Multidisciplinary Approaches to Cancer Symposium

Cutaneous Immune Related Adverse Events (cirAEs)

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Disclosures

- Consultant for Merck.
- On the Speakers Bureau for Regeneron, and Sanofi Genzyme.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Cutaneous immune related adverse reactions can appear differently based on baseline skin type.*
- *It is possible to misdiagnose skin reactions due to lack of familiarity with rashes in different ethnic skin types.*

Immune checkpoint inhibitors are widely prescribed

Original Investigation | Oncology

May 3, 2019

Alyson Haslam, PhD[1]; Vinay Prasad, MD, MPH[2,3,4,5]

JAMA Netw Open. 2019;2(5):e192535. doi:10.1001/jamanetworkopen.2019.2535

Estimation of the Percentage of US Patients With Cancer Who Are Eligible for and Respond to Checkpoint Inhibitor Immunotherapy Drugs

Key Points

Question What is the estimated percentage of US patients with cancer who are eligible for and respond to checkpoint inhibitor drugs approved for oncology indications by the US Food and Drug Administration?

Findings This cross-sectional study found that the estimated percentage of US patients with cancer who are eligible for checkpoint inhibitor drugs increased from 1.54% in 2011 to 43.63% in 2018. The percentage of patients estimated to respond to checkpoint inhibitor drugs was 0.14% in 2011 and increased to 12.46% in 2018.

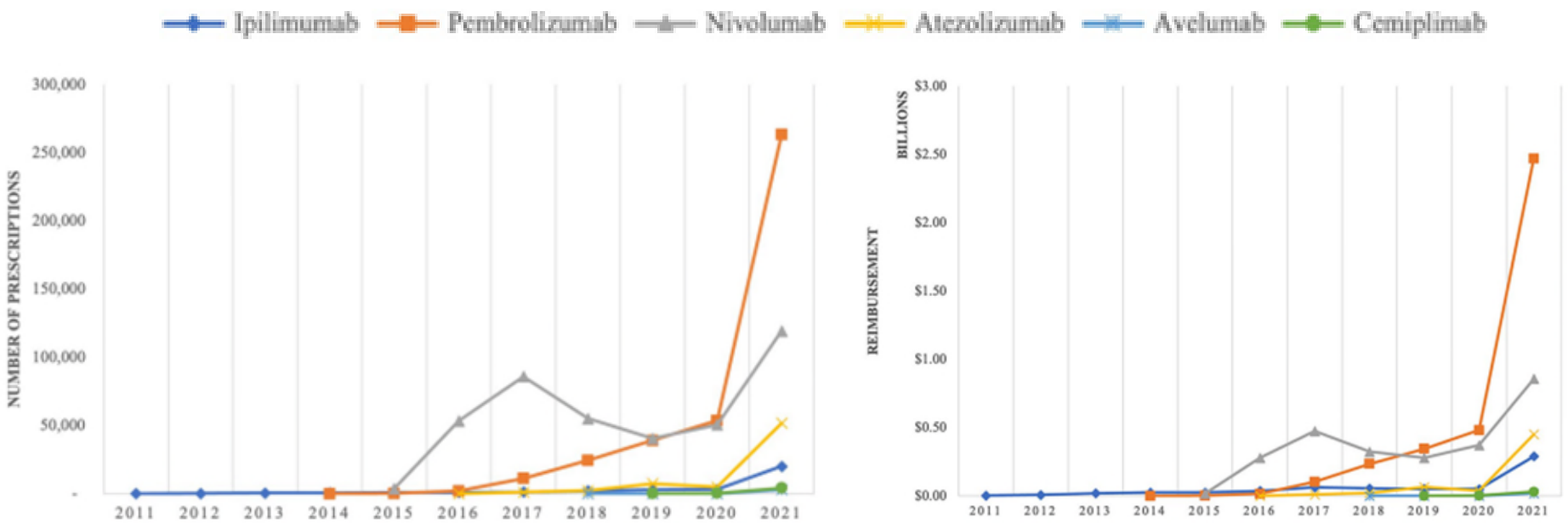
Meaning The estimated percentages of patients who are eligible for and who respond to checkpoint inhibitor drugs are higher than reported estimates for drugs approved for genome-driven oncology but remain modest.

Haslam, et al. JAMA Netw Open. 2019. doi:10.1001/jamanetworkopen.2019.2535

Immune checkpoint inhibitors are widely prescribed

Table 1 ICIs approved by the US FDA, 2011–21

Drug category	Generic name	Brand name	Approval date	Patent expiry	Manufacturer
CTLA-4 inhibitor	Ipilimumab	Yervoy®	3/25/2011	2023 [41]	Bristol Myers Squibb
PD-1 inhibitor	Pembrolizumab	Keytruda®	9/4/2014	2036 [41]	Merck
PD-1 inhibitor	Nivolumab	Opdivo®	12/22/2014	2027 [41]	Bristol Myers Squibb
PD-L1 inhibitor	Atezolizumab	Tecentriq®	5/18/2016	2028 [41]	Genentech
PD-L1 inhibitor	Avelumab	Bavencio®	3/23/2017	2033 [42]	Merck, Pfizer
PD-L1 inhibitor	Durvalumab	Imfinzi®	5/1/2017	2030 [43]	AstraZeneca
PD-1 inhibitor	Cemiplimab	Libtayo®	9/28/2018	2035 [44]	Regeneron, Sanofi



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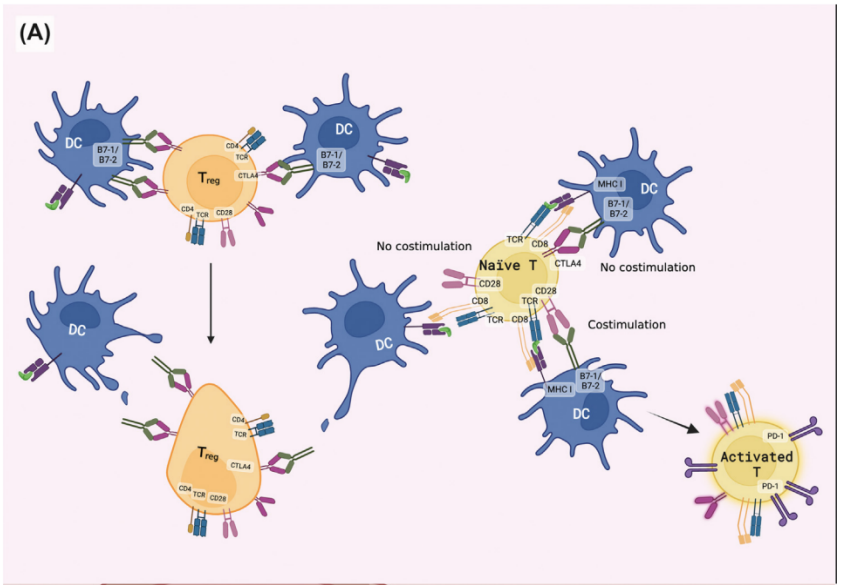
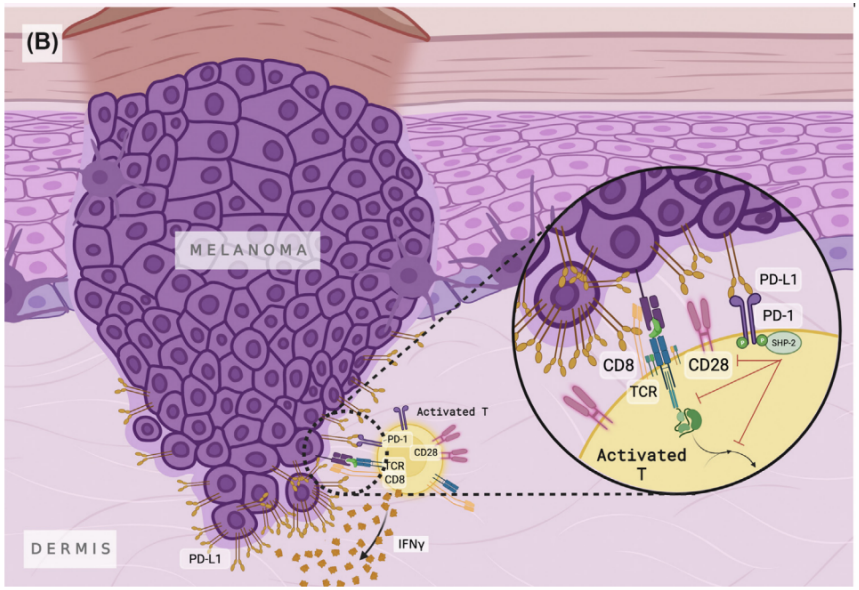
Shin, et al. Clin Drug Investig. 2023. PMID: 37005969

Mechanism of Action

CTLA-4



PD-1



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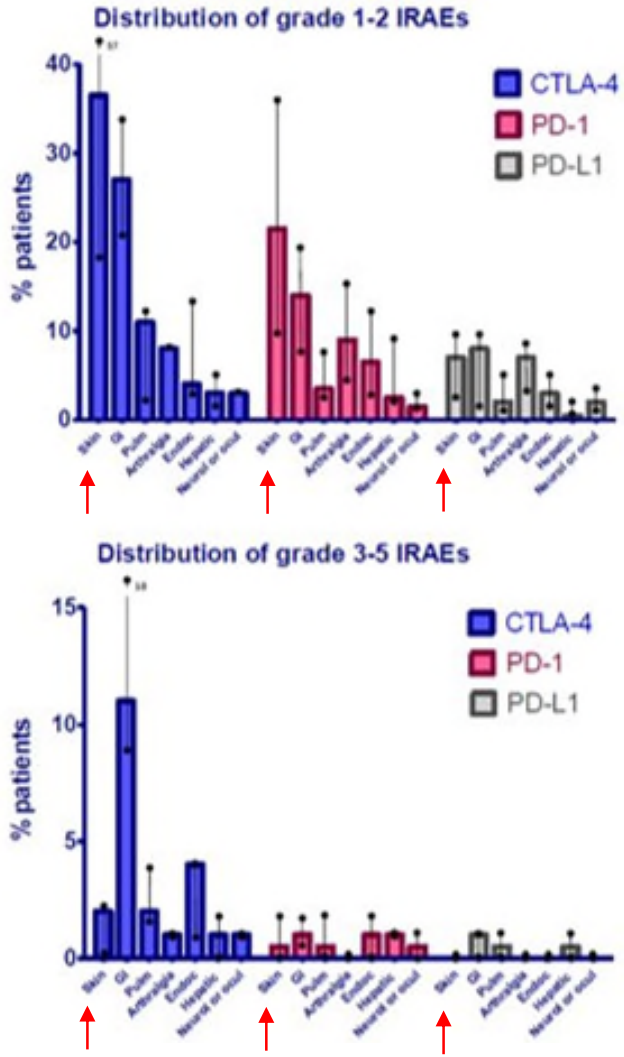
Wang, et al. “Immune mechanisms of toxicity from checkpoint inhibitors.” Trends in Cancer. 2023.

Immune Related Adverse Events (irAEs)



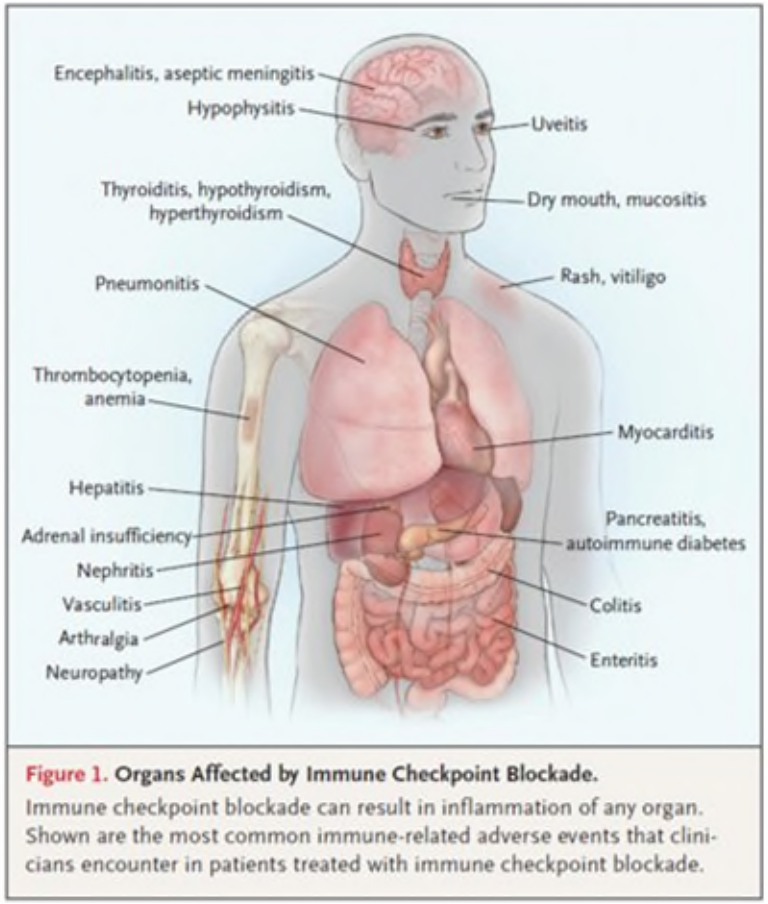


Figure 1. Organs Affected by Immune Checkpoint Blockade.
Immune checkpoint blockade can result in inflammation of any organ. Shown are the most common immune-related adverse events that clinicians encounter in patients treated with immune checkpoint blockade.

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Postow, et al. "Immune-Related Adverse…." NEJM. 2018. PMID: 29320654
Michot, et al. "Immune-related adverse events…." Eur J Cancer. 2016. PMID: 26765102

Cutaneous irAEs

Table I. Summary of patient demographics, associated immunotherapy class, rash characteristics, and other irAE

	Demographics		Immunotherapy class, n			Rash characteristics			
Rash type	No. patients, (M, F)	Age, y, mean	Anti–CTLA-4	Anti–PD-1 or PD-L1	Both	Latency, mon, mean (range)	Pruritus, n	Grade, median (range)	Other irAE,* n
Lichenoid	26 (17, 9)	64	2	23	1	6.2 (0.5-20)	25	1 (1-3)	9
Maculopapular	18 (5, 13)	61	2	11	5	1.0 (0.2-5.7)	16	2 (1-3)	7
Psoriasiform	17 (8, 9)	67	1	12	4	5.7 (0.2-28.8)	10	1 (1-3)	8
Eczematous	12 (6, 6)	66	0	9	3	5.8 (0.6-25)	12	1 (1-3)	5
Immunobullous	8 (4, 4)	68	0	8	0	4.5 (0.5-10)	8	3 (2-3)	2
Prurigo	7 (3, 4)	71	0	6	1	10.1 (1.8-16)	7	1 (1-3)	3
Grover-like	4 (4, 0)	71	0	4	0	4.2 (0.2-14.4)	4	1 (1-2)	1
Acneiform	4 (3, 1)	47	0	4	0	4.3 (0.2-11)	1	1 (1-2)	1
Granulomatous	3 (0, 3)	65	0	2	1	17.7 (7-36)	0	1	0
SJS-like	2 (1, 1)	62	0	0	2	1.4	2	4	2
PR-like	1 (1, 0)	75	0	1	0	0.2	1	2	0
PRP-like	1 (1, 0)	63	0	1	0	0.46	1	3	0
Total	103 (54, 49)	65	5	81	17	5.13 (0.1-36)	77	1 (1-4)	36†

- Cohort: 98 patients on ICI, 2016-2018, at Yale New Haven Hospital
- Findings:
  - Wide spectrum of inflammatory dermatoses
  - Immunobullous and exfoliative dermatoses were most common reason for discontinuation of immunotherapy

Coleman, et al. “Inflammatory eruptions associated….” JAAD. 2018. PMID: 30399387.

Cutaneous irAEs are associated with longer survival

- Cohort:
  - 3,731 ICI recipients at Mass General, Brigham & Dana-Farber Cancer Institute, all cancer types
- Findings:
  - 18.1% cirAE rate
  - CirAE development was associated with a **13%** decrease in mortality (HR = 0.87; 95% CI, 0.79-0.98), living on average **10.5 months** longer than those that do not develop cirAEs
  - Melanoma patients who developed vitiligo ircAEs had a **33% decreased risk of mortality** compared to melanoma patients who did not develop CirAE

Table 4: Association of CirAE Morphology with Overall Survival

Cutaneous Morphology[a]	Hazard Ratio	95% Confidence Interval	P-value[b]
Vitiligo	0.29	0.12, 0.71	0.007*
Acneiform Eruption	0.34	0.13, 0.87	0.025*
Lichenoid Eruption	0.51	0.36, 0.73	<0.001*
Psoriasiform Eruption	0.52	0.33, 0.82	0.005*
Rash NOS	0.68	0.57, 0.81	<0.001*
Isolated Pruritus Without Visible Manifestation of Rash	0.71	0.55, 0.91	0.007*
Eczematous Eruption	0.71	0.50, 1.01	0.056
Drug Hypersensitivity NOS	0.79	0.52, 1.21	0.3
Maculopapular Eruption	0.82	0.66, 1.03	0.084
Bullous Eruption	0.87	0.45, 1.68	0.7
Other CirAE Morphologies	0.98	0.64, 1.50	>0.9

[a]Each row corresponds to a separate multivariable time-varying Cox proportional hazards model for the association of cirAE morphology with overall survival by comparison to patients without cirAEs, adjusting for age at ICI initiation, gender, race, CCI, cancer type, ICI type, and year of ICI initiation.

[b]P-values that remain significant after Benjamini-Hochberg multiple comparison adjustment are marked with an asterisk.

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Zhang, et al. "Cutaneous immune-related adverse events…." JAAD. Jan 2023. PMID: 36736626.

Oncologic Society Management Recs

NCCN, SITC, ASCO, MASCC, ESMO

- Is it mild, moderate, or severe?
  - Mild: < 10% BSA
  - Moderate: 10-30% BSA
  - Severe: > 30% BSA
- Are there blisters present?
  - If so, the severity is upgraded (generally)
  - ASCO guidelines tease out BSA and whether blister is due to bullous pemphigoid or due to SJS/TEN
- Patient tolerability should also be a consideration

Chang, et al. "Immunotherapy for keratinocytic cancers…." JAAD. 2022.

Oncologic Society Management Recs

NCCN, SITC, ASCO, MASCC, ESMO

Mild

- Continue ICI
- Topicals
  - Steroids
  - Calcineurin-inhibitors
- Consider systemic steroids

Moderate

- Hold ICI
- Topicals
  - Steroids
  - Calcineurin-inhibitors
- Systemic steroids
- Dermatology consult

Severe

- Permanently discontinue ICI
- Topicals
  - Steroids
  - Calcineurin-inhibitors
- Systemic steroids
- Consider steroid sparing agent
- Dermatology consult

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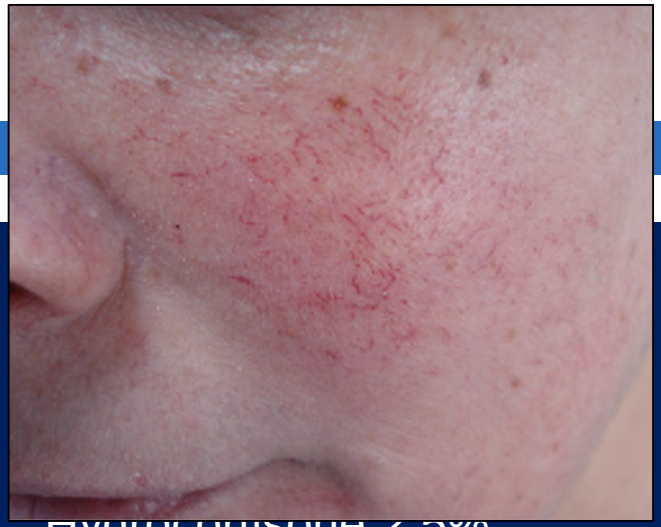
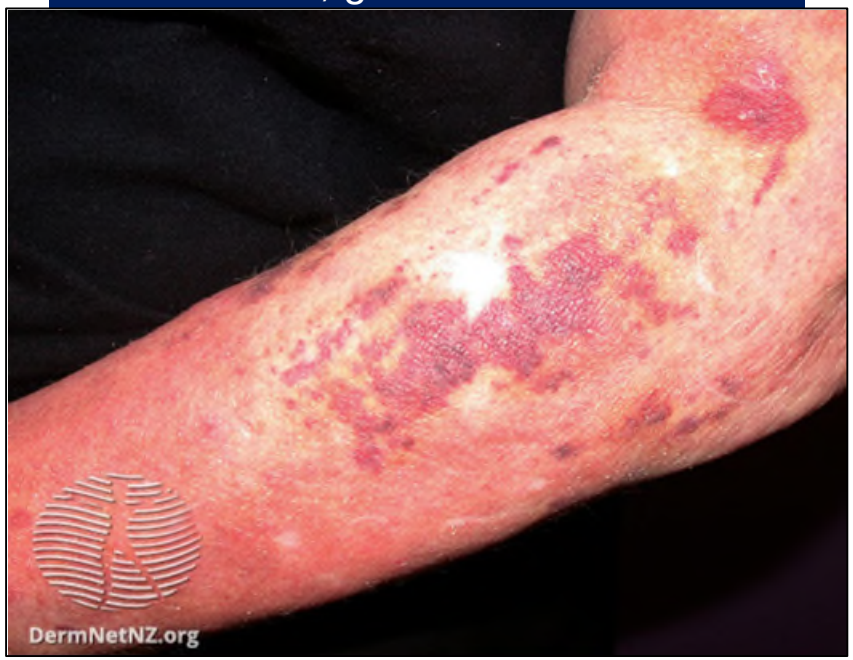
Chang, et al. "Immunotherapy for keratinocytic cancers…." JAAD. 2022.

Topical Therapies



- Emollients
- Topical steroids
  - Potency: mild to super-potent
  - Vehicle: ointment, cream, solution
  - Site specific: skin thickness, ease of use
  - Side effects: skin atrophy
- Topical calcineurin inhibitors
  - Safe alternative to topical steroids
  - Expensive

- Hydrocortisone 2.5%
  - Face, genitals

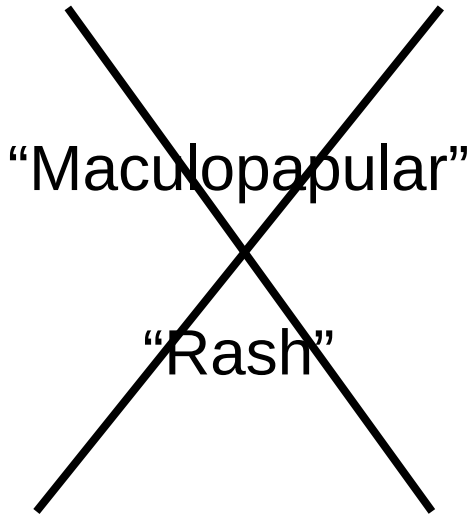


Goal of this talk

- This is a practical / clinical talk
- Cutaneous irAE management is based on consensus guidelines. These recommendations derive from clinical trial experience, expert opinion, and emerging **retrospective** data.
- There are no prospective comparative analyses.

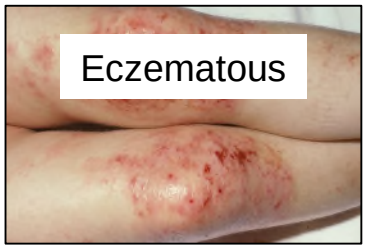
Goal of this talk

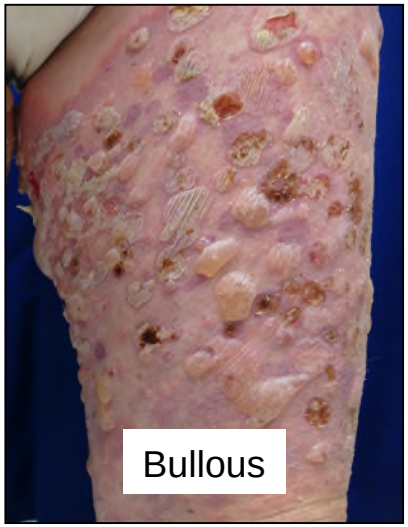
- To categorize the common ICI-induced rashes into phenotypes based on the **clinical** and **histologic** data

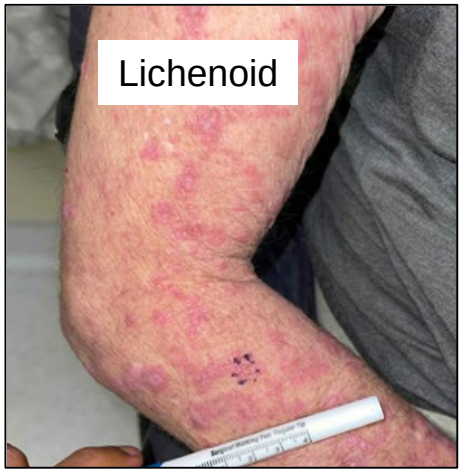


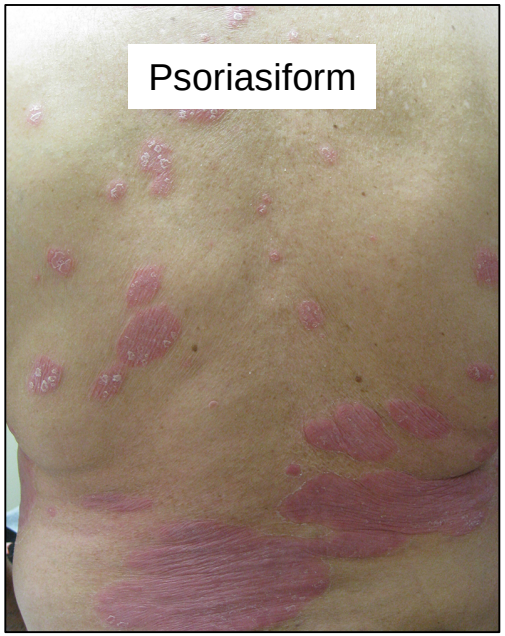
Pruritus without rash
Eczematous
Morbilliform
Lichenoid
Psoriasiform
Pigmentary
Bullous

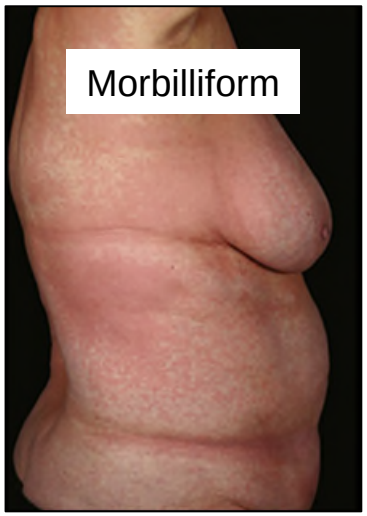
- Equip you with a phenotype-based management approach

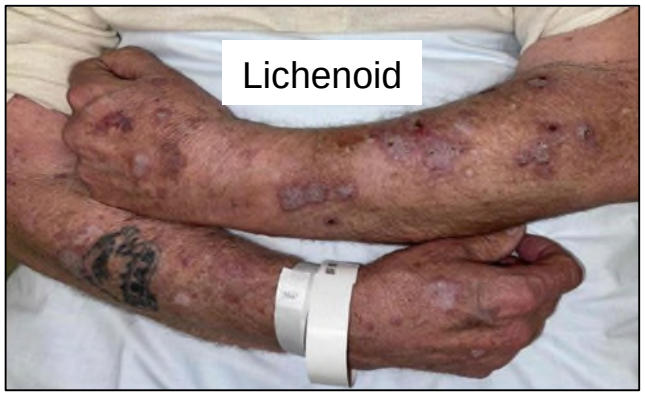

Eczematous

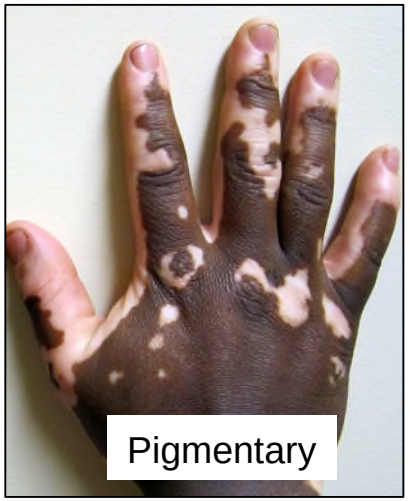

Bullous


Lichenoid


Psoriasiform


Morbilliform


Lichenoid


Pigmentary

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Severe CAE:
- 30% TBSA and/or
- Medically significant including limited self-care/ADLs, life-threatening, or requiring hospitalization

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Skin Biopsy to classify histology:
If bullous morphology or refractory pruritus, send DIF

↓

	Histologic type:	psoriasiform	bullous*,+	spongiotic	lichenoid
1st line	Steroids: topical	X	X	X	X
	systemic	X	X	X	X
2nd line and/or chronic usage	Retinoids: acitretin	X			X
	Steroid-sparing agents (controversial): methotrexate or	X			X
	cyclosporine			X	X
	Biologics: dupilumab		X	X	
	omalizumab (if serum IgE is high)			X	
	tocilizumab (if serum IL-6** is high)		(X)		
	rituximab		X		
	apremilast	X			
	risankizumab***	X			
	infliximab	X			X
	IVIG		X		

↓

Immunotherapy dose hold if no improvement on above

↓

Consider immunotherapy re-challenge if cutaneous IRAE resolves to mild-moderate severity

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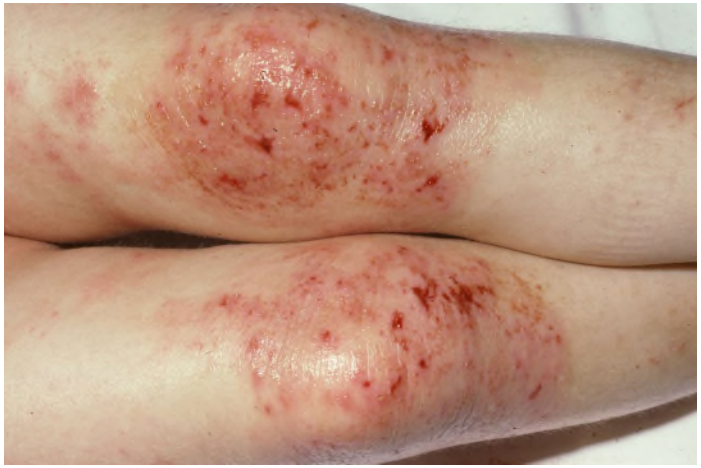
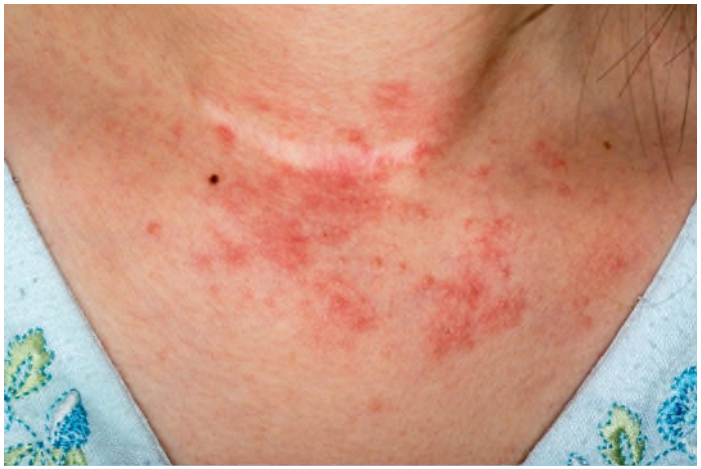
Chang, et al. "Immunotherapy for keratinocytic cancers…." JAAD. 2022.

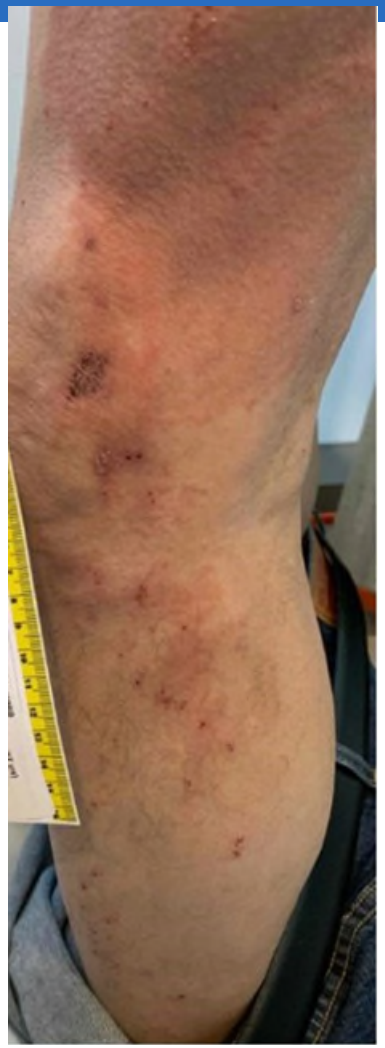
Eczematous

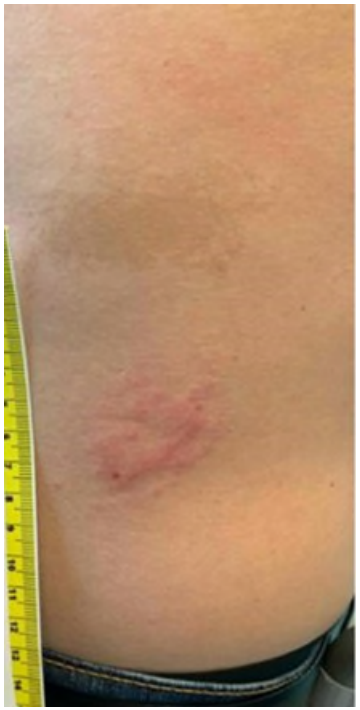


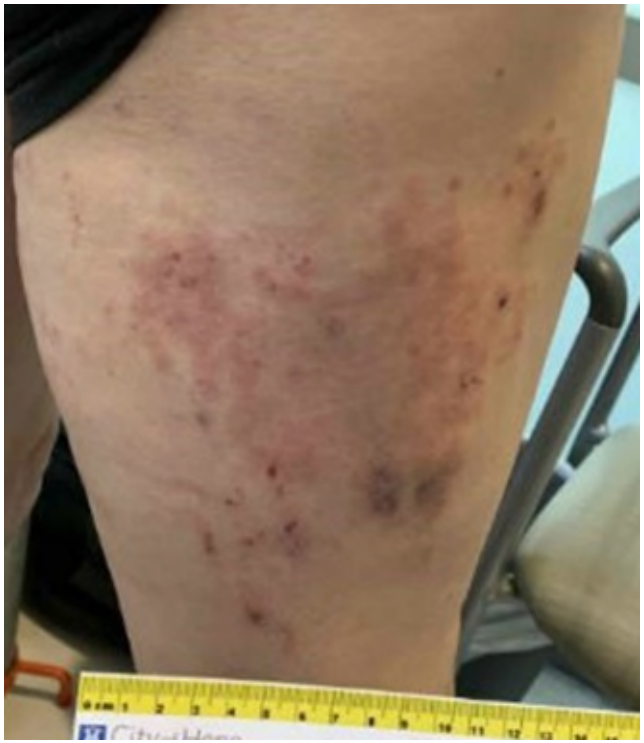


- Pruritic, excoriated papules
- Bx: Eosinophilic spongiosis
- Responds well to topical steroids, moisturizers, and phototherapy
- For refractory or severe cases, consider dupilumab

Eczematous







Final Diagnosis

A. SKIN, LEFT THIGH, PUNCH BIOPSY:

- Mild spongiotic dermatitis and dermal mixed inflammation with numerous eosinophils (see comment)

Electronically signed by Parekh, Vishwas P, MD on 4/28/2023 at 1512

Comment

The histomorphologic features of mild eczematous dermatitis and numerous dermal eosinophils are more suggestive of a hypersensitivity reaction to a medication or other allergens. In the current clinical context, **PD-1 inhibitor-associated rash** is favored. The eczematous component could be part of the rash pathophysiology or superimposed. Allergic contact dermatitis remains in the histologic differential diagnosis. Clinical correlation is recommended.

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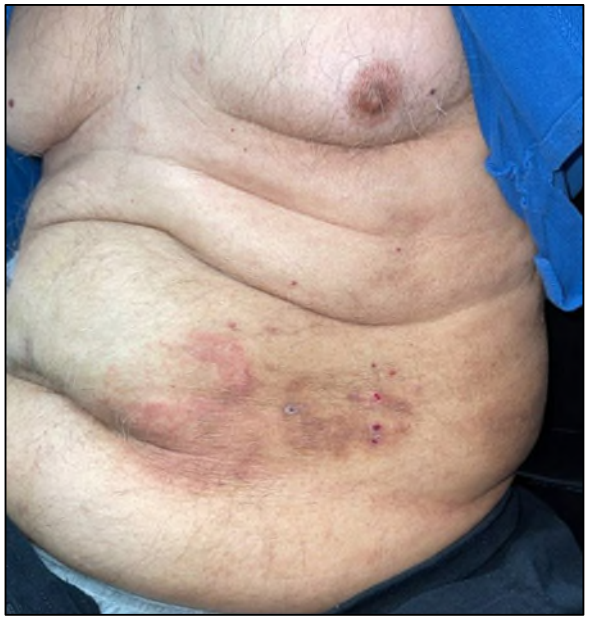
Eczematous

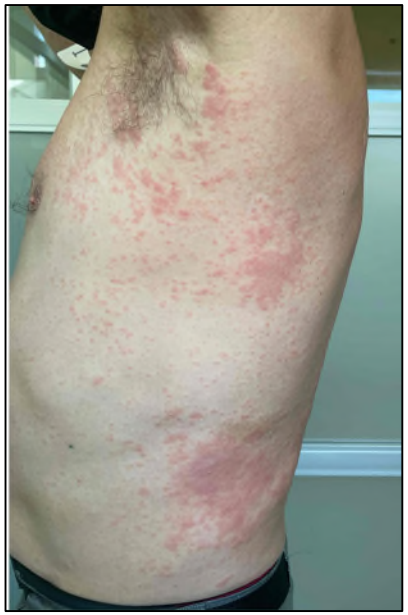
80yoM h/o stage IV oral-pharyngeal SCC, treated with nivolumab.

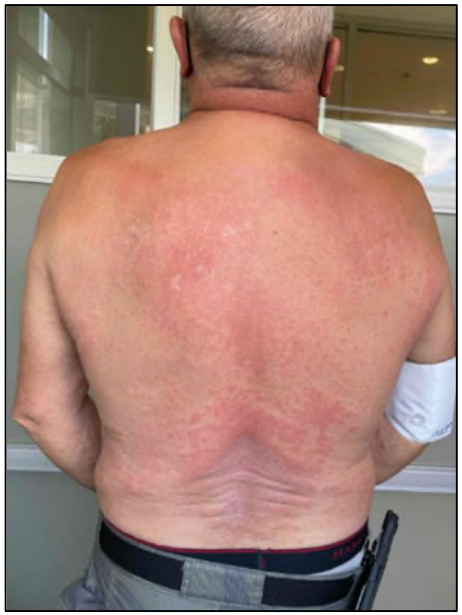


- ICI-induced eczematous dermatitis. +++Pruritus, not improved with topicals
- Also developed ICI-induced diabetes and wanted to avoid systemic steroids.
- ICI discontinued, but skin symptoms persisted
- Improved with methotrexate and ultimately switched to dupilumab

Morbilliform

67yoM h/o stage IVB follicular lymphoma, treated with pembrolizumab on clinical trial. Rash after 2 cycles.





Final Diagnosis

A. SKIN, RIGHT ARM, PUNCH BIOPSY:

•Mixed pattern dermatitis with dermal eosinophils (see comment)

Electronically signed by Parekh, Vishwas P, MD on 7/30/2023 at 1007

Comment

The histomorphologic features of mild spongiotic and interface changes ~~and dermal perivascular~~ mixed inflammation with numerous eosinophils is most suggestive of a **hypersensitivity reaction to a medication** or other allergens. Clinical correlation is recommended.

ICI discontinued due to widespread BSA, intense pruritus

Responded to prednisone, but re-flared after 2 attempts at a steroid taper

Given eosinophils on biopsy, dupilumab was initiated (off-label) and patient has been able to taper off prednisone without flare of rash

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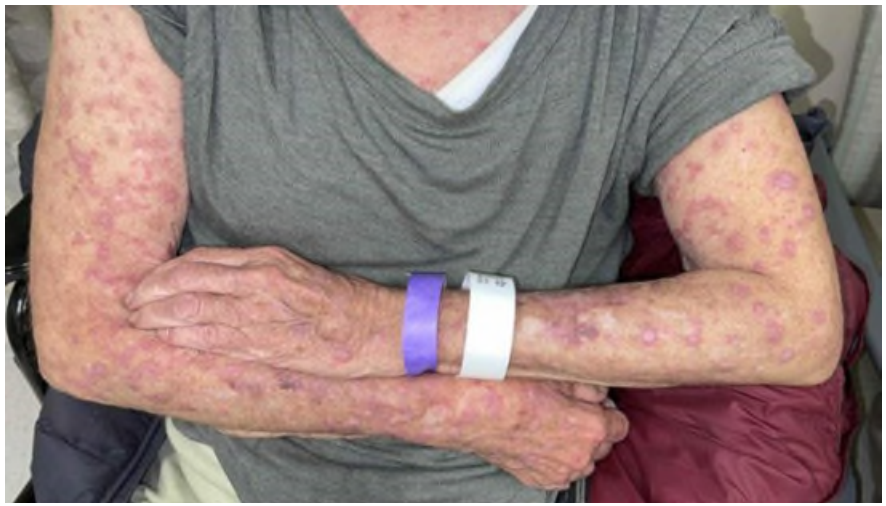
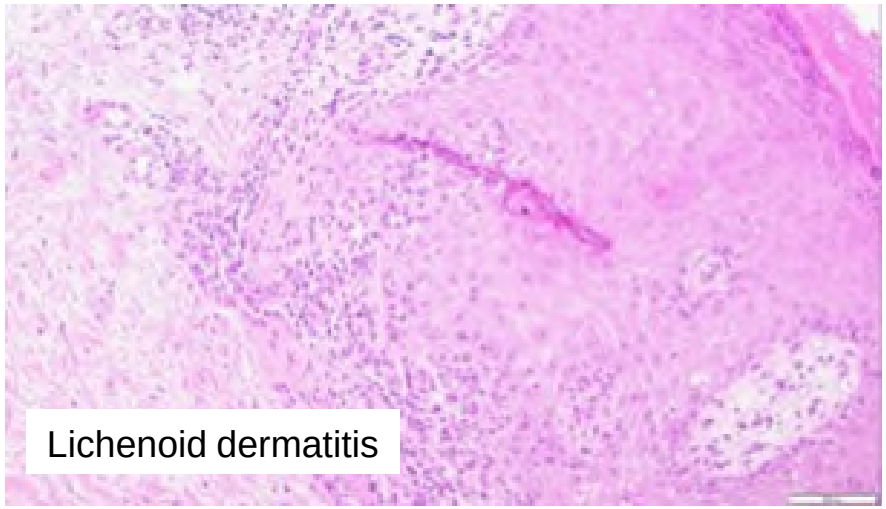
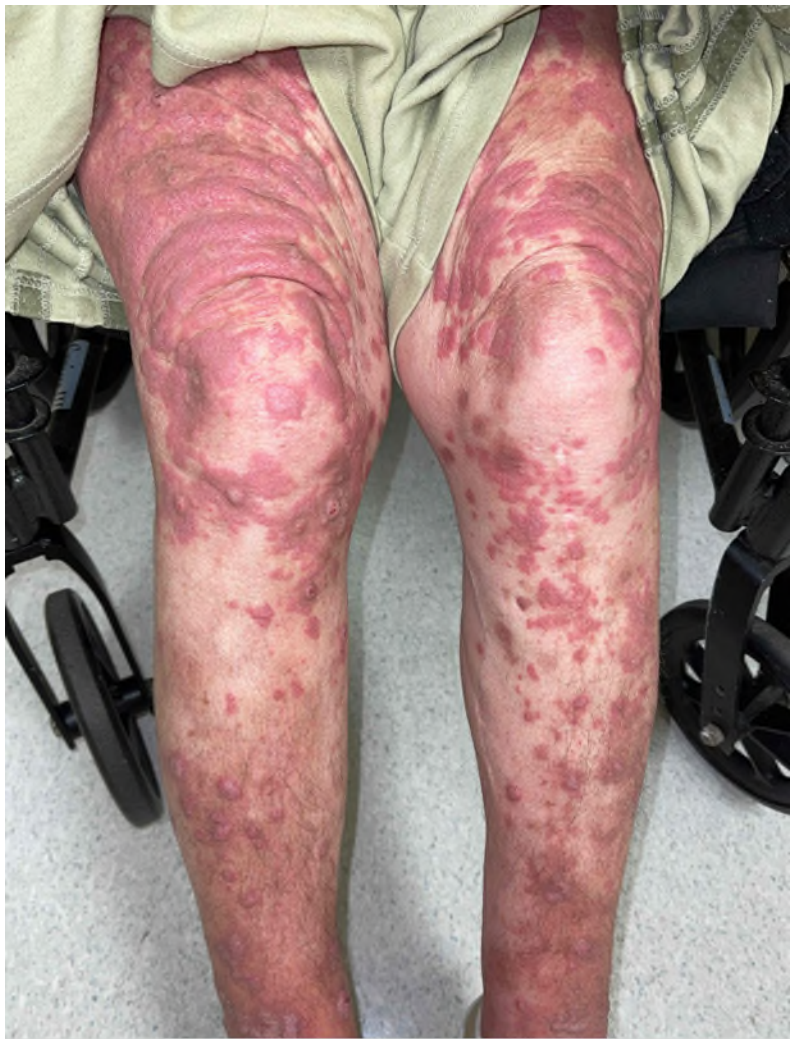
Lichenoid

66yoF h/o stage IV Lung SCC p/w widespread pruritic rash after 4 cycles of pembrolizumab.





Lichenoid dermatitis



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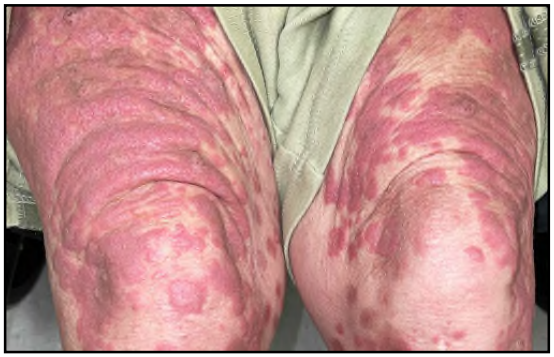

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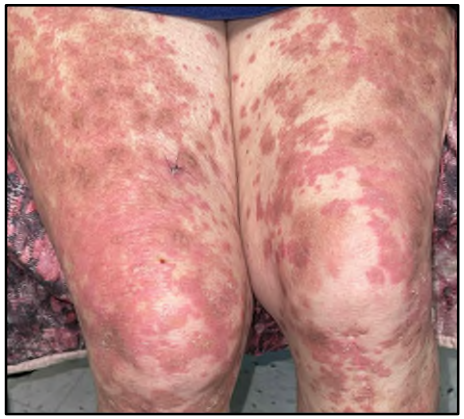

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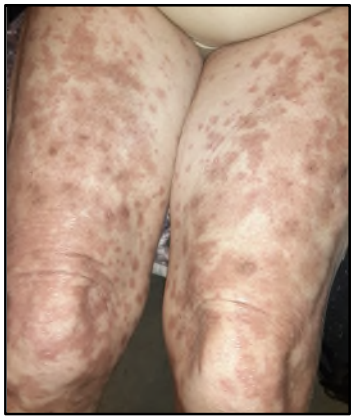

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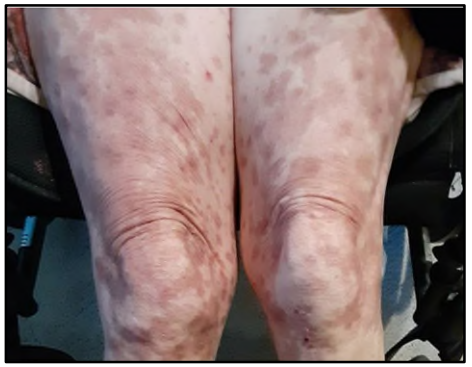

8.8.23

- Pembrolizumab discontinued
- Rash not improved after 1mg/kg prednisone x 6 weeks

- Started **Acitretin 10mg/d** & Triamcinolone 0.1% ointment x 2 weeks

PET-CT 9.1.23

IMPRESSION:

1. There is no focal area of hypermetabolic activity suspicious for residual or metastatic hypermetabolic neoplastic pathology. Findings of the current study are most consistent with stable complete response to treatment administered for the lung and breast carcinomas.

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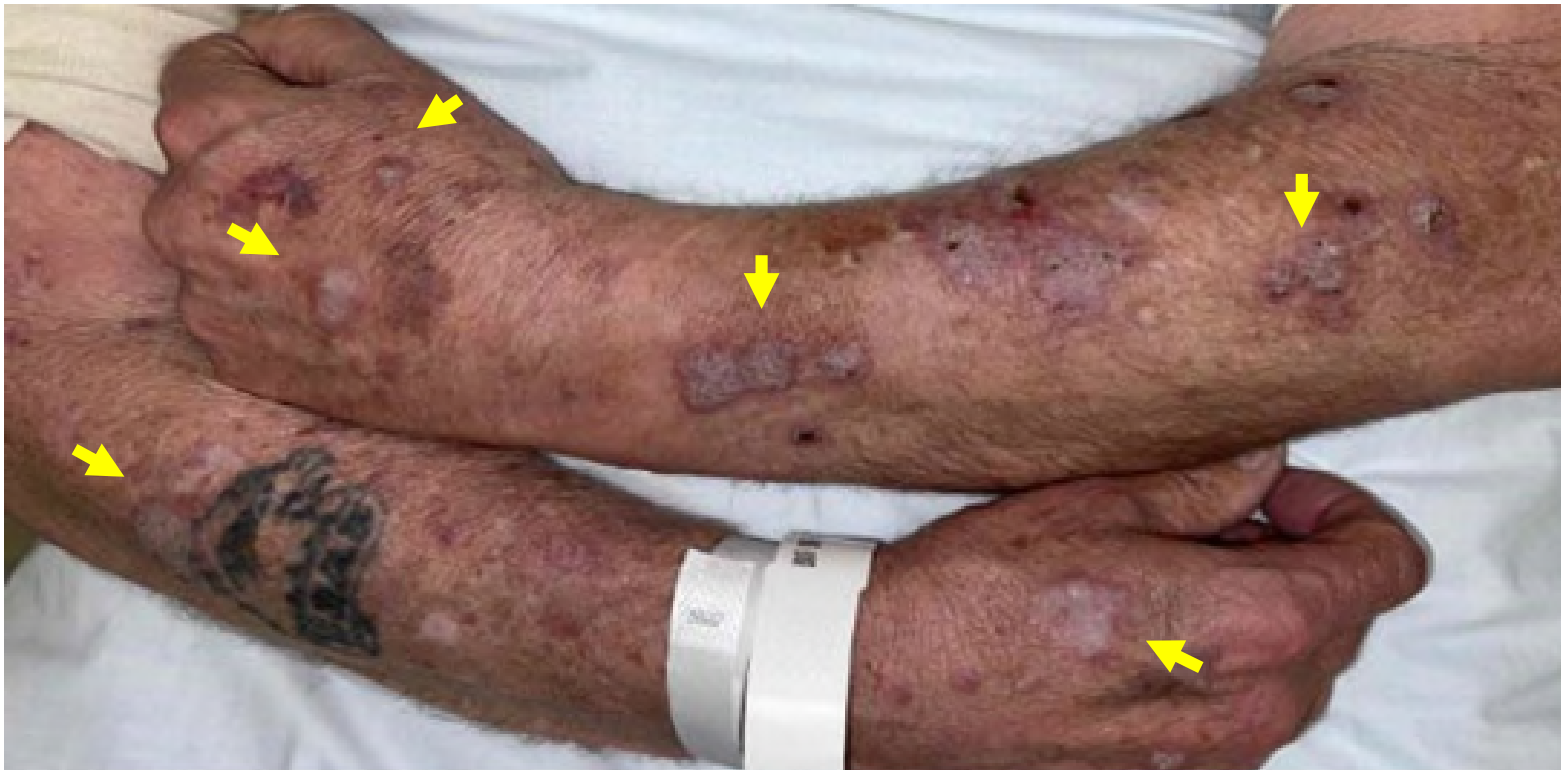
Eruptive squamous atypia

73yoM h/o stage IV merkel cell carcinoma on pembrolizumab, develops new lesions on extremities.



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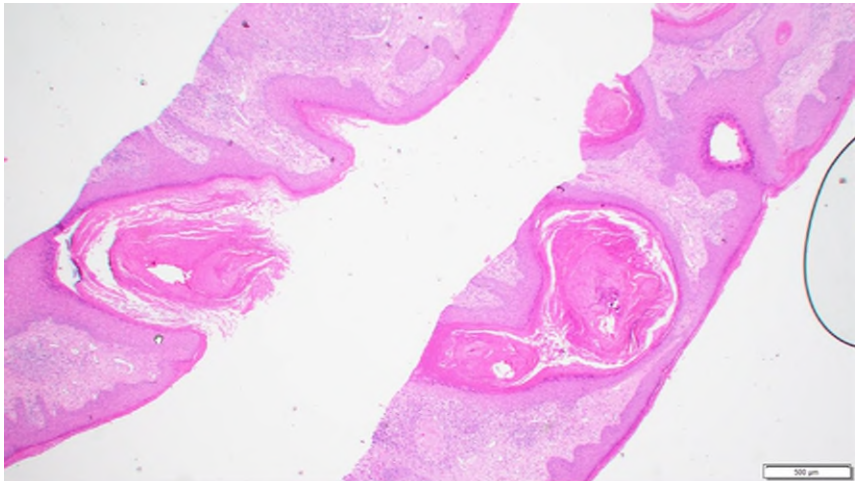
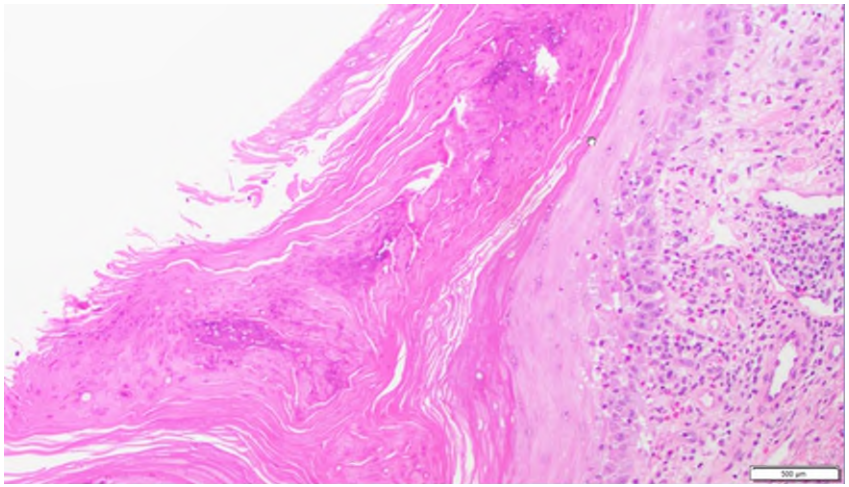
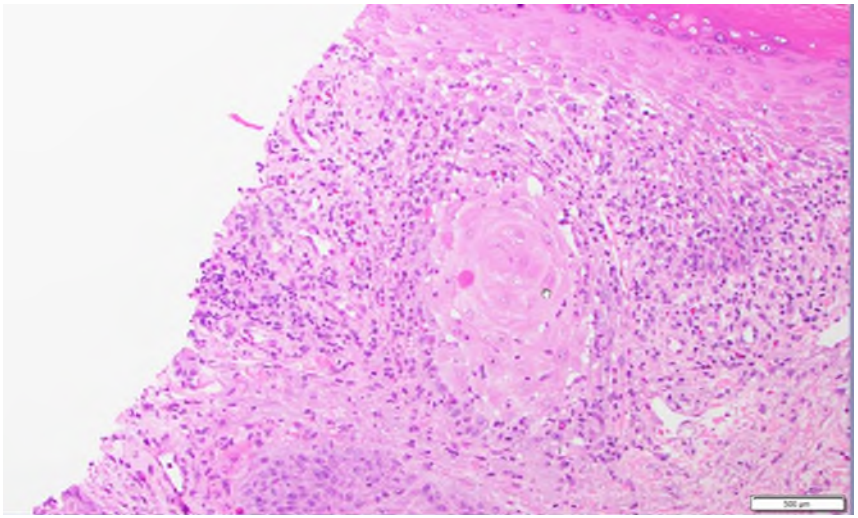






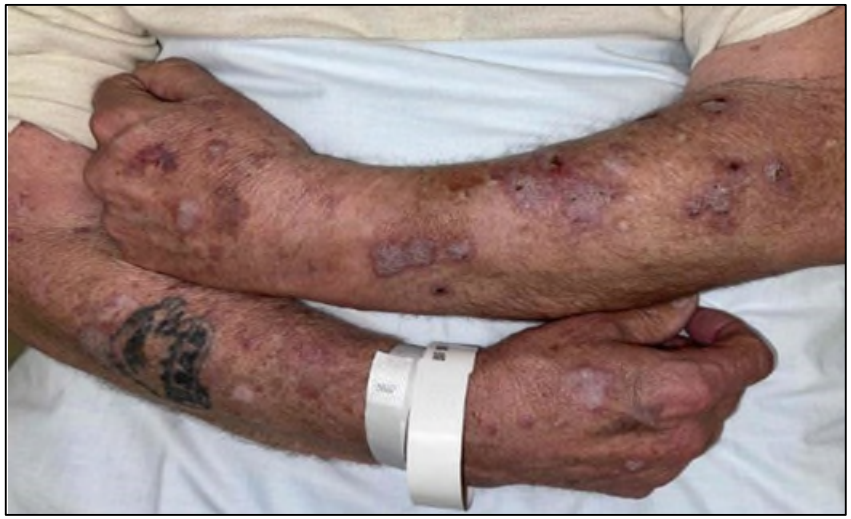
Component
Final Diagnosis
A. SKIN, RIGHT FOREARM, SHAVE BIOPSY: • Squamous cell carcinoma, well-differentiated, keratoacanthoma type • Present at deep tissue edge
Electronically signed by Vishwas P Parekh, MD on 7/18/2022 at 1018
Microscopic Description
The sections show a folliculocystic well-differentiated keratinocytic proliferation composed of atypical enlarged squamous cells glassy eosinophilic cytoplasm and filled with mildly parakeratotic keratin plug. Peripheral elastic fiber trapping is noted. There is mild chronic inflammatory infiltrate. The tumor is present at the dee tissue edge.

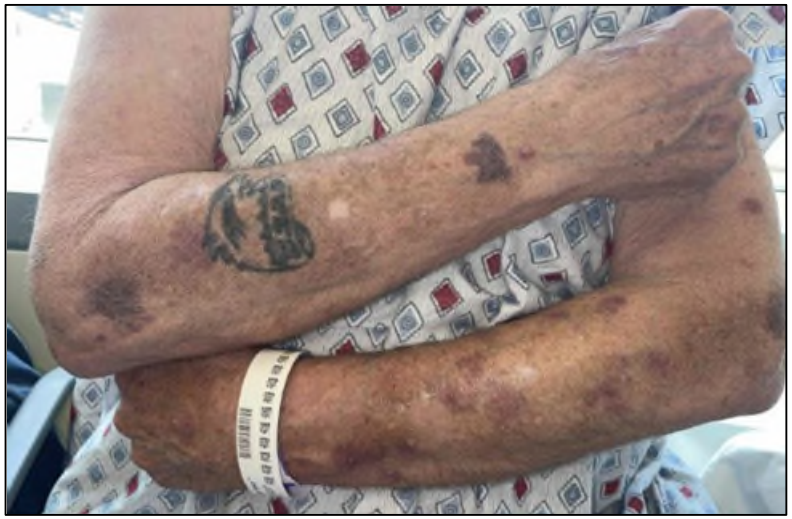
Eruptive squamous atypia

- Sudden onset of multiple firm, keratotic papules
- Histologically, may mimic squamous cell carcinoma
- Diagnosis is made by recognition of the synchronous presentation of multiple lesions on the legs > arms. These are commonly misdiagnosed as squamous cell carcinoma due to histology showing a hyperplastic epidermis and often leads to unnecessary excision
- Often improves with high-potency topical steroids (like clobetasol) under occlusion
- Consider acitretin

Marsh, et al. “Formation of eruptive cutaneous squamous cell carcinoma…. JAAD Case Rep. 2020. PMID: 32382626

Eruptive squamous atypia

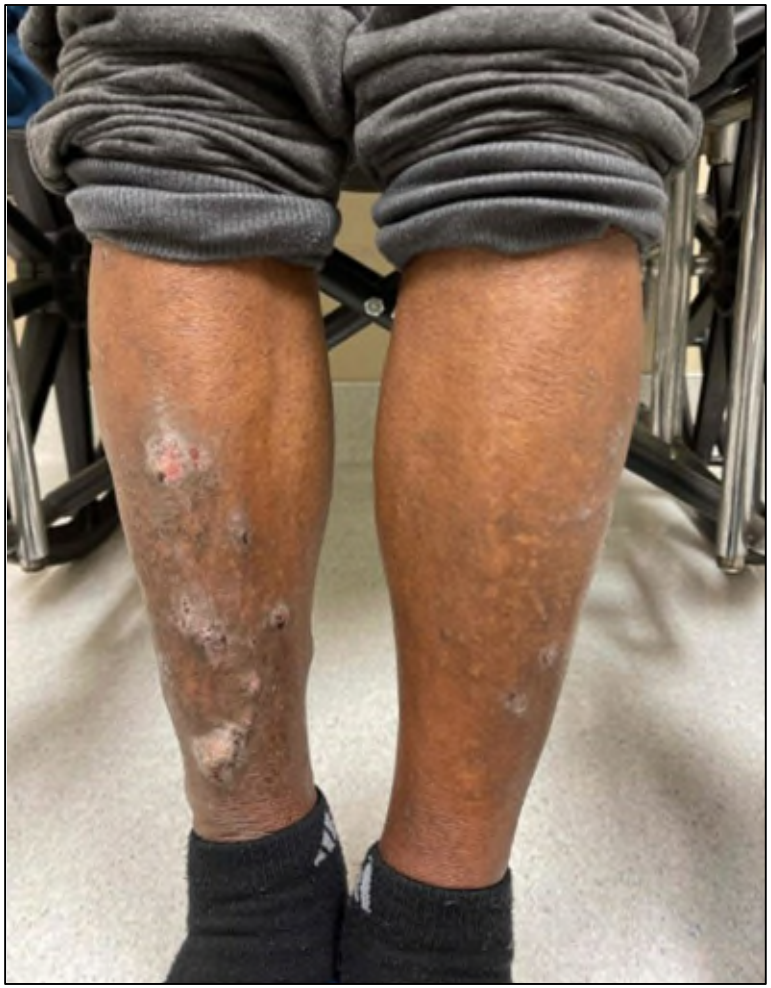


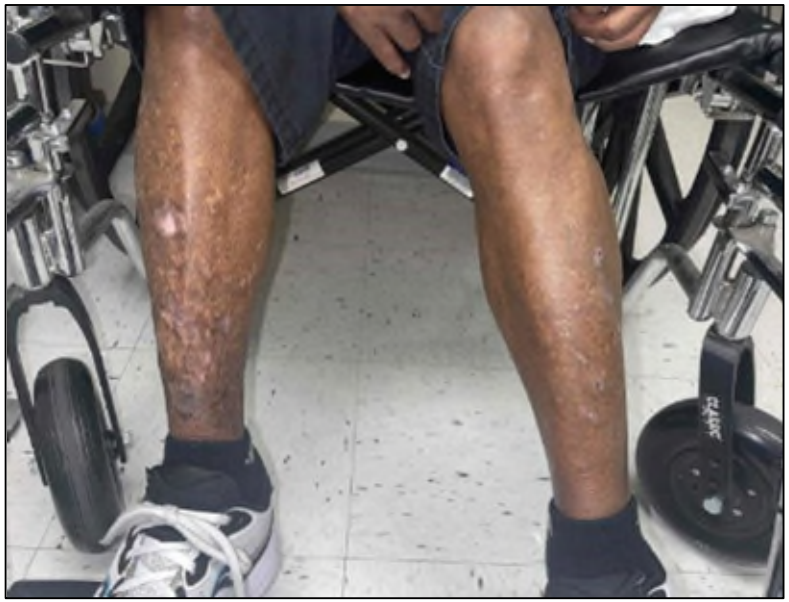


6 weeks of topical steroids & oral acitretin

No excisions

Eruptive squamous atypia



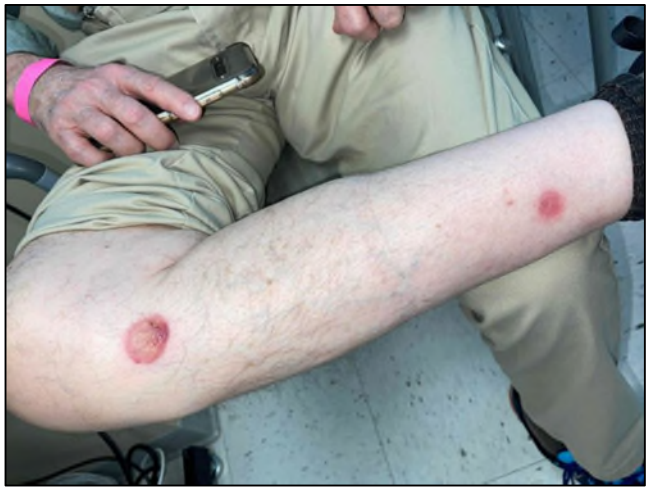


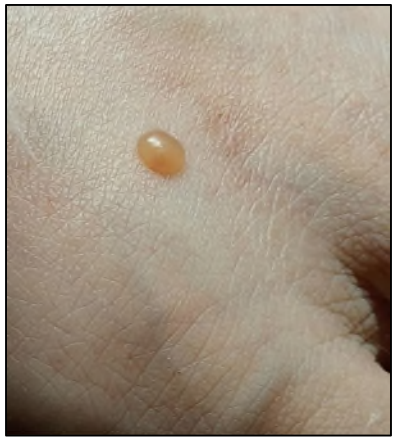
Bullous

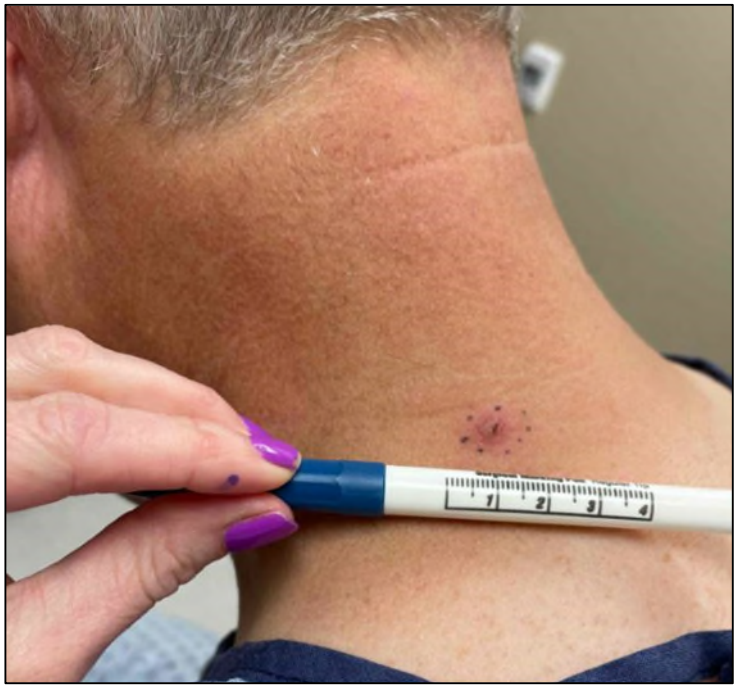
- Important to recognize, as this type of cirAE is the most likely to lead to discontinuation of ICI
- Categorize in disease severity – mild or severe involvement?
- Causes of the blister:
  - **Eosinophilic inflammation** that leads to a split between the dermis and the epidermis, but the cells are viable → BULLOUS PEMPHIGOID
  - **Cytotoxic inflammation** that leads to necrotic keratinocytes → SJS / TEN (usually also has mucosal involvement)

Mild bullous pemphigoid

53yoM h/o stage IV renal cell carcinoma on nivolumab for ~24mo







Final Diagnosis

A. SKIN, POSTERIOR NECK, PUNCH BIOPSY

- Bullous dermatosis with eosinophils, see comment

Electronically signed by Querfeld, Christiane S, MD PhD on 8/29/2023 at 1719

Comment

The patient's history of metastatic renal cell carcinoma, blistering rash for several months while on treatment regimen with nivolumab is noted. The morphologic findings of current biopsy are compatible with a bullous dermatosis such as bullous pemphigoid or a bullous pemphigoid-like drug eruption, the latter is favored in the setting of patients' history and treatment regimen with nivolumab. Bullous skin eruptions with immune checkpoint inhibitors targeting PD-1 and PD-L1 have been reported, blisters are mainly subepidermal (bullous pemphigoid [BP] -like) in nature (Naidoo J et al. Cancer Immunol res, 2016). Correlation with direct immunofluorescence and indirect immunofluorescence testing and clinical findings is recommended. DPAs stain was negative for fungal organisms.

Treated with topicals

Stayed on ICI, but ultimately discontinued given stable scans and patient had received 2 years of treatment

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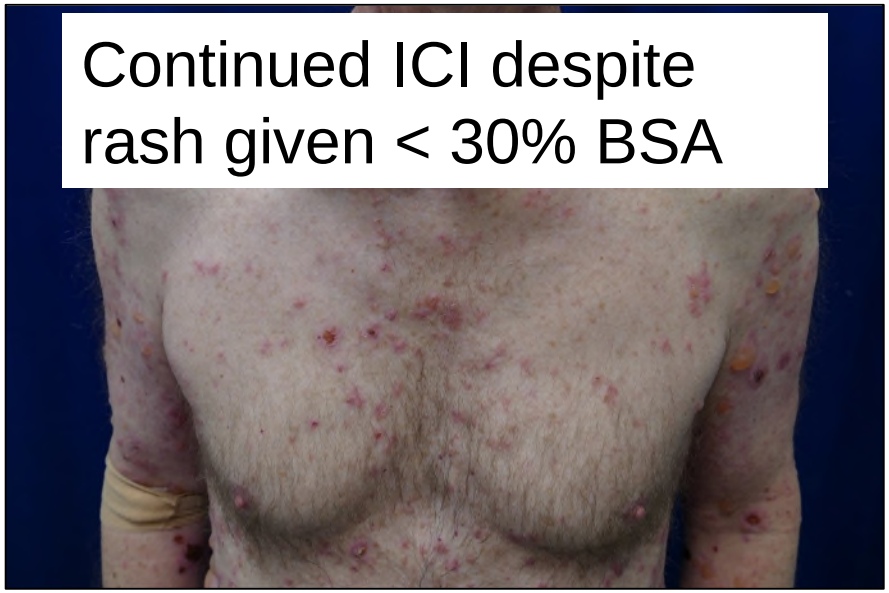
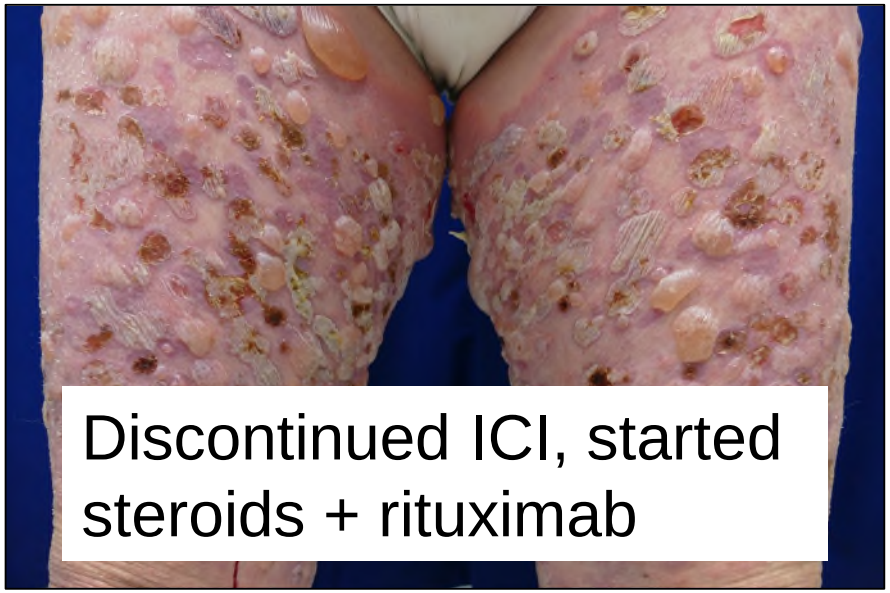
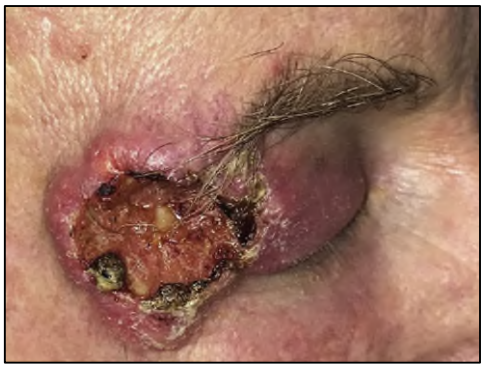
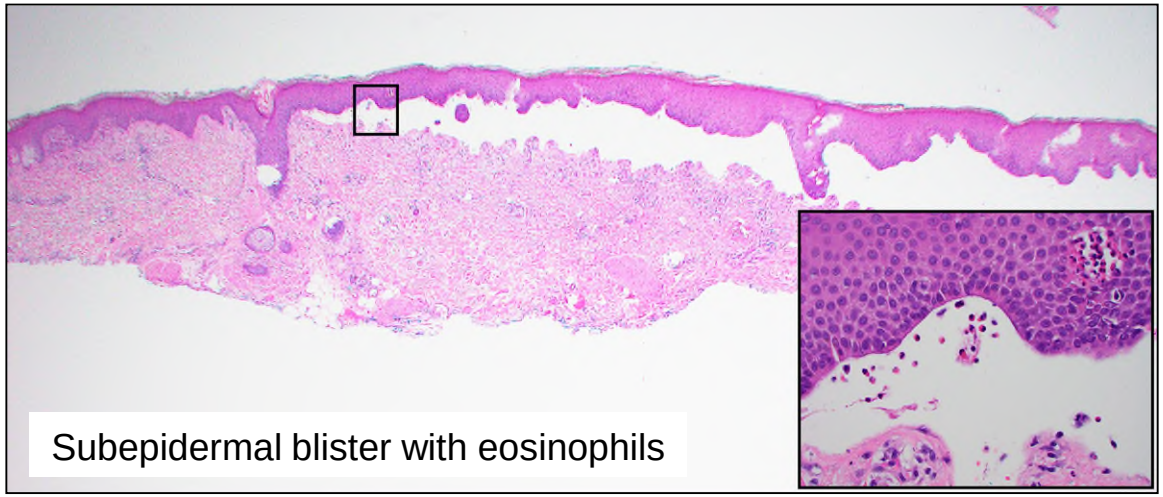
Severe bullous pemphigoid

68yoM h/o locally advanced skin SCC on cemiplimab for ~3 cycles









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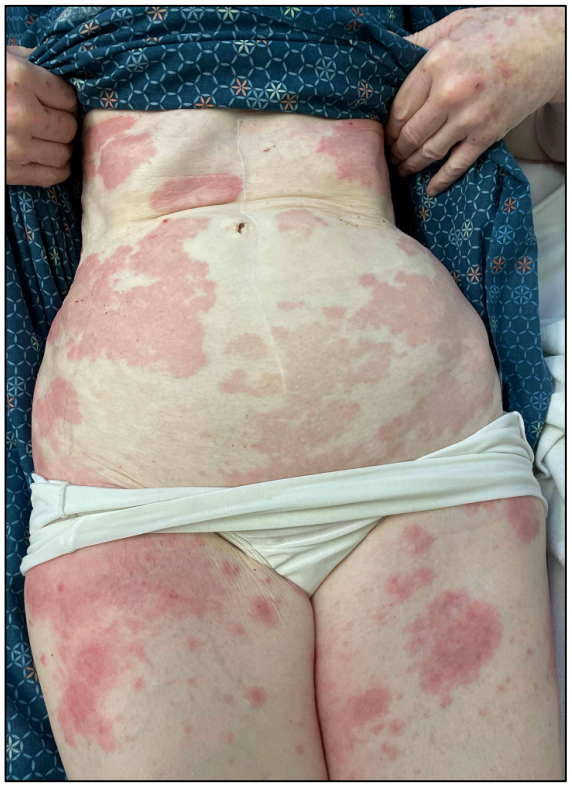
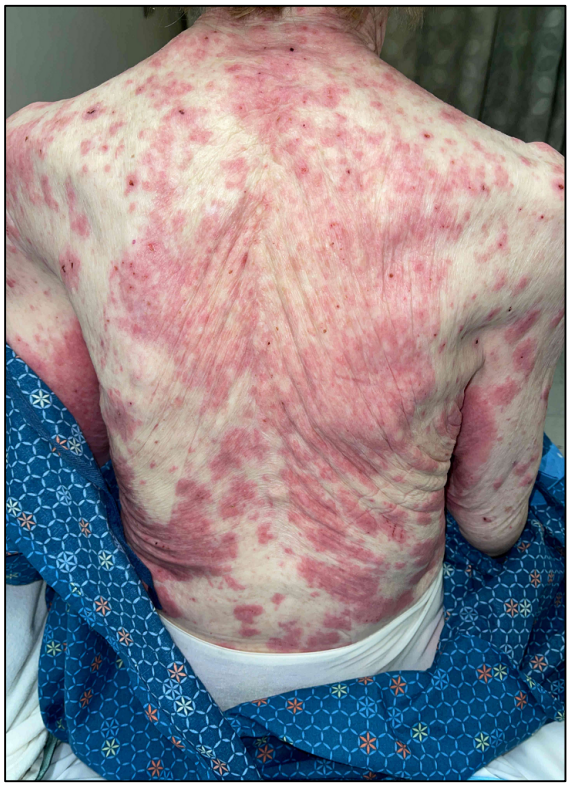
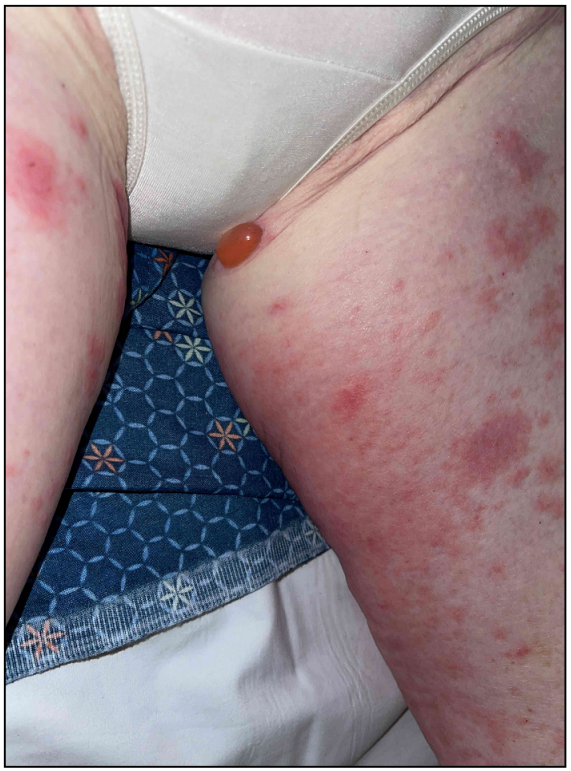
Severe bullous pemphigoid

84yoF stage IV RCC on nivolumab for ~1 year, presented with pruritic rash and blisters







- ICI discontinued
- Prolonged prednisone course due to flaring of rash when tapered below 20mg per day.
- Dupilumab initiated

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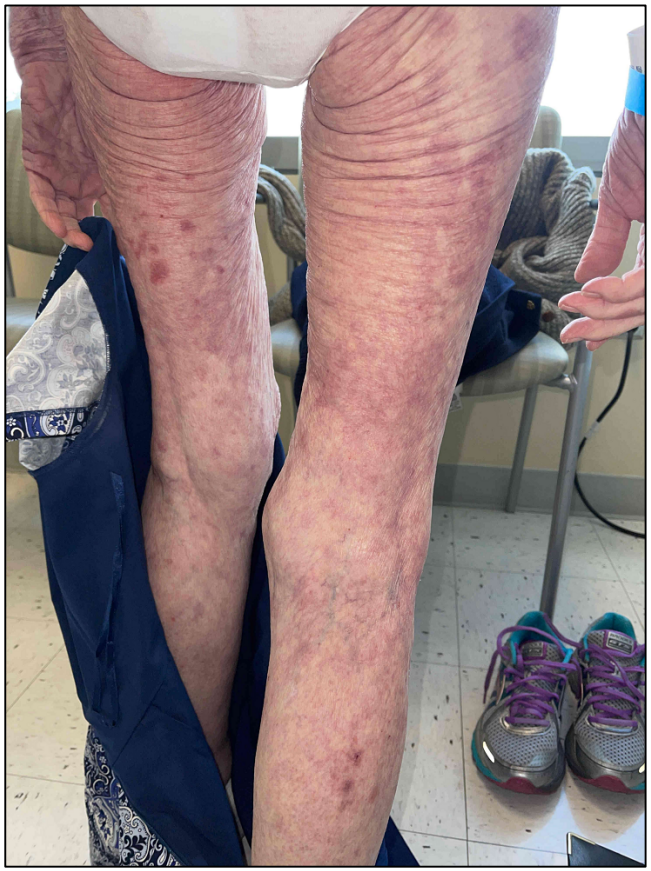
Steroids successfully tapered off, remains on dupilumab



- Being monitored off therapy with no evidence of disease progression on imaging

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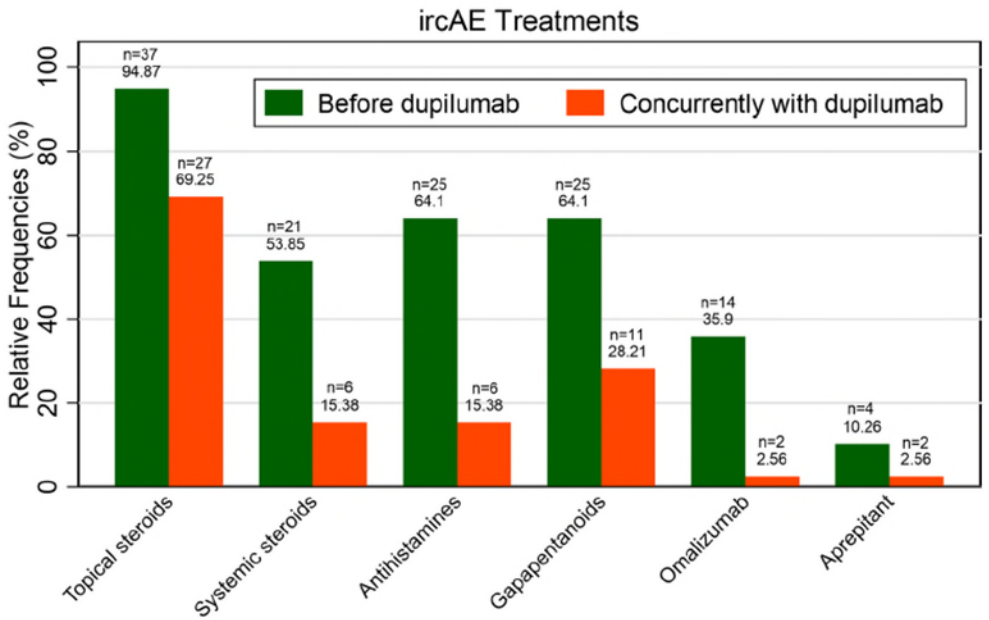
Dupilumab for ircAEs (off-label)

- IgG4 monoclonal antibody that binds to IL4 & IL13, targeting the Th2 axis.
- FDA approved for atopic dermatitis, asthma, eosinophilic esophagitis

- Retrospective review of 39 patients with ICI-associated **steroid refractory/dependent** ircAEs treated with dupilumab.
  - All tumor types, all ICIs
  - 41% eczematous, 41% morbilliform, 18% other (lichenoid, bullous, etc)

90% of patients improved, especially eczematous, morbilliform, and pruritic subtypes



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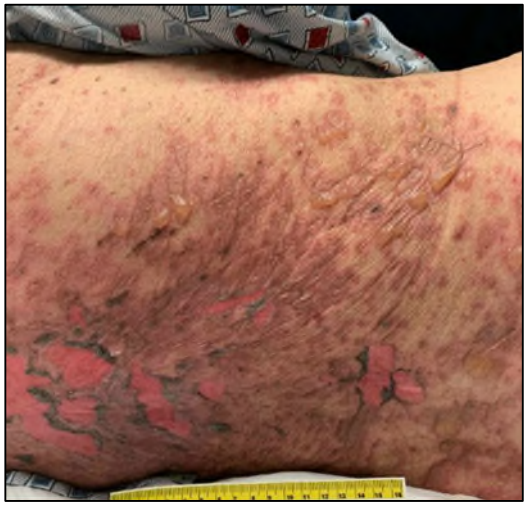
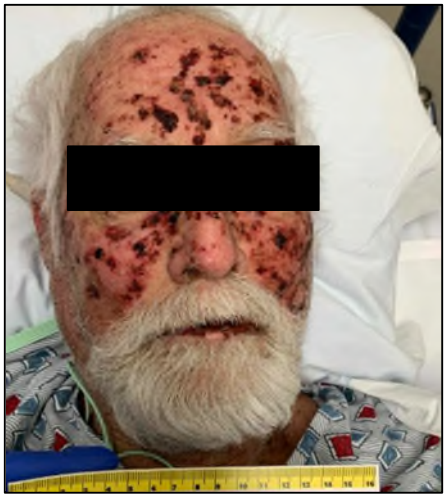
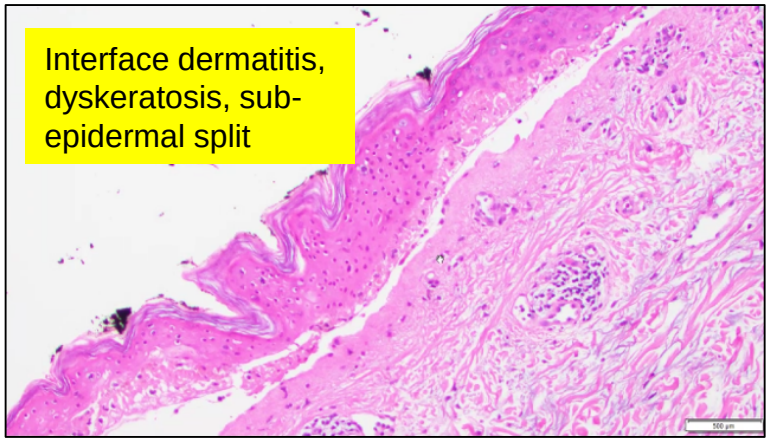
Kuo AM-S, Gu S, Stoll J, et al. Management of immune related cutaneous adverse events with dupilumab. Journal for Immunotherapy of Cancer 2023;11:e007324. doi:10.1136/ jitc-2023-007324

Cytotoxic blistering (SJS/TEN)

81yoM stage IV lung adenocarcinoma, received 1 dose of pembrolizumab







- ICI discontinued
- Prednisone 1mg/kg started, tapered over 3 months

Final Diagnosis

A. SKIN, ABDOMEN, PUNCH BIOPSY:

•Interface dermatitis with subepidermal clefting and necrotic epidermis (see comment)

Electronically signed by Parekh, Vishwas P, MD on 5/2/2023 at 0928

Comment

In the current clinical context, the histomorphologic features seen in these biopsy specimen are most consistent with **Stevens-Johnson syndrome / toxic epidermal necrolysis**. Histologic features of pemphigus vulgaris or bullous pemphigoid are not seen.

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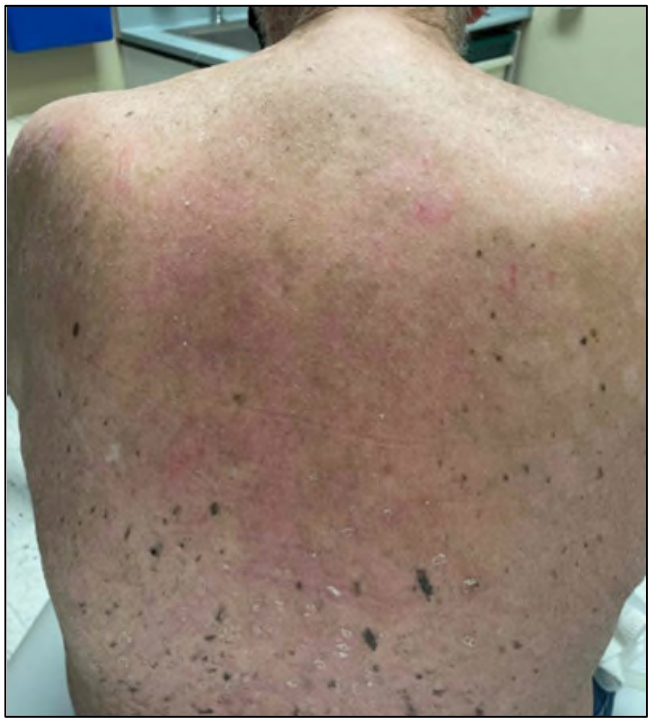
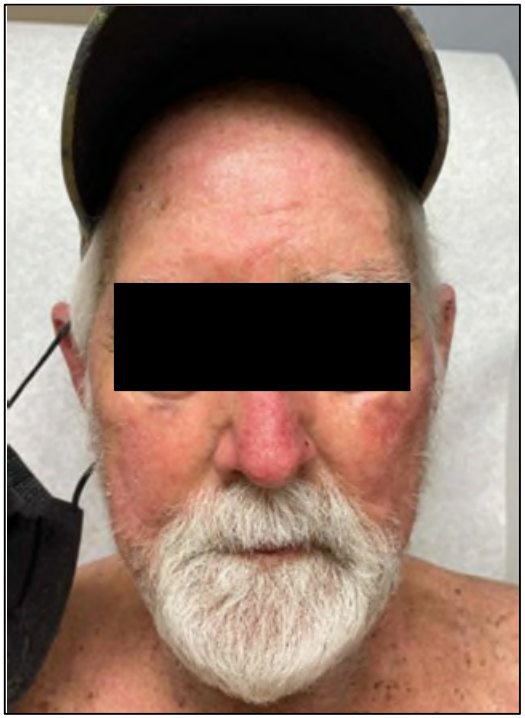
Cytotoxic blistering (SJS/TEN)

81yoM stage IV lung adenocarcinoma, received 1 dose of pembrolizumab





- Partial response on PET, duration of response ~4 months, but eventually developed oligo-progressive disease

SJS/TEN immune-related dermatologic reaction secondary to immune checkpoint inhibitor pembrolizumab in skin of color

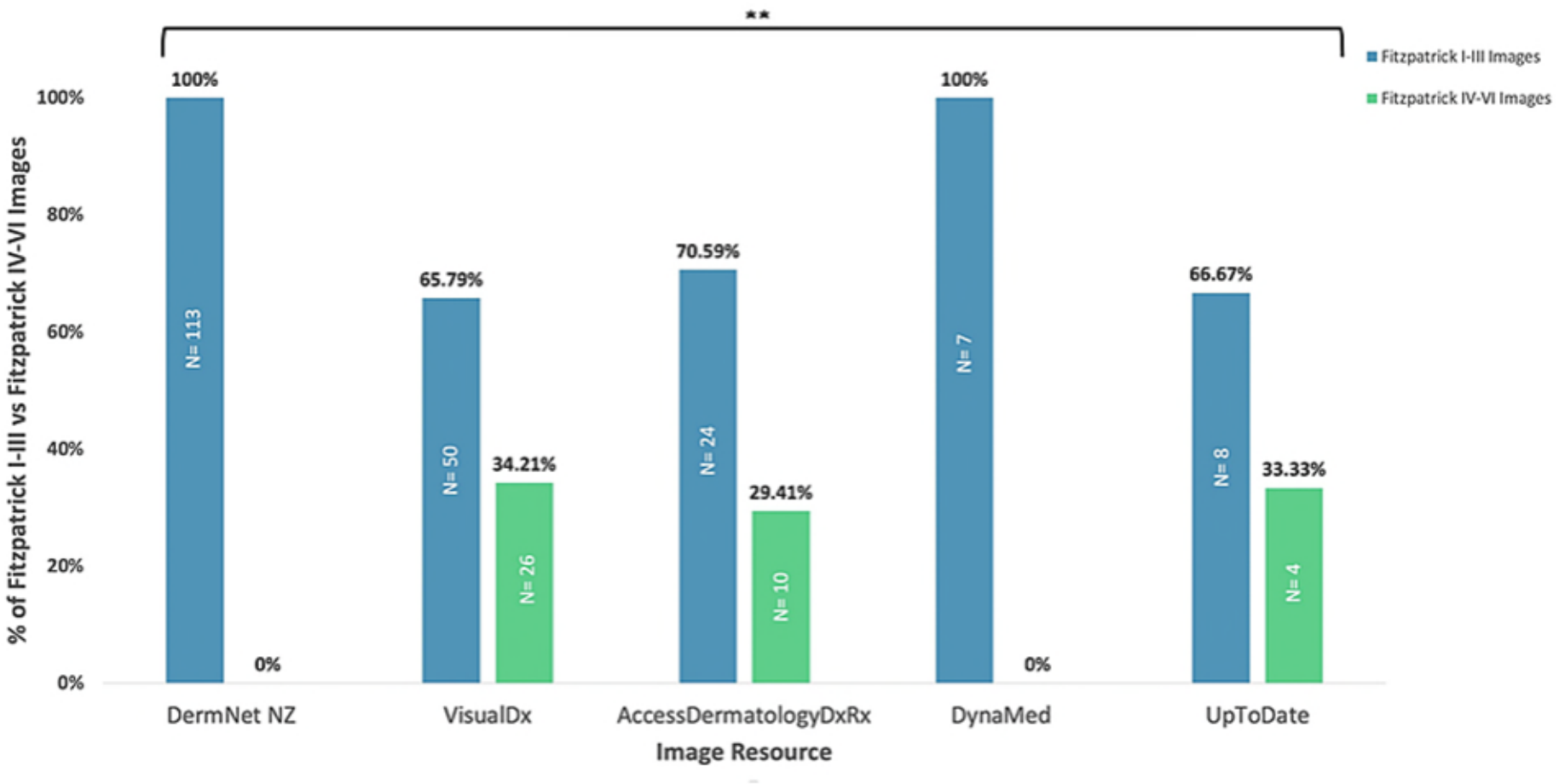


Figure 2: Total percentage of Fitzpatrick I-III vs. Fitzpatrick IV-VI images of SJS in medical education resources

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Pierre, et al. "SJS/TEN immune-related…." Gynecologic Oncology Reports. 2023. PMID: 37868017.
Diep, et al. "SJS in a patient of color…." Cureus. 2022. PMID: 35340465.

Summary: cutaneous immune related adverse events

- Immune checkpoint inhibitors (ICI) are increasingly being used in management of cancer, in advanced setting and in earlier lines of treatment
- Immune related adverse events (cirAEs) arise in majority of patients receiving ICI. Cutaneous irAEs are the most common irAEs
- Assessment:
  1. Categorize the type of reaction
  2. Assess the severity of reaction by body surface area and presence of blistering
- Management:
  - Skin directed therapies: topical corticosteroids, topical calcineurin inhibitors, phototherapy
  - Systemic therapy:
    - Corticosteroids
    - Phenotype specific therapies: dupilumab for eczematous reactions, acitretin for lichenoid, etc.
  - Consult Dermatology
- Goal: manage skin side effects so patients can remain on ICI, and know when the side effects are severe enough to warrant discontinuing ICI

- Thank you! Questions?
- Email: bamodi@coh.org

- Emollients twice daily
  - Aquaphor (oint)
  - Eucerin (thick cream)
- Hydrocortisone 2.5%
  - Face, genitals
- Triamcinolone 0.1%
  - Trunk, extremities
- Fluocinolone 0.1%
  - Scalp
- Clobetasol 0.05%
  - Hands/feet
- Topical tacrolimus (oint), pimecrolimus (cream)