Treatment of Pemphigus Foliaceous with Dupilumab

Carlos Vieira, MD
Cooper Medical School of Rowan University
Department of Dermatology
PGY-3

Cooper University Health Care

Cooper Medical School of Rowan University

1

2018:

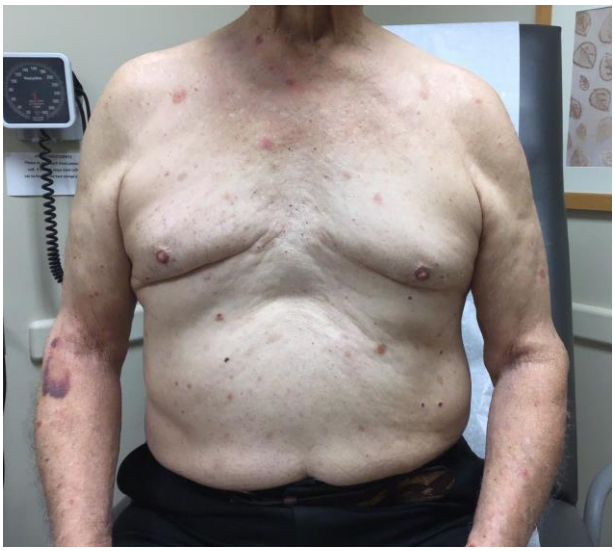
80-year-old male with a PMHx significant for hypothyroidism and prostate cancer presents to the clinic for a pruritic rash of the proximal upper extremities and trunk for 4 weeks.

Cooper University Health Care

Cooper Medical School of Rowan University

2

Physical exam:
Urticarial pink papules and erosions on central trunk and proximal upper extremities



Cooper University Health Care

Cooper Medical School of Rowan University

3

DDx:

Acute Urticaria

Bullous Pemphigoid

Atypical Sweet Syndrome

Arthropod Assault

Cooper University Health Care

Cooper Medical School of Rowan University

4

Diagnosis:
Epigastric skin - BULLOUS PEMPHIGOID, URTICARIAL STAGE, PROBABLE

Note:
The differential diagnosis includes the urticarial stage of superficial pemphigus. Step-sections have been examined. PAS stain is negative for hyphae.

Microscopic Description
There is a perivascular and interstitial, mixed-cell infiltrate of lymphocytes and numerous eosinophils, many of the latter being present in the papillary dermis.
All controls are appropriate
L12.0

DIAGNOSIS

Epigastric skin: **CELL SURFACE MEMBRANE STAINING, SEE NOTE**

Microscopic Description:
Epigastric skin - The sections were reacted with antibodies to IgG, IgA, IgM, C3, and fibrinogen. The biopsy shows focal acantholysis within the epidermis. Cell surface membrane staining is identified using IgG and C3. No significant or specific IgA, IgM or fibrinogen is identified. Overall, these findings are most consistent with pemphigus vulgaris. Correlation with routine histologic is recommended. This case has been reviewed with another member of the Dermatopathology group.

Cooper University Health Care

Cooper Medical School of Rowan University

5

Serologies revealed:

LIST OF RESULTS PRINTED IN THE OUT OF RANGE COLUMN:			
BULLOUS PEMPHIGOID BP230			EZ
IGG	9 H	<9 U/mL	
DESMOGLEIN 1 ANTIBODY	75 H	U/mL	EZ
	Reference Range:		
	NEGATIVE: <14		
	EQUIVOCAL: 14-20		
	POSITIVE: >20		

Cooper University Health Care

Cooper Medical School of Rowan University

6

	Bullous Pemphigoid	Pemphigus Foliaceus	Pemphigus Vulgaris
Antibody Target	BP 180 +/- BP 230	Desmoglein 1 (+/- 3)	Desmoglein 3 (+/- 1)
Split?	Subepidermal	Intraepidermal	Intraepidermal
Characteristic Histology	Eosinophils	Acantholysis in upper epidermis	Supra-basilar epidermal acantholysis (tombstoning), "chicken-wire" IgG and C3 deposition of lower epidermis of DIF
Distribution	Flexural or generalized	Seborrheic	Mucosal sites +/- skin
Morphology	Urticarial papules, eczematous patches, erosions or tense bullae	Superficial vesicles and bullae, erosions, crust	Erosions, mucositis, flaccid bullae
Epidemiology	Significant pruritis, older adults, history of neurologic disease or other autoimmune conditions	Favors adults, history of other autoimmune conditions	Favor adults
Associations	furosemide, captopril, NSAIDs, gliptins, etc.	penicillamine	penicillamine

Cooper University Health Care

Cooper Medical School of Rowan University

7

Treatment:

Topical Triamcinolone 0.1% ointment BID

Mycophenolate Mofetil up to 1500 mg/day with improvement:

discontinued 2/2 to recurrent URIs

Doxycycline 100 mg BID + nicotinamide 500 mg TID:

discontinued 2/2 to photosensitivity

Minocycline 100 mg BID:

discontinued 2/2 to drug induced hyperpigmentation

Cooper University Health Care

Cooper Medical School of Rowan University

8

Interval History (2022):
New diagnosis of metastatic lung adenocarcinoma

FINAL REPORT (12/20/2022)

Diagnosis:
Chest - DIRECT IMMUNOFLUORESCENCE POSITIVE FOR PEMPHIGUS, FAVORING SUPERFICIAL PEMPHIGUS OVER PEMPHIGUS VULGARIS (SEE ENCLOSED REPORT FOR DETAILS)

DESMOGLEIN 1 ANTIBODY	192 H	U/mL
	Reference Range:	
	NEGATIVE:	<14
	EQUIVOCAL:	14-20
	POSITIVE:	>20
DESMOGLEIN 3 ANTIBODY	16 H	U/mL
	Reference Range:	
	NEGATIVE:	<9
	EQUIVOCAL:	9-20
	POSITIVE:	>20

Cooper University Health Care

Cooper Medical School of Rowan University

9

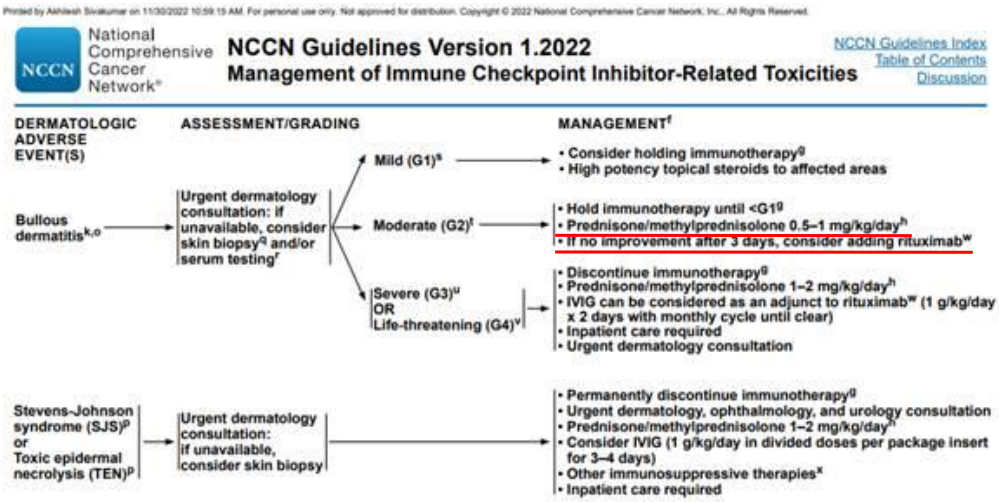
- Common treatments for Pemphigus Foliaceus:
  - High-potency topical steroids
  - Prednisone 1.0 - 1.5 mg/kg/day
  - Mycophenolate Mofetil 1-3 g/day
  - Azathioprine 2.5 mg/kg/day
  - Cyclophosphamide 50-100 mg/day
  - Rituximab
  - IVIG

Contraindicated in the setting of active malignancy

Cooper University Health Care

Cooper Medical School of Rowan University

10



Cooper University Health Care

Cooper Medical School of Rowan University

11

Multicenter Study > Clin Cancer Res. 2021 Nov 1;27(21):5993-6000.

doi: 10.1158/1078-0432.CCR-21-1283. Epub 2021 Aug 10.

Early Use of High-Dose Glucocorticoid for the Management of irAE Is Associated with Poorer Survival in Patients with Advanced Melanoma Treated with Anti-PD-1 Monotherapy

- Multicenter retrospective analysis of patients treated with anti–PD-1 monotherapy between 2009 and 2019
- 509 (54%) developed irAEs
- Early-onset irAE (within 8 weeks of anti–PD-1 initiation) with high-dose GCC use (≥60-mg prednisone equivalent once a day) was independently associated with poorer progression free survival and overall survival (HR 5.37 and 5.95, respectively) when compared to patients who did not receive high dose steroids

Cooper University Health Care

Cooper Medical School of Rowan University

12

Dupilumab

- Human monoclonal antibody that inhibits IL-4 R α subunit which blocks IL-4 and IL-13 signaling and dampens Th2 mediated inflammation
- FDA approved for Atopic Dermatitis, Prurigo Nodularis, Asthma, Chronic Rhinosinusitis with Polyposis and Eosinophilic Esophagitis
- Off-label, dupilumab has demonstrated efficacy in treating Bullous Pemphigoid in multiple case series (disease clearance or satisfactory response was achieved in 92.3% of the patients in one multisite case series)

Immune checkpoint inhibitor-bullous pemphigoid is characterized by interleukin-4 and interleukin-13 expression and responds to dupilumab treatment.
Shipman WD, et al. Br J Dermatol. 2023. PMID: 37140007 No abstract available.

Dupilumab for the treatment of nivolumab-induced **bullous pemphigoid**: a case report and review of the literature.
Klepper EM, Robinson HN.
Dermatol Online J. 2021 Sep 15;27(9). doi: 10.5070/D327955136.
PMID: 34755978 Review.
Immune **checkpoint inhibitors**, a relatively new class of drugs, are used to treat a variety of malignancies. ...We present a case of nivolumab-induced **bullous pemphigoid** that was successfully treated with **dupilumab**....

Immune **checkpoint inhibitor-bullous pemphigoid** is characterized by interleukin-4 and interleukin-13 expression and responds to **dupilumab** treatment.
Shipman WD, Singh K, Cohen JM, Leventhal J, Damsky W, Tomayko MM.
Br J Dermatol. 2023 May 4:ljad149. doi: 10.1093/bjd/ljad149. Online ahead of print.
PMID: 37140007 No abstract available.

Cooper University Health Care

Cooper Medical School of Rowan University

13

Case Reports > JAAD Case Rep. 2022 Nov 5;31:16-18. doi: 10.1016/j.jdcr.2022.10.035. eCollection 2023 Jan.

Dupilumab monotherapy suppresses recalcitrant pemphigus vulgaris

Angela Y Moore [1 2 3 4 5], Kara Hurley [5]

Affiliations + expand
PMID: 36478983 PMCID: PMC9720249 DOI: 10.1016/j.jdcr.2022.10.035
Free PMC article

No abstract available

Keywords: Dsg, desmoglein; IL, interleukin; PV, Pemphigus vulgaris; case report; drug response; dupilumab; general dermatology; medical dermatology; oncology; pemphigus; vesiculobullous.

- 41-year-old woman who presented with superficial bullae and crusted erosions on head, oral mucosa, trunk and extremities.
- Biopsy revealed dermal inflammatory infiltrate with scattered eosinophils
- Loading dose 600 mg SC
- Maintenance dose 300 mg SC q 2 weeks cleared skin disease.
- Increasing to weekly 300 mg dose cleared mucosal erosions.

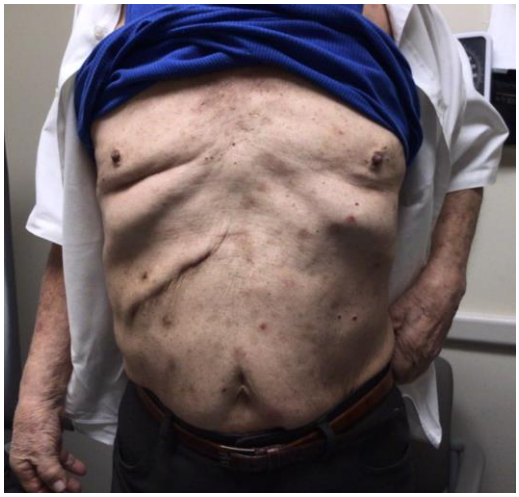
Cooper University Health Care

Cooper Medical School of Rowan University

14

Back to our patient...

- Loaded with 600 mg SC dupilumab on day 0
- Maintenance dosing: 300 mg SC q 2 weeks
- After two months of therapy, pruritis resolved and > 50% decrease in active lesions



Cooper University Health Care

Cooper Medical School of Rowan University

15

Take Home Points

- Use of high dose systemic steroids must be carefully considered in patients with irAEs as they may contribute to morbidity.
- Dupilumab has demonstrated efficacy in treating autoimmune bullous dermatoses, particularly Bullous Pemphigoid.
- Presence of eosinophils in the dermis may be a useful histological marker to gage utility of dupilumab in other autoimmune blistering disorders such as Pemphigus Foliaceous.

Cooper University Health Care

Cooper Medical School of Rowan University

16

Cooper University Health Care

Cooper Medical School of Rowan University

17

References

- Abdat R, Waldman RA, de Bedout V, Czernik A, Mcleod M, King B, Gordon S, Ahmed R, Nichols A, Rothe M, Rosmarin D. Dupilumab as a novel therapy for bullous pemphigoid: A multicenter case series. J Am Acad Dermatol. 2020 Jul;83(1):46-52. doi: 10.1016/j.jaad.2020.01.089. Epub 2020 Mar 13. PMID: 32179082.
- Bai X, Hu J, Betof Warner A, Quach HT, Cann CG, Zhang MZ, Si L, Tang B, Cui C, Yang X, Wei X, Pallan L, Harvey C, Manos MP, Ouyang O, Kim MS, Kasumova G, Cohen JV, Lawrence DP, Freedman C, Fadden RM, Rubin KM, Sharova T, Frederick DT, Flaherty KT, Rahma OE, Long GV, Menzies AM, Guo J, Shoushtari AN, Johnson DB, Sullivan RJ, Boland GM. Early Use of High-Dose Glucocorticoid for the Management of irAE Is Associated with Poorer Survival in Patients with Advanced Melanoma Treated with Anti-PD-1 Monotherapy. Clin Cancer Res. 2021 Nov 1;27(21):5993-6000. doi: 10.1158/1078-0432.CCR-21-1283. Epub 2021 Aug 10. PMID: 34376536; PMCID: PMC9401488
- Culton DA, Liu Z, Diaz LA. Bullous pemphigoid. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS, eds. *Fitzpatrick's Dermatology*. 9th ed. New York, NY: McGraw-Hill Education; 2019
- Moore AY, Hurley K. Dupilumab monotherapy suppresses recalcitrant pemphigus vulgaris. JAAD Case Rep. 2022 Nov 5;31:16-18. doi: 10.1016/j.jdcr.2022.10.035. PMID: 36478983; PMCID: PMC9720249.
- Murrell DF, Peña S, Joly P, Marinovic B, Hashimoto T, Diaz LA, Sinha AA, Payne AS, Daneshpazhooh M, Eming R, Jonkman MF, Mimouni D, Borradori L, Kim SC, Yamagami J, Lehman JS, Saleh MA, Culton DA, Czernik A, Zone JJ, Fivenson D, Ujiie H, Wozniak K, Akman-Karakaş A, Bernard P, Korman NJ, Caux F, Drenovska K, Prost-Squarcioni C, Vassileva S, Feldman RJ, Cardones AR, Bauer J, Ioannides D, Jedlickova H, Palisson F, Patsatsi A, Uzun S, Yayli S, Zillikens D, Amagai M, Hertl M, Schmidt E, Aoki V, Grando SA, Shimizu H, Baum S, Cianchini G, Feliciani C, Iranzo P, Mascaró JM Jr, Kowalewski C, Hall R, Groves R, Harman KE, Marinkovich MP, Maverakis E, Werth VP. Diagnosis and management of pemphigus: Recommendations of an international panel of experts. J Am Acad Dermatol. 2020 Mar;82(3):575-585.e1. doi: 10.1016/j.jaad.2018.02.021. Epub 2018 Feb 10. PMID: 29438767; PMCID: PMC7313440.
- Thompson JA, Schneider BJ, Brahmer J, Achufusi A, Armand P, Berkenstock MK, Bhatia S, Budde LE, Chokshi S, Davies M, Elshoury A, Gesthalter Y, Hegde A, Jain M, Kaffenberger BH, Lechner MG, Li T, Marr A, McGettigan S, McPherson J, Medina T, Mohindra NA, Olszanski AJ, Oluwole O, Patel SP, Patil P, Reddy S, Ryder M, Santomasso B, Shofer S, Sosman JA, Wang Y, Zaha VG, Lyons M, Dwyer M, Hang L. Management of Immunotherapy-Related Toxicities, Version 1.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022 Apr;20(4):387-405. doi: 10.6004/jnccn.2022.0020. PMID: 35390769..

18