

Immunobullous Disease

Tips for Management

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Relevant Disclosures

- Advisory Board and Speakers Bureau: Regeneron
- Off label treatments will be discussed

Objectives

- At the conclusion of this presentation, participants will be able to:
 - Develop treatment plans for immunobullous patients which will lead to the best outcomes
 - Understand the appropriate diagnostic tools for different clinical scenarios
 - Recognize atypical presentations of rare and potentially life threatening immunobullous diseases

Pemphigus, Bullous Pemphigoid, and other forms of Pemphigoid

Tip 1

- Use steroids
 - Appropriate dosing
 - Appropriate taper

Case 1

- 70 year old female
- Diagnosed with BP 9/2022
 - PMH significant for T2DM
- No new medications
- Initial therapy
 - Doxycycline 100mg BID
 - Prednisone 20mg x 5 days, 10mg x 10 days
- 10/5 – Minocycline/clobetasol
- 10/26 – 14 day prednisone taper
- 11/22 – Mycophenolate and triamcinolone



Case 2

- 46 year old female
- Nonspecific H&E findings, DIF negative x 2
- No new medications, no significant PMH
- Prednisone tapers
 - August - 19 day taper
 - September - 15 day taper
 - October - 28 day taper
 - Doxycycline and mycophenolate started in November (no prednisone)
 - December – ELISA for desmogleins 1 and 3
 - Dsg 1 - 54
 - Dsg 3 - 173



September



October



November

Case 3

- 38 year old male
- Diagnosed with pemphigus foliaceus
- No new medications, no significant PMH
- Prednisone taper
 - 40 – 20 – 10, 5 days at each dose



Use of prednisone in AIBD

- Avoid rapid tapers!
 - Decreases in prednisone should be on the order of 5 – 10mg every 2-4 weeks (for BP, pemphigus, and pemphigoid with significant scarring)
- Even with the addition of steroid sparing therapy (excluding rituximab), be cautious about stopping prednisone in the setting of active disease
- Work closely with patient's primary care provider to manage potential corticosteroid induced side effects
- Think months, not weeks

Prednisone in BP

- 70 year old female
- Diagnosed with BP
- PMH notable for T2DM
- No new medications around the time that BP was diagnosed
- Being treated with topical steroids, doxycycline 100mg BID
- Started on 40mg x 2 weeks, 30mg x 2 weeks, 20mg for 4 weeks, 10mg for 2 months
- Doxycycline was discontinued
- Sliding scale insulin was added when patient was on higher doses of prednisone



Prednisone in BP

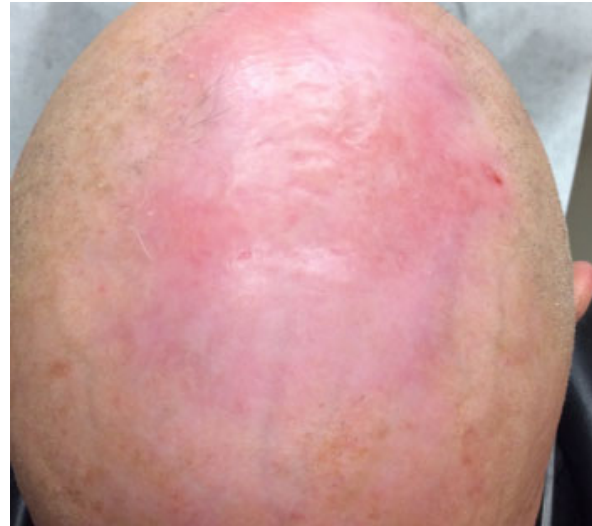
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Prednisone in (non-BP) pemphigoid



- Started on prednisone 60mg daily for 2 wks, then 50mg daily for 2 wks, then decrease by 10mg every month



- Consistent response to moderate to high dose oral prednisone
- Inconsistent response to adjuvant therapy:
 - Pulse dexamethasone (30mg daily for 3 days)
 - Mycophenolate mofetil
 - Azathioprine
 - Dapsone
 - Intralesional corticosteroid injection
 - Topical corticosteroids
 - Rituximab was denied by insurance

Pemphigus, Bullous Pemphigoid, Scarring MMP

Tip 2

- Get patients off steroids
- Rituximab

Pemphigus

Limitations of steroid sparing therapies (That aren't rituximab)

Treating Pemphigus Vulgaris with Prednisone and Mycophenolate Mofetil: A Multicenter, Randomized, Placebo-Controlled Trial

Stefan Beissert¹, Daniel Mimouni^{2,3}, Amrinder J. Kanwar⁴, Neil Solomons⁵, Veena Kalia⁵ and Grant J. Anhalt⁶

- Percentage of patients reaching the primary endpoint (disease control on ≤ 10 mg prednisone) was the same between patients taking prednisone + MMF versus prednisone + placebo (69% vs. 63.9%)

Rituximab

First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial

Pascal Joly, Maud Maho-Vaillant, Catherine Prost-Squarcioni, Vivien Hebert, Estelle Houivet, Sébastien Calbo, Frédérique Caillot, Marie Laure Golinski, Bruno Labeille, Catherine Picard-Dahan, Carle Paul, Marie-Aleth Richard, Jean David Bouaziz, Sophie Duvert-Lehembre, Philippe Bernard, Frederic Caux, Marina Alexandre, Saskia Ingen-Housz-Oro, Pierre Vabres, Emmanuel Delaporte, Gaëlle Quereux, Alain Dupuy, Sébastien Debarbieux, Martine Avenel-Audran, Michel D'Incan, Christophe Bedane, Nathalie Bénétou, Denis Jullien, Nicolas Dupin, Laurent Misery, Laurent Machet, Marie Beylot-Barry, Olivier Dereure, Bruno Sassolas, Thomas Vermeulin, Jacques Benichou, Philippe Musette, and the French study group on autoimmune bullous skin diseases

- Anti-CD20 monoclonal antibody
- 1000mg on days 1 and 14, 500mg at months 12 and 18
- Patients in the rituximab group underwent a more rapid taper of their prednisone
 - 3 and 6 months versus 12 and 18 months in the prednisone alone group
- Patients in complete remission off therapy at month 24
 - 89% of rituximab patients versus 34% of prednisone alone

Rituximab

Rituximab versus Mycophenolate Mofetil in Patients with Pemphigus Vulgaris

V.P. Werth, P. Joly, D. Mimouni, E. Maverakis, F. Caux, P. Lehane, L. Gearhart,
A. Kapre, P. Pordeli, and D.M. Chen, for the PEMPHIX Study Group*

- 1000mg on days 1, 15 with 2 additional doses at 6 months (2 weeks apart)
- Sustained complete remission at week 52
 - 40% rituximab patients versus 10% mycophenolate patients

Rituximab

- 2 doses of 1000mg, 2 weeks apart
- Follow up doses as needed
- Should be offered to almost all patients with pemphigus vulgaris and most patients with pemphigus foliaceus
- Should be considered in BP patients not responding to moderate to high-dose prednisone
 - Literature review of 122 BP patients treated with rituximab
 - Complete remission in 70.5%
 - Partial remission in 23.8%

Severe pemphigus vulgaris



Mild pemphigus vulgaris



Pemphigus foliaceus



Rituximab

- Just initial 2 doses? **Yes**
- Routine follow up doses? **No – not routinely**
- Use of antibody titers to determine redosing? **Sometimes**

Rituximab

- Lymphoma versus RA protocol for pemphigus
 - Literature review demonstrated CR in 66.66% of the lymphoma protocol patients compared to 75% of the RA protocol patients
 - Single institution retrospective study demonstrated that patients receiving the lymphoma protocol had a higher odds ratio of achieving complete remission off therapy
- Standard follow up doses versus “as needed” follow up dosing
 - Retrospective study comparing just initial two doses of 1000mg versus the initial dose plus 500mg at months 6 and 12
 - 71% relapse rate versus 40% relapse rate

Rituximab

- Vaccination recommendations
 - Prior to immunosuppression
 - ≥ 2 weeks for non-live vaccines
 - ≥ 4 weeks for live vaccines
 - Following rituximab therapy
 - For non-live vaccines, wait at least 3 months, ideally 6 months
 - Avoid live vaccines

Using titers in disease management

- 46 year old female
- Baseline titers
 - Dsg 1 - 54
 - Dsg 3 - 173
- Initial treatment
 - Prednisone, 60 – 50 – 40 – 30, 2 weeks at each dose, then one month each of 20mg, 10mg
 - Rituximab 1000mg x 2 doses while taking the 20mg



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3 months post rituximab
Prednisone tapered to 0mg



Using titers in disease management

- 25 year old female
- Approximately 8 months of oral erosions/blisters
- Prednisone improved lesions – had never been prescribed a longer course of medication
- Biopsy – “intraepithelial separation”, DIF unable to be performed because of denuded epithelium
- Antibody titers
 - Dsg 3 – 158
 - Dsg 1 – 16
- Initial treatment
 - Prednisone taper – 40mg x 2 weeks, 30mg x 2 weeks, then 20mg for a month
 - Rituximab 1000mg x 2 doses, 2 weeks apart



Using titers in disease management

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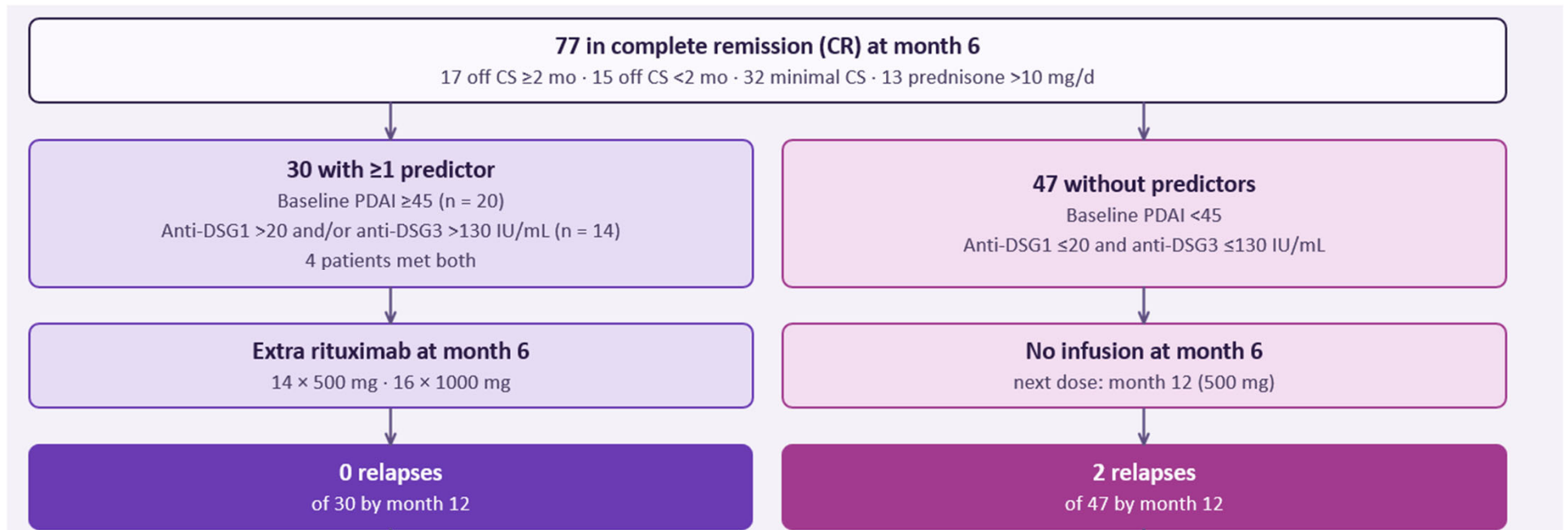


One month following rituximab
Prednisone 10mg

Using titers in disease management

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 - Dsg 1 – 16
- Initial treatment
 - Prednisone taper – 40mg x 2 weeks, 30mg x 2 weeks, then 20mg for a month
 - Rituximab 1000mg x 2 doses, 2 weeks apart
- One month after rituximab
- Patient still complaining of gingival sloughing
- Still developing oral blisters while on 10mg prednisone
- Repeat titers
 - Dsg 3- 140
 - Dsg 1 - <19
- Repeat rituximab, 500mg x 1 dose

Predictors of Relapse in Pemphigus



Bullous Pemphigoid

Limitations of steroid sparing therapies (That aren't rituximab)

- Bullous pemphigoid
 - Cochrane Database of Systemic Reviews (updated August 2023)
 - “The effectiveness of the addition of plasma exchange, azathioprine, mycophenolate mofetil, dapsone, or mepolizumab to prednisolone or prednisone has not been established”

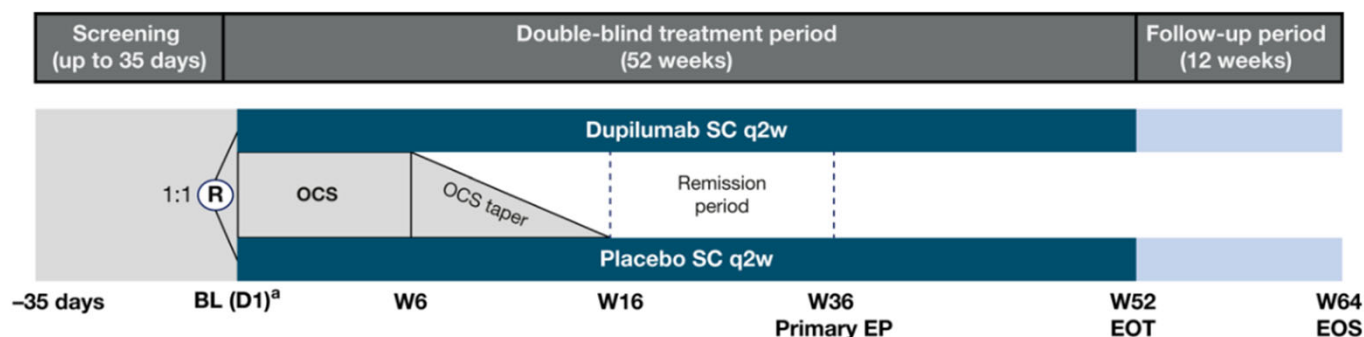
Doxycycline in bullous pemphigoid patients

Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: a pragmatic, non-inferiority, randomised controlled trial

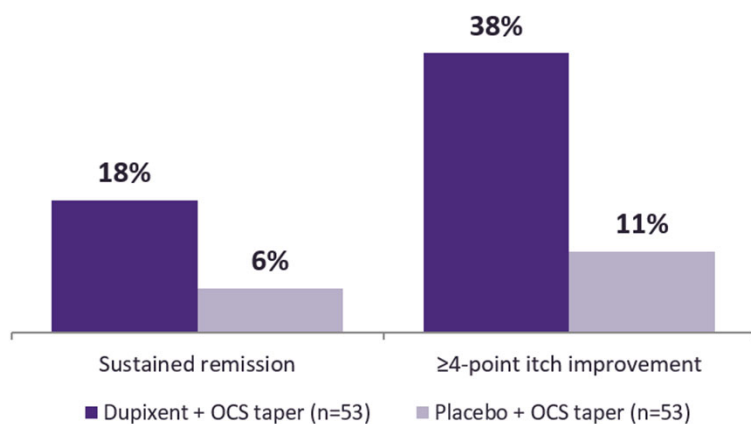
*Hywel C Williams, Fenella Wojnarowska, Gudula Kirtschig, James Mason, Thomas R Godec, Enno Schmidt, Joanne R Chalmers, Margaret Childs, Shernaz Walton, Karen Harman, Anna Chapman, Diane Whitham, Andrew J Nunn, on behalf of the UK Dermatology Clinical Trials Network BLISTER Study Group**

- Control of blister development at week 6
 - 74% of doxycycline patients versus 91% of prednisolone patients
- Severe, life-threatening, and fatal events
 - 18% of doxycycline patients versus 36% of prednisolone patients
- Doxycycline is a reasonable addition to prednisone in all BP patients and could be considered as monotherapy in the mildest cases of BP

Dupilumab



Patients achieving endpoint at Week 36 (%)



Median cumulative OCS dose, Week 36

2.8 g vs **4.1 g** Dupixent vs placebo

Sustained remission = complete remission, off OCS by Week 16, no relapse after taper, and no rescue therapy through Week 36. Remission difference 12.2% (95% CI -0.8, 26.1): did not meet statistical significance. Itch (Peak Pruritus NRS) difference 27.8% (95% CI 11.6, 43.4): secondary endpoint, not multiplicity-controlled

UPMC LIFE CHANGING MEDICINE

Murrell DF et al. Adv Ther. 2024 Jul;41(7):2991-3002.

Food and Drug Administration. Regeneron Pharmaceuticals, Inc. and sanofi-aventis U.S. LLC; 2026

Bullous Pemphigoid Tip

- Take a good medication history

BP Case 2

- 80 year old male
- Referred for management of BP
- Multiple prednisone tapers over the previous several months
- Started linagliptin around the time of the start of his BP
- Linagliptin discontinued, slow prednisone taper
- Able to completely taper prednisone



BP Case 2

- 78 year old male
- Diagnosed with metastatic urothelial carcinoma
- On month 10 of a planned 1 year course of nivolumab
- Subepidermal bullae with eosinophils, IgG and C3 at the BMZ
- BPAg 180 – 53
- BPAg 230 - <9



Drug Associated BP

A Systematic Review of Drug-associated Bullous Pemphigoid

Matthew J. VERHEYDEN¹, Asli BILGIC^{2,3} and Dédée F. MURRELL^{2,4}

¹School of Medicine, University of Notre Dame, ²St George Hospital, Department of Dermatology, Sydney, Australia, ³Antalya Research and Training Hospital, Antalya, Turkey and ⁴Faculty of Medicine, University of New South Wales, Sydney, Australia

- 250 case reports
- DPP4-inhibitors and PD-1/PD-L1 inhibitors made up ~25% of reported cases
- Treatment
 - Withdraw medication
 - Prednisone, rituximab

Paraneoplastic Pemphigus

Tip 1

- Have a high degree of suspicion for PNP in the setting of certain clinical and histologic findings

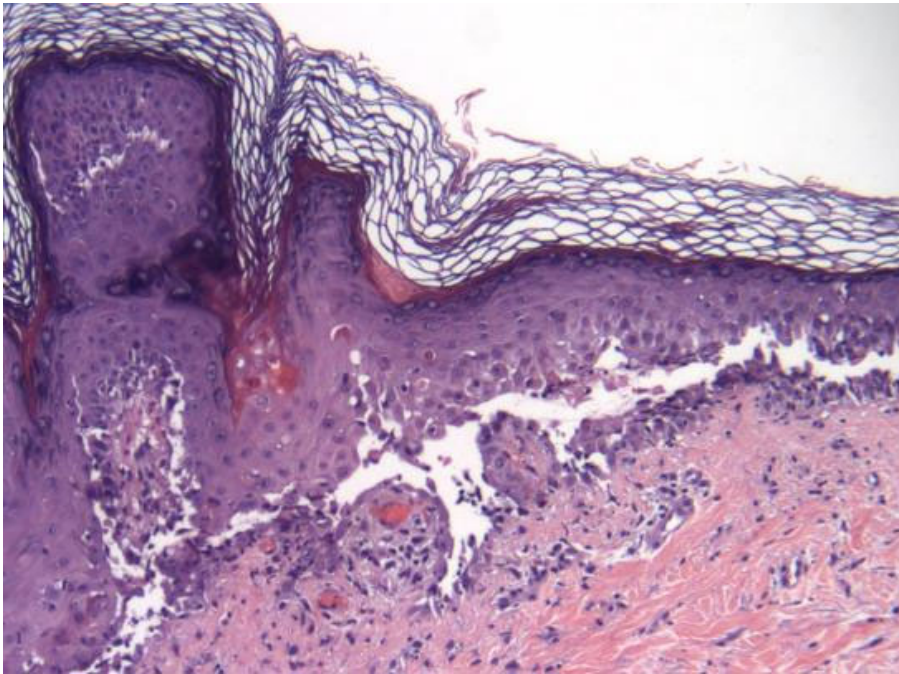
PNP Case 1

- 56 year old male with rash, blisters, oral erosions
- No new medications
- No significant PMH

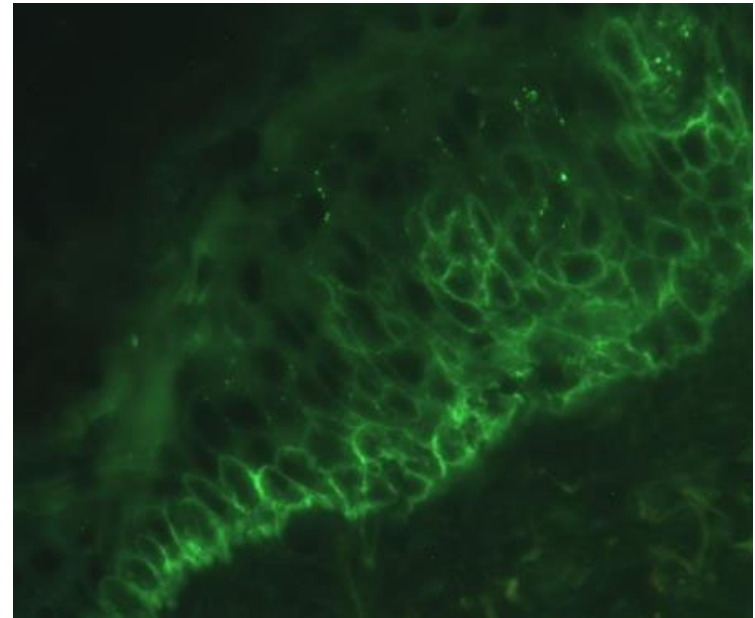


PNP Case 1

Suprabasal clefting with acantholysis



Intracellular IgG and C3



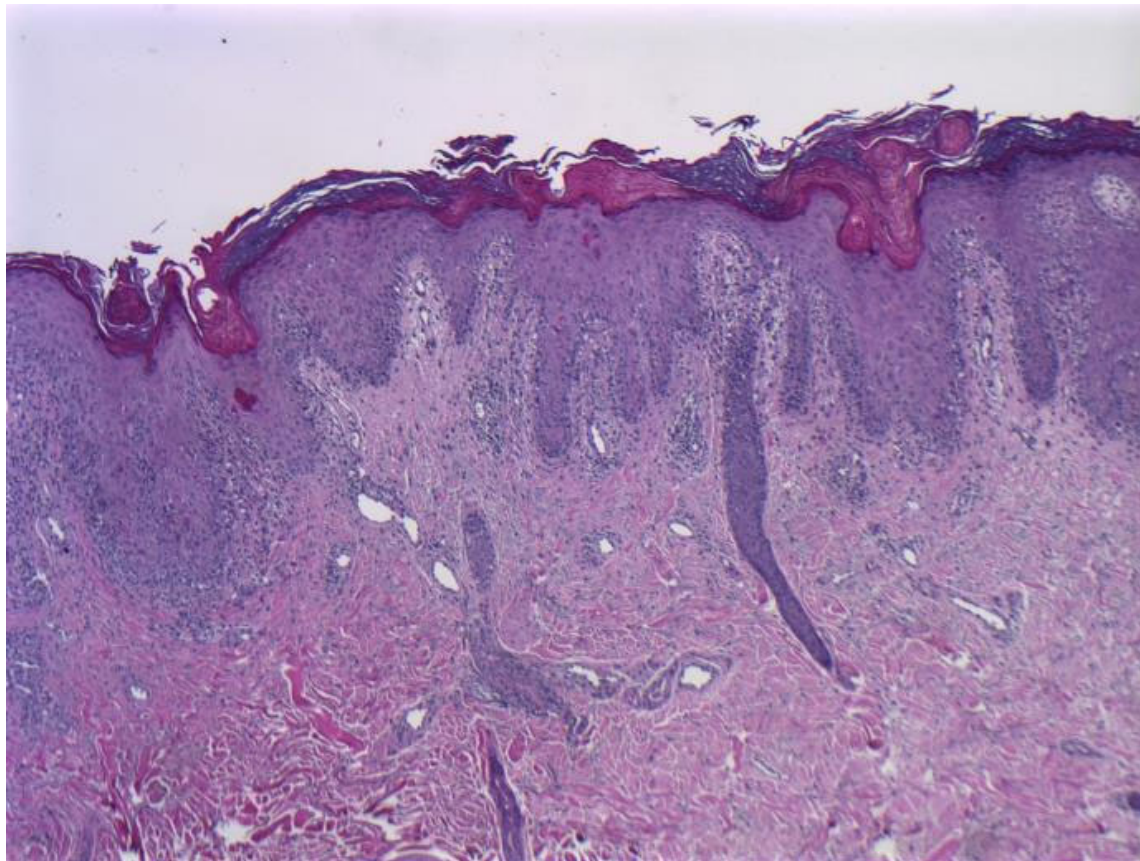
PNP Case 1

- Initial improvement with corticosteroids
- Worsening rash with tapering doses of corticosteroids



PNP Case 1

Lichenoid reaction pattern



Paraneoplastic Pemphigus

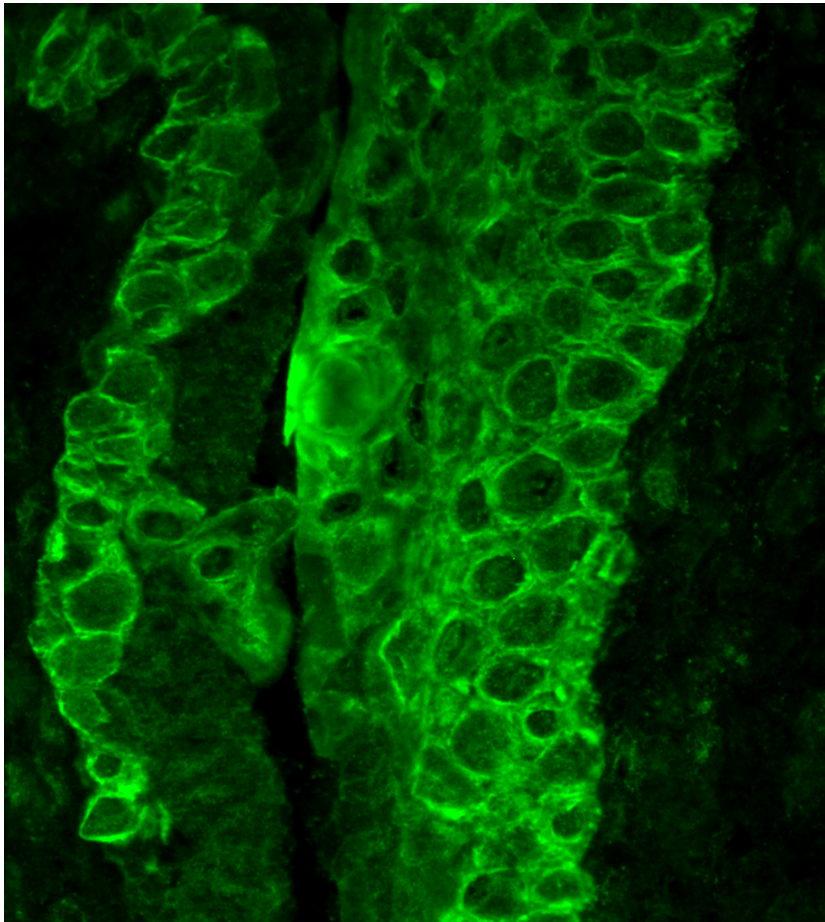
- Autoimmune bullous disease in which antibodies are directed against multiple epithelial antigens in addition to desmogleins
- Also known as Paraneoplastic Autoimmune Multiorgan Syndrome (PAMS)
- Occurs in association with multiple malignancies
 - NHL
 - CLL
 - Castleman's
 - Waldenstrom's
 - Thymoma
- Involves both humoral and cell mediated autoimmunity

Paraneoplastic Pemphigus

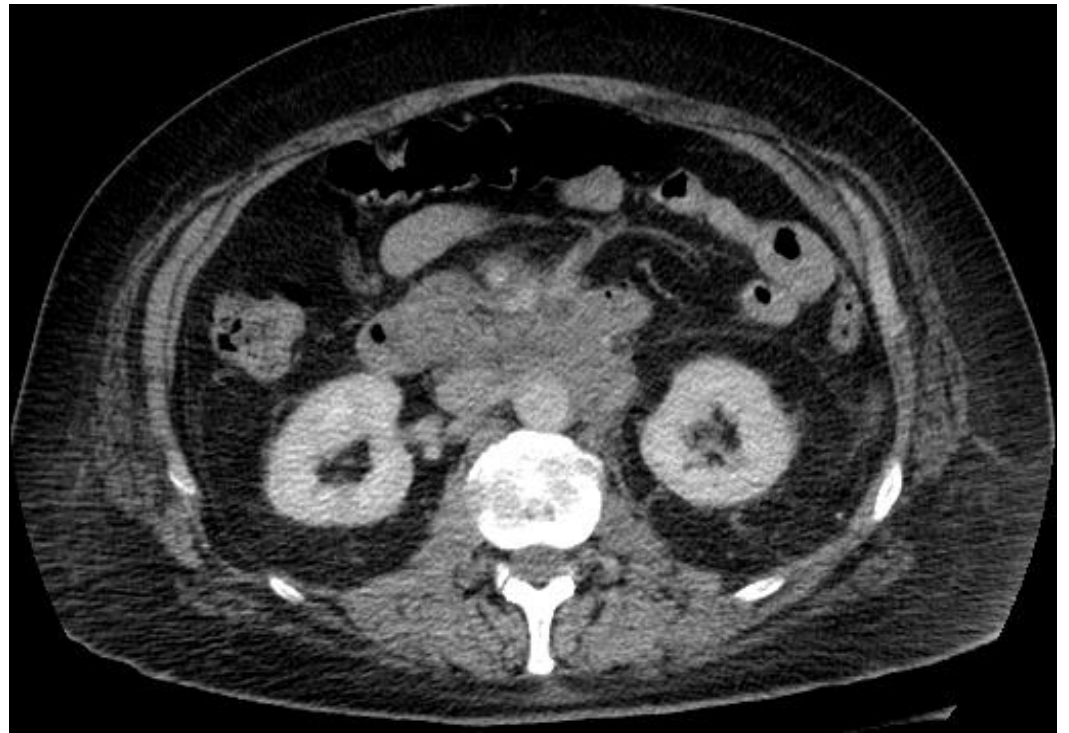
Diagnosis

- In addition to suprabasal clefting classically found in PV, PNP patients may also show lichen planus-like or EM-like changes
 - This may be the first indication of PNP and workup for malignancy should be considered
 - CT scan of chest, abdomen, pelvis
 - CBC, SPEP
- Specific DIF findings (immunoreactants at both epithelial cell surface and basement membrane zone) may only be present in less than half of PNP patients
- IIF on murine bladder and ELISAs to envoplakin and periplakin are sensitive tests, but may not be immediately available

PNP Case 1



IIF on murine bladder



Paraneoplastic Pemphigus

Tip 2

- Be aware of lichenoid PNP in patients that have received rituximab
- Initial immunofluorescence testing may be negative

PNP Case 2

- 63 year old female with SJS from rituximab
- Patient with CLL, was initiated on a regimen of fludarabine, cyclophosphamide, rituximab and developed a severe mucositis
- Diagnosed with SJS secondary to rituximab, treated with dexamethasone for close to 2 years
- Multiple skin biopsies demonstrated lichen planus-like reaction



PNP Case 2

- 2 years following diagnosis SJS secondary to rituximab, biopsy performed for DIF on buccal mucosa
 - Negative
- IIF on human skin
 - Negative
- Desmoglein ELISA
 - Dsg3 titers: 44 U/ml (Normal <20)
- IIF on rat bladder
 - Positive

PNP Case 3



- 71 year old male
- CLL – diagnosed with SJS secondary to rituximab
- Initial antibody testing negative
- IIF on rat bladder – positive
- Envoplakin ELISA - positive



PNP without antibodies

Lichenoid paraneoplastic pemphigus in the absence of detectable antibodies

Deborah L. Cummins, MD,^a Daniel Mimouni, MD,^b Julia Tzu, BS, Nicole Owens, MD,^c
Grant J. Anhalt, MD,^a and Jon H. Meyerle, MD^a
*Baltimore, Maryland; Petah Tikva and Tel Aviv, Israel;
and Fort Sam Houston, Texas*

- 4 patients that had received rituximab for the treatment of CLL
- Severe mucosal erosions/ulcerations
- Lichenoid pattern of inflammation
- DIF, IIF, immunoprecipitation all failed to demonstrate antibodies

PNP without antibodies



Lichenoid PNP

- PNP is both a B-cell and T-cell mediated disease
- When patients receive rituximab, the B-cell component of the disease is rendered inactive
 - Negative antibody testing
- All three patients were diagnosed with SJS secondary to their chemotherapy
 - Importance of correct diagnosis – chemotherapy can be continued in these patients

Mucous Membrane Pemphigoid

Tip 1

- Utilize subspecialists

Case

- 63 year old female
- 5 month history of oral ulcers
- Biopsy results demonstrating “inflammation”
- Repeat biopsy with nonspecific H&E findings, negative DIF
- IIF testing was negative
- Trial of hydroxychloroquine without improvement
- Patient referred to dental surgeon for repeat gingival biopsy



Pemphigoid Algorithm

H&E – submucosal split
Immunoglobulins at the mucosal/submucosal
junction
Prominent lichenoid infiltrate not present

IgA only

Linear IgA Disease

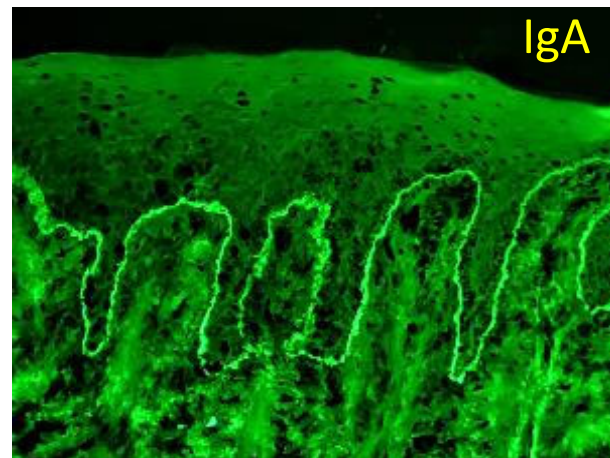
IgG, +/- IgA, +/-C3

Mucous Membrane Pemphigoid
Epidermolysis Bullosa Acquisita

If DIF is negative and suspicion for an immunobullous disease is still
high, the best option is to probably repeat the DIF
Indirect IF is often negative in MMP patients

Case

- 63 year old female
- 5 month history of oral ulcers
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Mucous Membrane Pemphigoid

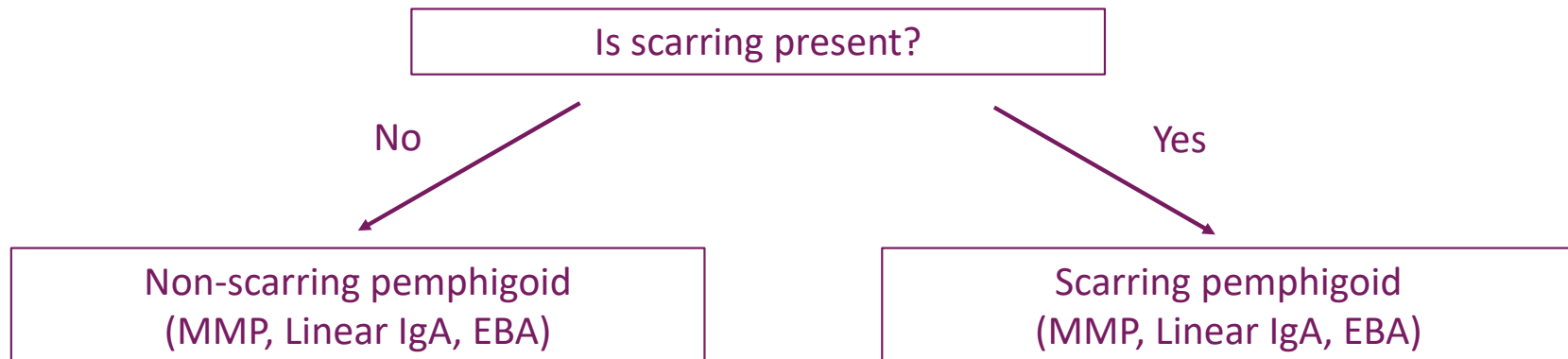
Tip 2

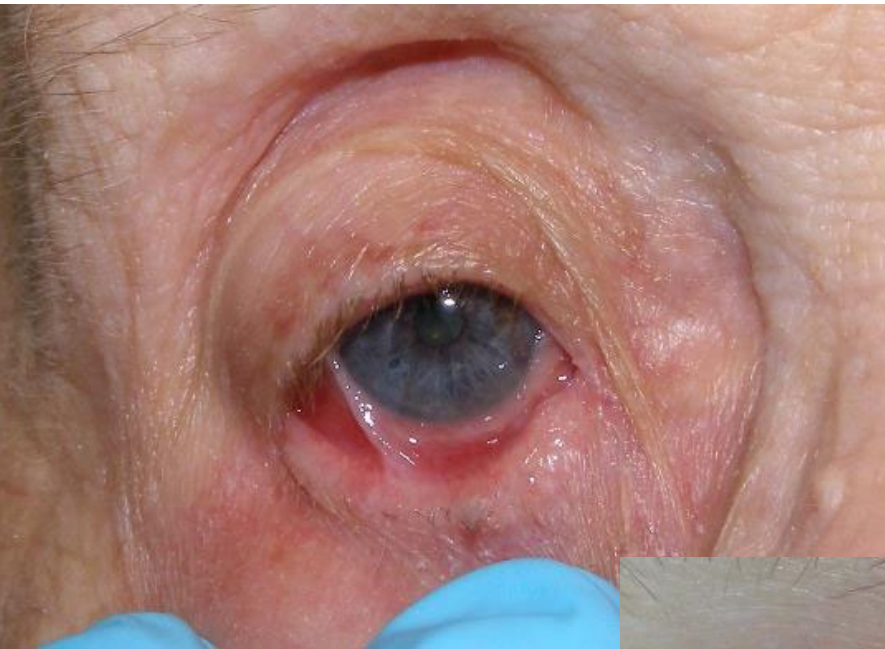
- Determine if patient has scarring or non-scarring disease

Pemphigoid Group

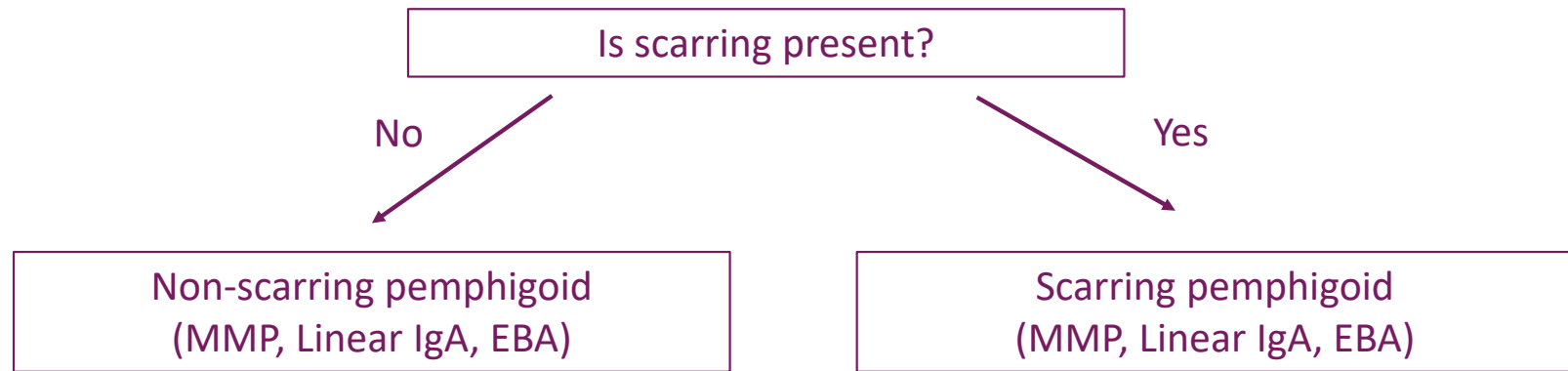
Diagnosis

- With predominant oral mucous membrane involvement, more important than the precise diagnosis (MMP versus EBA versus Linear IgA) is assessing whether or not scarring is present
- Eyes, esophagus, larynx, genital
- Take a good history – history of regurgitation, stridor, foreign body sensation
- Eye exam should be done in all patients with oral pemphigoid lesions





Pemphigoid Group Therapy

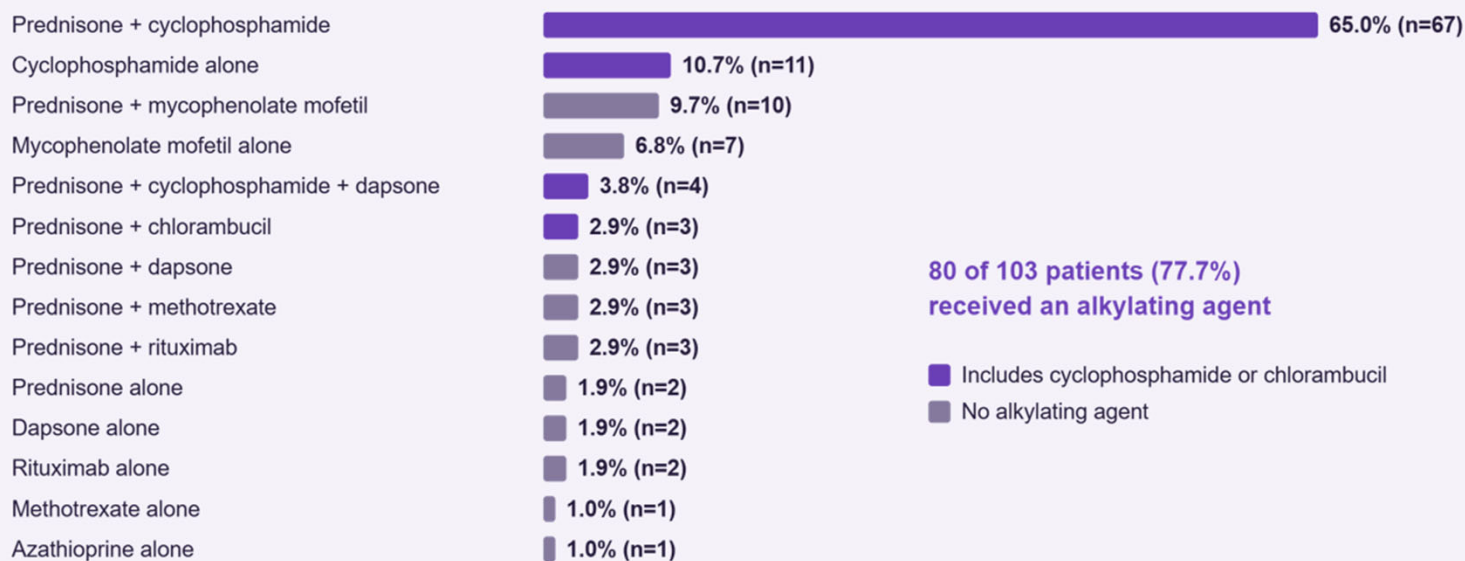


Usually only affects the oral mucosa
Can be symptomatic
Initial treatments should be non-aggressive
Topical corticosteroids, doxycycline,
dapsons, colchicine

Serious sequelae can develop if not treated
aggressively (blindness, esophageal stenosis,
laryngeal stenosis)
Systemic corticosteroids + cyclophosphamide +
rituximab

Scarring MMP

Treatments received by patients with ocular MMP



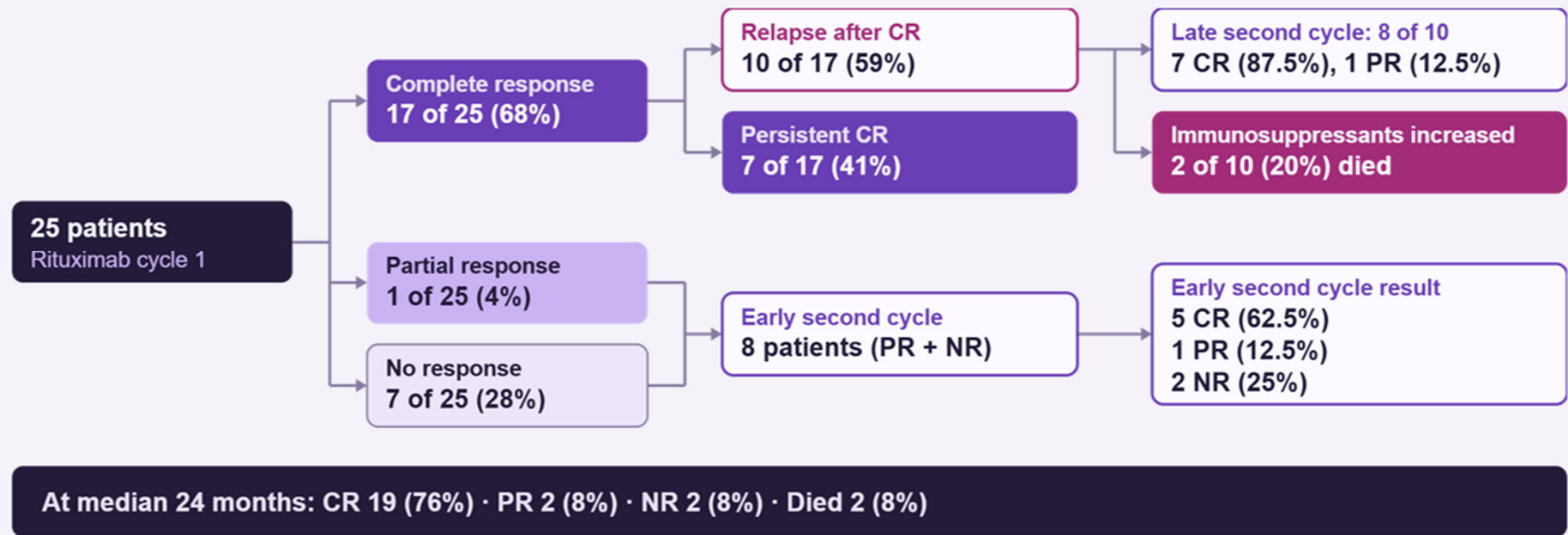
Treatment and outcome

- Cyclophosphamide: remission HR 3.84; relapse HR 0.32 (P = .05)
- Alkylating agent or rituximab vs others: any-site relapse HR 0.17, ocular HR 0.11
- Rituximab: 5 of 5 remitted, no relapses (median 3.6 years after remission)

Shifera AS et. Am J Ophthalmol. 2021 Mar;223:21-27

Scarring MMP

Response to rituximab, cycle by cycle







The End