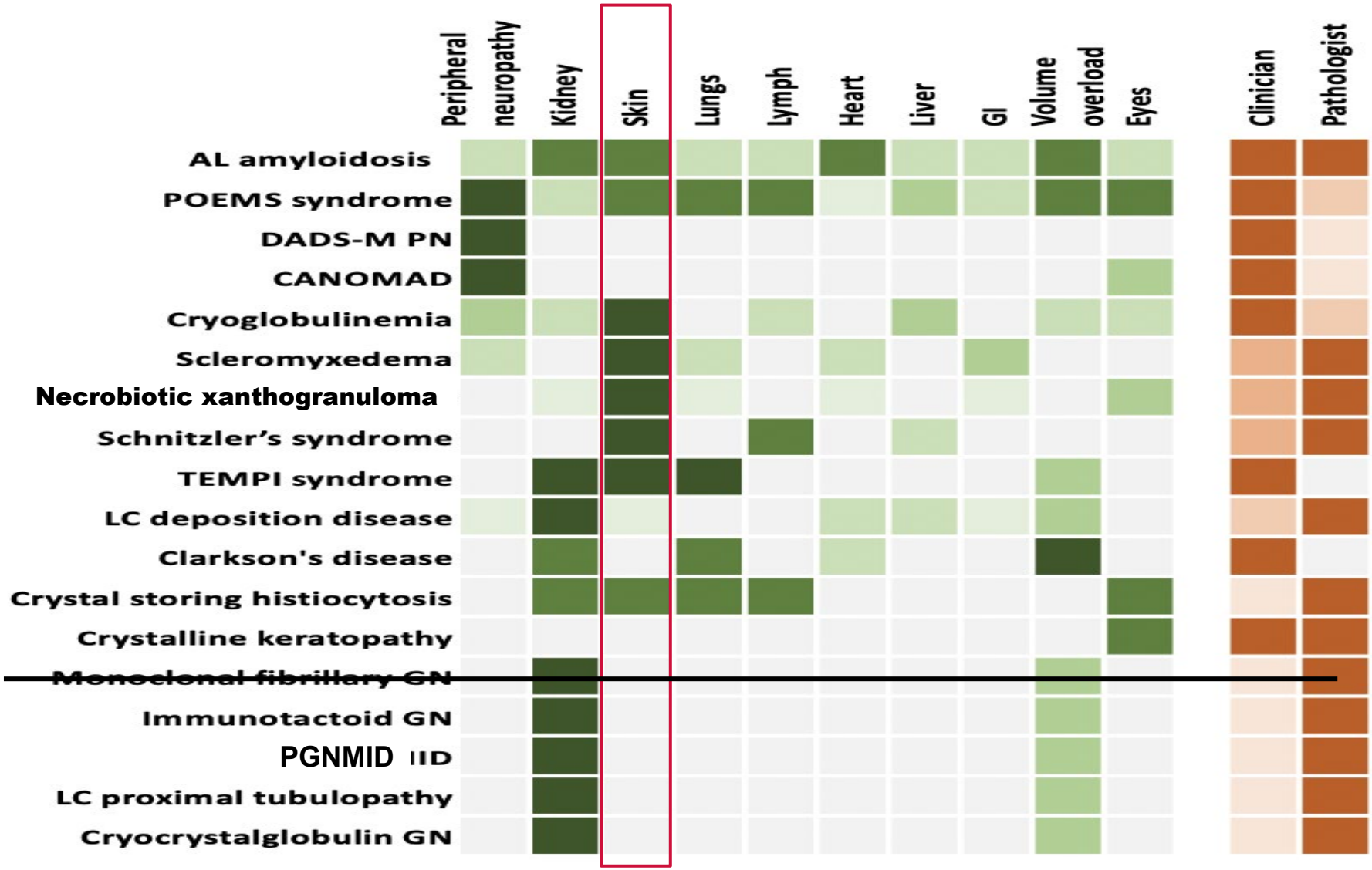
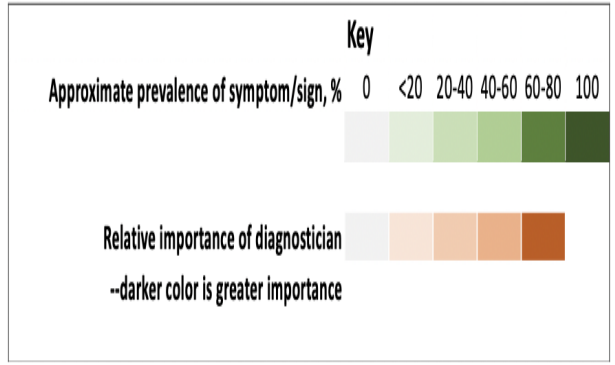
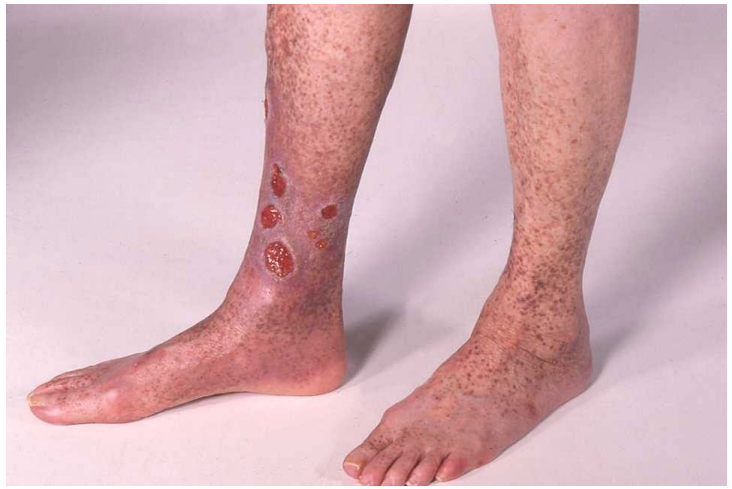




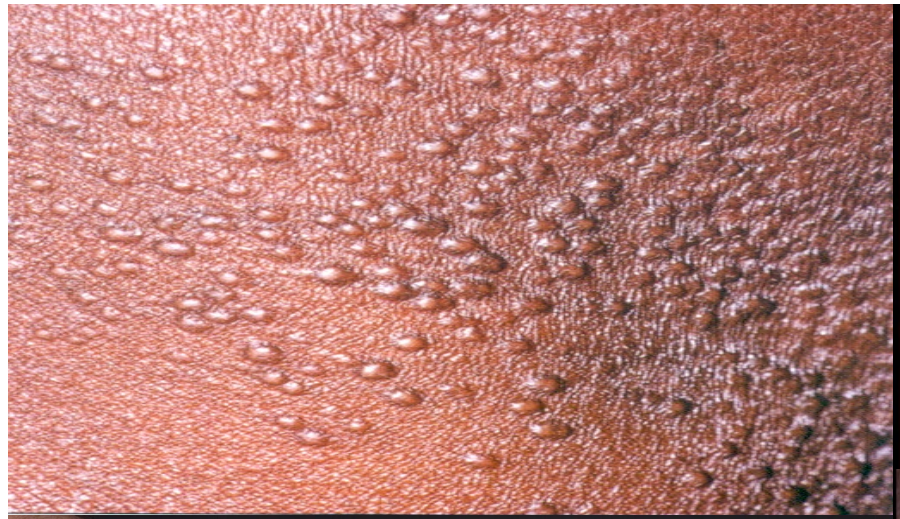
9. Cold agglutinin disease
10. Acquired cutis laxa
11. Neutrophilic dermatosis

DADS, distal acquired demyelinating symmetric neuropathy with M protein; CANOMAD, chronic ataxic neuropathy, ophthamoplegia, IgM, cold agglutinins, and disialosyl antibodies; PGNMID, proliferative glomerulonephritis with monoclonal immunoglobulin deposits

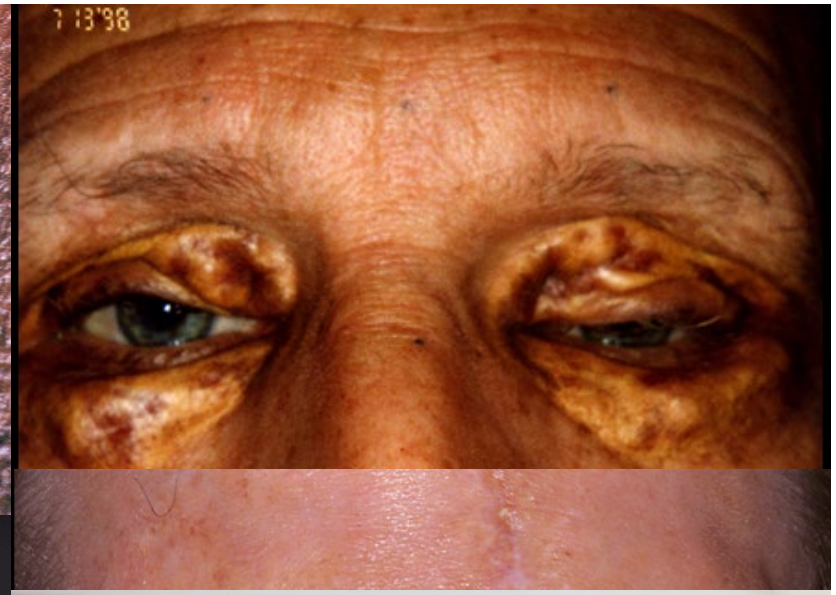
Cryoglobulinemia



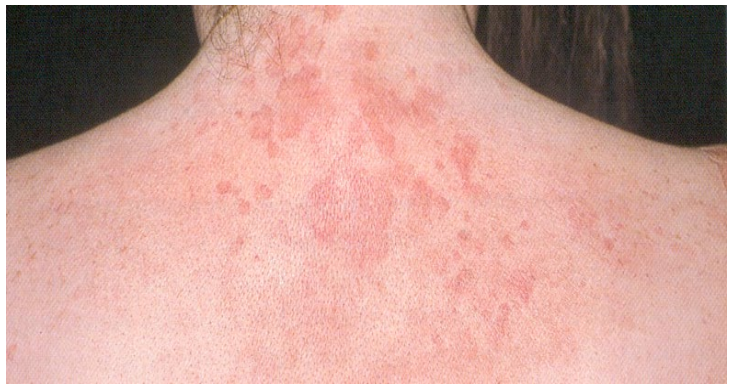
Scleromyxedema [2]

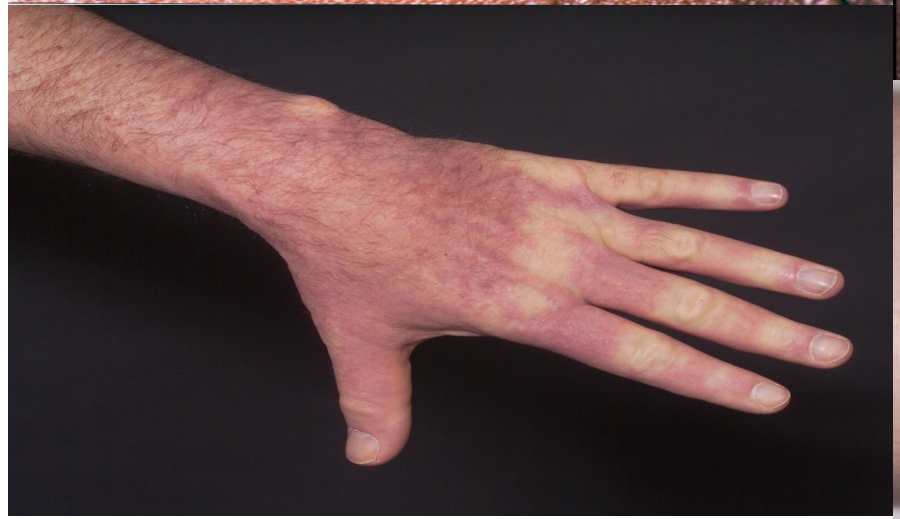


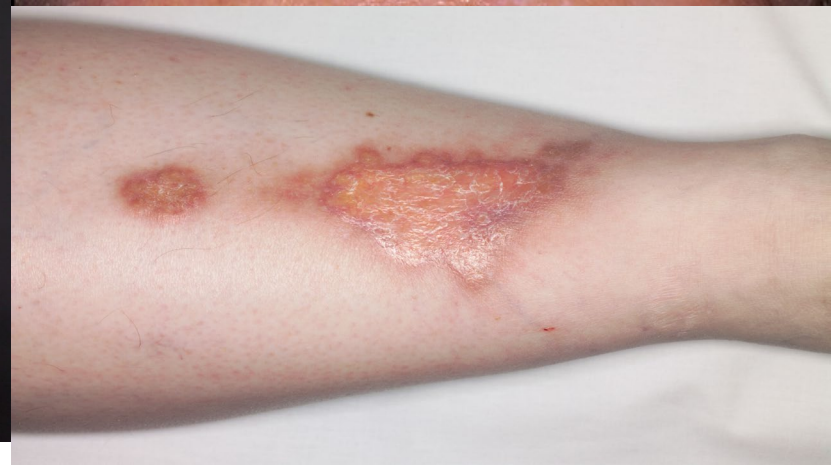
Necrobiotic Xanthogranuloma [3]



Schnitzler's syndrome [1]







[1] Simon A. *Allergy*. 2013;68(5):562-568. 2020;156(3):270-279.

[2] Rongioletti F. *J Am Acad Dermatol*. 2016;74(6):1194-1200. [3] Nelson CA. *JAMA Dermatol*.

TEMPI SYNDROME

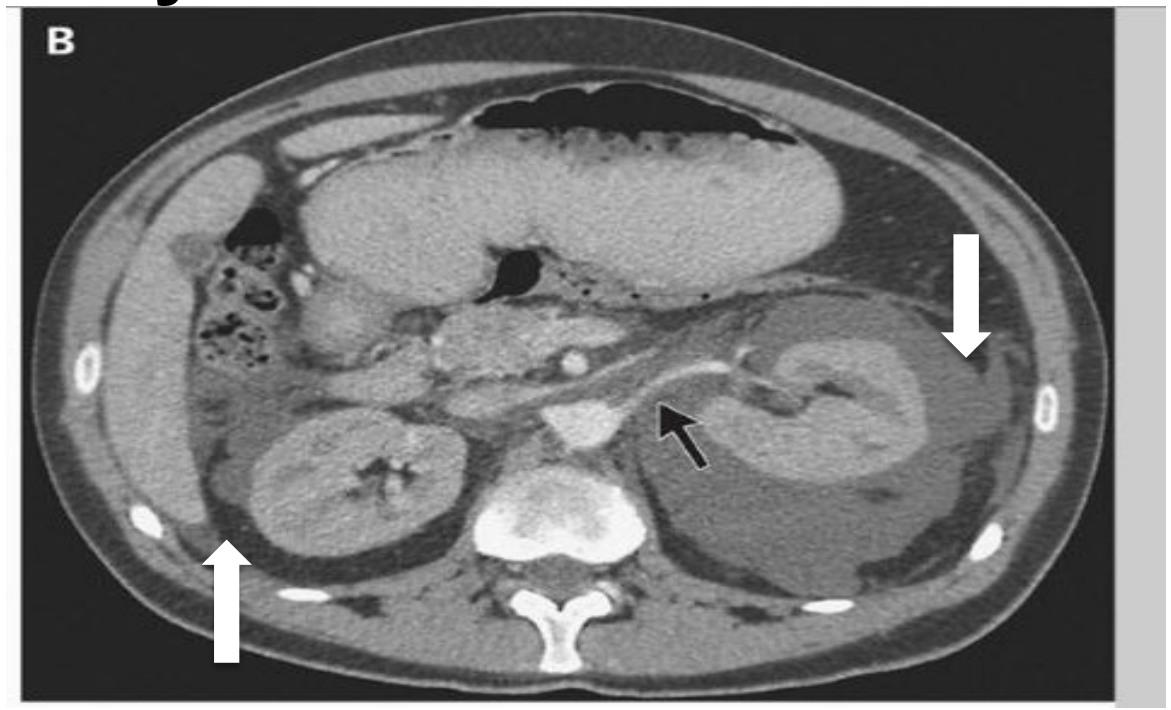
Telangiectasias

Elevated erythropoietin & erythrocytosis

Monoclonal gammopathy

Perinephric-fluid collections

Intrapulmonary shunting



N Engl J Med 2010; 363:463-475

THERAPY OF MGCS *(SKIN)*
MOSTLY ANECDOTAL

	1st line	2nd line	Other
Scleromyxedema	Intravenous gammaglobulin	Clone directed therapy	
Necrobiotic xanthogranuloma	Intravenous gammaglobulin	2nd line (bortezomib or lenalidomide)	
Capillary leak	Intravenous gammaglobulin		Supportive care
Schnitzler's syndrome	Anti-IL1 mAb	Clone directed therapy	
Cryoglobulinemia	Treat underlying cause	Rituximab	Severe disease, Medrol, chemo, PE
TEMPI syndrome	Clone directed therapy		