DERMATOLOGIC TOXICITIES ASSOCIATED WITH IMMUNOTHERAPIES AND MANAGEMENT STRATEGIES

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28-30 JUNE
VIENNA, AUSTRIA
SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE

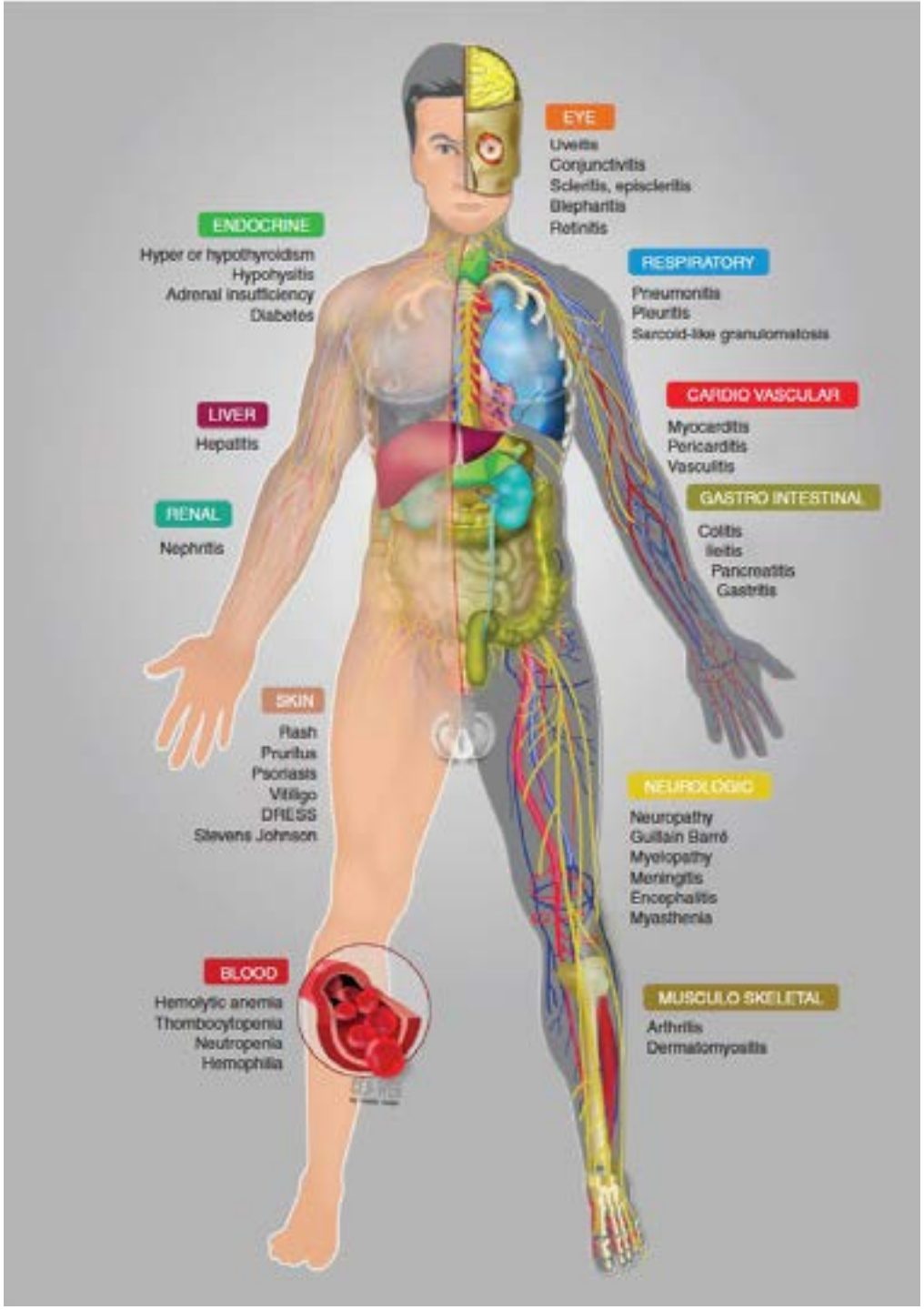
DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Jennifer N. Choi, MD

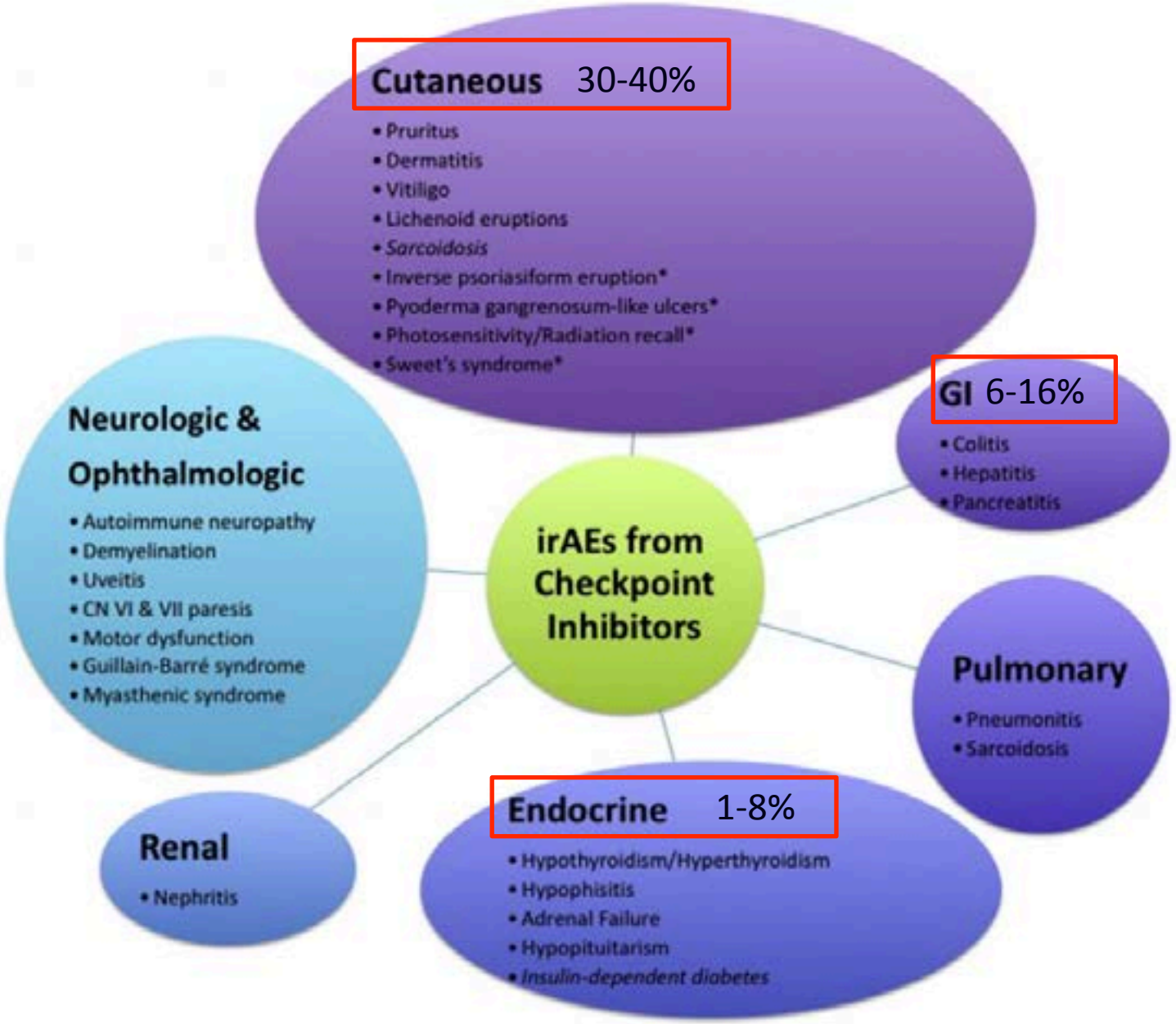
DISCLOSURES

Biotest AG: Consultant – Honoraria
Bayer: Speaker – Honoraria
Incyte: Principal Investigator – Research
Veloce Pharmaceuticals: Principal Investigator – Research

Spectrum of immune-related Adverse Events (irAEs)



Annals of Oncology 27: 559–574, 2016



Suozzi KC, et al. JAAD Case Rep. 2016 Jul 14;2(3):264-8
Hofmann L, et al. Euro J Cancer. 60 (2016): 190-209

Dermatologic Adverse Events to Anti-PD-1 Therapies

Adverse Event	Percent (Grade 3-4)
Rash	34-39% (2%)
Pruritus	17-21% (0.5-1%)
Vitiligo	9-11% (0%)

N Engl J Med. 2013 Jul;369(2):134-44
N Engl J Med. 2015 Jan;372(4):320-330
J Clin Oncol 2015; 33
N Engl J Med. 2015; 372:2521-2532

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N Engl J Med. 2013 Jul;369(2):134-44
N Engl J Med. 2015 Jan;372(4):320-330
J Clin Oncol 2015; 33
N Engl J Med. 2015; 372:2521-2532

Nivolumab + Ipilimumab

Adverse Event	Percent (Grade 3-4)
Rash	44-65% (6-7%)
Pruritus	17-65% (0%)

N Engl J Med. 2013 Jul 11;369(2):122-33

Rash

Median time to onset = 4-6 weeks

Eczema

Interface, perivascular and periadnexal lymphocytic dermatitis

Few plasma cells and eosinophils

Lichenoid dermatitis

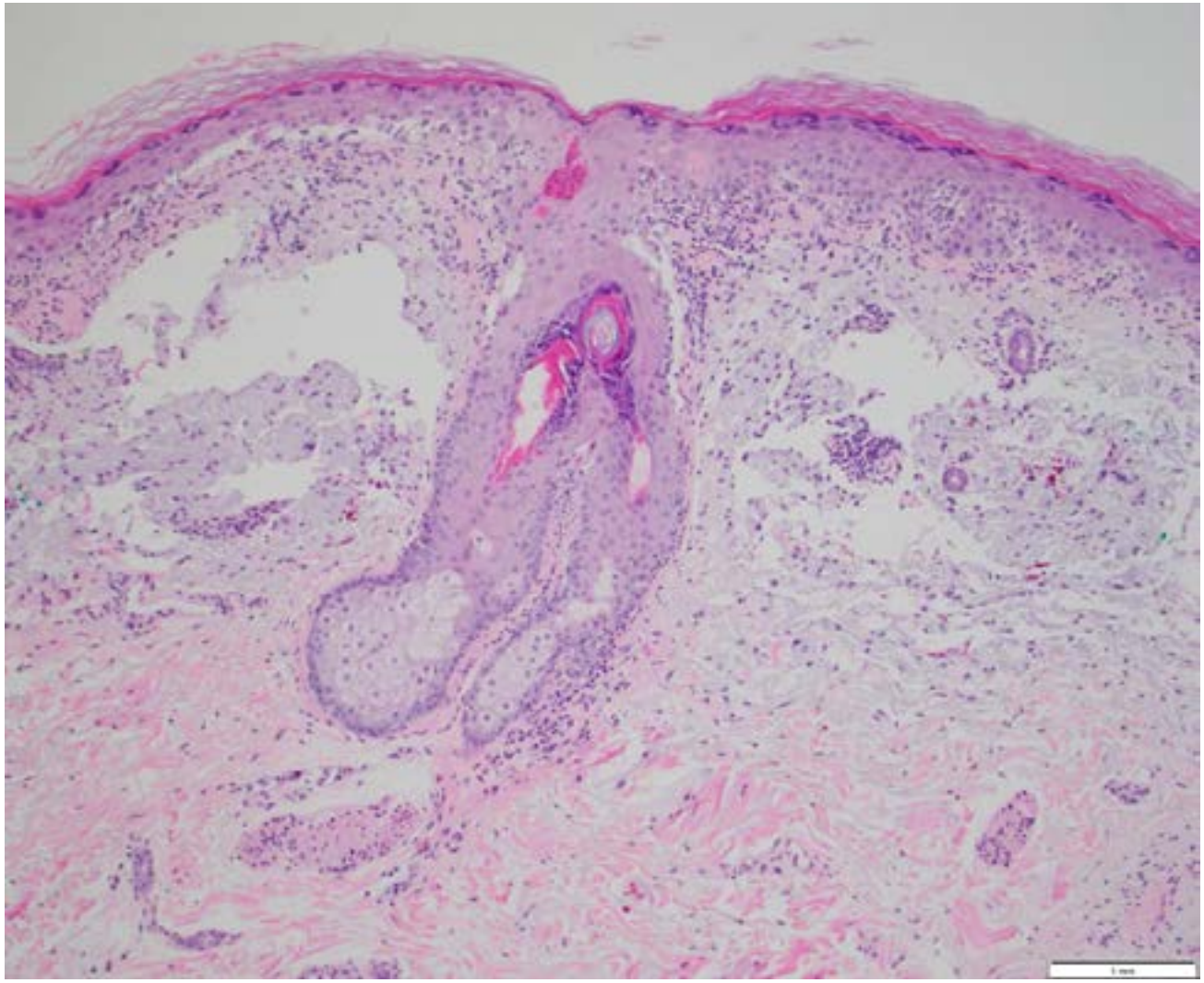
Band-like lymphocytic infiltrate along DEJ

Vacuolar interface

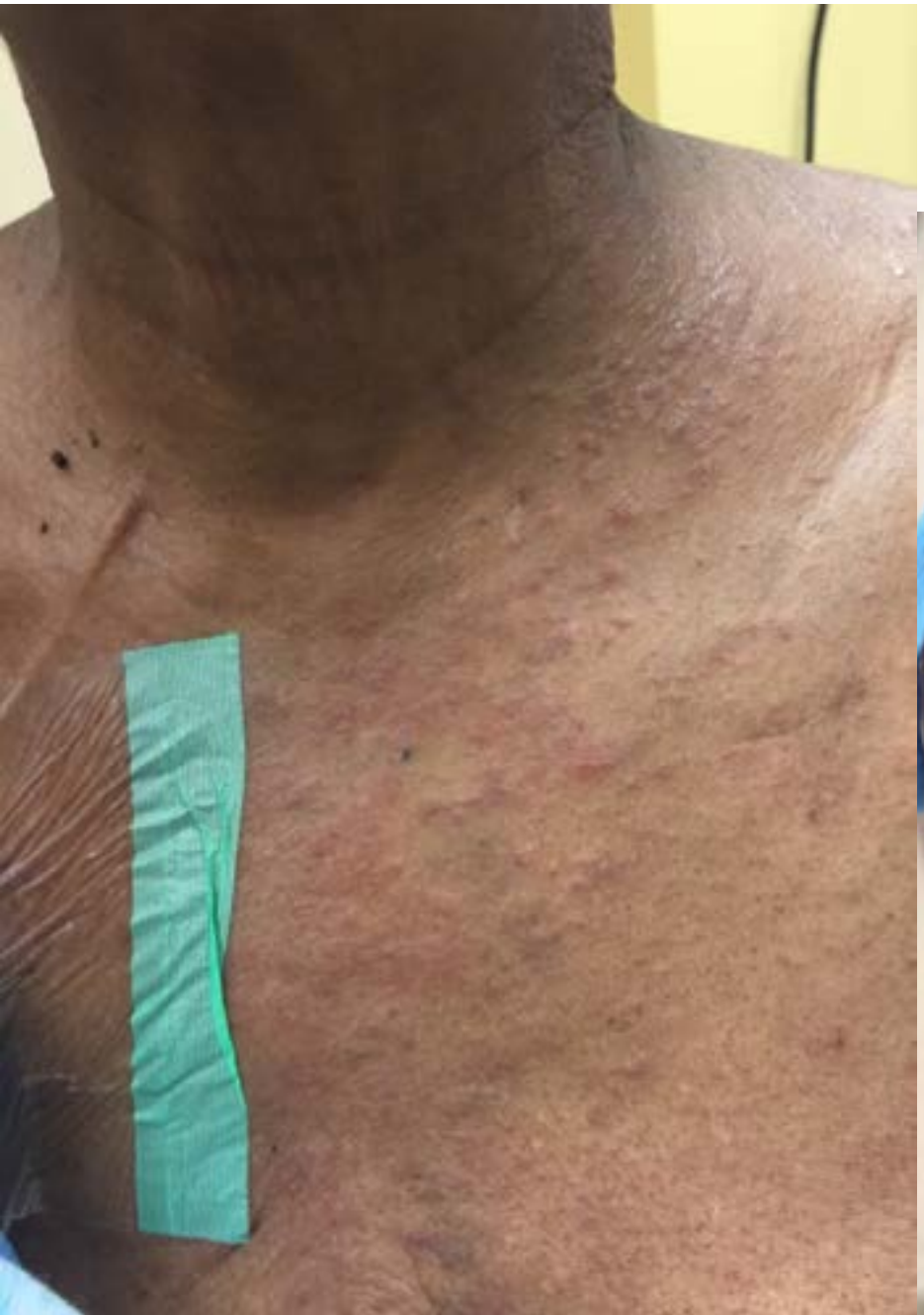
Coexisting spongiosis

Hwang S, et al. J Am Acad Dermatol. 2016 Mar;74(3):455-461
Shi VJ, et al. JAMA Dermatology. 2016;152(10):1128-1136
Sibaud V, et al. Curr Opin Oncol 2016, 28:254-263
Hofmann L, et al. Europ J Cancer. 2016, 60:190-209
Belum VR, et al. Europ J Cancer. 2016, 60:12-25

Eczematous/spongiotic dermatitis

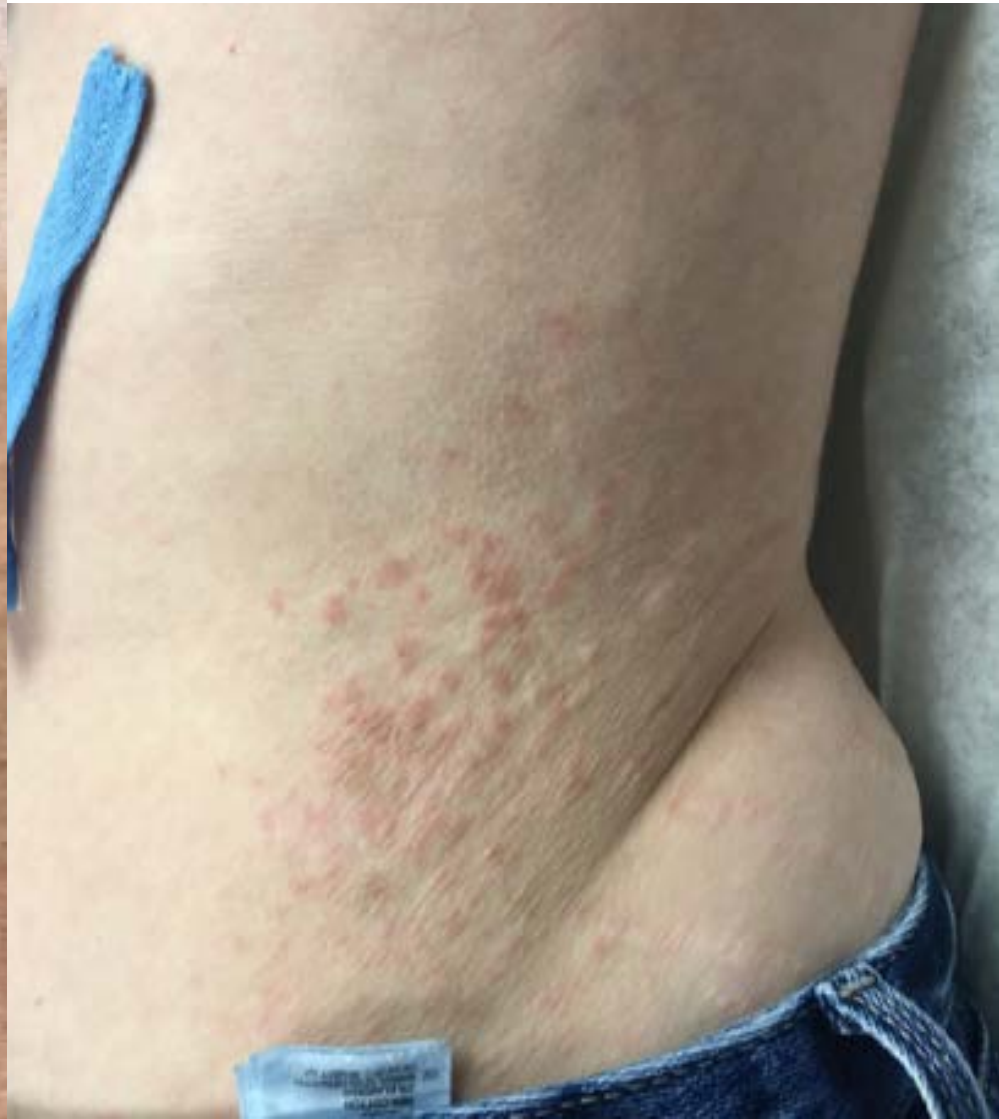


Belum VR et al. Eur J Cancer 2016 June; 60:12-25.



Eczematous

- Generalized
- Localized



Eczematous

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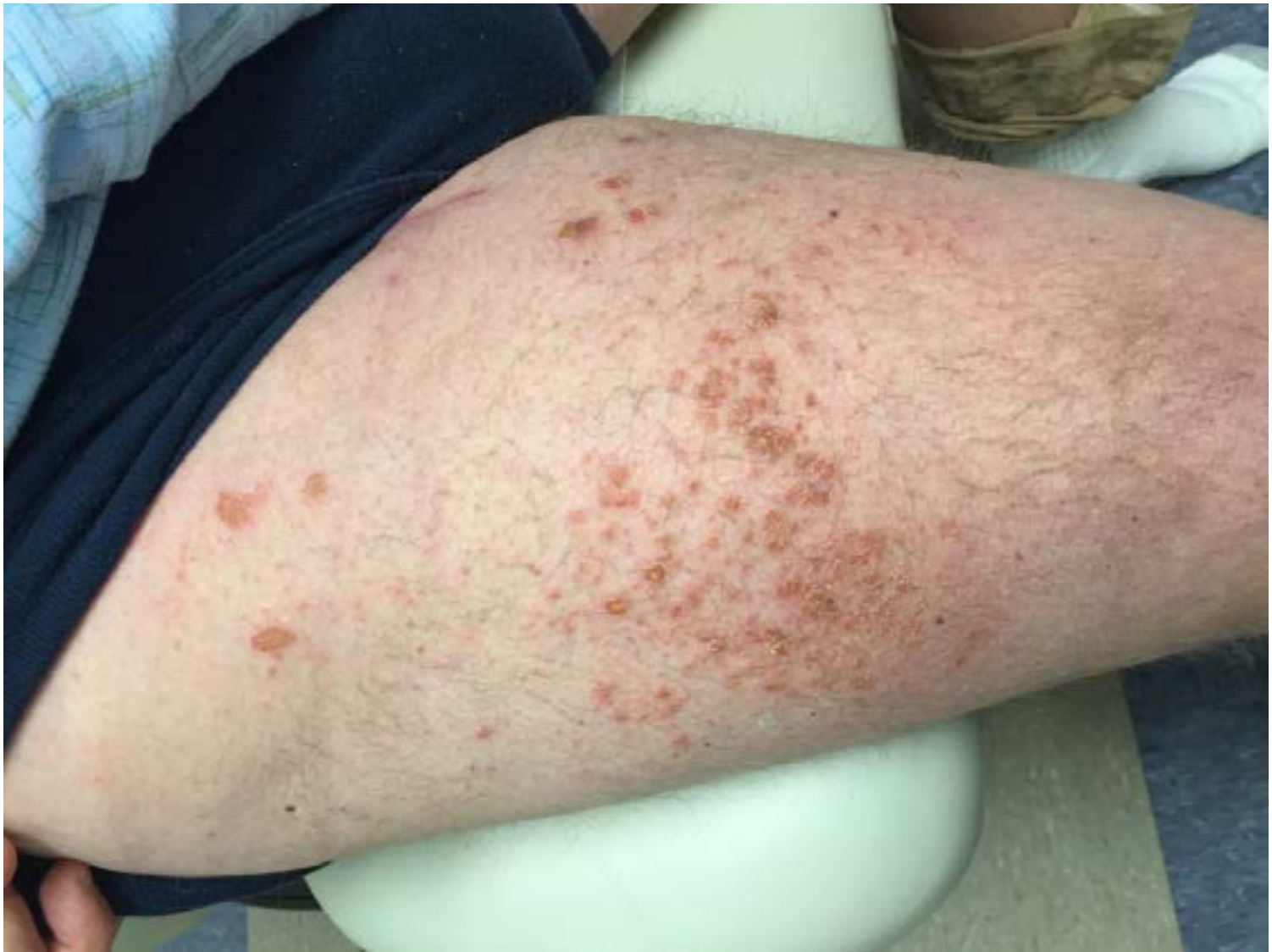
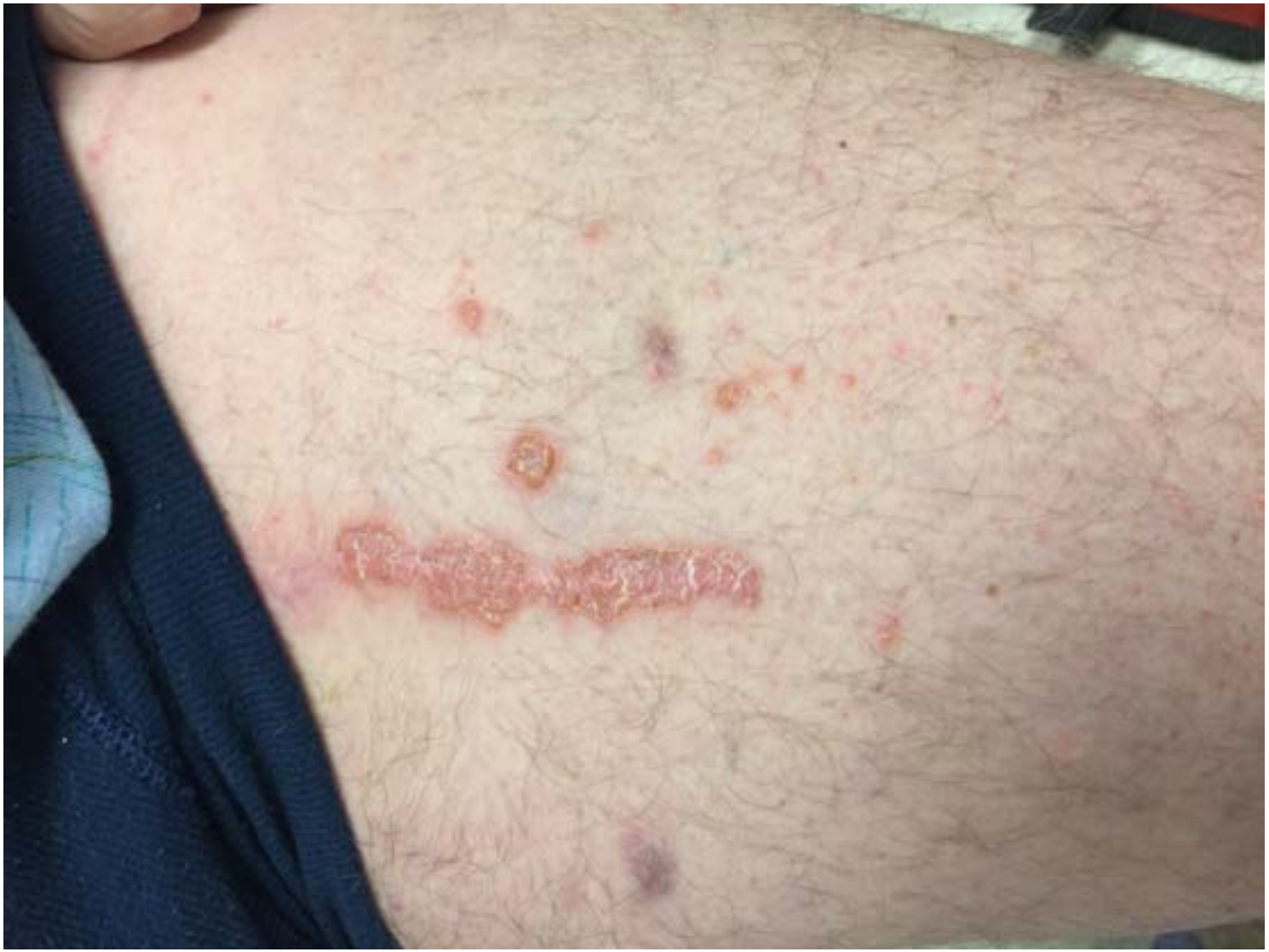
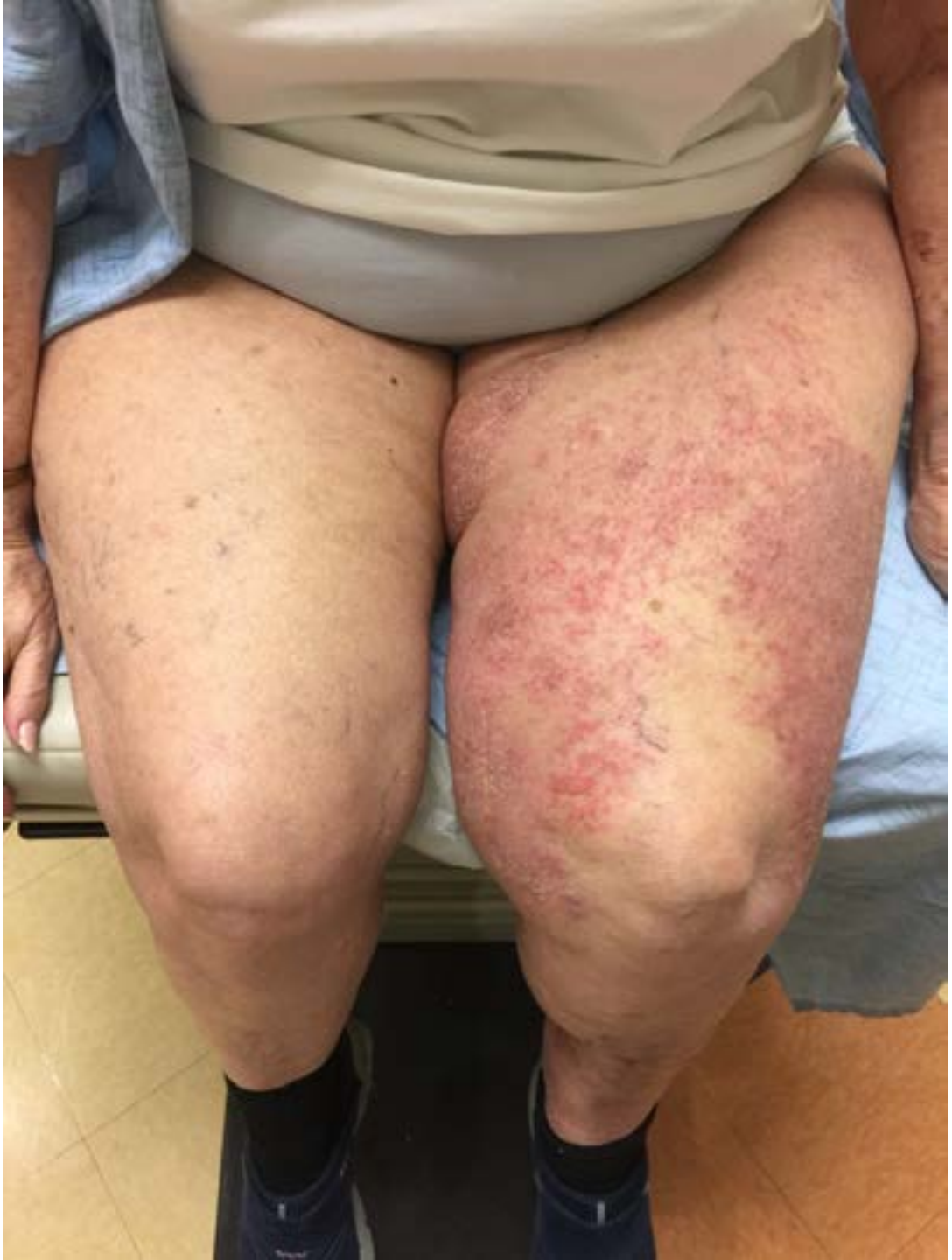




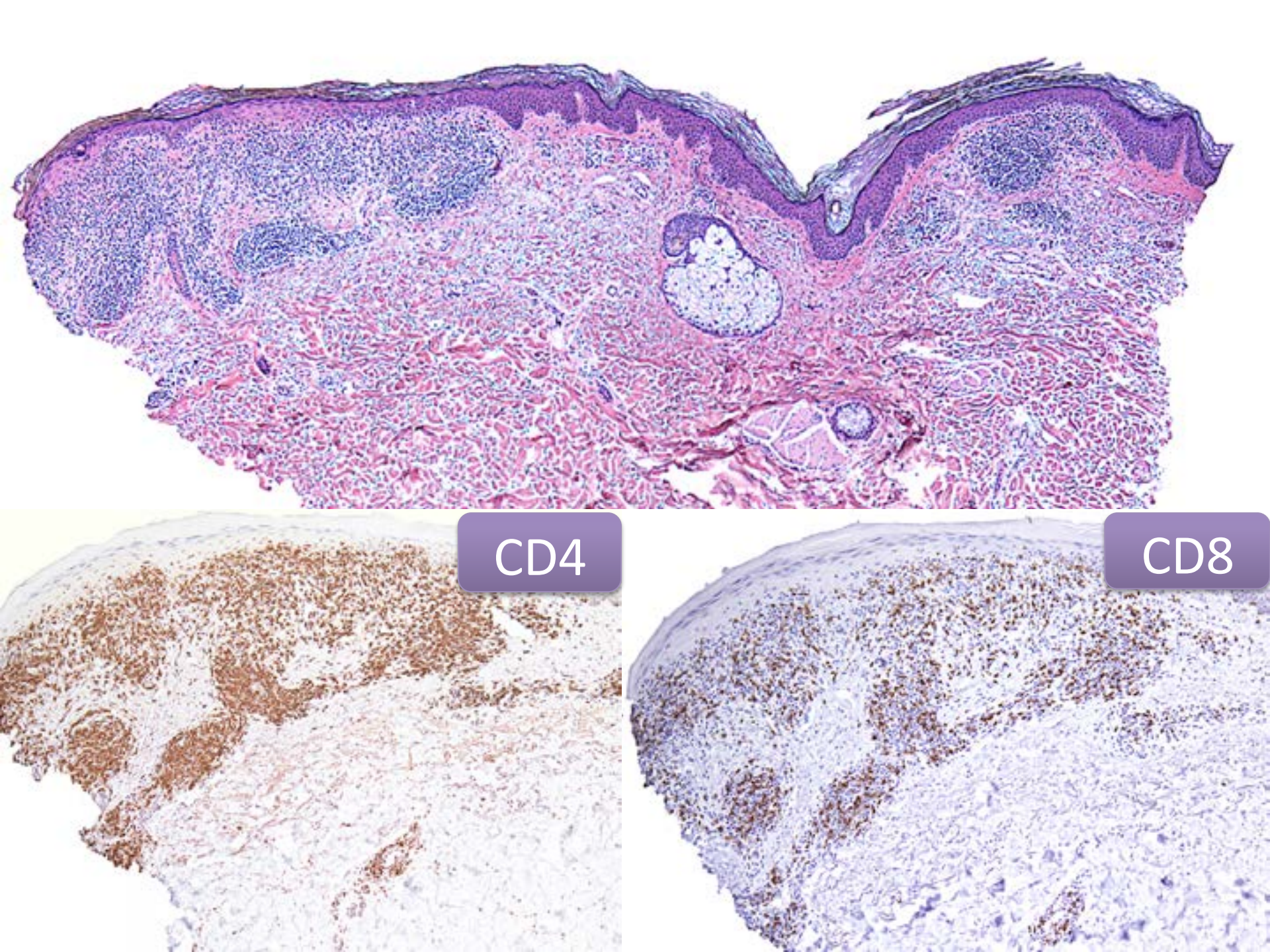


Eczematous

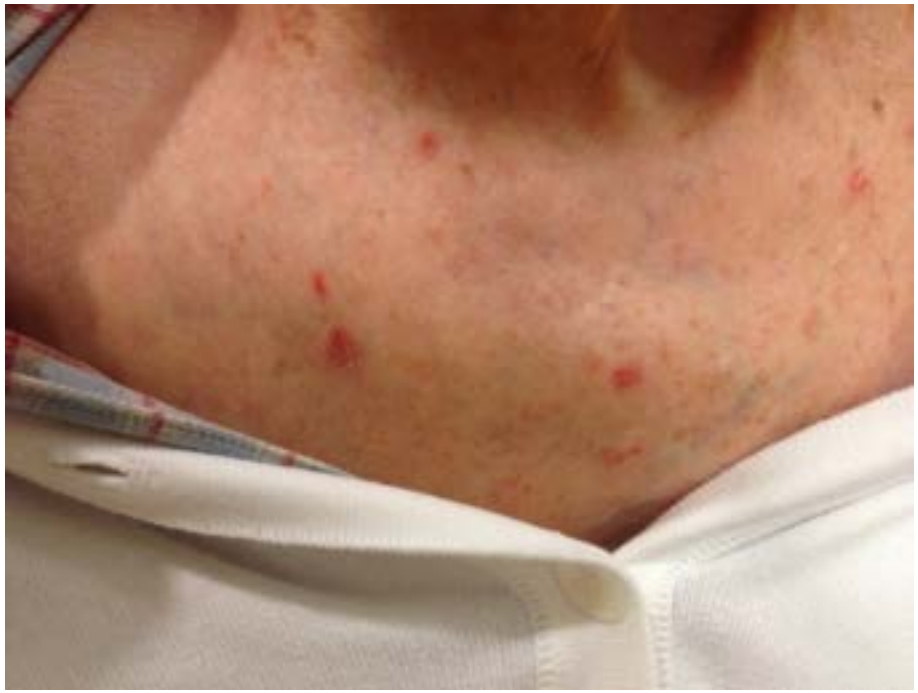
- Generalized
- Localized

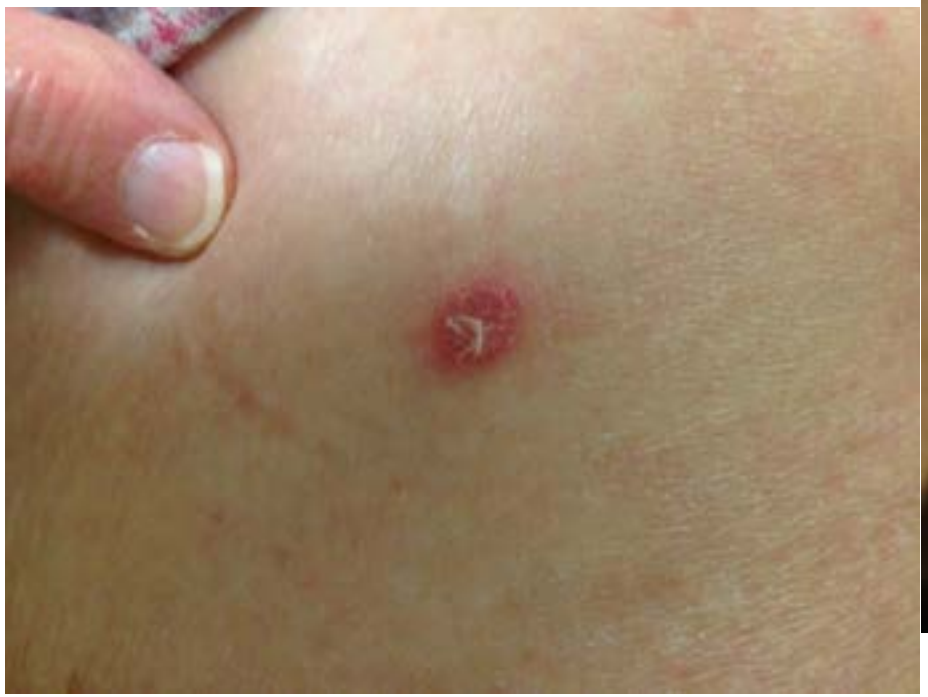
Clinical Patterns of Lichenoid Dermatitis

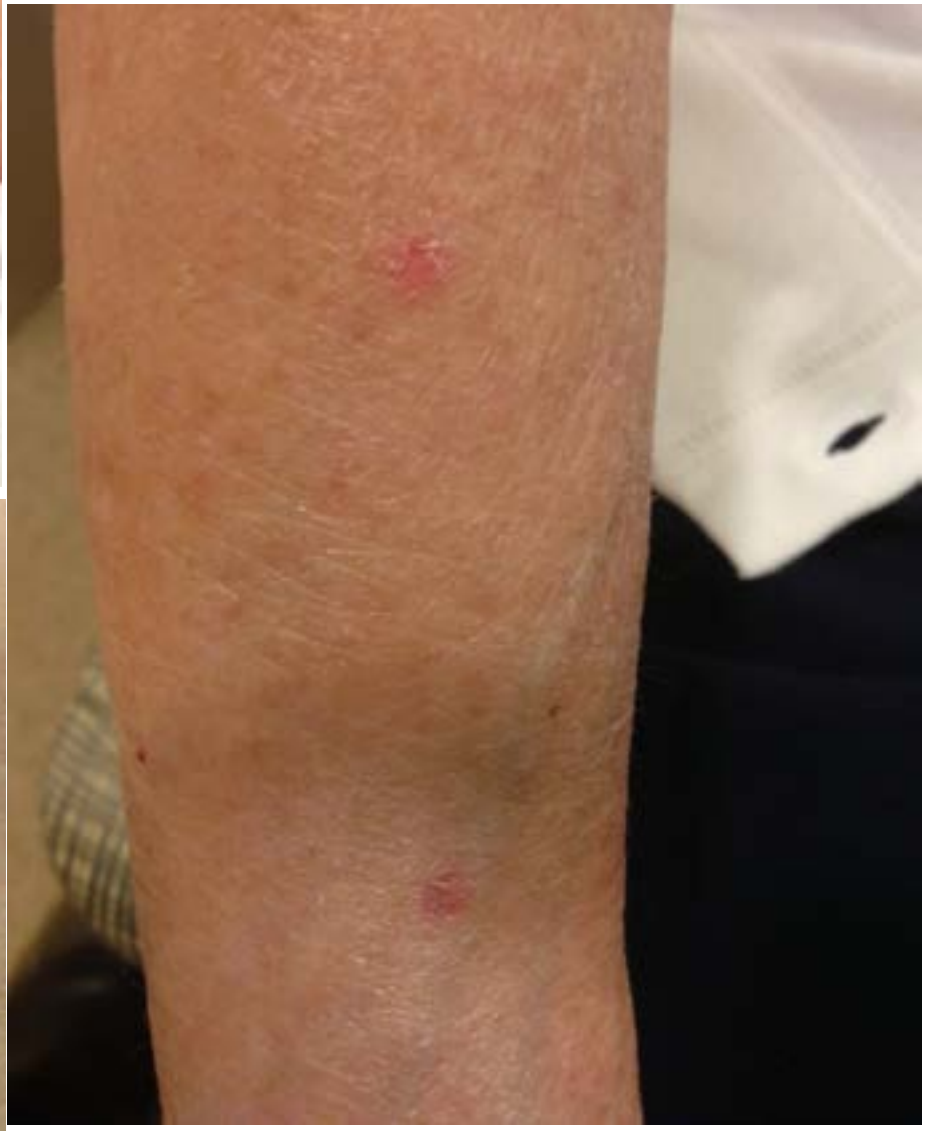
- Discrete
- Localized
- Inverse
- Generalized
- Palmoplantar
- Mucosal


CD4
CD8

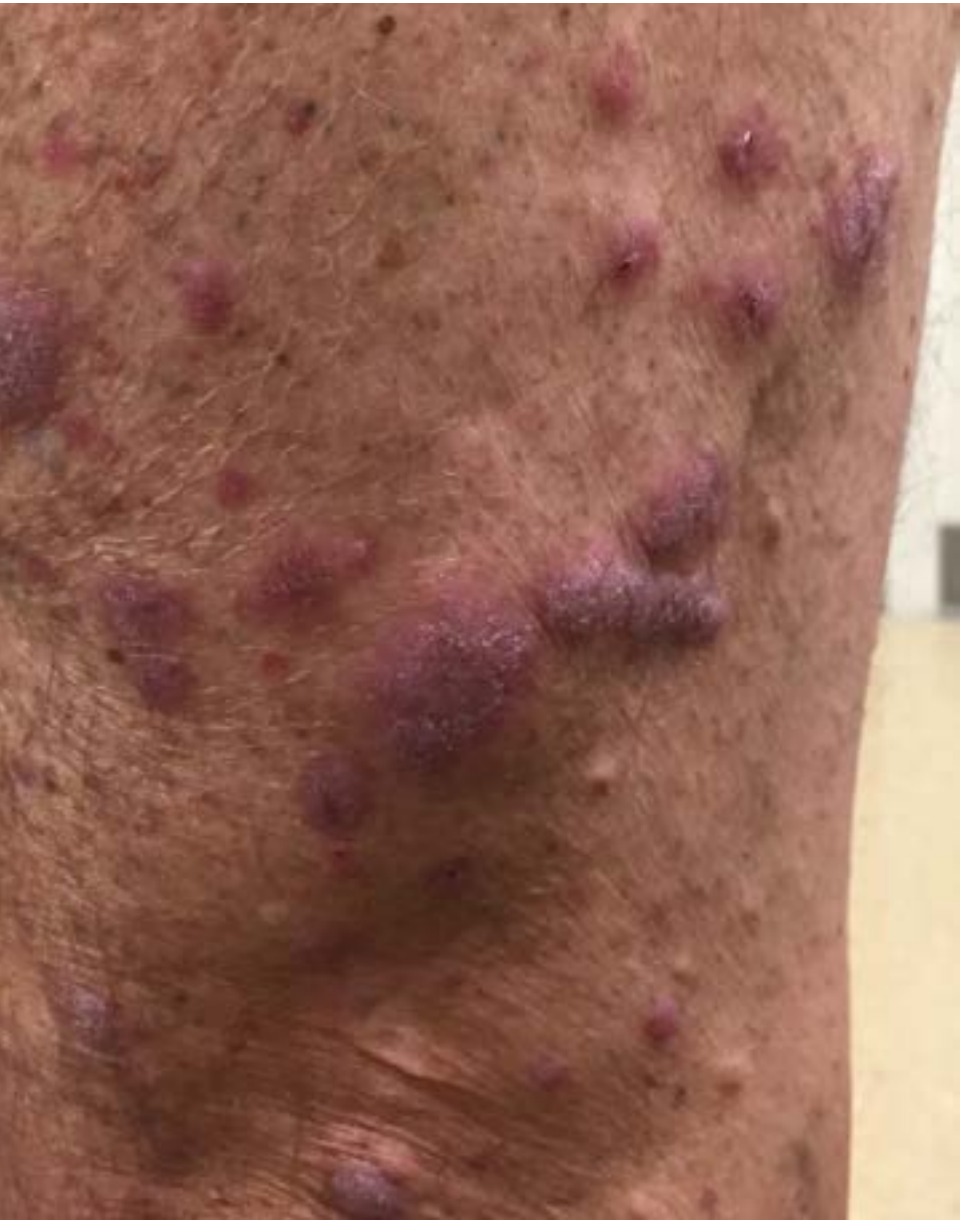
Lichenoid: Discrete

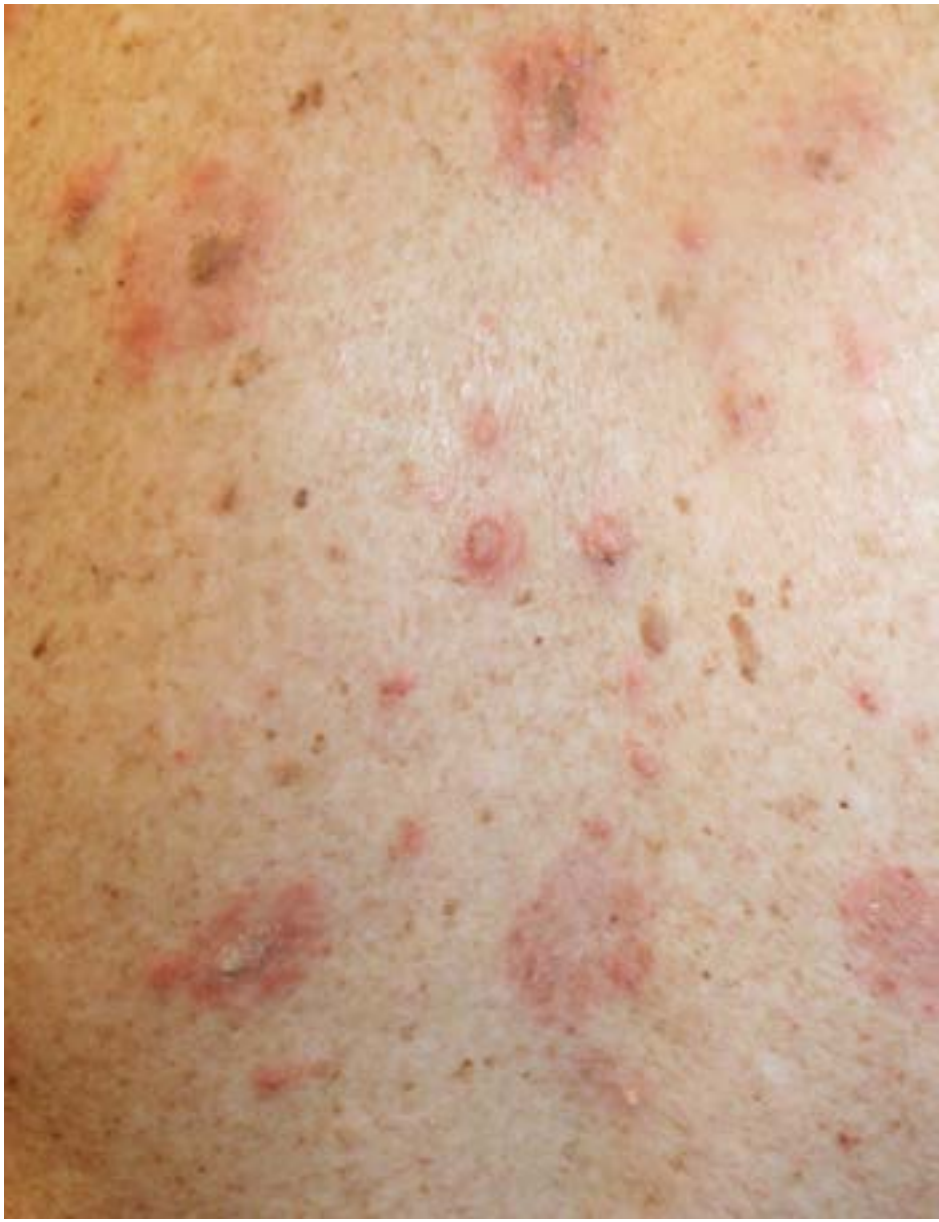




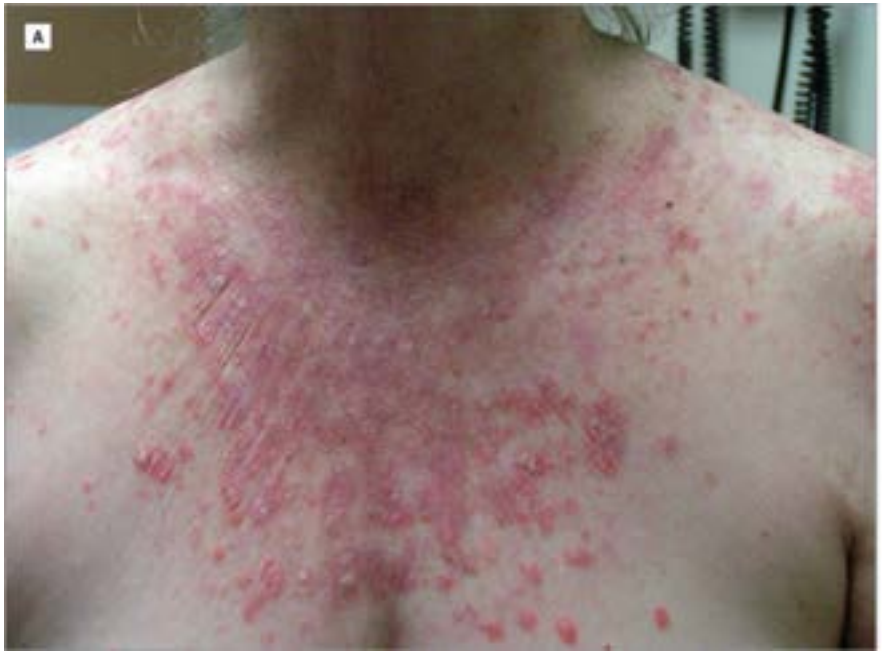


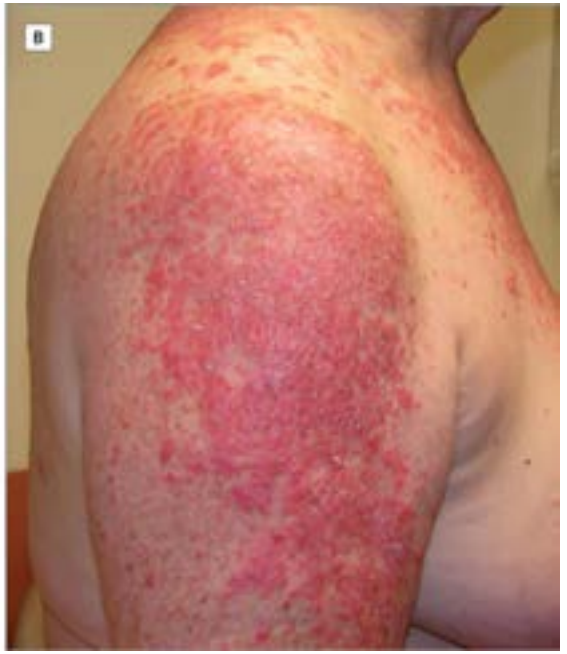
Lichenoid: Discrete



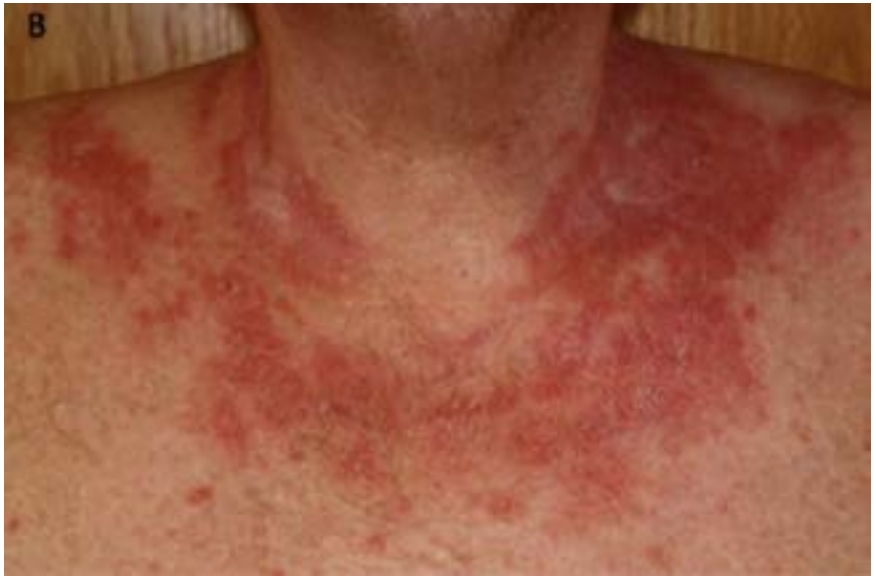


Lichenoid: Localized



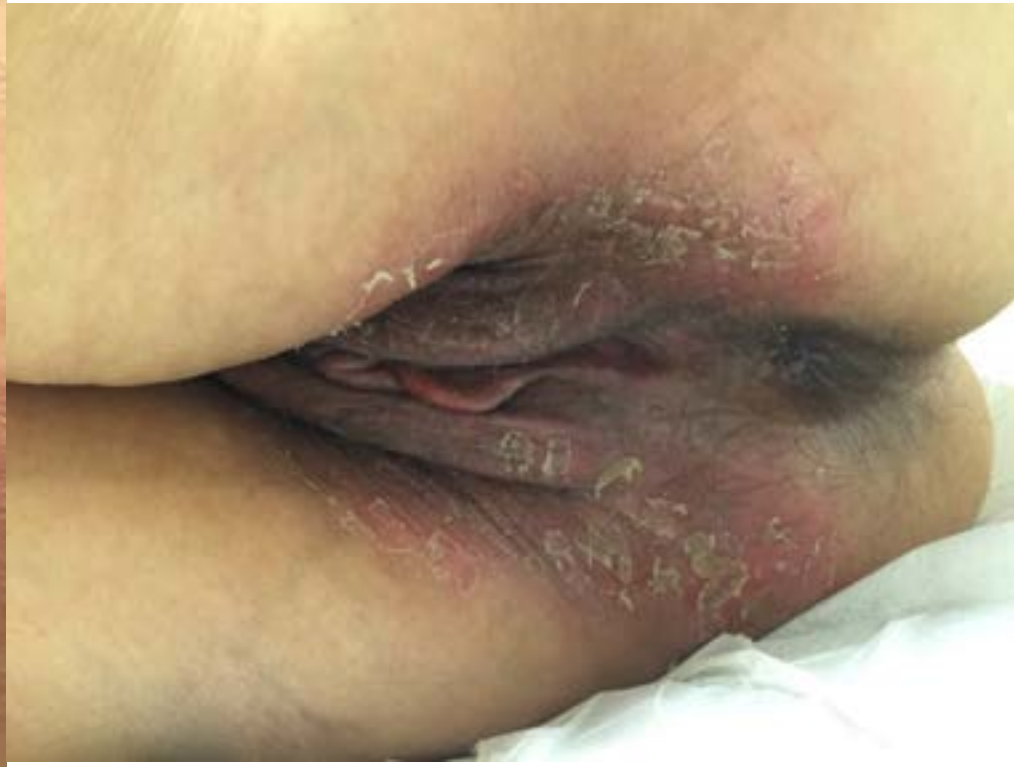


JAMA Dermatol. 2015;151(11):1206-1212.



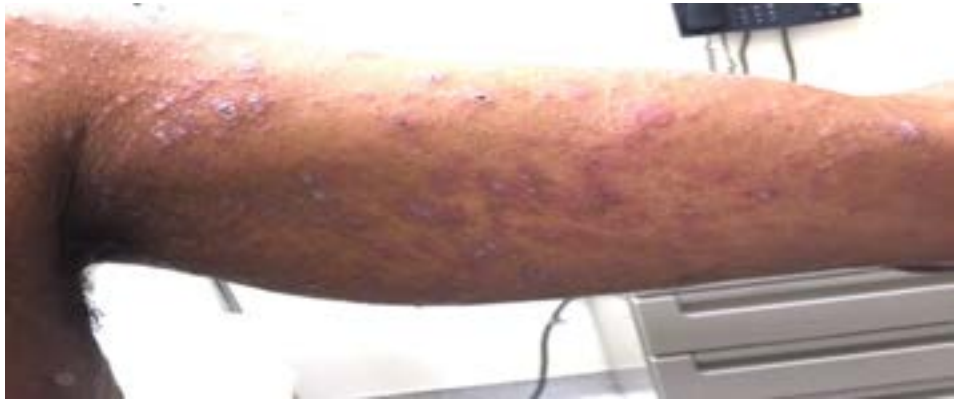
Lichenoid: Localized

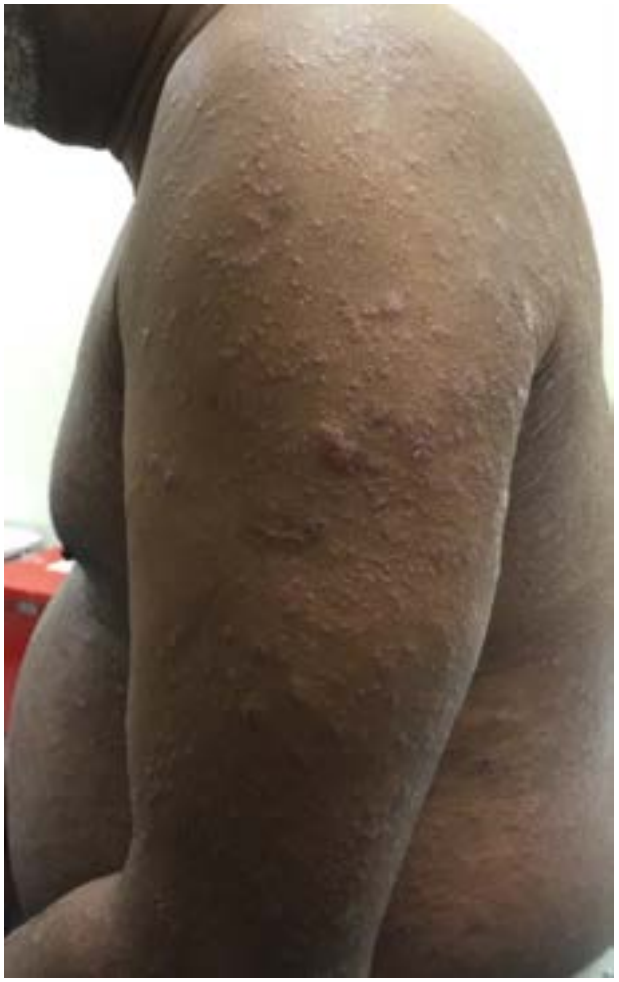
- Inverse

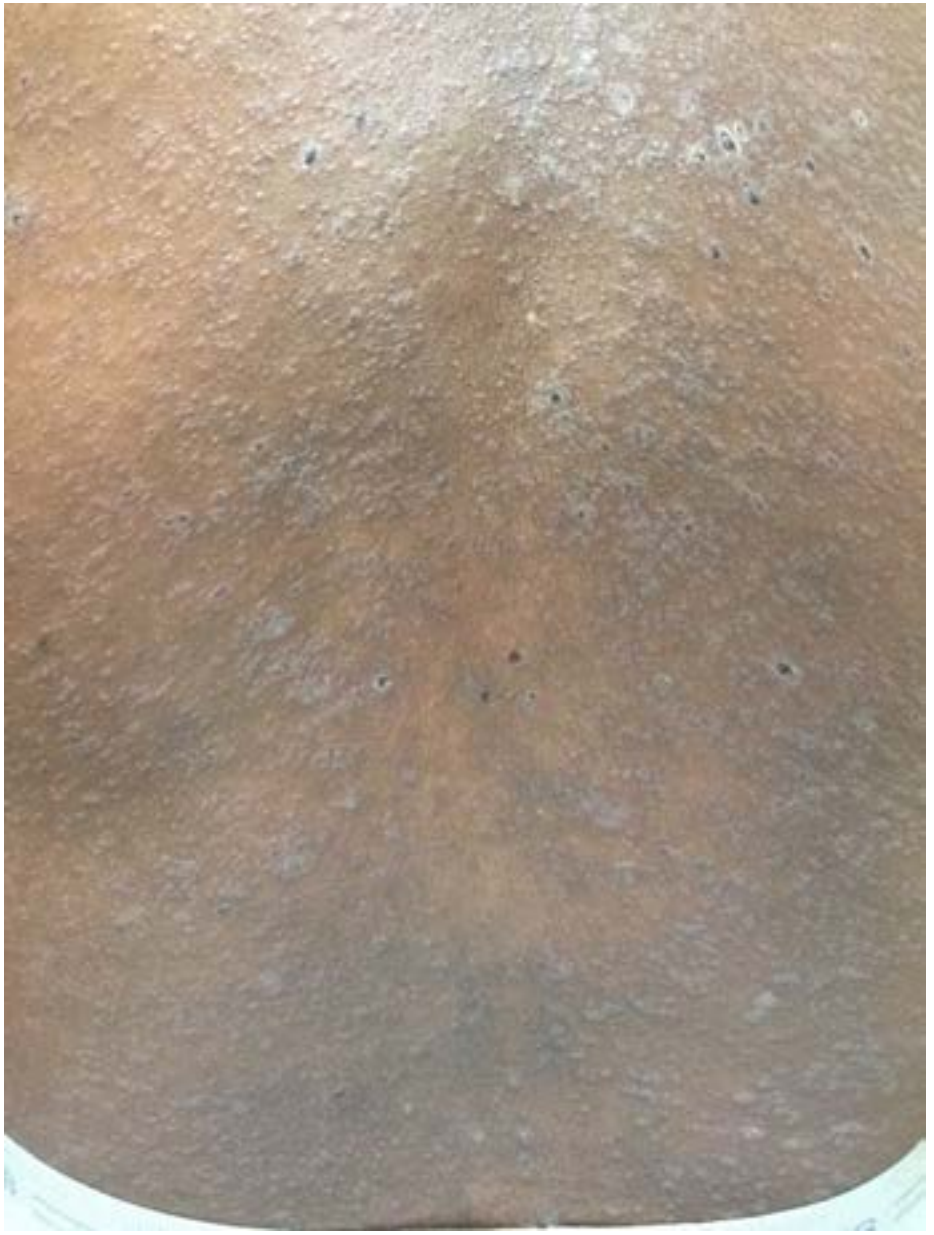


JAAD Case Rep. 2017 Jan; 3(1): 7–9.

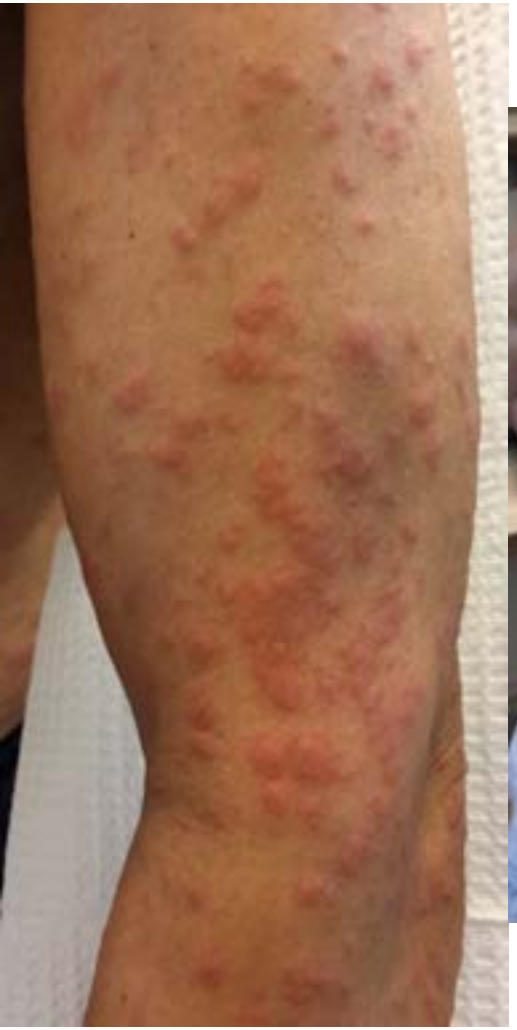
Lichenoid: Generalized

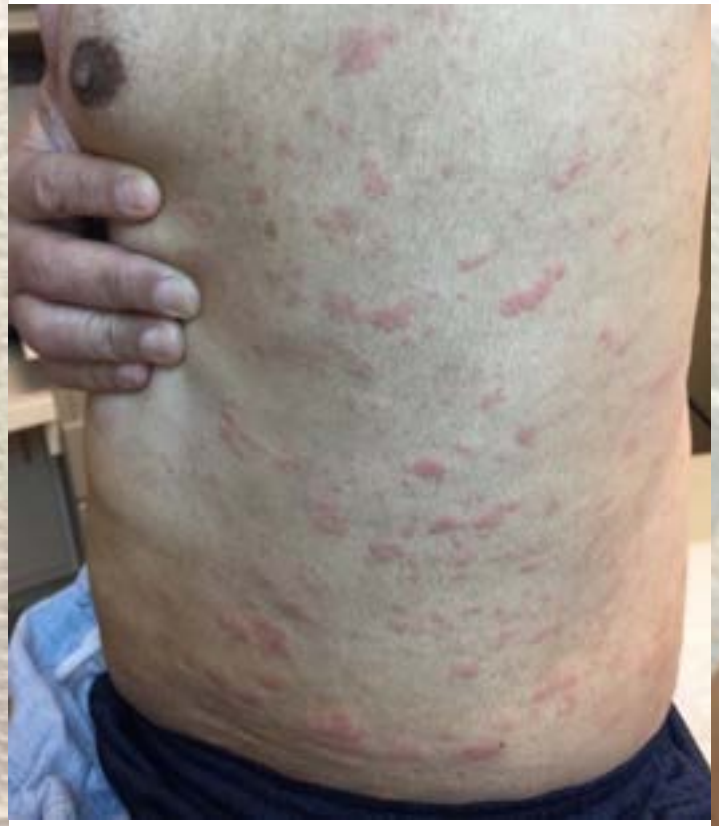


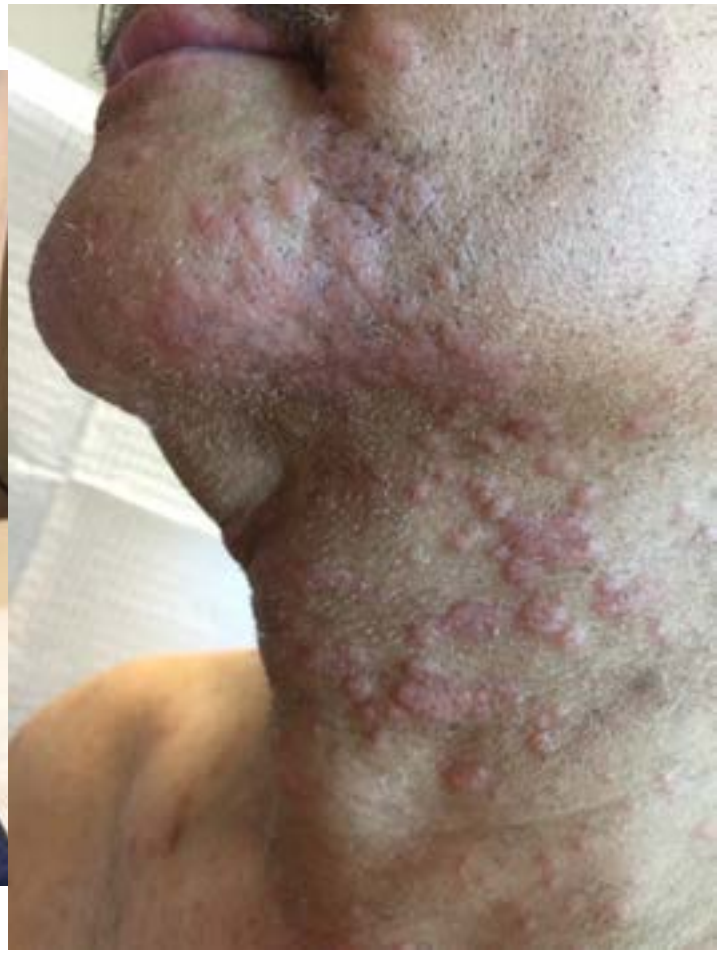




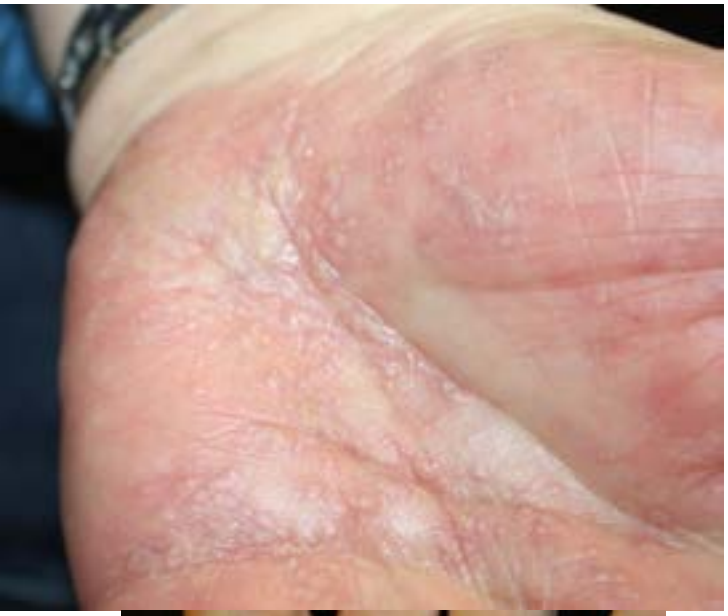
Lichenoid: Generalized

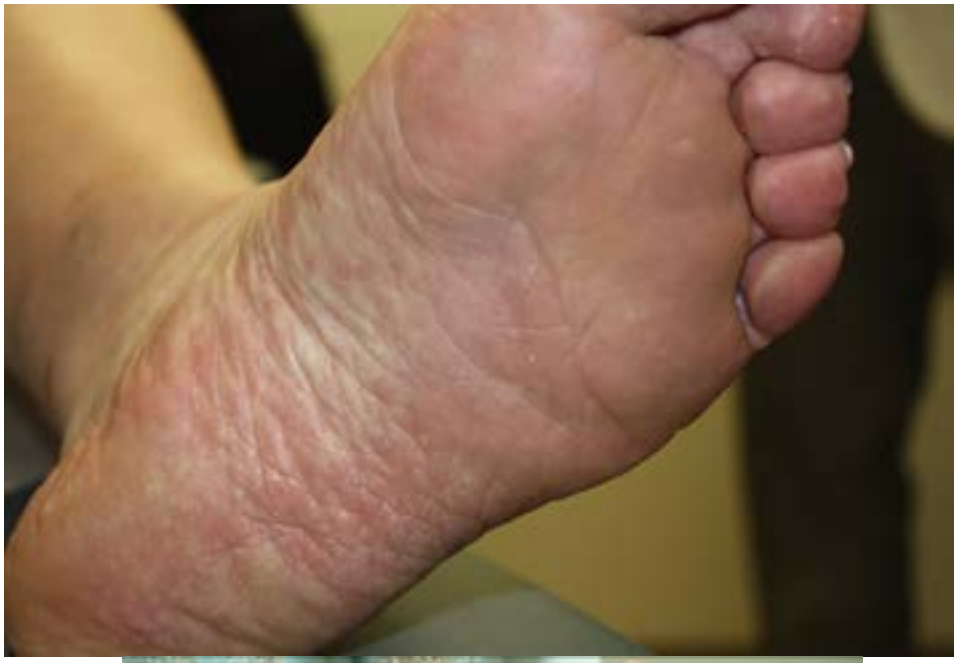


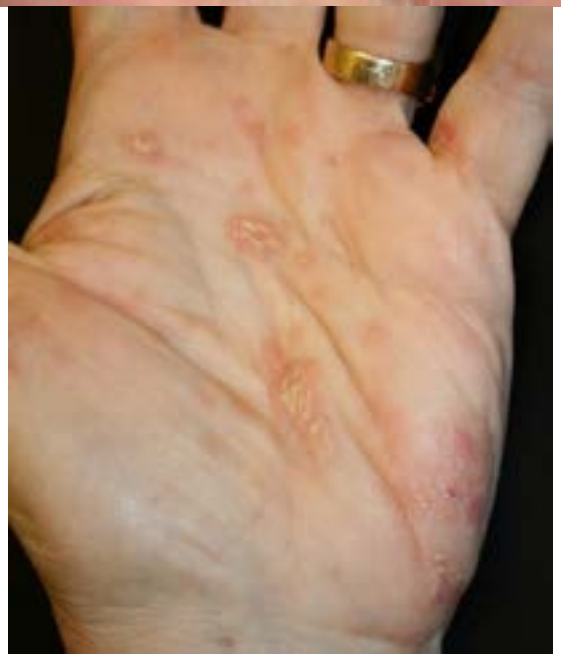


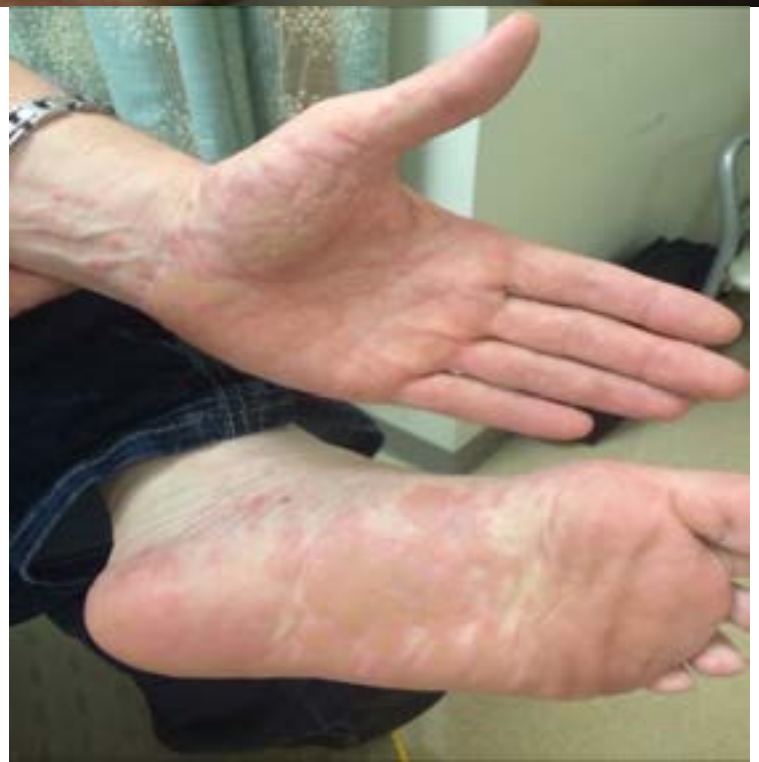


Lichenoid: Palmoplantar

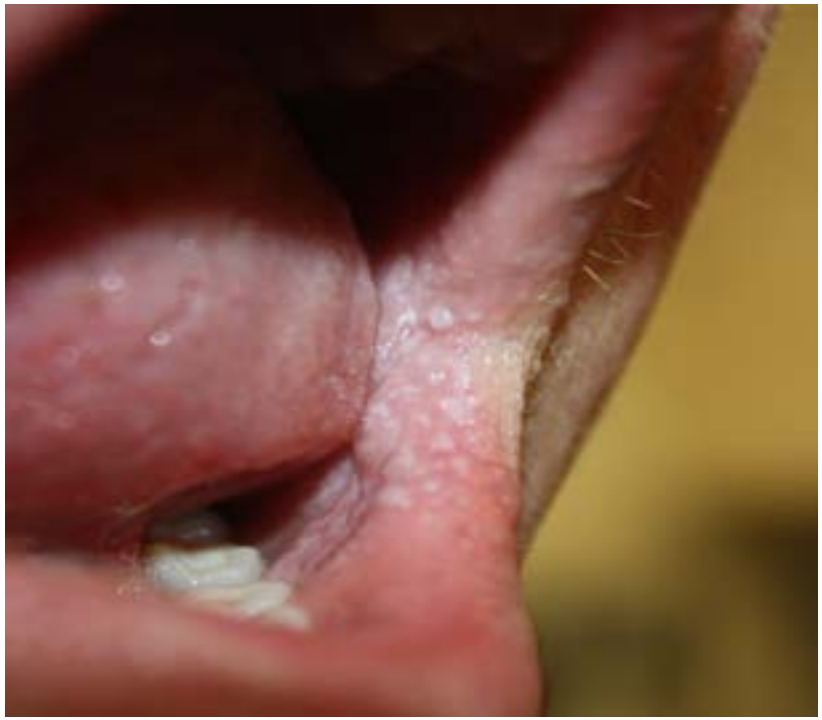


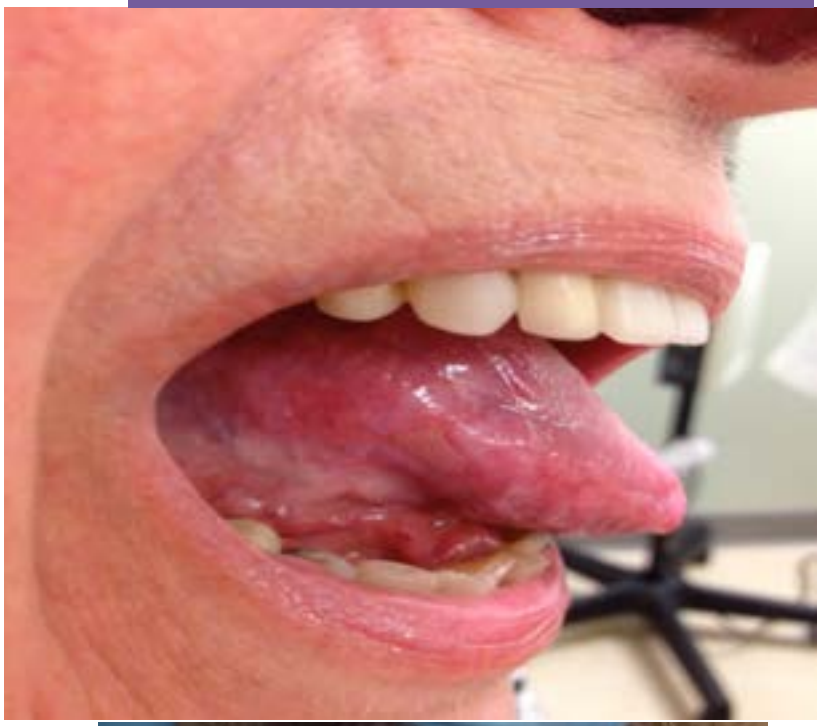


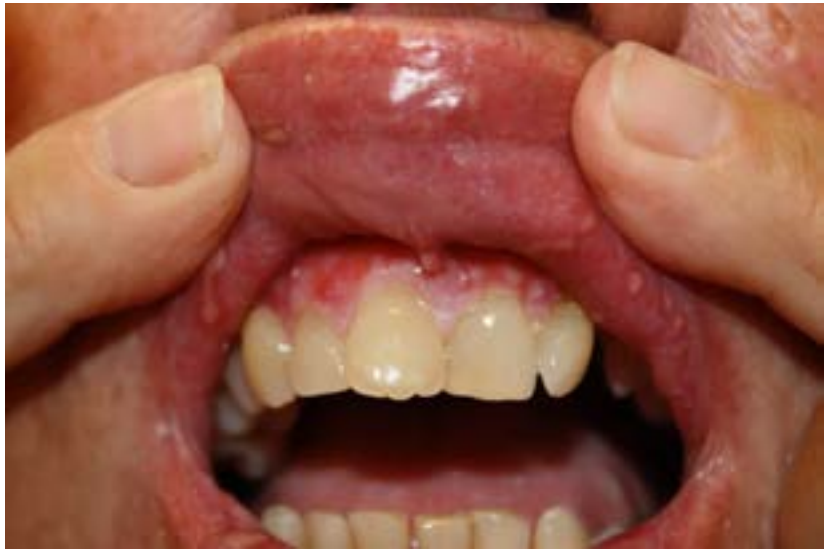


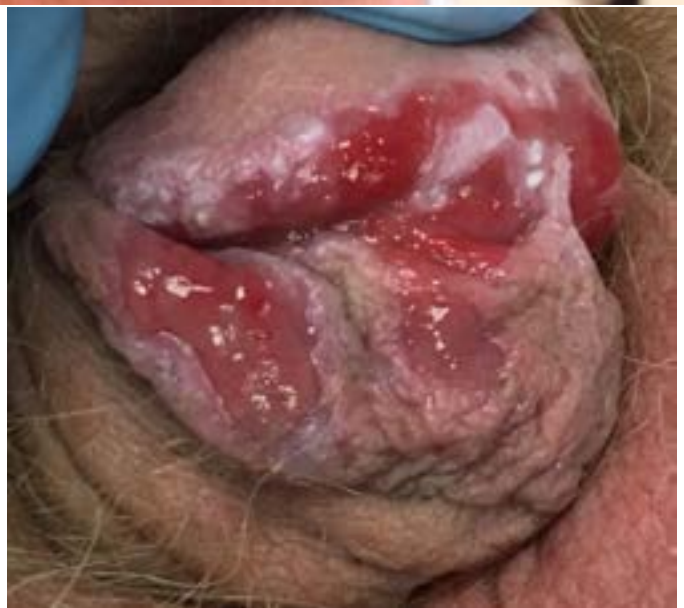


Lichenoid: Mucosal









JAMA Dermatology | Original Investigation

Clinical and Histologic Features of Lichenoid Mucocutaneous Eruptions Due to Anti–Programmed Cell Death 1 and Anti–Programmed Cell Death Ligand 1 Immunotherapy

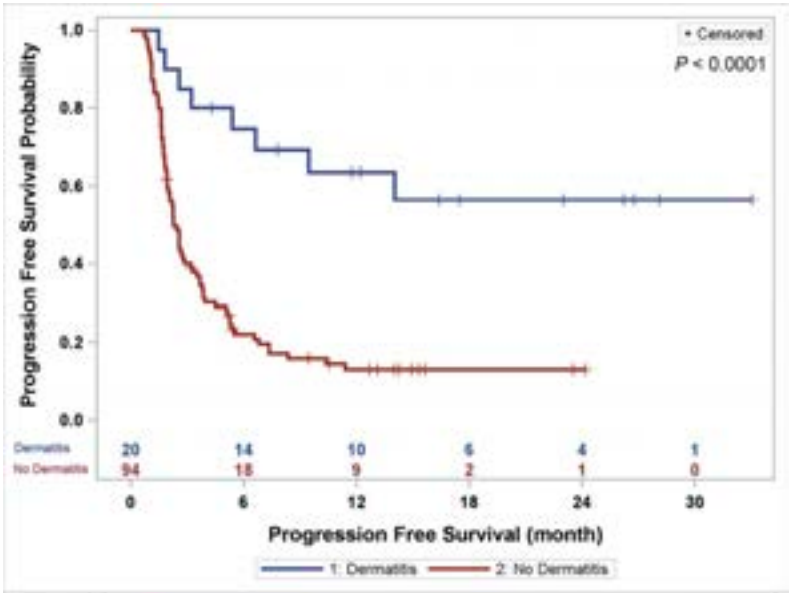
Veronica J. Shi, MD; Nemanja Rodic, MD, PhD; Scott Gettinger, MD; Jonathan S. Leventhal, MD; Julia P. Neckman, MD; Michael Girardi, MD; Marcus Bosenberg, MD, PhD; Jennifer N. Choi, MD

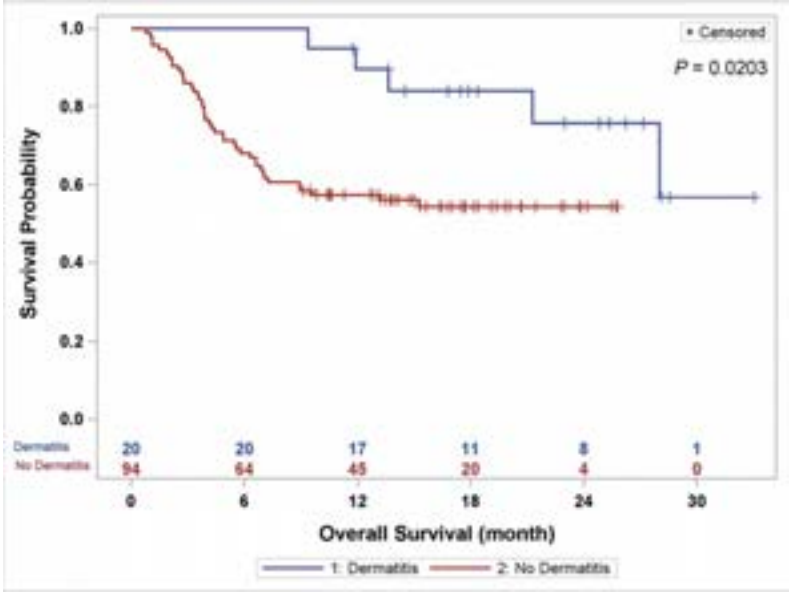
- 20 patients
- Time to onset: 3 days to 13 months
- 16/20 (80%): erythematous papules with scale
  - 11/20 (55%): Localized on trunk or extremities
  - 9/20 (45%): Generalized distribution
- 16/17 (94%): lichenoid histology
- 8/16 (50%): lichenoid + spongiotic histology
- 4/20 (20%): peripheral eosinophilia
- 16/20 (80%) on concurrent medications previously reported to cause lichenoid drug eruptions

JAMA Dermatology. 2016;152(10):1128-1136

Association of Dermatitis after PD-1/PD-L1 Inhibitor Therapy and Progression Free Survival and Overall Survival

Lee CK et al. JAAD May 2018





NCCN Guidelines Version 1.2018
Management of Immunotherapy-Related Toxicities

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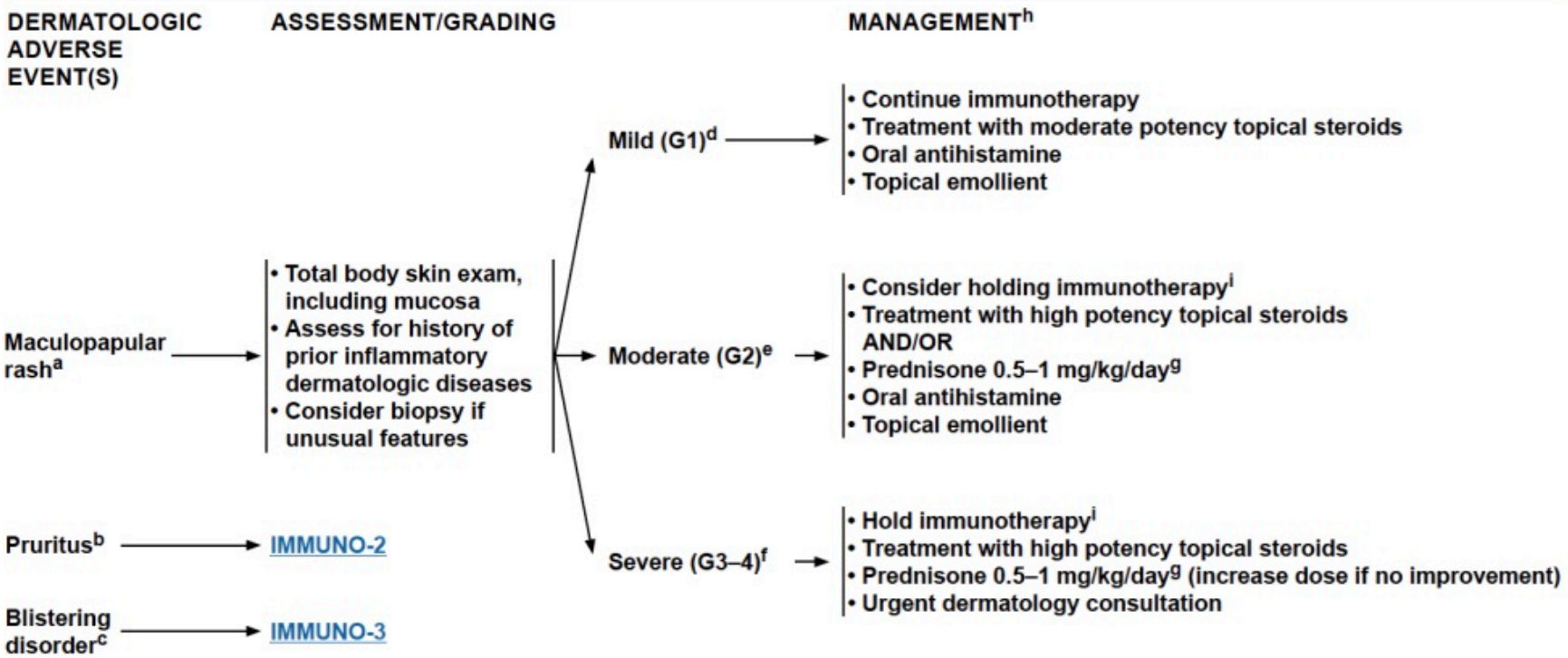
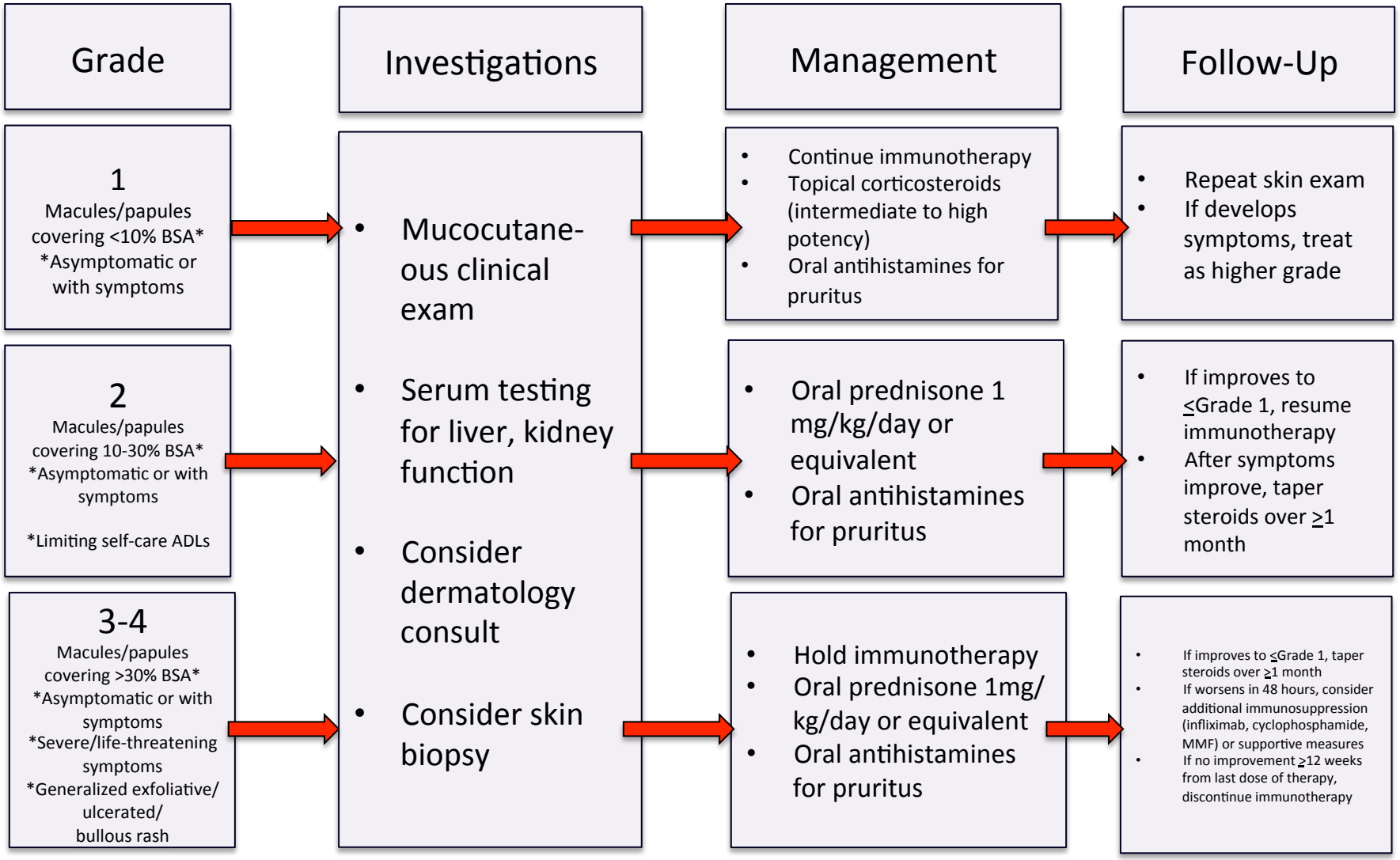


[a]Characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and may be associated with pruritus.
[b]Characterized by an intense itching sensation.
[c]Characterized by inflammation of the skin and the presence of bullae, which are filled with fluid.
[d]Macules/papules covering <10% body surface area (BSA) with or without symptoms (eg, pruritus, burning, tightness).
[e]Macules/papules covering 10%–30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental activities of daily living (ADLs).
[f]Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADLs.
[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Management of Rash by Immune Checkpoint Blockade

Naidoo et al. Ann Oncol 2015 Sept 14

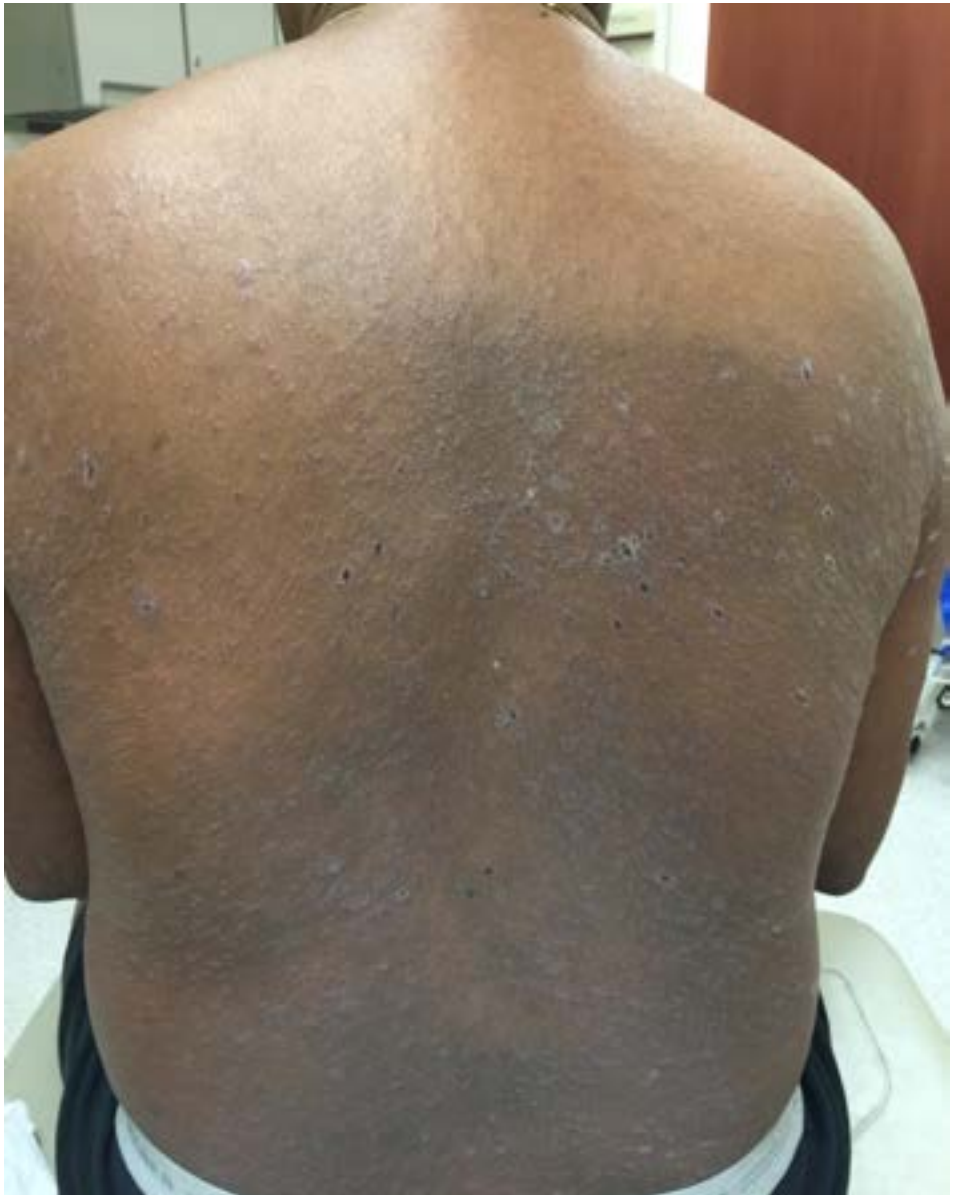


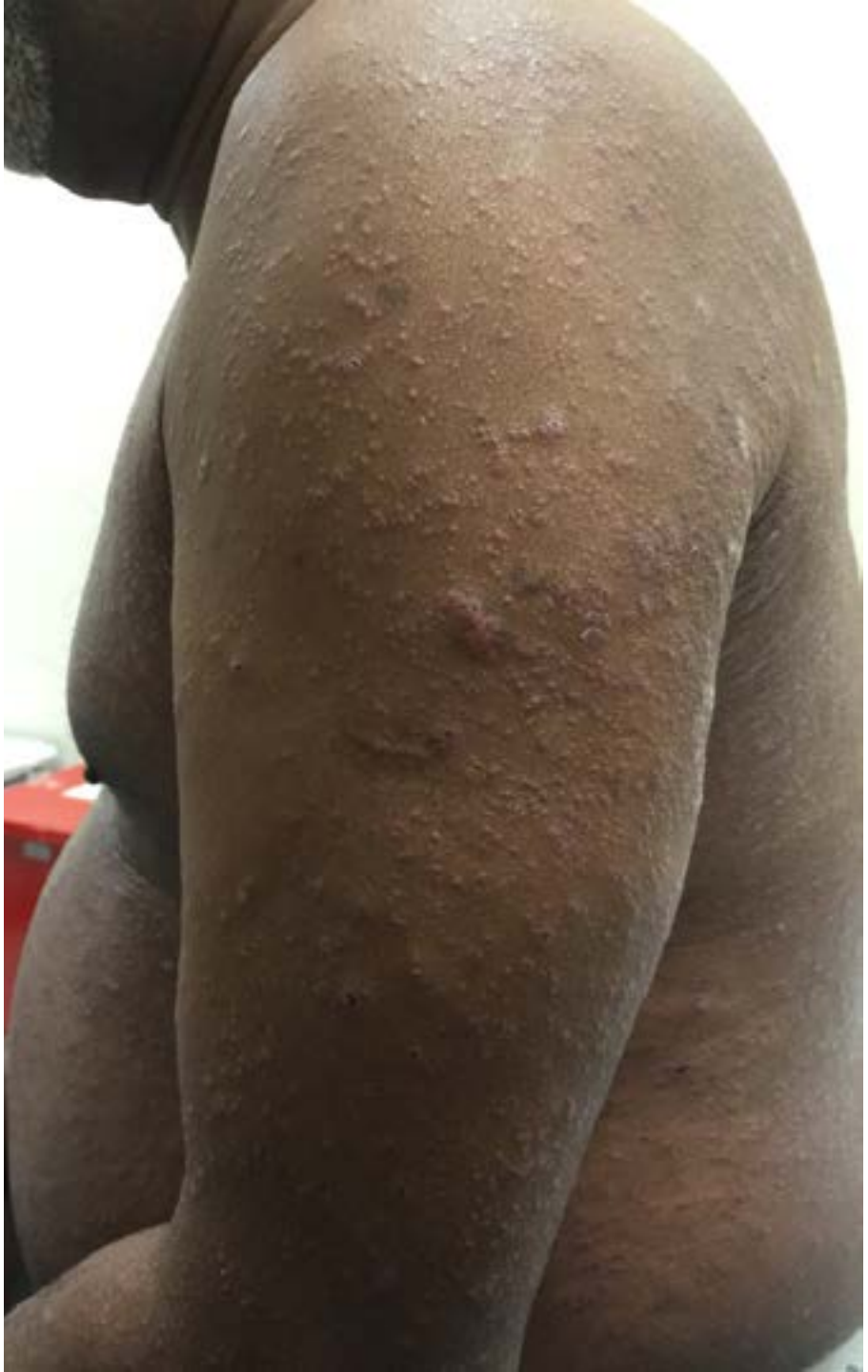
Treatment of Severe and Steroid-Refractory Immune-Related Adverse Events

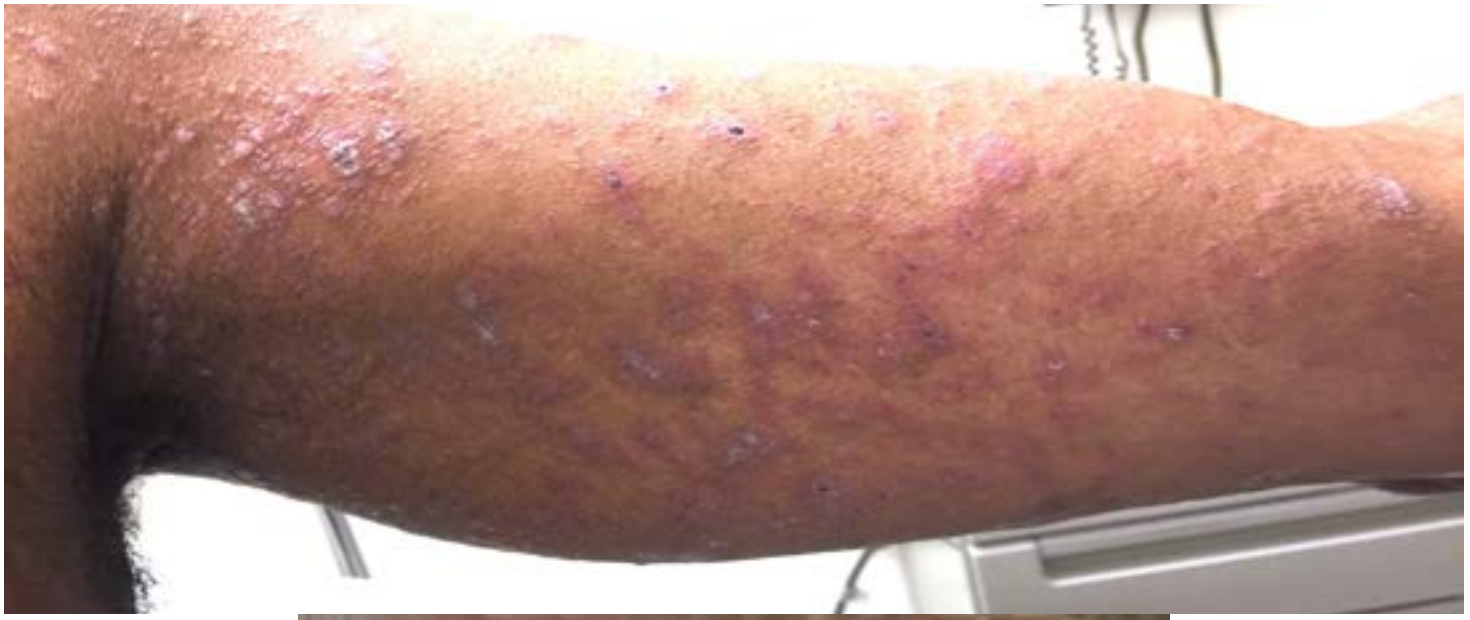
Type and Severity of irAE	Initial Management	Additional Immunosuppression	Immunosuppression Tapering Schedule
Colitis and/or diarrhea Grade 3-4 • Increase of ≥7 stools per day over baseline • Abdominal pain, fever, and change in bowel habits	• Admit to hospital for intravenous corticosteroid therapy (methylprednisolone 1-2 mg/kg daily dose) • Supportive care including intravenous fluids, supplemental oxygen, and antibiotics as needed • Withhold hepatotoxic drugs • Consider further diagnostic imaging or procedures	**Colitis and/or diarrhea** • If no improvement after 3 days, give infliximab 5 mg/kg • Can redose infliximab after 2 weeks if needed	**Colitis and/or diarrhea** • Rapidly tapering course of steroids as tolerated over 4-6 weeks • Increase steroids if diarrhea flares and then restart tapering
Hepatitis Grade 3-4 • Aspartate transaminase and/or alanine transaminase levels >5 times ULN • Total bilirubin level >3 times ULN		**Hepatitis** • If no improvement after 3 days, start mycophenolate mofetil 500-1000 mg every 12 hours	**Hepatitis** • Rapidly tapering course of steroids as tolerated; discontinue mycophenolate mofetil once tapered to prednisone 10 mg daily
Pneumonitis Grade 3-4 • Severe, life-threatening symptoms • Worsening hypoxia		**Pneumonitis** • If no improvement after 48 hours, start additional agent as above or cyclophosphamide	**Pneumonitis** • Taper steroids slowly over 6 weeks • Mycophenolate mofetil management as above if needed

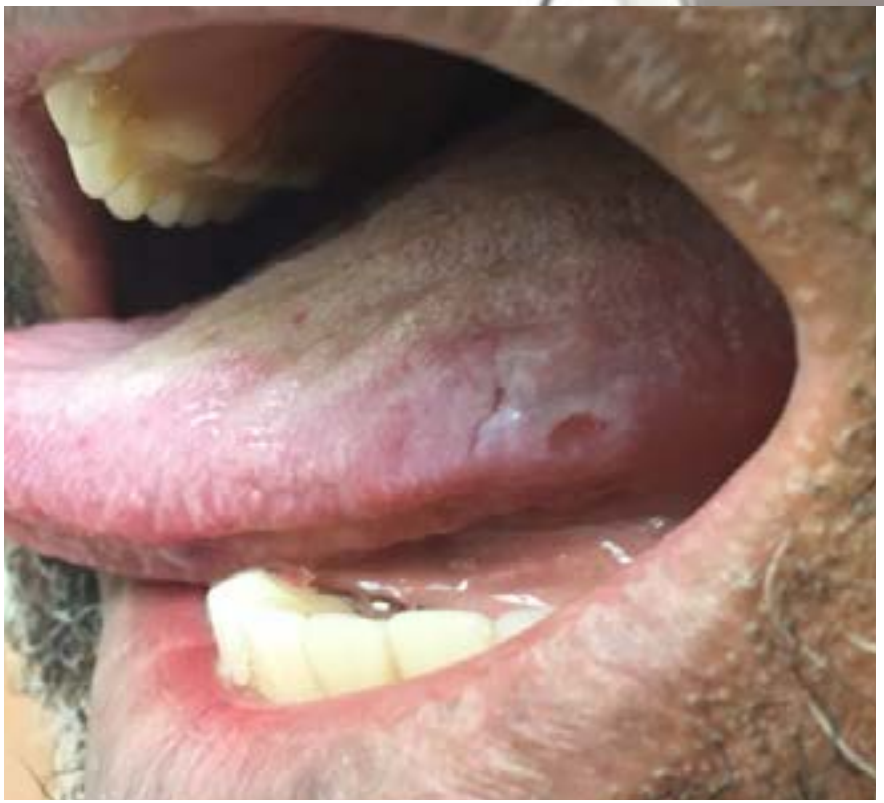
Treatment of the Immune-Related Adverse Effects of Immune Checkpoint Inhibitors: A Review

Friedman CF, et al. JAMA Oncol. 2016;2(10):1346-1353.



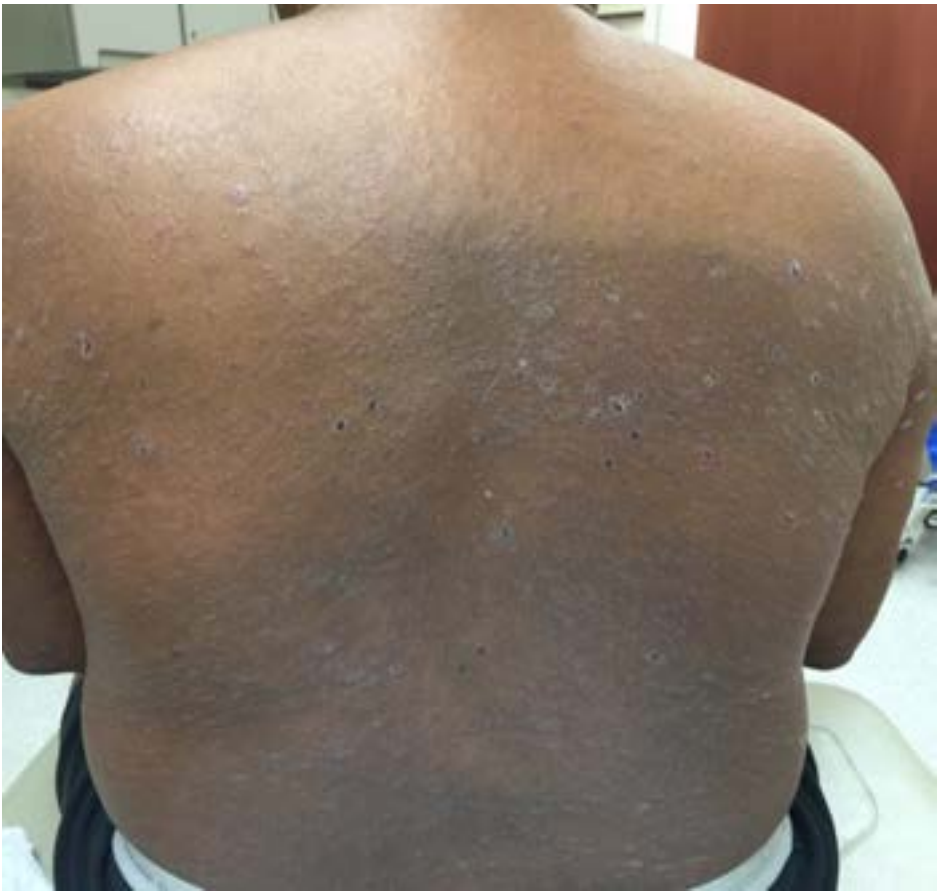


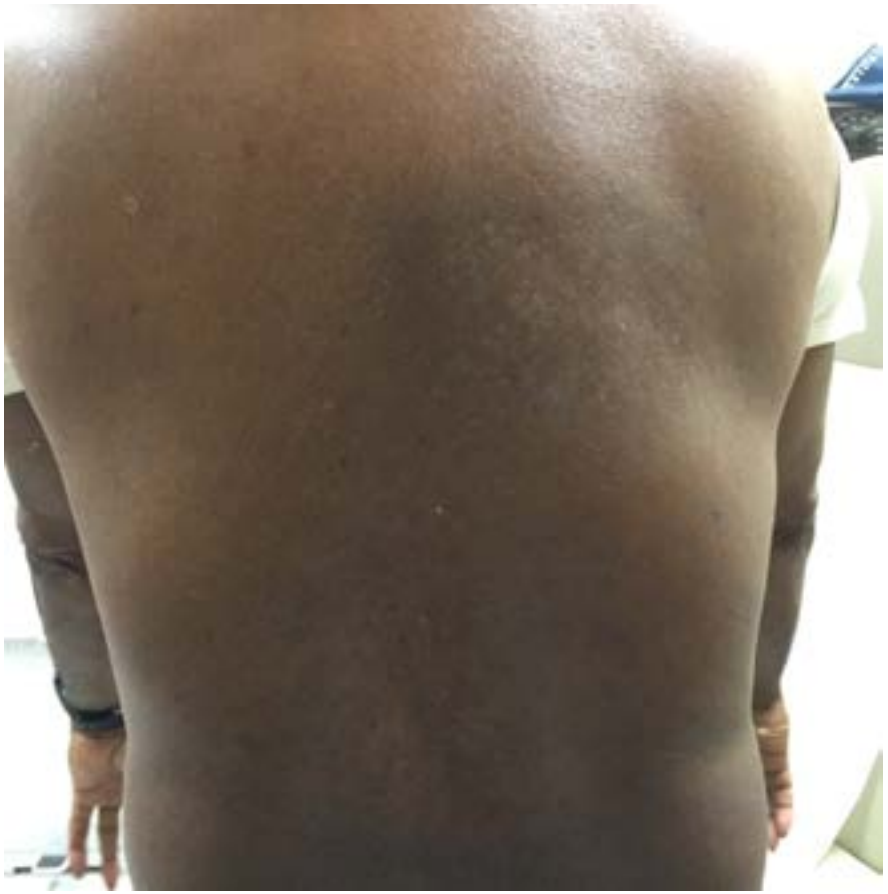




Patient Course

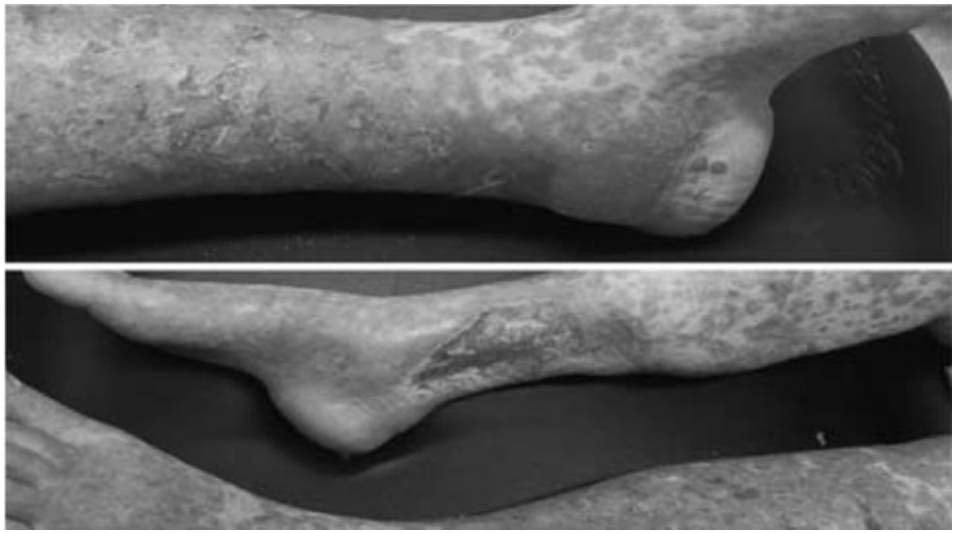
- Started on prednisone 80 mg daily with 3-4 week taper
- Clobetasol ointment BID x 2 weeks to genital area and oral ulceration; resolved and did not recur
- After prednisone dose reached 10 mg QD, rash and pruritus always recurred.
- Started narrowband ultraviolet B phototherapy 2-3 times a week – treated for 3 months
- Able to stop phototherapy and was maintained on prednisone 4 mg daily, then discontinued prednisone completely 2 months later.
- Still on pembrolizumab with stable disease.
- No recurrence of rash or pruritus for past 12 months.



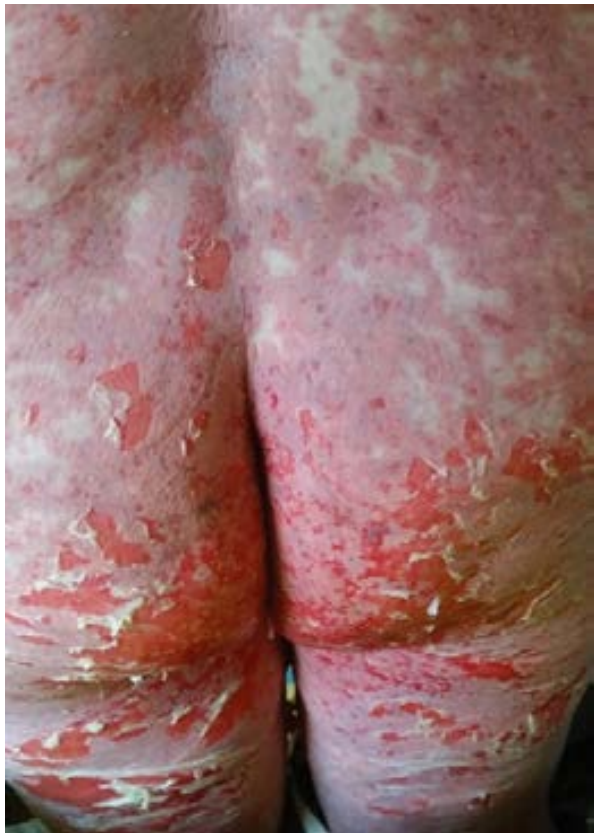


Anti-PD-1 Cutaneous Eruptions
Severe/life-threatening

TEN-like reaction associated with nivolumab following ipilimumab



J Immunother 2016, 39(3):149-152



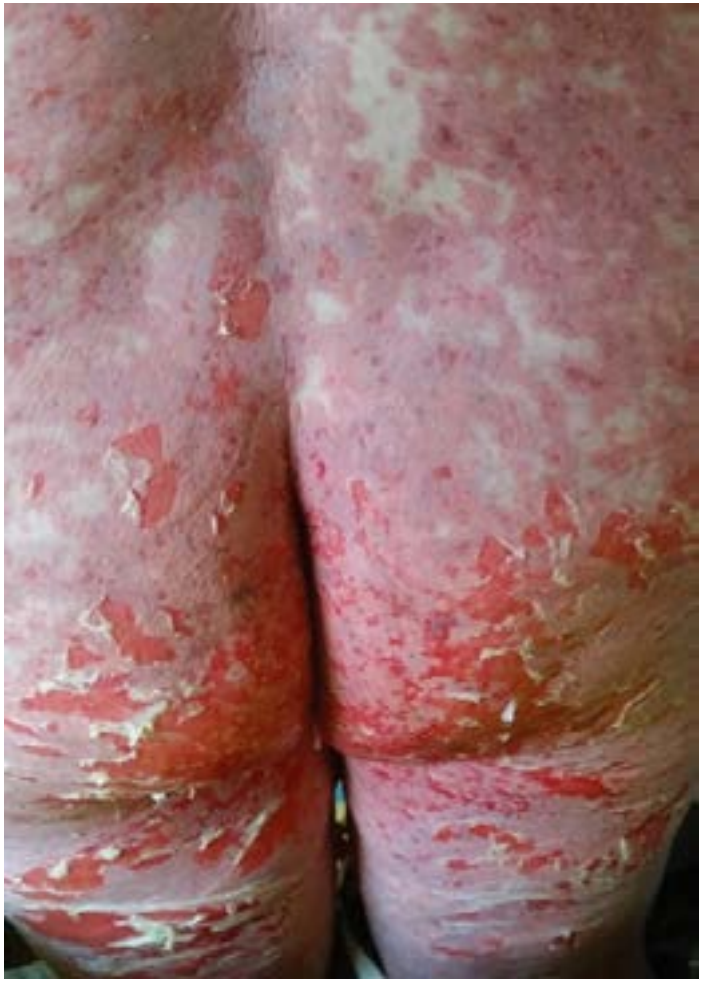
TEN due to nivolumab

J Cutan Pathol 2017; 00:1–4

- Diffuse morbilliform eruption -> slow progression over weeks to months
- Marked increase in PD-L1 staining expression in epidermis

- Pembrolizumab: 8 SJS, 2 TEN

- 50 yo woman, metastatic melanoma
- 3 months prior to admission, started ipilimumab + nivolumab x 1 cycle -> diffuse morbilliform, grade 2.
- Ipilimumab stopped.
- 2 more cycles of nivolumab -> slow progression. Short course of systemic steroids after each dose with some improvement. After 3rd dose nivolumab, treatment held. Started prednisone 1 mg/kg.
- Biopsy: mild interface dermatitis with rare necrotic keratinocytes. PD-L1 staining in few scattered keratinocytes and weak expression along epidermis.
- On admission, 90% BSA with 10% Nikolsky sign. Extensive conjunctival, oral, and genital desquamation. Immunohistochemical analysis demonstrated CD8+ cells aggregated at the dermal-epidermal junction and epidermal exocytosis of CD8+ cells. PD-L1 expression was markedly increased in the epidermis. Direct immunofluorescence was negative. Dx: TEN.
- Infliximab, prednisone 1 mg/kg. 2 days later, started IVIG x 3 doses. Developed septic shock and multiorgan failure. Died on hospital day 6.



J Cutan Pathol 2017; 00:1–4

*Ability of anti-PD-1 antibodies to induce TEN without the classic clinical morphology or time course of the disease

Immunotherapy-Induced Pruritus

- Approximately 30% of patients
- Associated with rash and xerosis
- Enhanced immune system activation in the skin

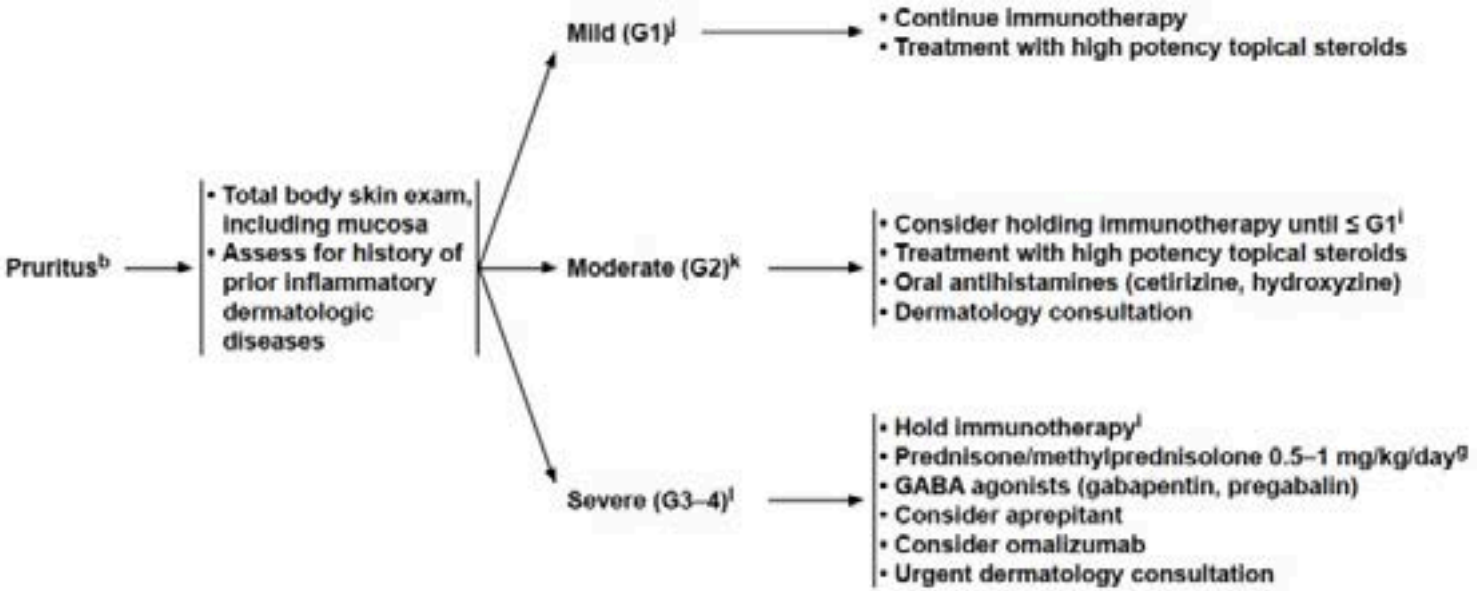
- Adversely affects quality of life

NCCN Guidelines Version 1.2018
Management of Immunotherapy-Related Toxicities

DERMATOLOGIC ADVERSE EVENT(S)

ASSESSMENT/GRADING

MANAGEMENT[h]



[b]Characterized by an intense itching sensation.
[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[j]Mild or localized.
[k]Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting instrumental ADLs.
[l]Intense or widespread; constant; limiting self-care ADLs or sleep. Assess serum IgE and histamine; consider oral antihistamines for increased histamine and omalizumab for increased IgE.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Lung Cancer 109 (2017) 58–61

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Case report

Aprepitant for refractory nivolumab-induced pruritus

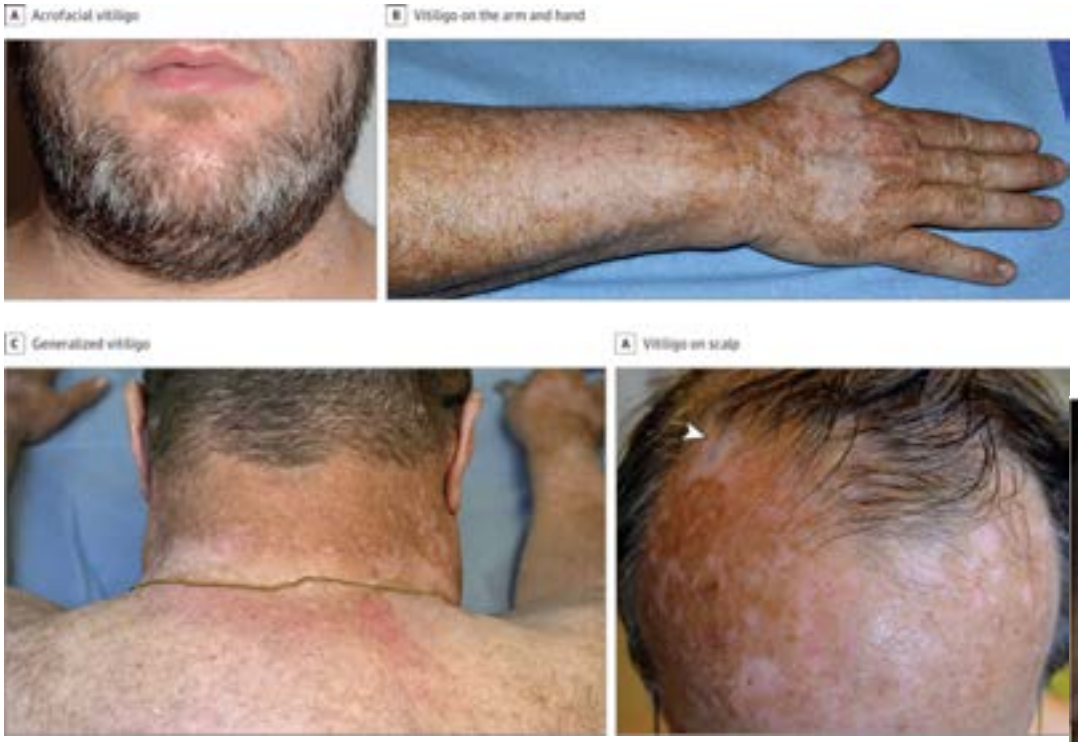
Jiro Ito[a,*], Daichi Fujimoto[a], Ayaka Nakamura[b], Tohru Nagano[b], Keiichiro Uehara[c], Yukihiro Imai[c], Keisuke Tomii[a]

[a] Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan
[b] Department of Dermatology, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan
[c] Department of Pathology, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan

76-year-old Japanese woman
Advanced NSCLC with nivolumab
Severe rash with mucosal involvement → SJS
Oral prednisolone 1 mg/kg
Rash resolved, but pruritus unremitting with emollients, antihistamines, steroids
Aprepitant 80 mg QD x 5 days

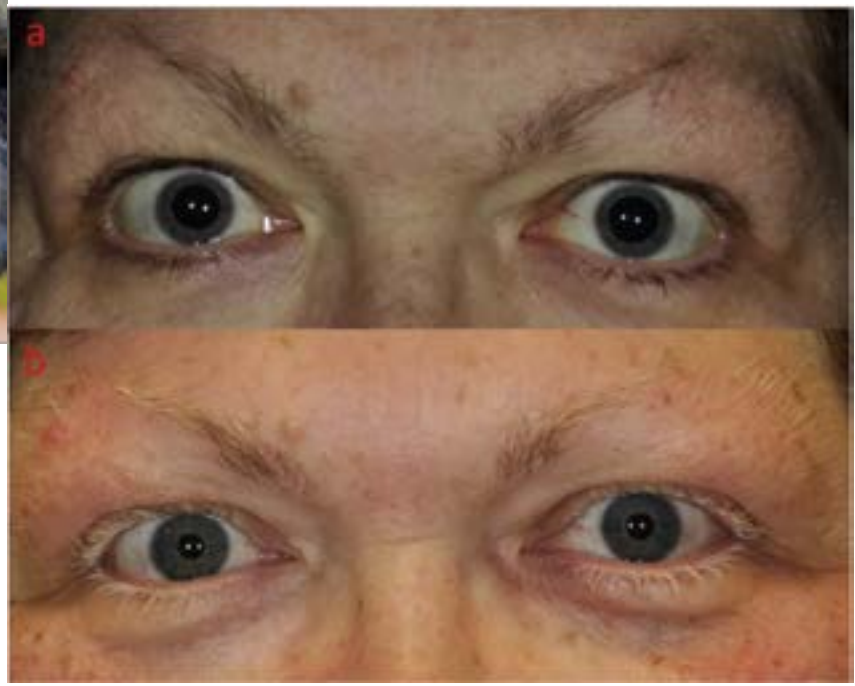
80 mg QD x 3-5 days; 120 mg, 80 mg, 80 mg

Vitiligo



JAMA Dermatol. 2016 Jan 1;152(1):45-51.

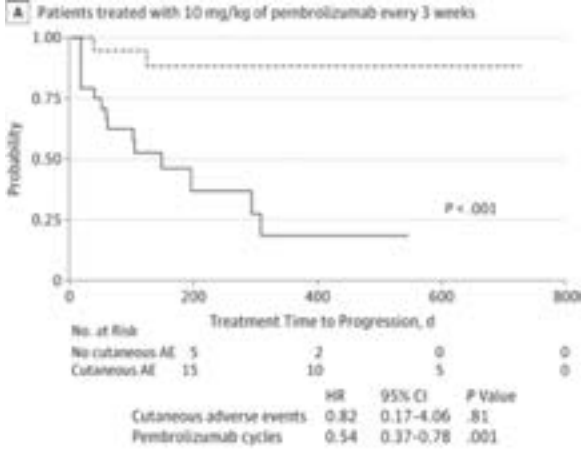
- 8-25% vitiligo
- 52 to 453 days to onset

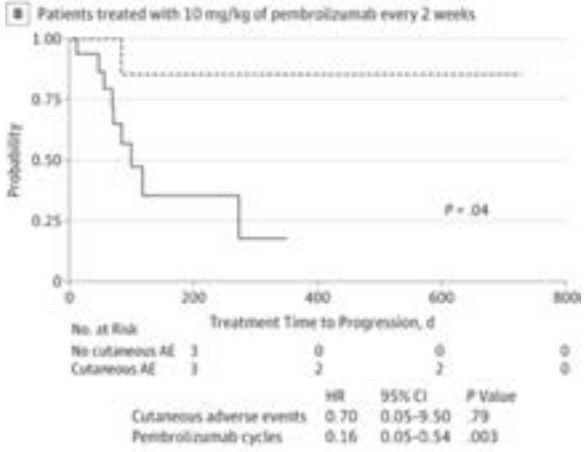


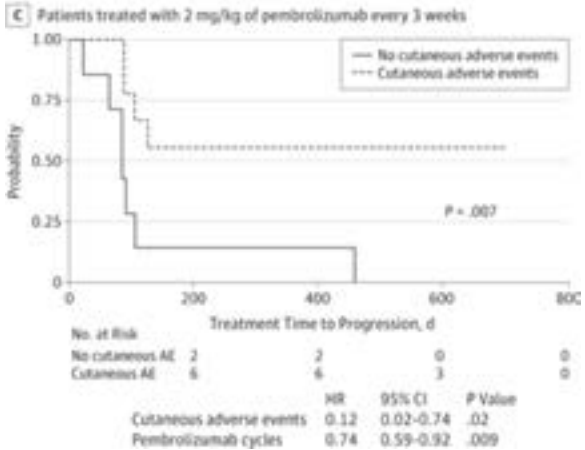
Hofmann L, et al. Europ J Cancer. 2016, 60:190-209

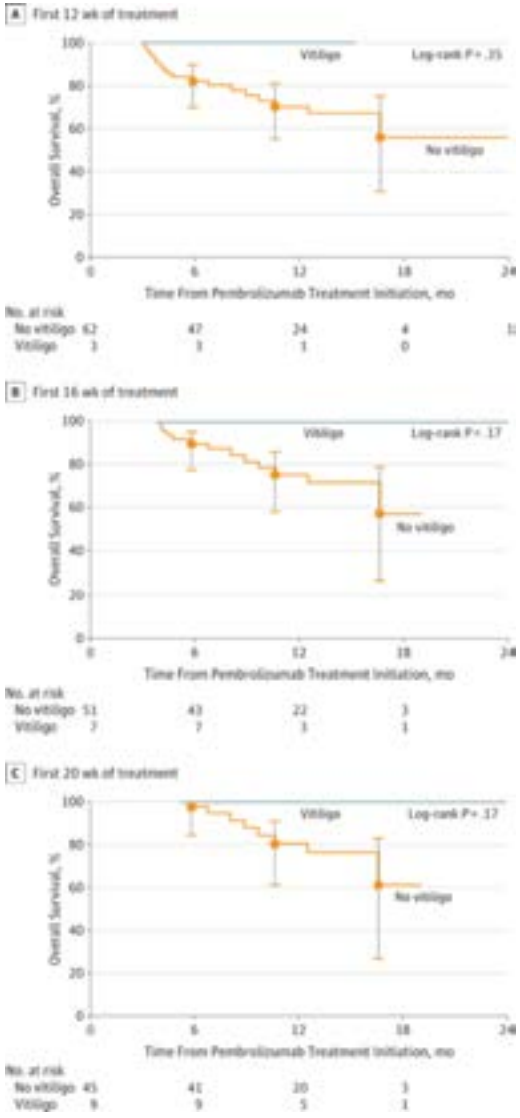
Association of Cutaneous AE and Vitiligo With Tumor Response in Patients With Metastatic Melanoma Treated With Pembrolizumab

JAMA Dermatol. 2016;152(1):45-51
JAMA Dermatol. 2015 Nov;151(11):1206-12



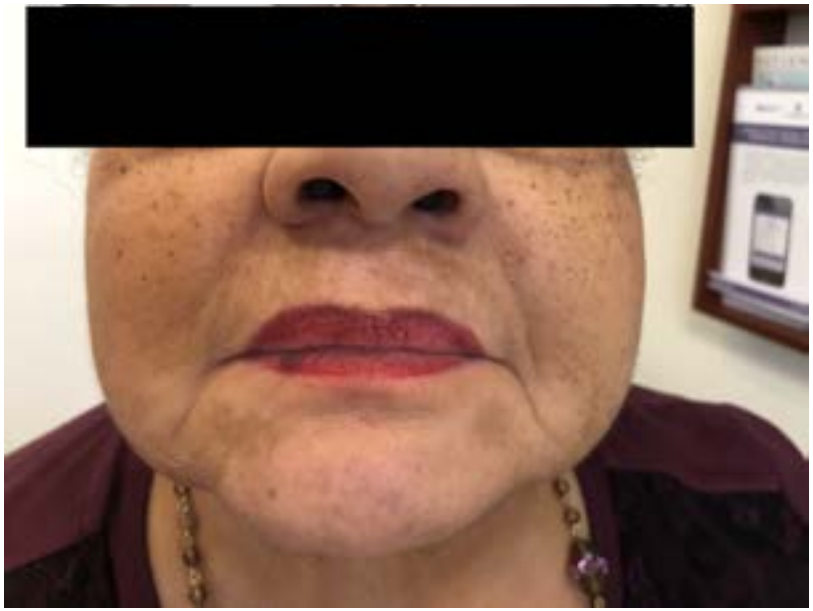


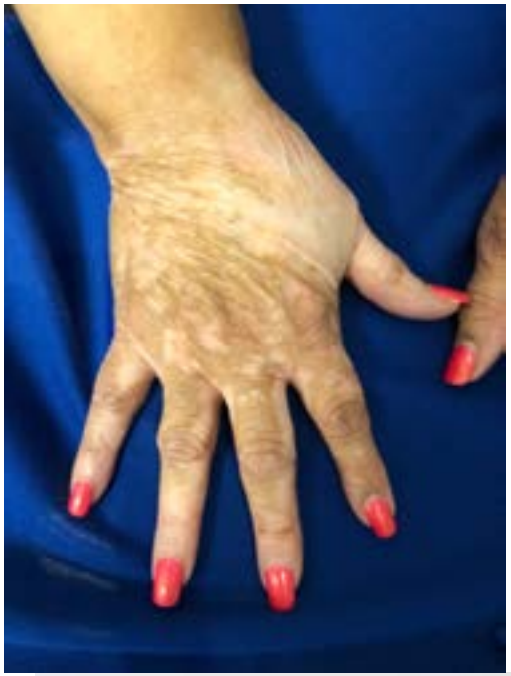




OR (complete or partial) associated with a higher occurrence of vitiligo: 71% vs 28%

Vitiligo in non-melanoma cancer patients





75 year old woman

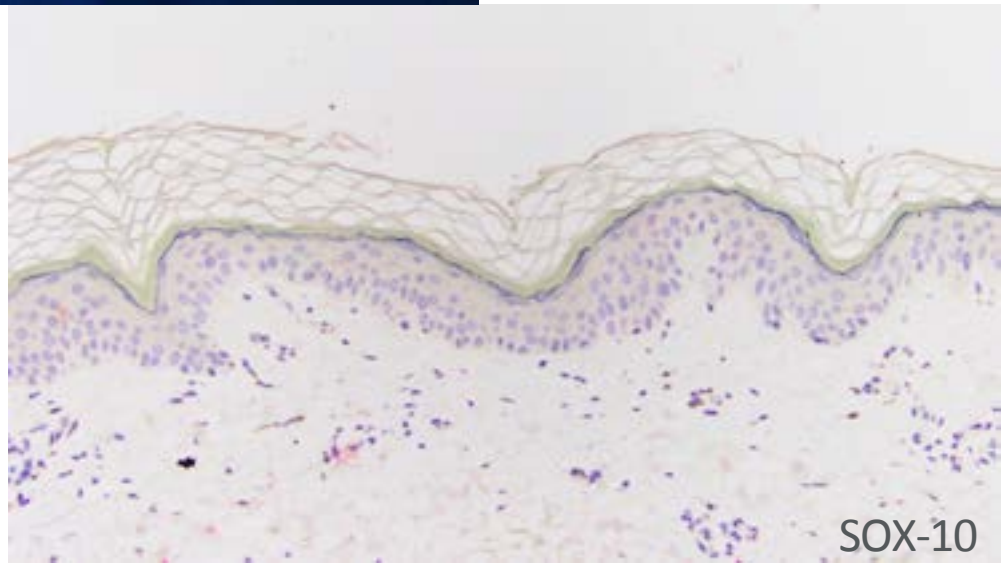
Stage IV NSCLC

Carboplatin + pemetrexed

4 months later, started on nivolumab

8 months after nivolumab initiation:

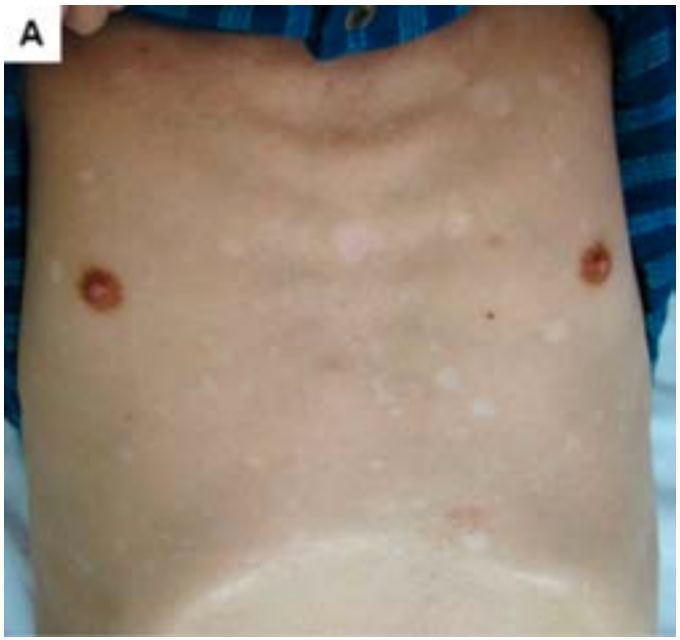
Patch of depigmentation on right hand

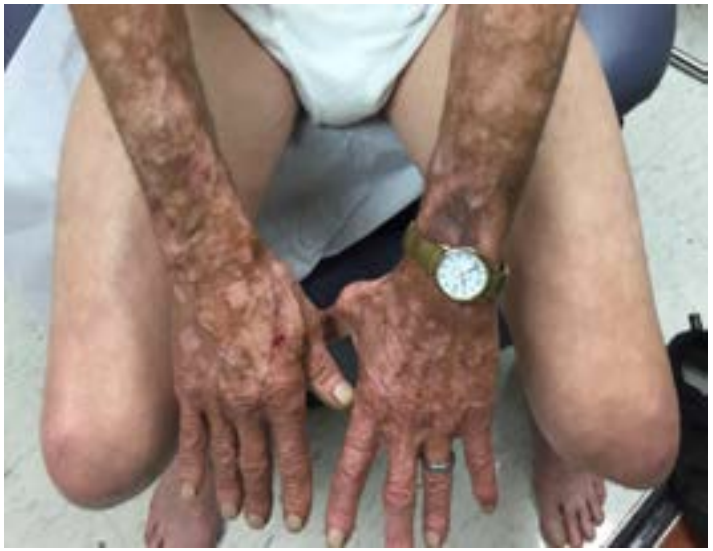


Vitiligo in non-melanoma cancer patients

- 75 yo man with stage 4 NSCLC, treated with docetaxel. Started nivolumab 3 months later due to progressive disease.
- 6 days later, vitiligo appeared on back, chest, abdomen, and extremities

- 66 yo man with AML in remission after chemotherapy and NSCLC previously treated with chemotherapy and local radiation
- On nivolumab as part of phase II clinical trial for prevention of AML recurrence
- Depigmentation starting 4 months after nivolumab initiation: arms, chest, face, neck



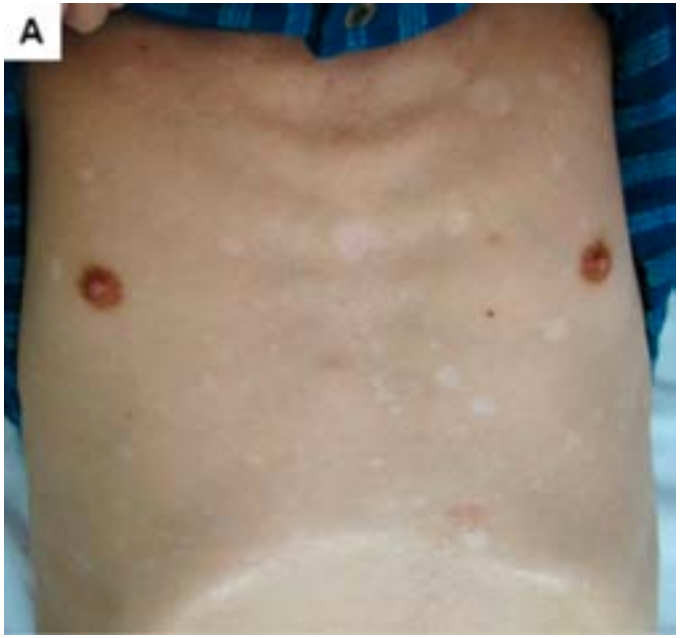


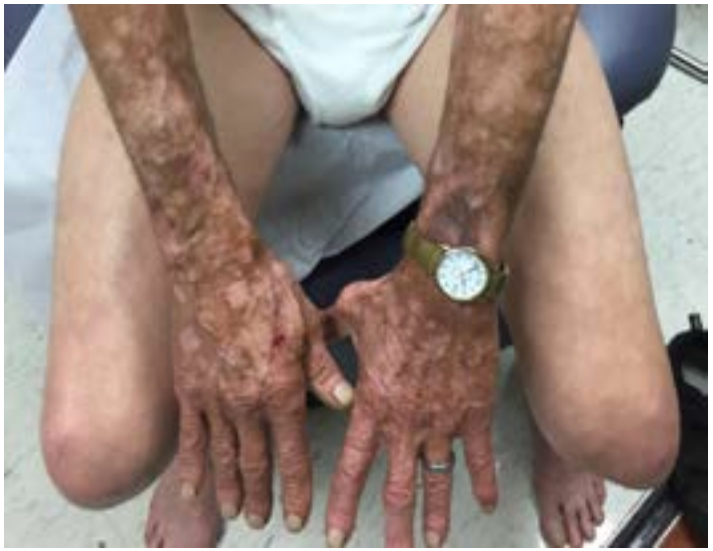
Northwestern Medicine® | Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Lung Cancer. 2017 Jul;109:42-44
JAAD Case Reports 2017;3:90-2

Vitiligo in non-melanoma cancer patients

- Cross-reaction with melanocyte differentiation antigens: gp100, MelanA/MART-1, tyrosinase?
- Another shared antigen between NSCLC and melanocytes?





JAMA Dermatology | Brief Report

Hair Repigmentation During Immunotherapy Treatment With an Anti-Programmed Cell Death 1 and Anti-Programmed Cell Death Ligand 1 Agent for Lung Cancer

Noelia Rivera, MD; Aram Boada, MD; M. Isabel Bielsa, MD, PhD; M. Teresa Fernández-Figueras, MD, PhD; Enric Carcereny, MD; M Teresa Moran, MD; Carlos Ferrándiz, MD, PhD

JAMA Dermatol. 2017 Jul 12.

- 13/14 patients with lung cancer
- 4 = squamous cell lung cancer
- 10 = lung adenocarcinoma
- 13/14 complete hair repigmentation to baseline hair color
- Nivolumab (n=11)
- Pembrolizumab (n=1)
- Atezolizumab (n=2)
- 13/14 partial response or stable disease

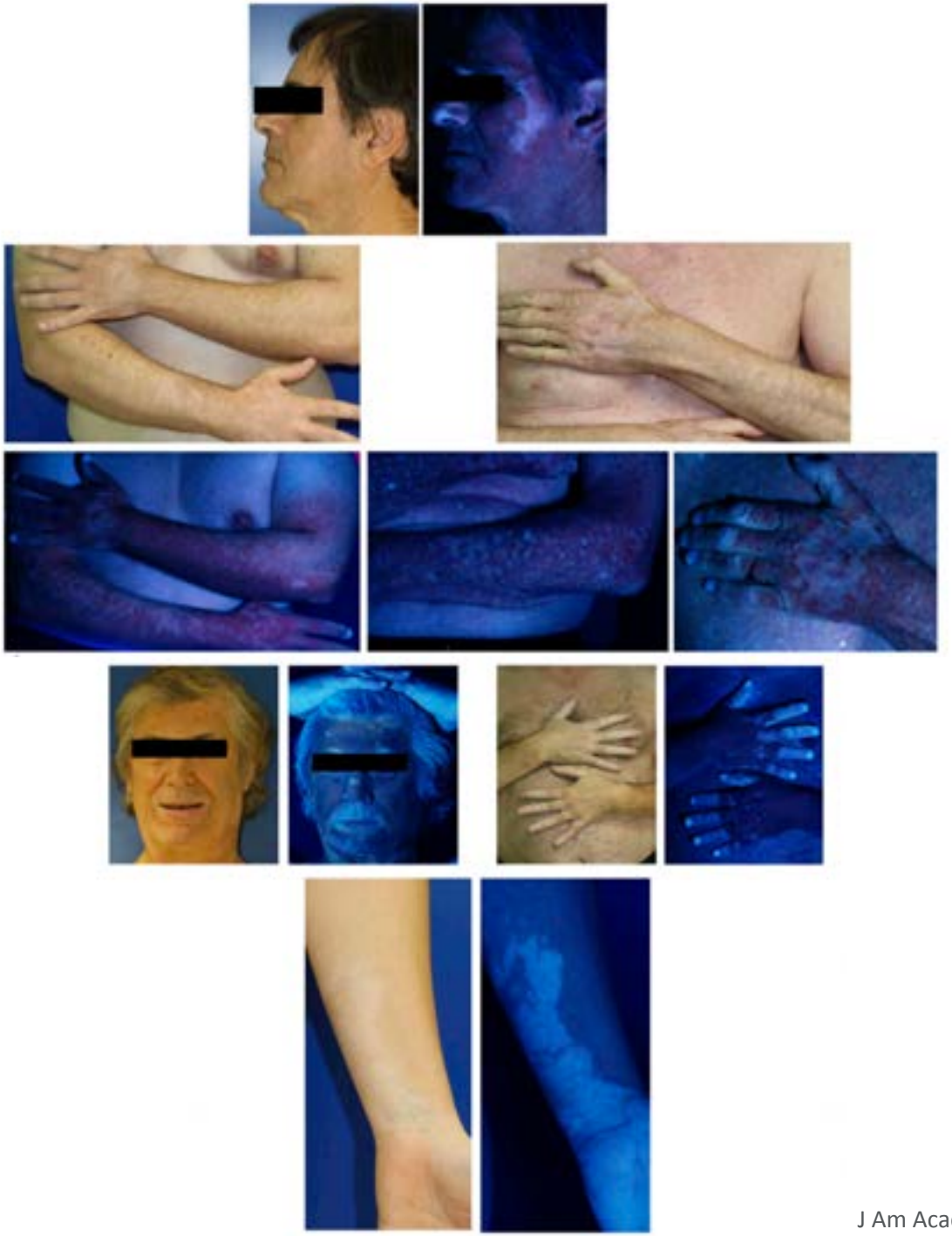
JAMA Dermatol. 2017 Jul 12.

Vitiligo-like lesions occurring in patients receiving anti-programmed cell death–1 therapies are clinically and biologically distinct from vitiligo

Maiana Larsabal, MD,[a] Aurélie Marti, MD,[a] Clément Jacquemin, PhD,[b] Jérôme Rambert, PhD,[b] Denis Thiolat, BS,[b] Léa Dousset, MD,[a] Alain Taieb, MD, PhD,[a,b] Caroline Dutriaux, PhD, MD,[a] Sorilla Prey, MD, PhD,[a] Katia Boniface, PhD,[a,b] and Julien Seneschal, MD, PhD[a,b]
Bordeaux, France

- 8 patients on anti-PD1 therapy vs 30 vitiligo controls
- Photoexposed areas with specific depigmentation pattern consisting of multiple flecked lesions
- No personal or family history of vitiligo, thyroiditis, or other autoimmune d/o
- Blood and skin samples:
  - Increased CXC motif ligand 10 levels in serum
  - Skin infiltration of CD8 T cells expressing CXC motif receptor 3 and producing elevated levels of IFN-γ and TNF-α
- Mean BSA 4.25% (1-9%)

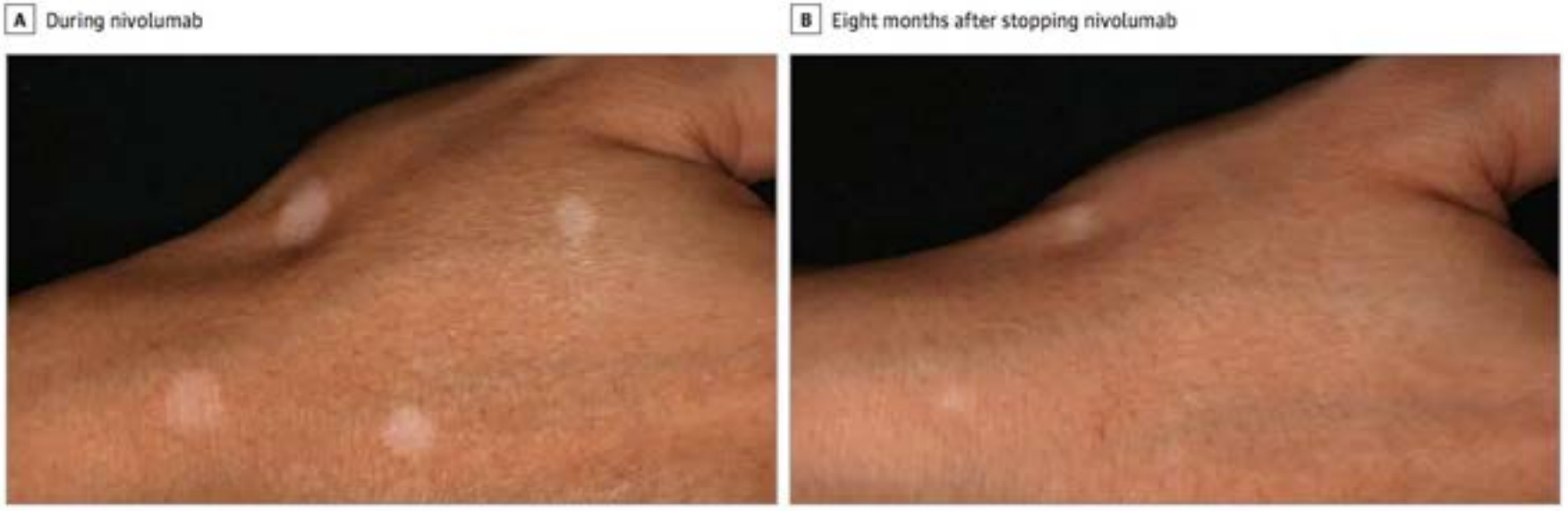
J Am Acad Dermatol 2017;76:863-70



J Am Acad Dermatol 2017;76:863-70

Repigmentation of Vitiligo Associated with Melanoma Relapse

Figure 2. Clinical Appearance of Treatment-Related Vitiligo and Repigmentation of Vitiligo in Association With Brain Metastases

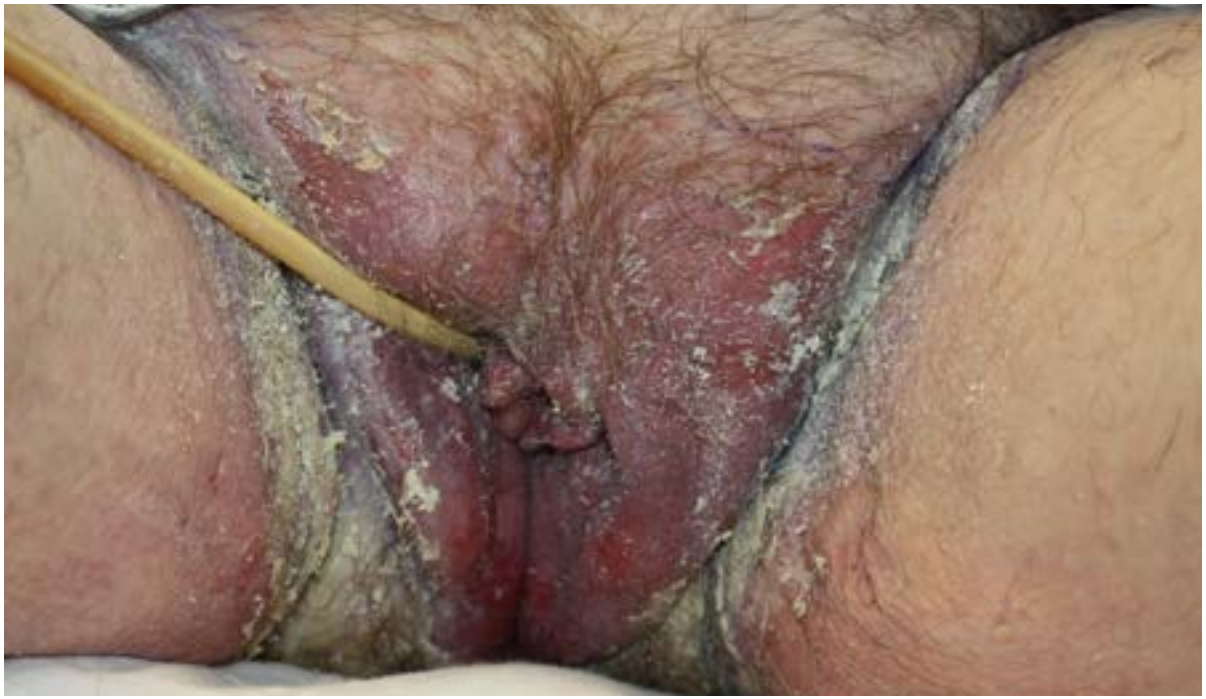


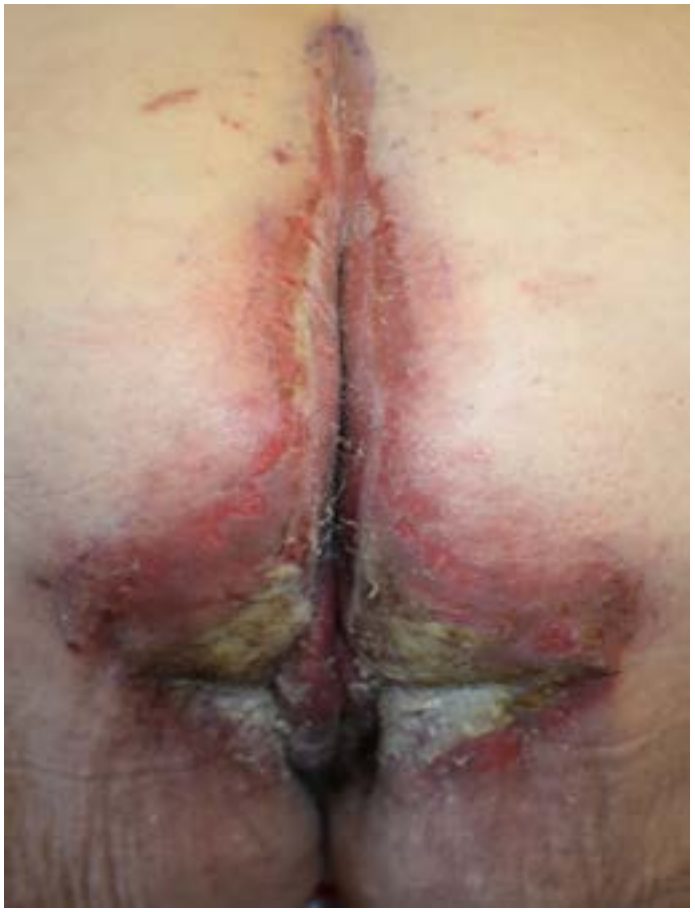
A, Multiple vitiligo areas appeared on the right dorsal hand during nivolumab therapy. B, Eight months after cessation of nivolumab treatment, repigmentation of vitiligo was observed.

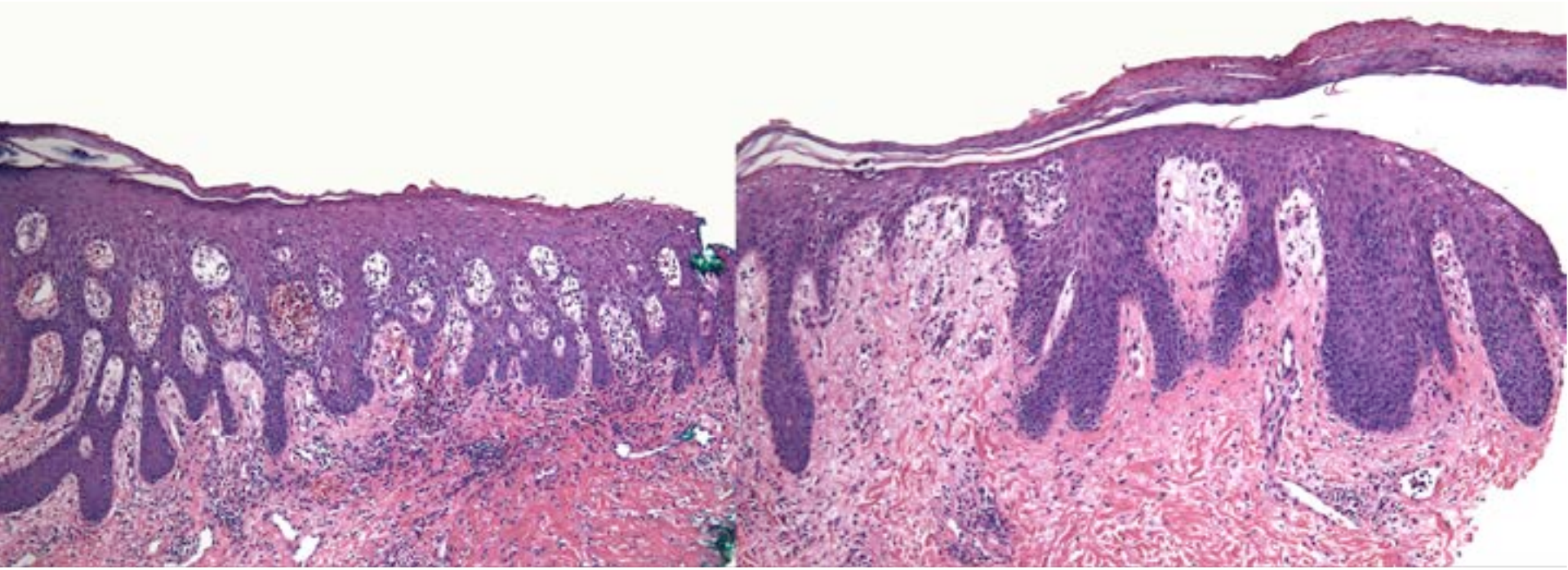
Nakamura Y et al. JAMA Dermatol. 2017 Sep 1;153(9):942-944

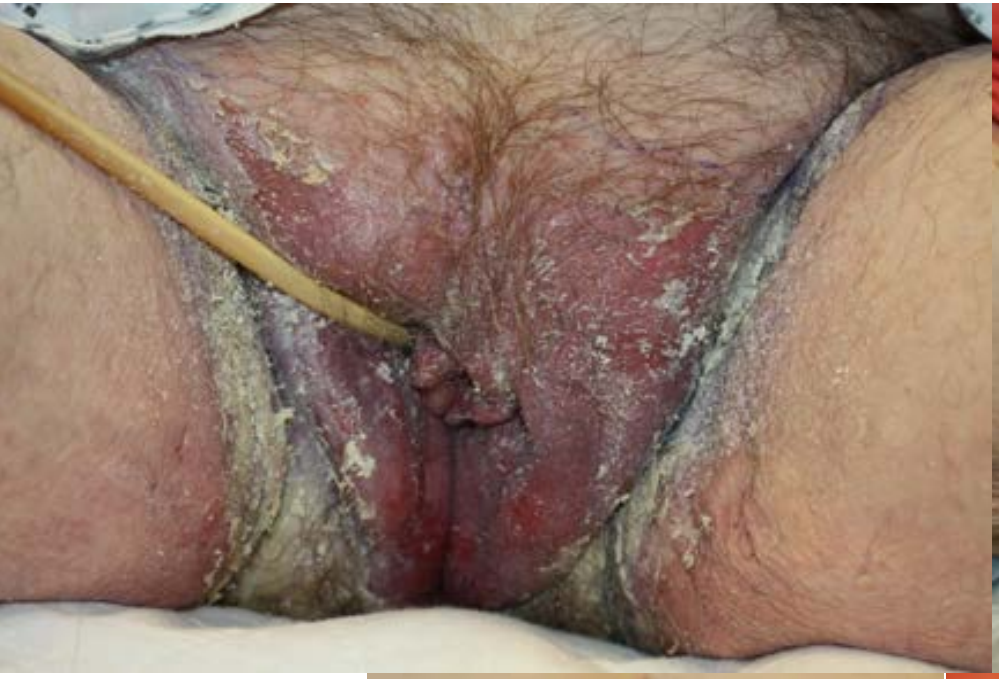
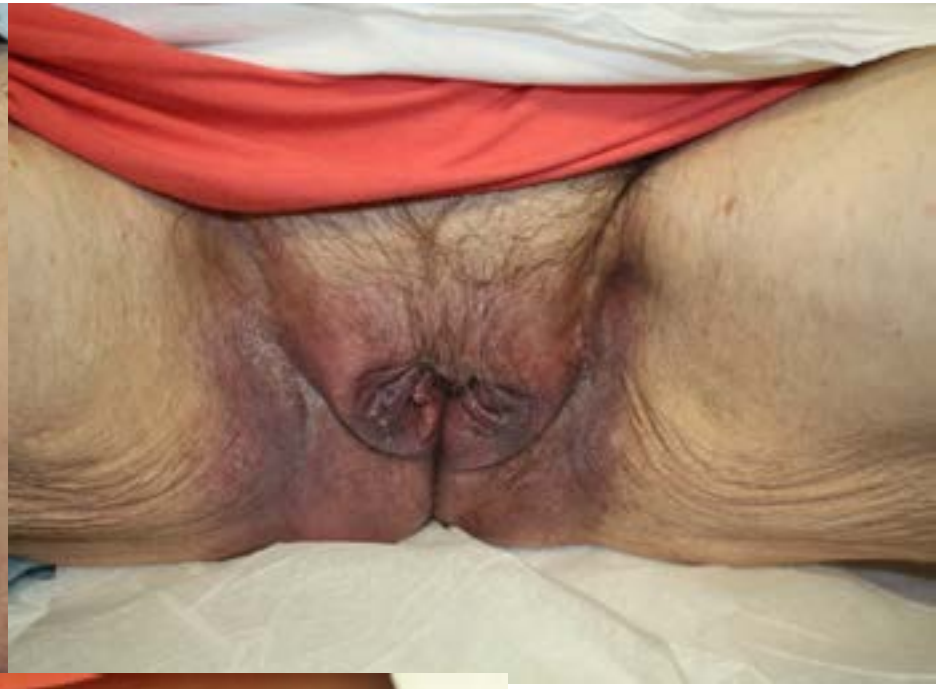
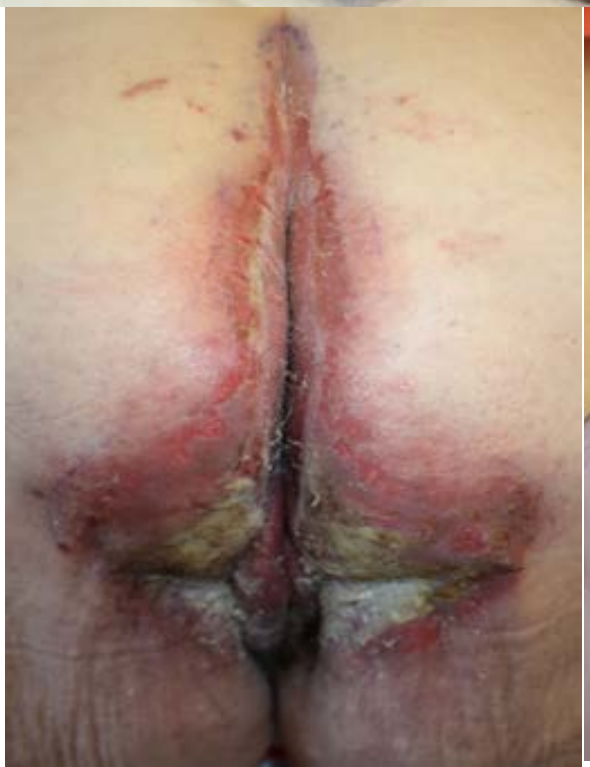
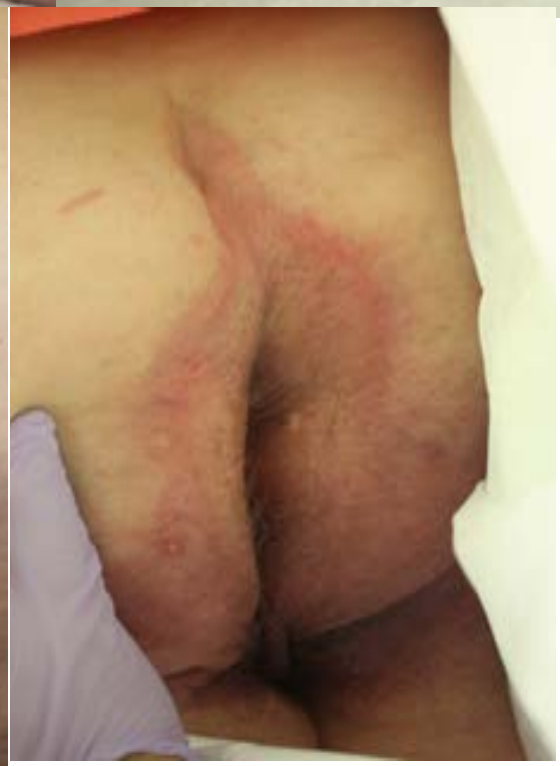
Case

- 83 year old Caucasian woman with metastatic melanoma to lung and spine
- Pembrolizumab 2 mg/kg IV every 3 weeks
- 2 month history of worsening vaginal and intergluteal eruption
- Onset between cycles 2 and 3
- Empiric systemic anti-fungal and antibacterial therapy with minimal response
- Consulted after admission to hospital for rash







Anti-PD-1 Cutaneous Eruptions

- Exacerbation of psoriasis
- Psoriasiform eruptions

J Eur Acad Dermatol Venereol. 2015 Sep 21

Acta Derm Venereol. 2015 Aug 13

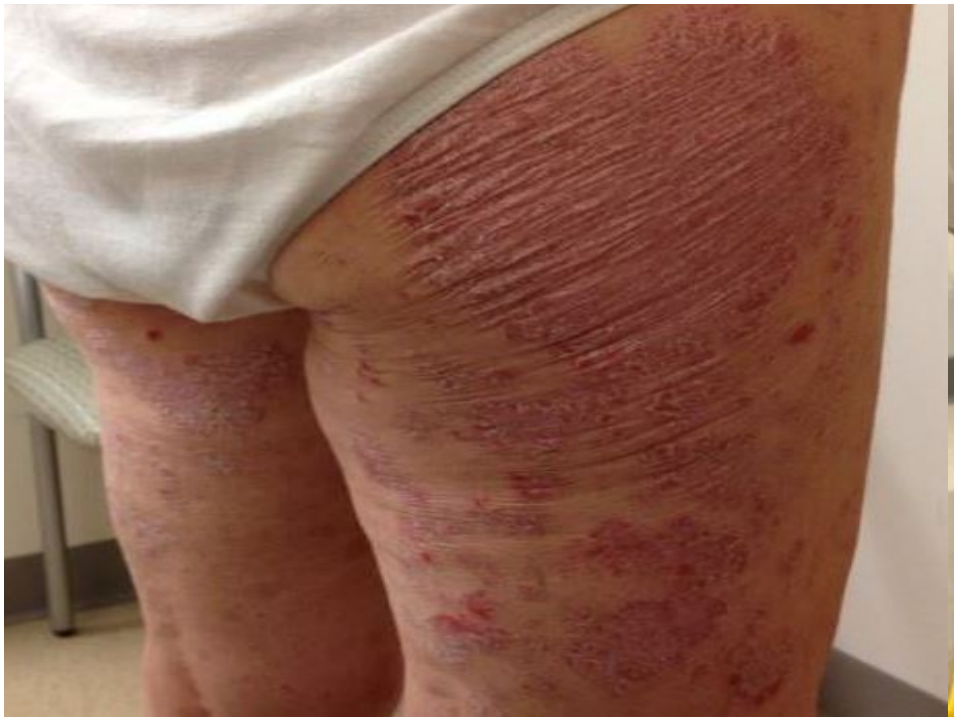
JAMA Dermatol. 2015 Jul;151(7):797-9
Curr Opin Oncol 2016,28:25-263
J Eur Acad Dermatol Venereol. 2016 Oct 14
JAMA Dermatol. 2016 May 1;152(5):590-2
Current Prob Cancer. 2017;41:407-412

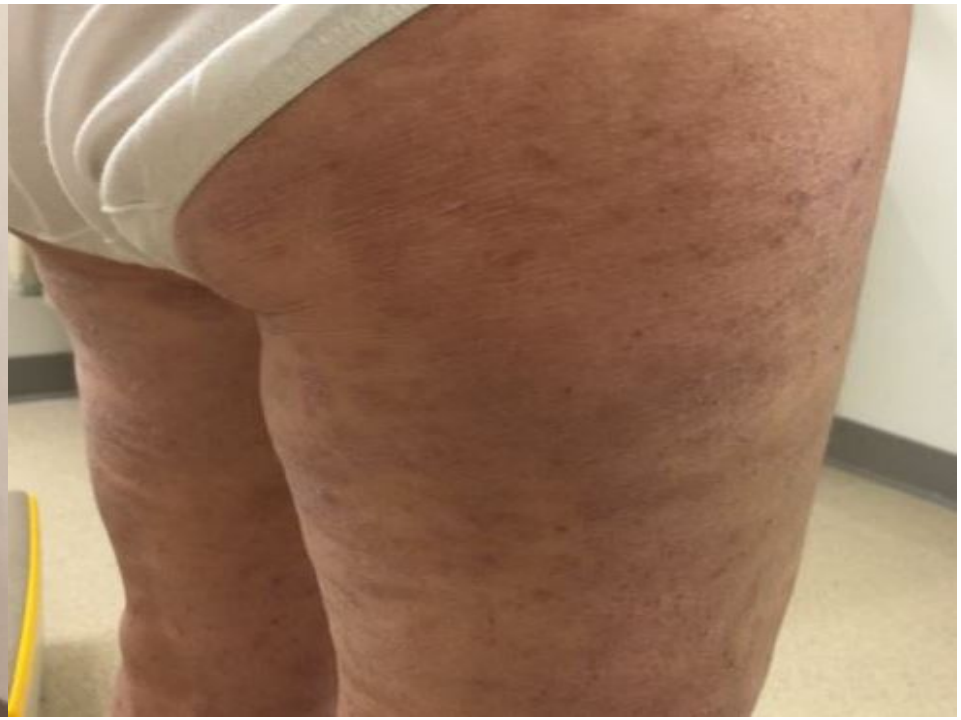
Anti-PD-1 Induced Psoriasis

- 21 patients
- 86% male
- 71% with history of psoriasis
- Mean time of onset between anti-PD1 initiation and psoriasis flare: 50 days
  - De novo psoriasis: 90 days
  - Preexisting psoriasis: 33 days
- 95% developed plaque psoriasis
  - + guttate: n=6
  - + palmoplantar: n=4
  - + pustular palmoplantar: n=1

- 81% topical treatment
- 10% systemic steroids
- 5% acitretin (5/17 patients required acitretin as second-line tx)
- 5% phototherapy
- 91% controlled by treatment; 9% worsened

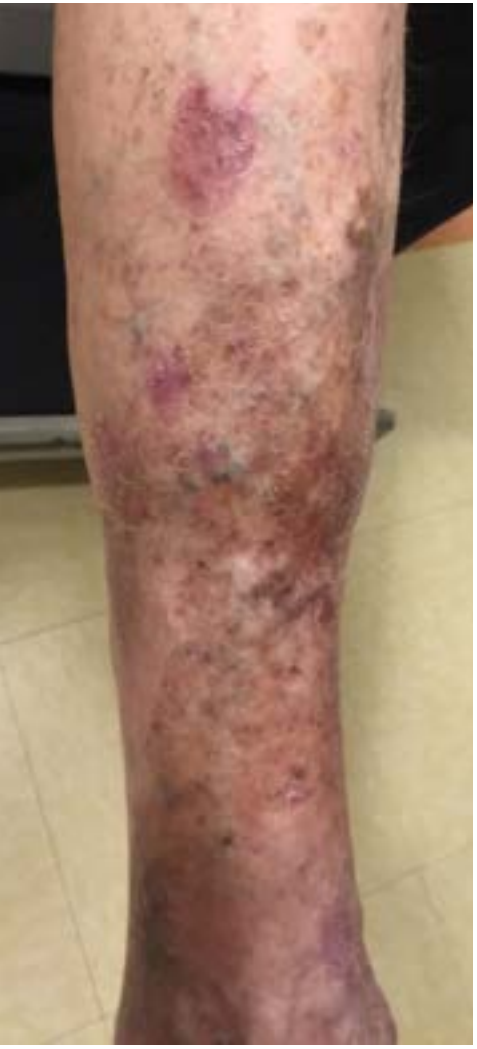
Bonigen J et al. Oct 2016 doi: 10.1111/jdv.14011



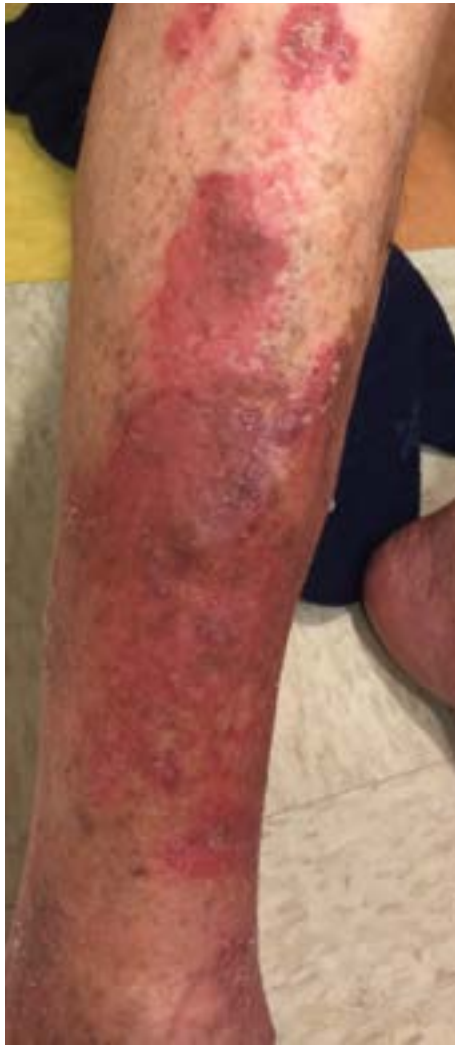


- If known history of psoriasis, make sure patients are followed carefully during immunotherapy.
- Initiate topical steroid treatment early on with a maintenance regimen:

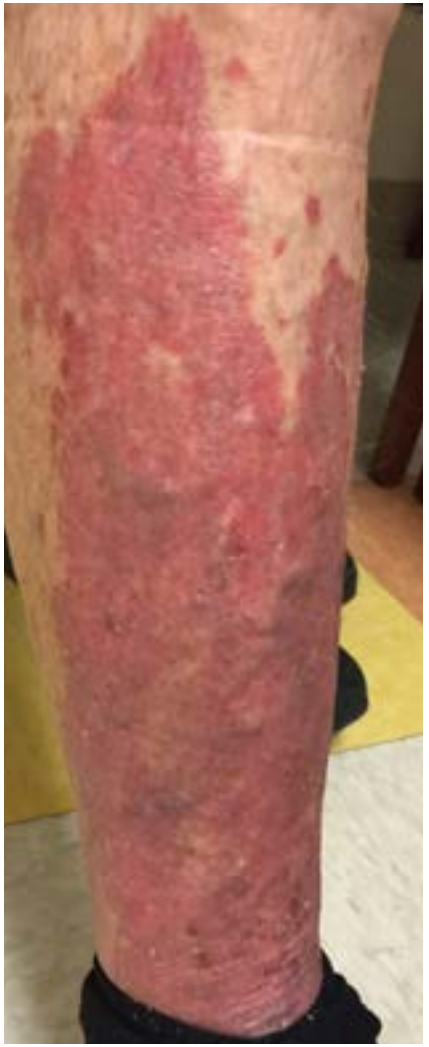
  E.g. Topical steroids BID x 2 weeks, then topical calcipotriene cream/ointment QD-BID during on weekdays and topical steroids QD-BID on weekends
- Low threshold to add on phototherapy while on immunotherapy.
- Can consider additional therapy: acitretin, low-dose methotrexate



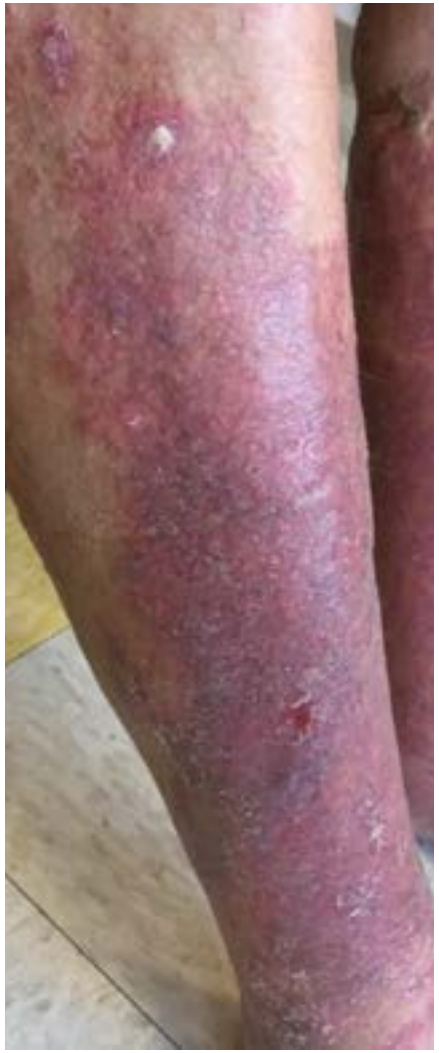
Feb



May



Aug



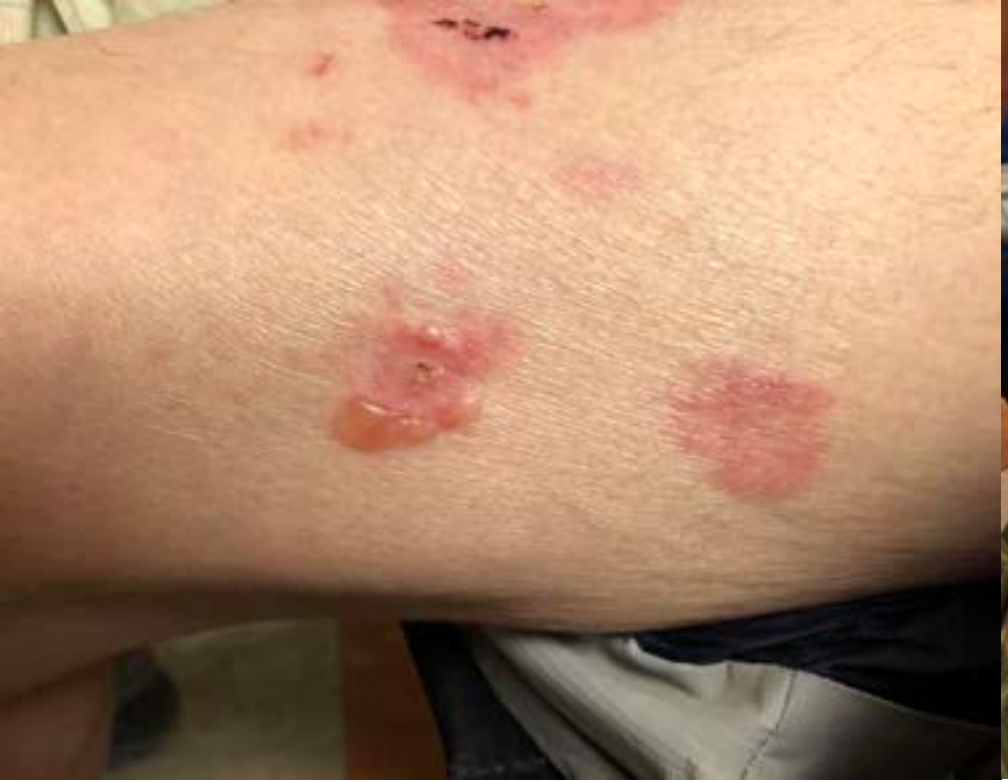
Oct

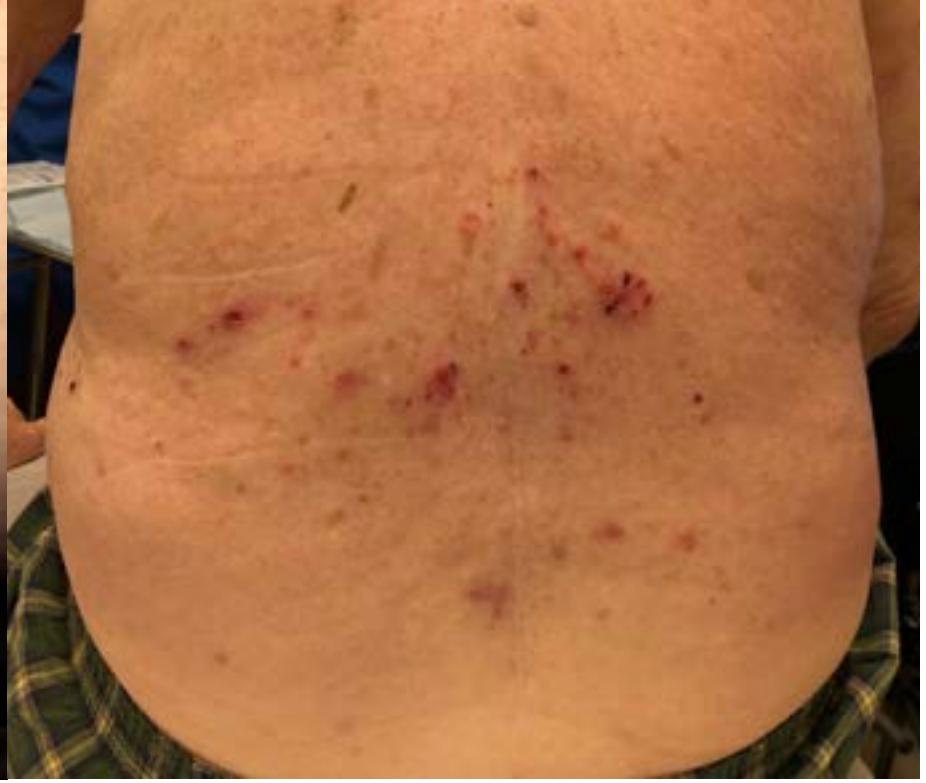
Anti-PD-1 Cutaneous Eruptions

- Autoimmune bullous skin disorders
  - Bullous pemphigoid

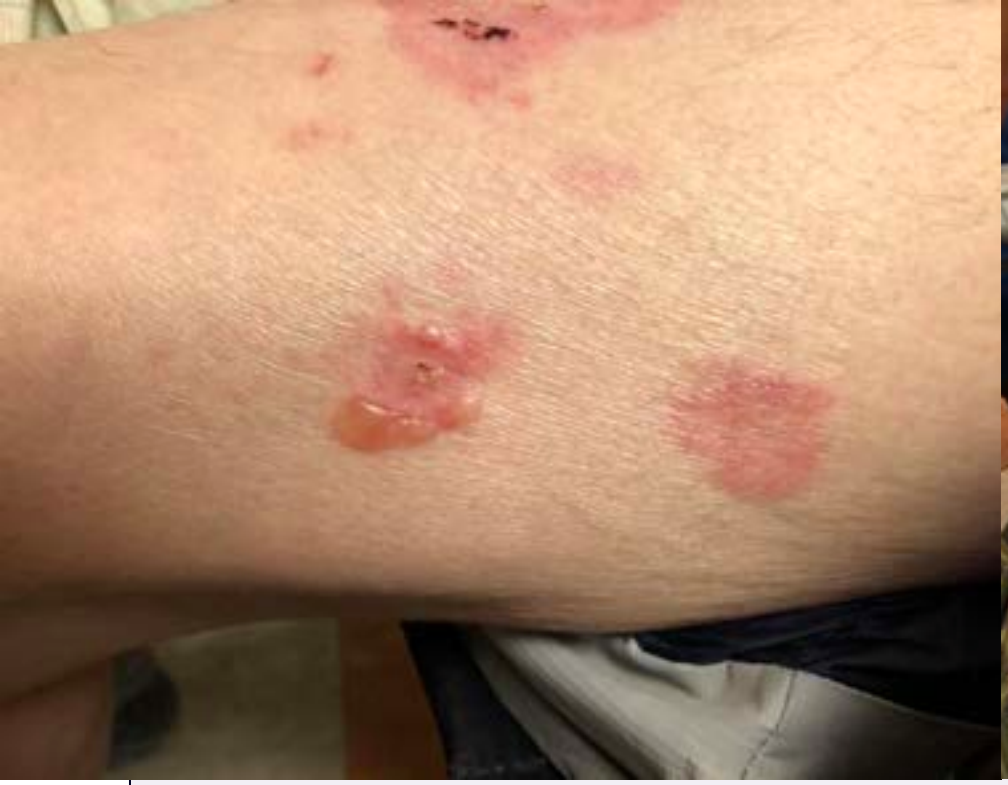
Cancer Immunol Res. 2016 Feb 29.

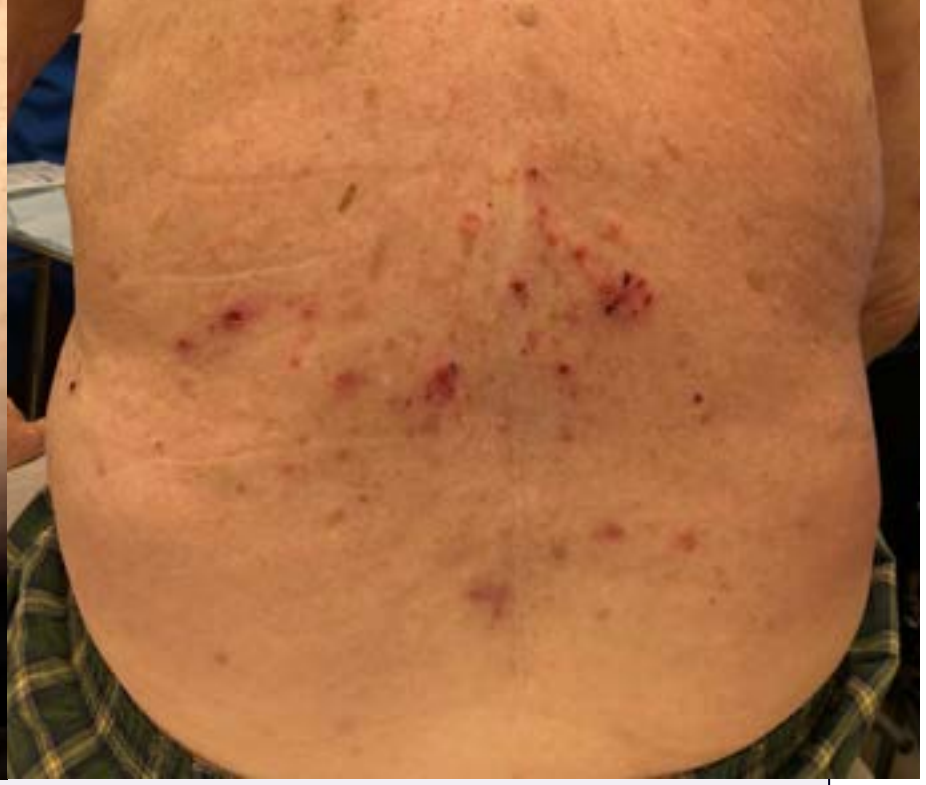
Melanoma Res. 2015 Jun;25(3):265-8.
Intl J Dermatolo. 2018;57:664-669.



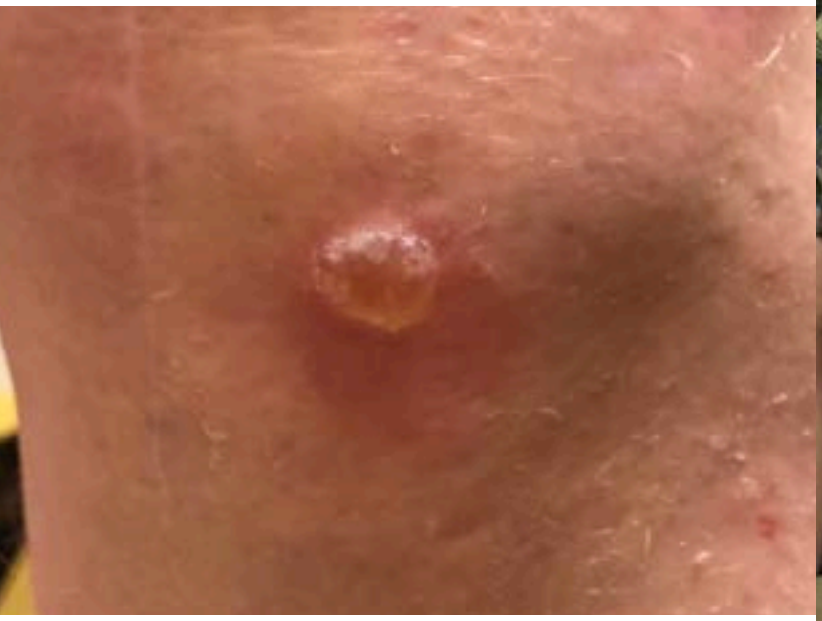


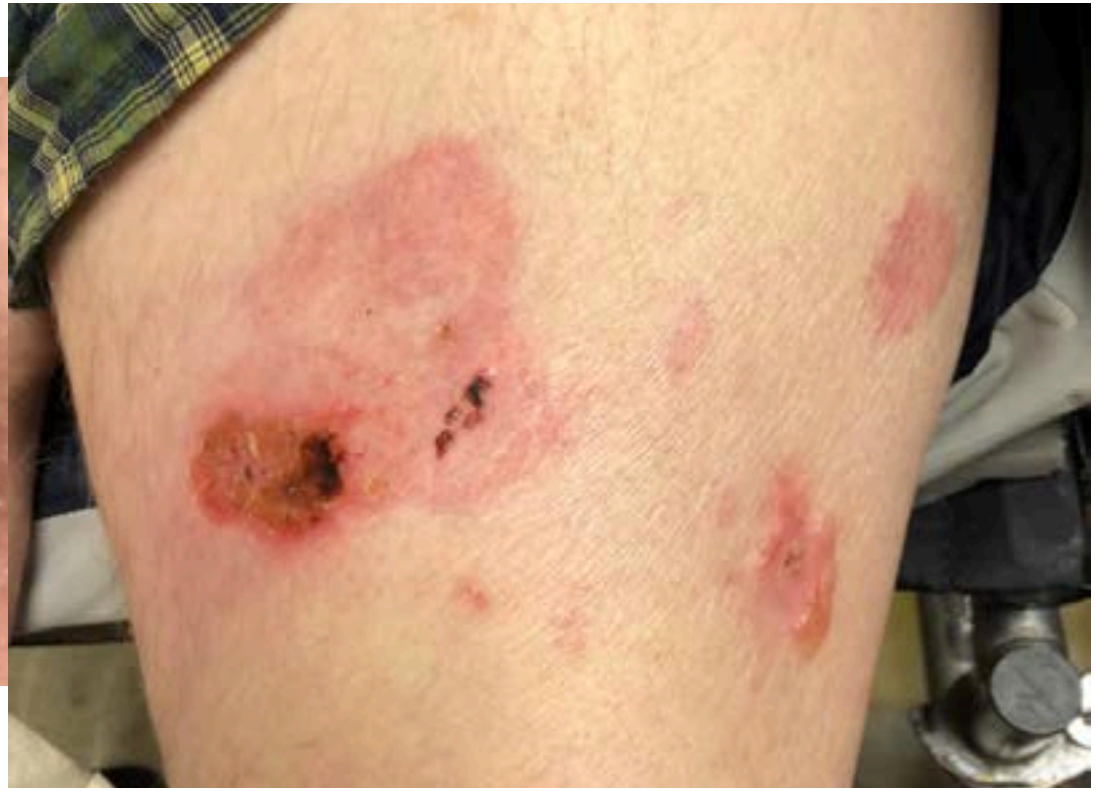
- At least 21 cases reported: pembro, nivo, durvalumab, atezolizumab
- Pruritus: prominent feature, preceding or concurrent
- Mean time to pruritus: 17 weeks
- Time to development of bullae: 6 to 80 weeks (median 24 weeks)
- Metastatic melanoma, head/neck SCC, lung adenocarcinoma, lung SCC, NSCLC, renal cell carcinoma, urothelial carcinoma
- Mean age: 71 years
- 6/21 patients = 29% had oral mucosal involvement





- Topical steroid monotherapy
- Oral steroids + topical steroids
- Doxycycline + niacinamide: n=1; + oral and topical steroids: n=3
- Rituximab: n=1
- Omalizumab: n=1
- 3/21 patients: prolonged courses of BP for 3-12 months after discontinuation of checkpoint inhibitor
- Discontinuation necessary in 16/21 cases = 76%
- 7/19 patients = 37% had cancer progression or patient death shortly after BP diagnosis and checkpoint inhibitor discontinuation





- <u>2 theories</u>:
  - Altered regulation of T-cells targeting collagen XVII/ BP180
  - Increased autoantibody production against BP180
- In patients with persistent or unusual pruritus, consider subclinical BP.
- Can take months to resolve due to autoimmune activation

NCCN Guidelines Version 1.2018
Management of Immunotherapy-Related Toxicities

NCCN Guidelines Index
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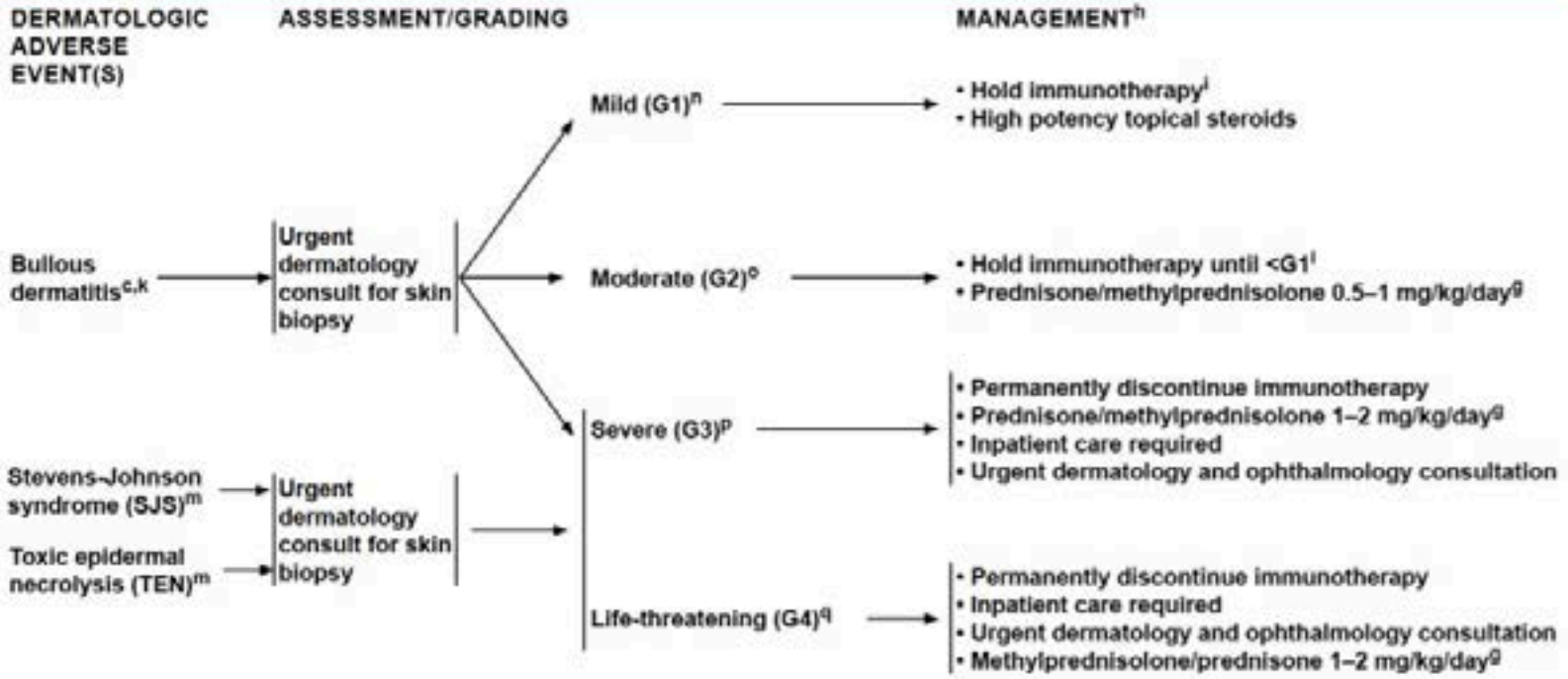
Discussion



[c]Characterized by inflammation of the skin and the presence of bullae, which are filled with fluid.
[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[k]Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting instrumental ADLs.

[m]Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) should be treated as grade 3–4 bullous dermatitis. SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10%–30%, and >30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.
[n]Asymptomatic; blisters covering <10% BSA.
[o]Blisters covering 10%–30% BSA; painful blisters; limiting instrumental ADLs.
[p]Blisters covering >30% BSA; limiting self-care ADLs.
[q]Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Other reported cutaneous side effects to checkpoint inhibitors

- Acneiform eruption
- Actinic keratosis
- Acute generalized exanthematous pustulosis (AGEP)
- Annular granuloma
- Alopecia areata, universalis
- Basal cell carcinoma
- Dermal hypersensitivity reaction (DHR)
- Dermatitis herpetiformis
- Dermatomyositis
- Drug rash with eosinophilia and systemic symptoms (DRESS)
- Eruptive keratoacanthoma
- Erythema
- Erythema-nodosum-like panniculitis
- Exfoliative reaction
- Grover's disease
- Hyperhidrosis

- Nail changes
- Necrotizing vasculitis
- Papulopustular rosacea
- Peritumoral inflammatory cellulitis
- Photosensitivity reaction
- Pityriasis lichenoides-like reaction
- Prurigo nodularis
- Pyoderma gangrenosum-like ulcerations
- Radiation-associated dermatitis
- Regression of melanocytic nevi
- Sarcoidosis
- Sclerodermoid reaction
- Seborrheic keratosis
- Sjögren’s syndrome
- Squamous cell carcinoma
- Sweet’s syndrome
- Tumoral melanosis
- Urticaria
- Xerosis

Eruptive keratoacanthomas

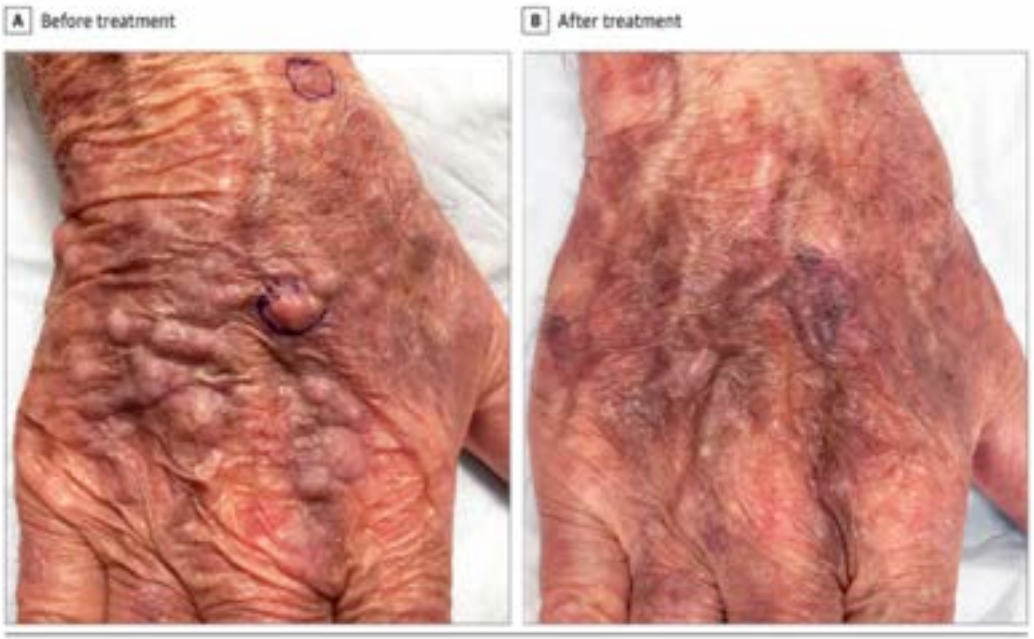
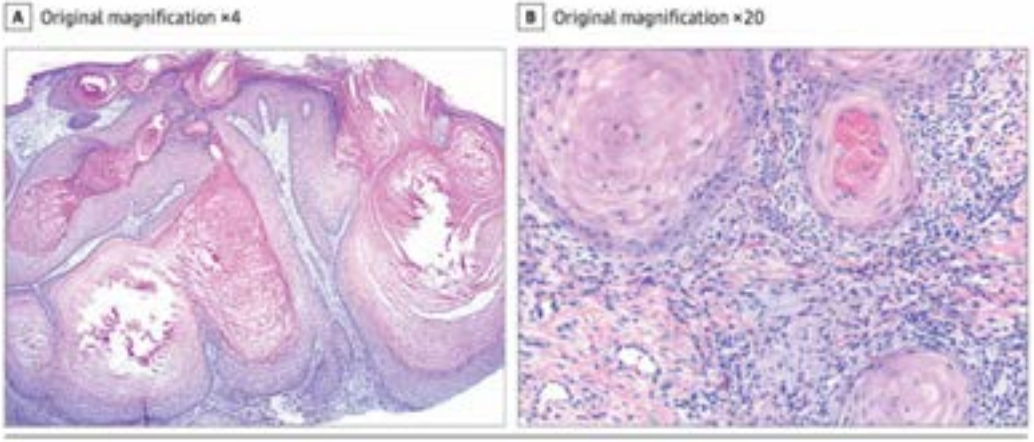


Figure 2. Hematoxylin-Eosin Biopsy Sections Showing a Multiloculated, Crateriform, Keratin-Filled Atypical Squamoproliferative Lesion



Cutaneous SCCs

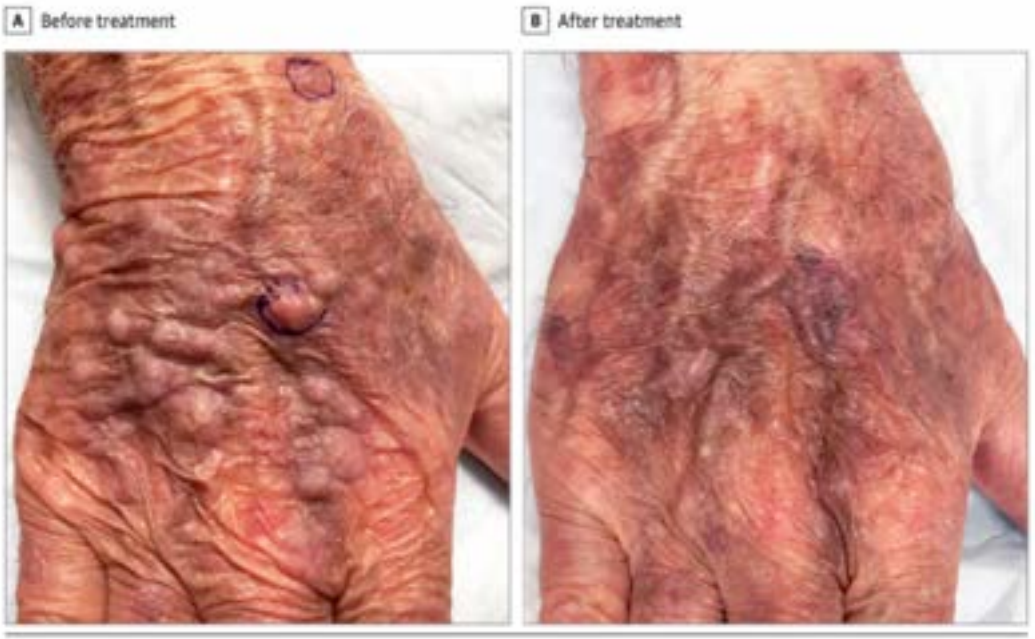
5/82 patients = 6.1%

Face, chest, arms

Older patients (73 yo vs 60 yo)

Hwang et al. J Am Acad Dermatol 2016; 74:455-61.

Eruptive keratoacanthomas



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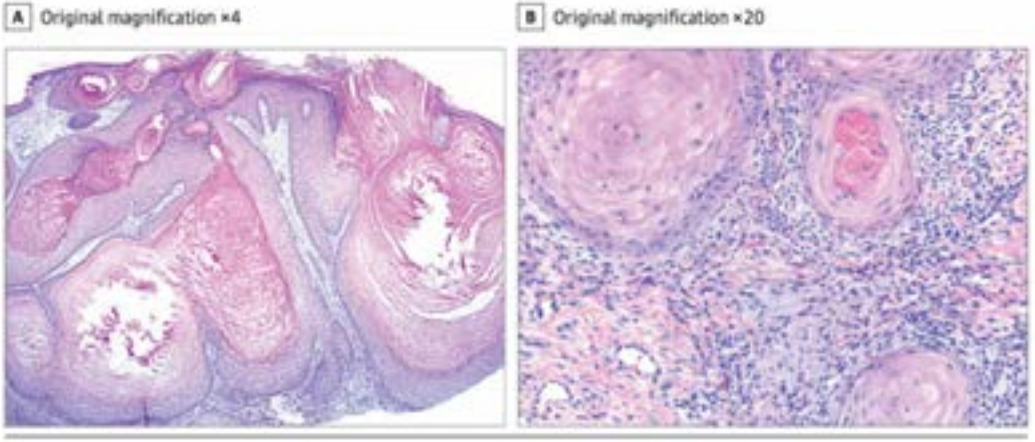


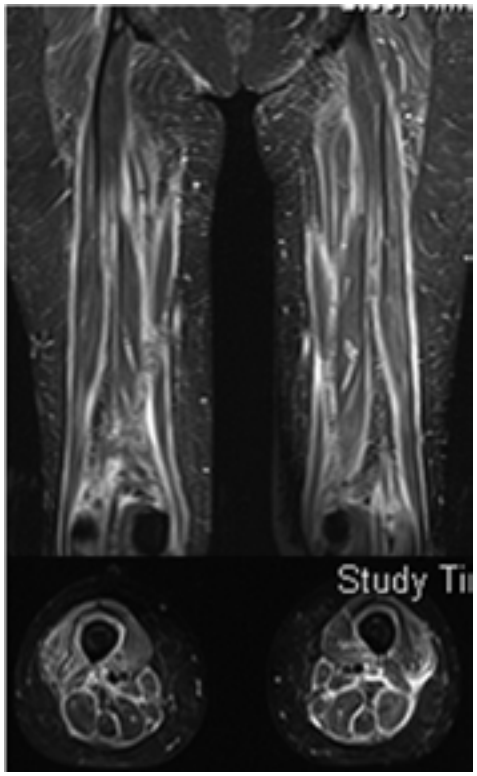
- 3 patients on pembrolizumab
- Sudden onset of multiple lesions on sun-exposed areas of extremities
- Median 13 months (4-18 mos)
- Pathology:
  Multiloculated, crateriform, keratin-filled lesions
  Squamous cells w/ glassy appearing cytoplasm and minimal cytologic atypia
  Distinct lichenoid infiltrate in underlying dermis w/ CD3+ T cells
- IL + topical steroids +/- cryotherapy

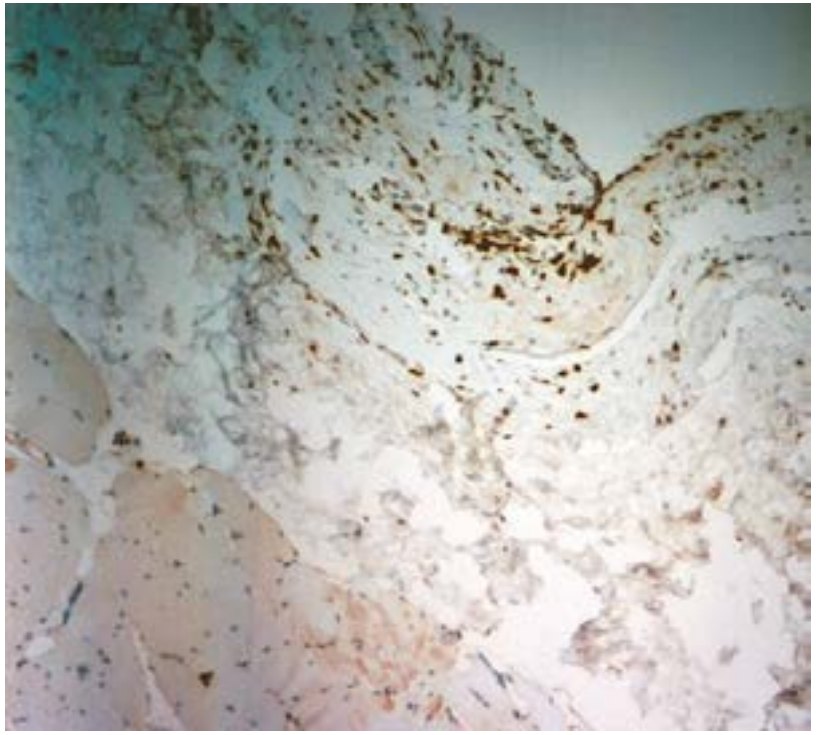
JAMA Dermatology. 2017 May 3

Autoimmune fasciitis

- 43-year-old woman with metastatic melanoma
- Started on nivolumab
- 14 months later: developed progressive fatigue, widespread myalgia of bilateral upper and lower limbs, progressive dysphagia
- Skin-muscle biopsy: focused fascial and perifascicular inflammatory infiltrate

Parker M et al. BMJ Case Rep 2018;Jan8



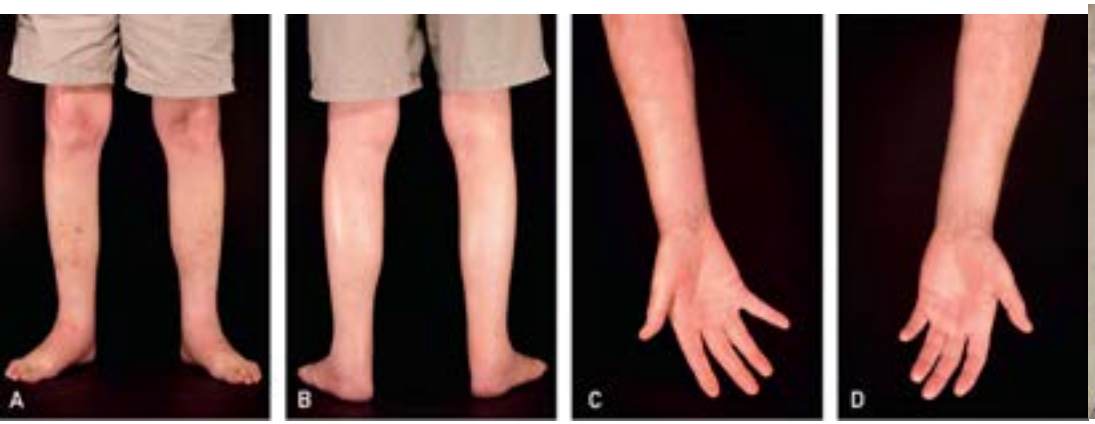


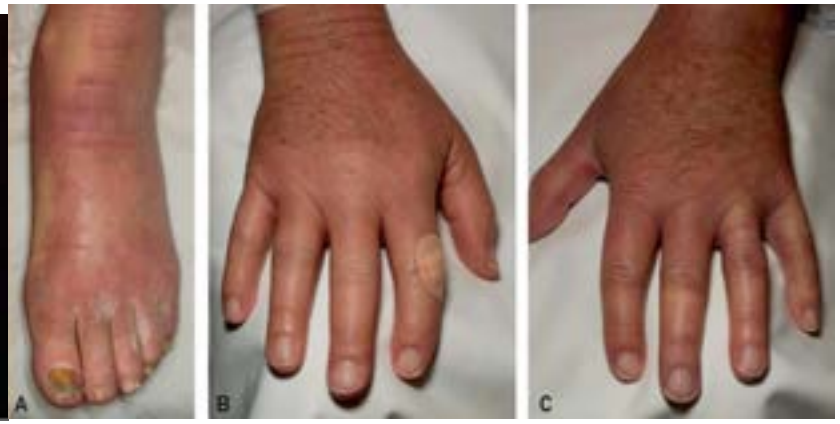
Pembrolizumab-induced scleroderma

- 66-year-old man with metastatic melanoma. Started on pembrolizumab. After cycle 13, developed fatigue and swelling of joints and ankles. Progression to burning and muscle weakness. Developed diffuse skin thickening over bilateral extremities and face.
- Treated with IVIG 5 days weekly per month and mycophenolate mofetil 1000 mg BID. Symptom improvement, then 14 weeks later, began to decline and died 2 months later.

- 79-year-old man with metastatic melanoma. Started on pembrolizumab. After cycle 5, severe stiffness of hands and feet. Pembrolizumab was discontinued.
- Treated with hydroxychloroquine 200 mg BID and oral prednisone. Improvement in symptoms.

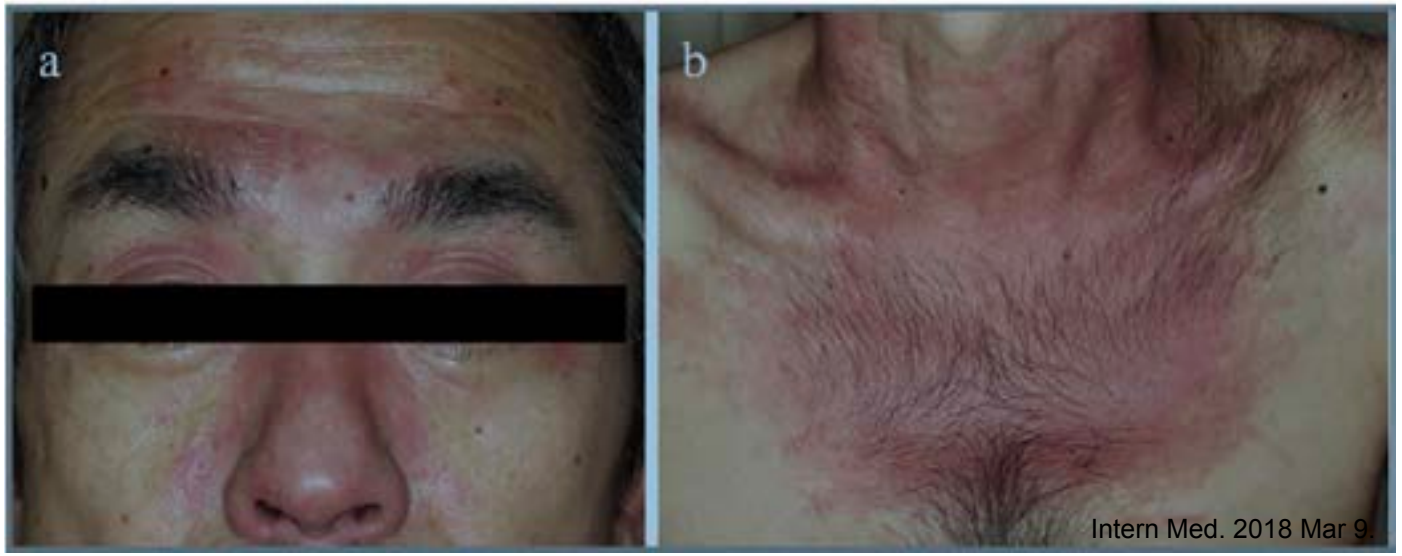
Mayo Clin Proc. 2017;92(7):1158-1163





Checkpoint inhibitor-induced dermatomyositis

- Ipilimumab : n=1
- Nivolumab: n=1
- 42-year-old man with stage IV lung adenocarcinoma. Treated with 4 cycles of cisplatin, pemetrexed, and bevacizumab -> 7 cycles of pemetrexed and bevacizumab -> 4 cycles of docetaxel. Started on nivolumab (3 mg/kg Q2 weeks).
- A few days after cycle 1: general fatigue and minor proximal limb muscle weakness
- 6 weeks later: clear proximal muscle weakness and skin findings
- MRI legs: abnormally high intensity areas in bilateral adductor and obturator muscles; EMG showed myogenic conversion.
- Treated with prednisolone 0.6 mg/kg QD -> slight temporary improvement
- Then diagnosed with spinal cord and meningeal dissemination 10 days later -> death



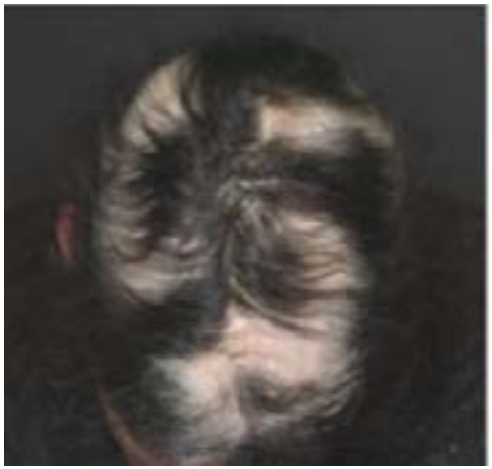
Intern Med. 2018 Mar 9.

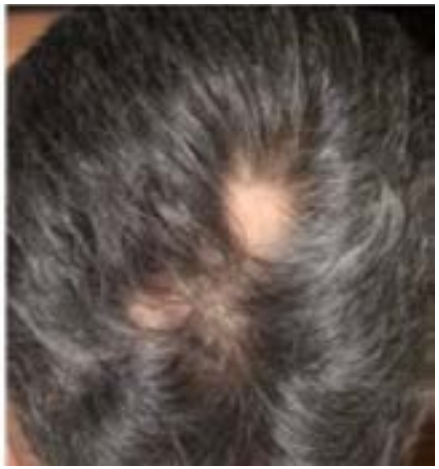
Erythema nodosum-like panniculitis

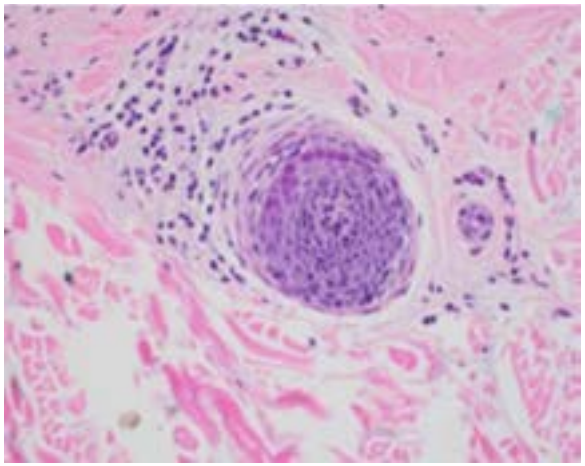
Sarcoidosis

Immunotherapy-induced alopecia areata

- 1-1.6% of patients on immunotherapy
- Anti-CTLA-4, PD-1, and PD-L1 inhibitors
- Scalp, face, eyebrows, eyelashes, trunk
- Areata and universalis
- Treatment with intralesional steroids (triamcinolone) and topical steroids (clobetasol)
- Resultant regrowth with poliosis







Br J Dermatol. 2017 June ; 176(6): 1649–1652.

Thank You

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