ECHO Program

Sclerotic Chronic GVHD

Moderator: **Steven Pavletic, MD, MS**

Senior Clinician and Head, Graft-Versus-Host Disease and Late Effects Section
Immune Deficiency Cellular Therapy Program
National Cancer Institute, Bethesda, MD

Presenter: **Annie Im, MD**
Associate Professor
University of Pittsburgh, Pittsburgh, PA

Commentator: **Edward Cowen, MD, MHSc**
Senior Clinician and Head, Dermatology Consultation Service
National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD

Case Presenter: **Yazan Migdady, MD, MSc**
Assistant Professor
Oregon Health & Science University, Portland, OR

ECHO Program

Welcome to the Third ECHO Program of the GVHD Interactive Provider Network

- The goal of the GVHD Interactive Provider Network ECHO is to connect GVHD specialists with community providers to share expertise, discuss cases, and improve patient care.
- The network is based on the ECHO Model™ (Extension for Community Healthcare Outcomes) which uses proven adult learning techniques and interactive video technology to connect community providers with specialists in collaborative sessions.
- The sessions, designed around case-based learning and mentorship, will help primary care and community-based practitioners gain the practical expertise required to care for GVHD patients. Questions and comments from the learners will be encouraged to facilitate discussion.

ECHO Program

Target Audience

This CE activity is intended for physicians of all specialties, nurse practitioners, physician assistants, and other healthcare professionals who treat patients with chronic GVHD.

Educational Objectives

After completing this CE activity, the participant should be better able to:

- Recognize signs and symptoms of sclerotic skin disease
- Discuss systemic treatment options for sclerotic skin disease
- Describe therapies specific to sclerotic skin disease

ECHO Program

Program Agenda

- Welcome and Introductions – Steven Pavletic, MD, MS
- Didactic presentation – Annie Im, MD
- Expert commentary – Edward Cowen, MD, MHSc
- Case presentation – Yazan Migdady, MD, MSc
- Q & A and Panel Discussion
- Closing Announcements

Accreditation, Support, and Credit

In support of improving patient care, this activity has been planned and implemented by Medical Learning Institute, Inc., and Aplastic Anemia and MDS International Foundation. Medical Learning Institute, Inc. is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physician Continuing Medical Education

Medical Learning Institute, Inc. (MLI) designates this enduring activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Support Statement

This CE activity is supported by an educational grant from Incyte Corporation.

Nursing Continuing Professional Development

Successful completion of this nursing continuing professional development activity will be awarded 1.0 contact hour and 1.0 contact hour in the area of pharmacology.

Interprofessional Continuing Education (IPCE) Statement

This activity was planned by and for the healthcare team, and learners will receive 1.0 Interprofessional Continuing Education (IPCE) credit for learning and change.

Disclosure & Conflict of Interest Policy

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Faculty Disclosures

Chair/Planner/Moderator
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Steve Pavletic, MD, MS, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

Planner/Moderator
Annie Im, MD
Associate Professor
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Annie Im, MD, has no relevant financial relationships with ineligible companies to disclose for this educational activity.
The following relationships have ended within the last 24 months:
Advisory Board/Consultant for Abbvie and CTI BioPharma
Research Grant from Incyte

Faculty Disclosures

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Edward Cowen, MD, MHSc has no relevant financial relationships with ineligible companies to disclose for this education activity.

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Yazan Migdady, MD, MSc, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

All relevant financial relationships of individuals for this activity have been mitigated.

Planning Committee and Content/Peer Reviewers

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ECHO Program

The GVHD Interactive Provider Network is administered by

the Aplastic Anemia and MDS International Foundation

Partner Organizations of the GVHD Interactive Provider Network:

Sclerotic skin chronic GVHD

Annie Im, MD
Associate Professor of Medicine
Director of Education and Fellowship Program Director
University of Pittsburgh, UPMC Hillman Cancer Center

Sclerotic skin chronic GVHD incidence

- Characterized by inflammation and progressive fibrosis of the dermis and subcutaneous tissues
- Mean onset >1 year after transplant
- Incidence reports vary – 13-20% overall; 50% in patients with severe chronic GVHD

GVHD Interactive PROVIDER NETWORK

Risk factors

- Peripheral blood graft
- Total body irradiation >450 cGy
- Younger age and multiple myeloma

- Decreased risk associated with use of ATG and cord blood graft

GVHD Interactive PROVIDER NETWORK

Martires KJ *et al.* Blood 2011; Inamoto Y *et al.* Blood 2013; Detrait MY *et al.* Bone Marrow Transplantation 2015

Clinical manifestations

- Localized disease (morphea-like)
- Deep sclerosis
- Panniculitis
- Fasciitis

- Can lead to joint contractures, skin breakdown, neuropathy, nerve compression syndrome and muscle cramps, myopathy, vascular insufficiency

GVHD Interactive PROVIDER NETWORK

Sclerotic skin GVHD

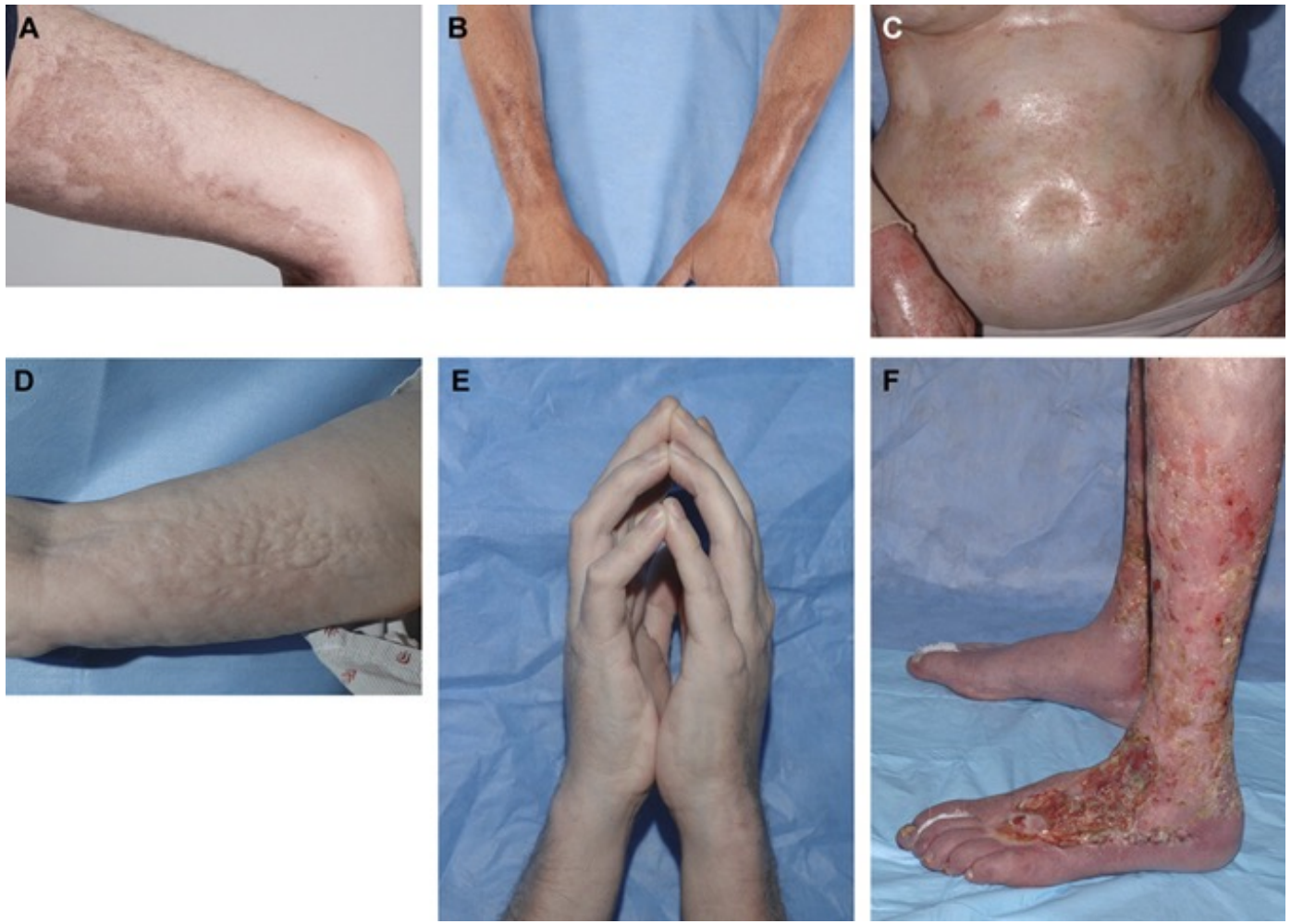
A. and B. Morphea/ localized scleroderma

C. Systemic sclerosis

D. Subcutaneous and fascial fibrosis

E. Joint contractures

F. Skin breakdown



GVHD Interactive PROVIDER NETWORK

Martires KJ *et al.* Blood 2011

Transplant outcomes with sclerotic skin chronic GVHD

- Functional impairment →joint range of motion, grip strength
- Distressing symptoms → change in skin color, increased skin thickness, sores on the skin, itchy skin, joint stiffness
- Longer time to withdrawal of immunosuppression

- Not associated with survival, non-relapse mortality, or relapse
- Greater body surface area may be related to poorer survival

GVHD Interactive PROVIDER NETWORK

Martires KJ *et al.* Blood 2011; Inamoto Y *et al.* Blood 2013

Systemic treatment

1st line: Steroids

2nd line: Ruxolitinib, Ibrutinib

3rd line: Belumosudil

4th line: Clinical trial, clinician choice

Ruxolitinib

- Overall response rate for all patients at 6 months: 50%

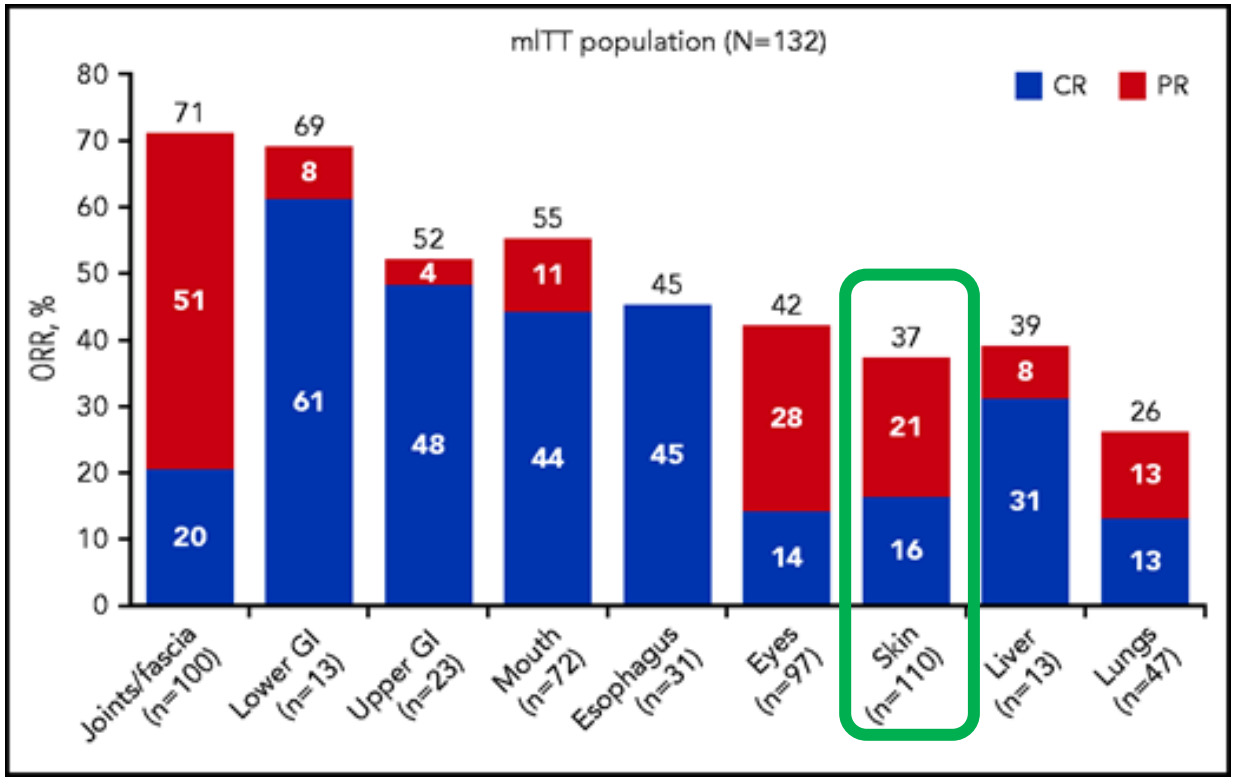
- 72% of patients had baseline skin involvement, score ≥2 60%
- Skin response rate – 41%

**Clinical trial of ruxolitinib in sclerotic skin is ongoing (NCT 03616184, PI: Vijaya Bhatt, MD)*

GVHD Interactive PROVIDER NETWORK

Zeiser R *et al.* N Engl J Med 2021

Belumosudil



83% skin involvement at baseline

37% ORR, 16% CR

41 patients with skin response:

- **24 had decrease in sclerosis**

GVHD Interactive PROVIDER NETWORK

Cutler C *et al.* Blood 2021

Treatments specific to sclerotic skin

Imatinib:

- 20 patients (14 evaluable for response) with steroid-refractory or dependent sclerotic skin GVHD treated with imatinib 100-400mg daily

- **5 with >25% improvement in ROM, 7 with stable disease**
- 8 patients reduced immunosuppression
- Several patients showed visible change in skin texture and anecdotally reported skin softening and improved flexibility

Baird K *et al.* Biol Blood Marrow Transplant 2015

Treatments specific to sclerotic skin

Imatinib or Rituximab:

- 72 patients (60 evaluable for response) with steroid-refractory sclerotic skin GVHD treated with **imatinib 200mg daily** or **Rituximab 375mg/m2 weekly x 4** in a randomized crossover study

- Imatinib: **ORR 26%** (19% success rate in crossover patients) and improvement in skin symptom burden

- Rituximab: **ORR 27%** (31% success rate in crossover patients)

Arai S *et al.* Clin Cancer Res 2016

Treatments specific to sclerotic skin

Extracorporeal photopheresis (ECP):

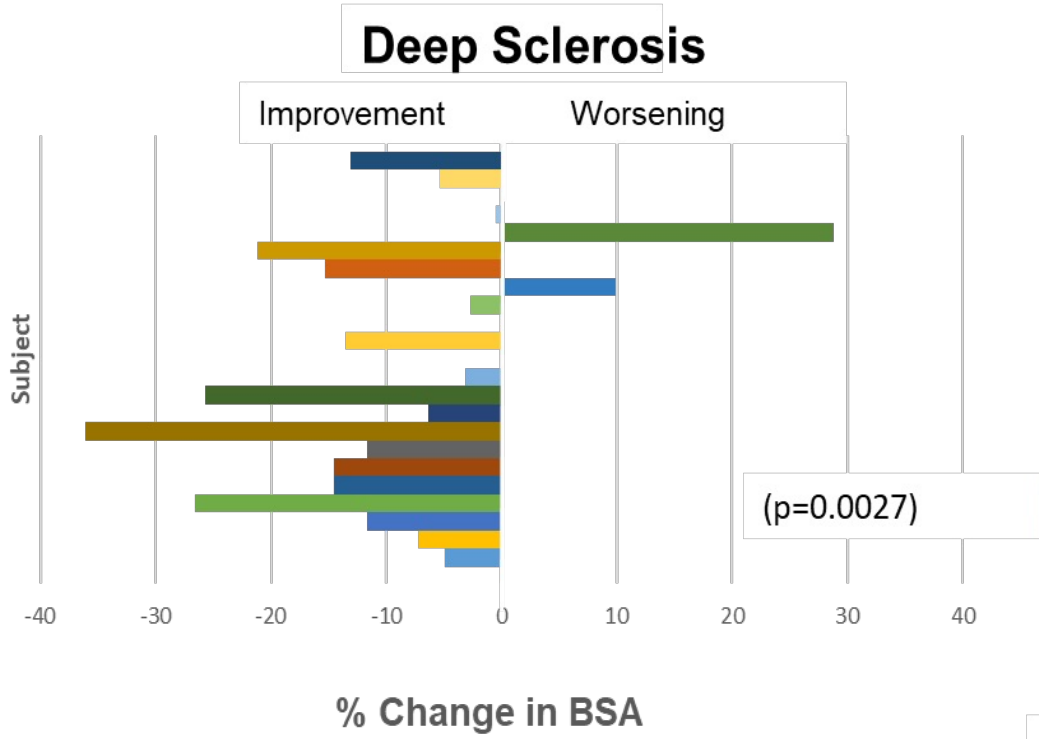
- 14 of 21 (67%) patients with sclerotic skin GVHD responded to ECP in a retrospective analysis
- 12 of 15 (80%) patients with cutaneous cGVHD had complete response, some with sclerotic skin; contractures partially resolved
- ECP associated with investigator-assessed response and reduction in steroid dose in randomized trial

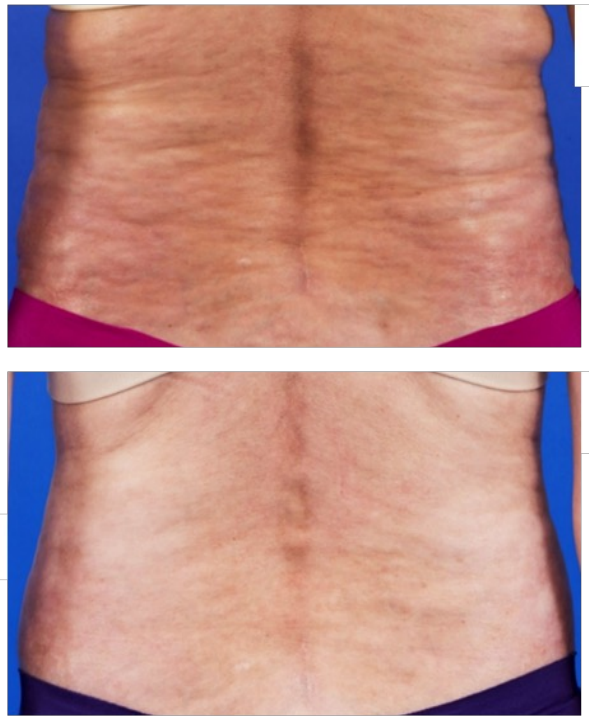
Couriel DR *et al.* Blood 2006; Greinix HT *et al.* Blood 1998; Flowers MED *et al.* Blood 2008

Treatments specific to sclerotic skin

Pomalidomide:

- 34 patients (24 evaluable) treated with pomalidomide 0.5mg or 2mg daily
- 32 patients had skin sclerosis (26 with >20% BSA with deep)
- ORR 67%





Improvement in skin GVHD hyperpigmentation and sclerosis after 1 year at 2mg

Curtis LM *et al.* Blood 2021

Treatments specific to sclerotic skin

Being studied:

- Glasdegib (hedgehog inhibitor)
  - NCT04111497, PI: Stephanie Lee, MD, MPH

- Ruxolitinib
  - NCT 03616184, PI: Vijaya Bhatt, MD

GVHD Interactive PROVIDER NETWORK

Axatilimab

- Anti-CSF1 receptor monoclonal antibody, targets macrophages

- Phase 1/2 trial, results of 40 patients reported at ASH 2021:
  - ORR 68% in advanced, refractory chronic GVHD

  - 28 had baseline skin involvement, 25 (81%) had severe skin sclerosis
  - 4 patients (16%) had improved sclerosis with treatment

GVHD Interactive PROVIDER NETWORK

Lee SJ *et al,* ASH Annual Meeting 2021

Ancillary therapy and supportive care

- Deep muscle/fascial massage

- Stretching exercises

Carpenter PA *et al.* Biol Blood Marrow Transplant 2015

Future directions

- Biology: better understanding of the pathophysiology that underlies transition from inflammation to dysregulated tissue remodeling
- Response: more sensitive response measures to determine extent of disease and improvement in sclerosis
- Treatments: exploration of treatments for other fibrotic diseases, and for delivery of topical therapies

Wolff D *et al.* Transplant Cell Ther 2021

Treatments specific to sclerotic skin

<u>Imatinib + Mycophenolate mofetil:</u>

- 13 pediatric patients with steroid-refractory or dependent sclerotic cGVHD treated with imatinib mg/m2/d and mycophenolate mofetil 15-20 mg/kg/d

- 3 months: 9 PR, 3 stable disease
- 1 year: 1 CR, 8 PR, 1 progressive disease → ORR 77%
- Median steroid dose 1.0 mg/kg/d → 0.21 mg/kg/d at 1 year

Choi JY *et al.* Transplant Cell Ther 2021

Sclerotic Chronic Graft-Versus-Host Disease

Steven Pavletic, MD

Annie Im, MD

Edward Cowen, MD

Yazan Migdady, MD, MSc

Case Presentation

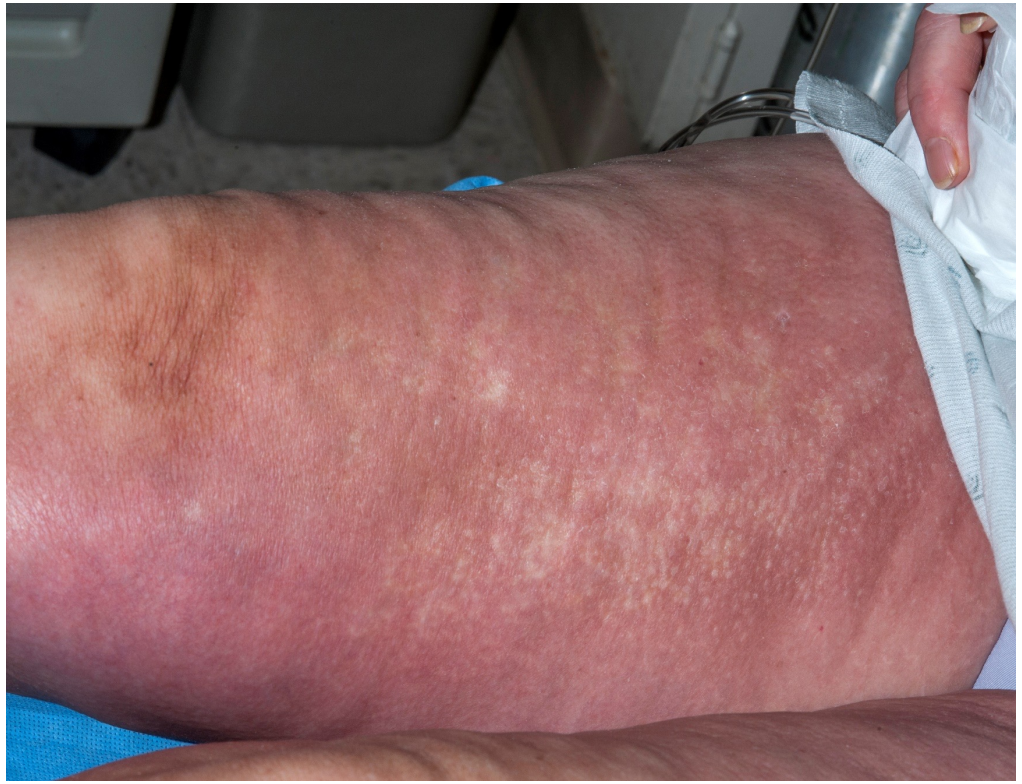
Case Presentation (1)

- A 64-year-old woman with MDS transformed to AML underwent HSCT in October 2013:
  - ***Donor***: HLA mismatched sibling donor
  - ***Conditioning regimen****:* RIC (fludarabine/melphalan)
  - ***Graft source***: PBSC
  - ***GVHD prophylaxis***: tacrolimus and methotrexate
- **Post-transplant course:**
  - Both acute skin/GI GVHD requiring prolonged steroid exposure, complicated by osteoporosis and multiple fractures
  - Patient developed chronic GVHD (eyes, mouth, and skin) and received multiple lines of therapy including steroids, tacrolimus and sirolimus, off IST since July 2019

Case Presentation (1)

- **February 2022:** was admitted for rhinovirus pneumonia. After she received IV contrast, she developed a generalized maculopapular erythematous rash; started on prednisone 1mg/kg followed by a quick steroid taper

- The new skin rash worsened after steroids tapered. Patient was restarted on prednisone 10 mg with mild improvement

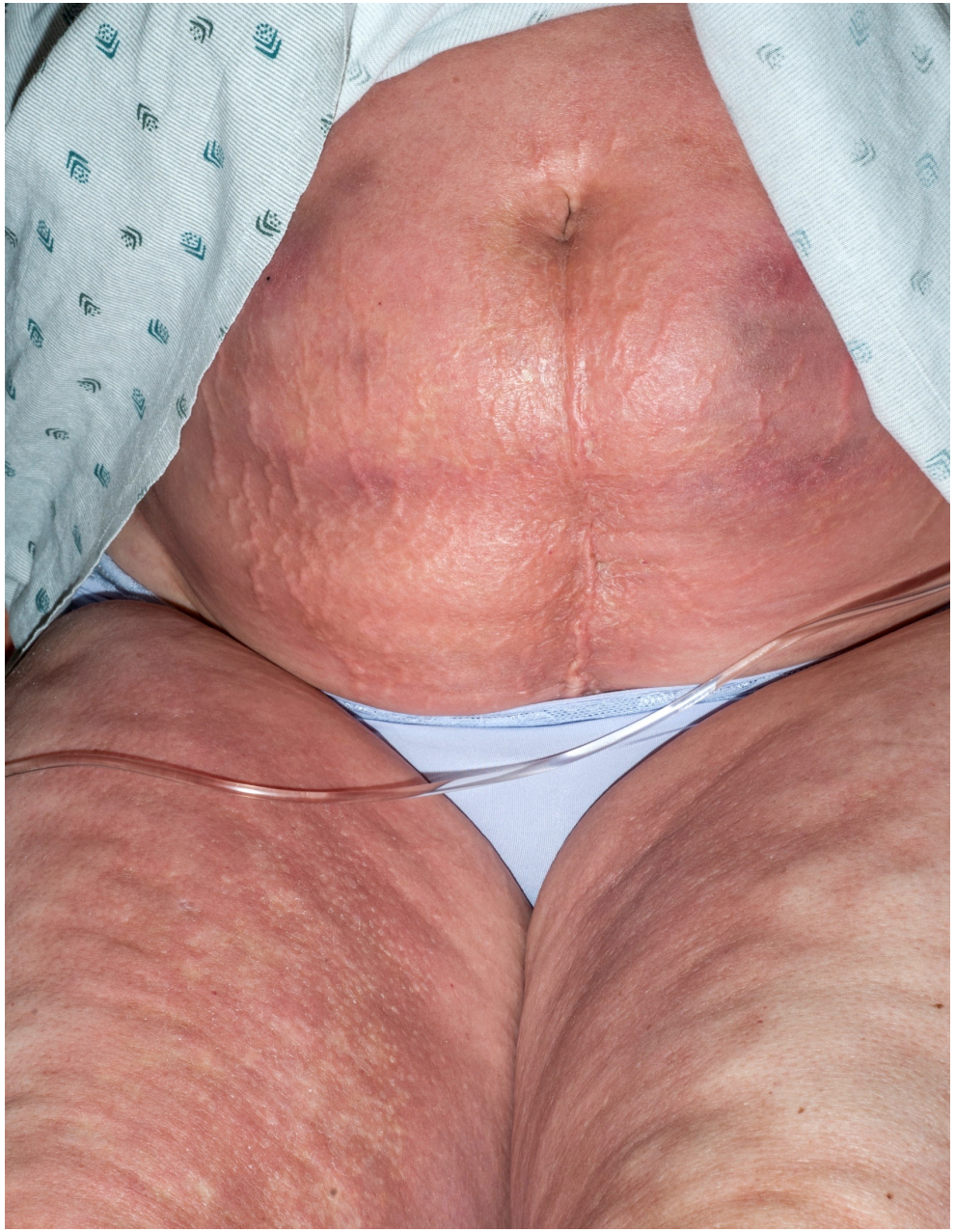


Case Presentation (1)

- She still has mild maculopapular rash in lower extremities and ongoing tightness (sclerotic changes) across her lower abdomen

- Global NIH score severe; (skin 3, mouth 1, eye 3)

What would you do next?

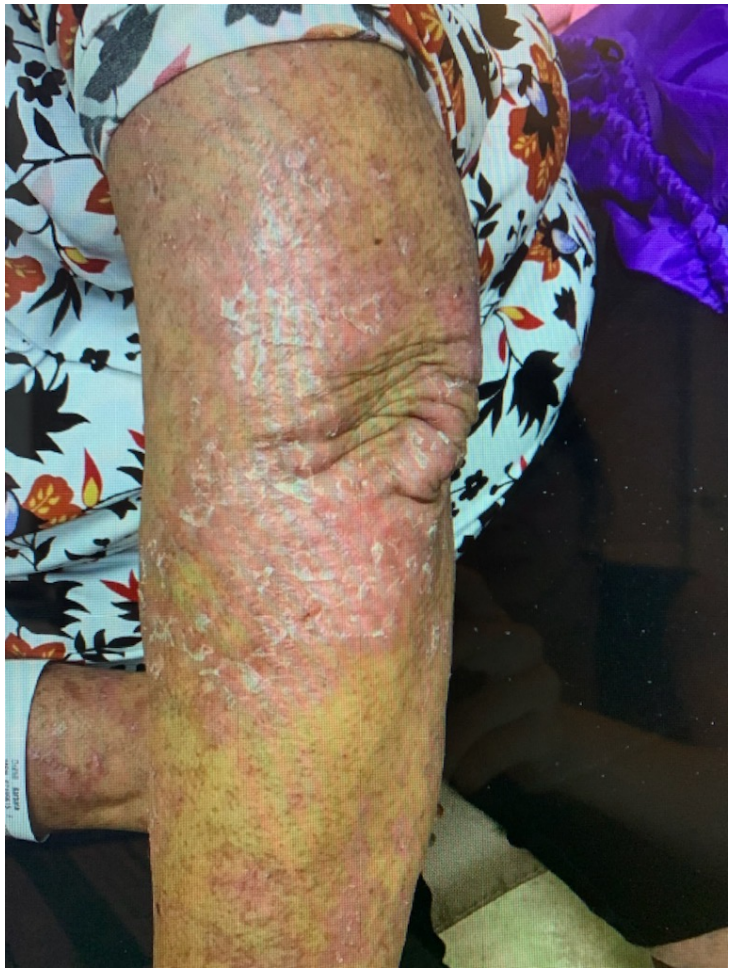


Case Presentation (2)

- A 77-year-old woman with a history of HR-MDS with *TP53* mutation underwent allogeneic HSCT in February 2020:
  - ***Donor***: HLA matched unrelated donor
  - ***Conditioning regimen****:* RIC (fludarabine/melphalan)
  - ***Graft source***: PBSC
  - ***GVHD prophylaxis***: tacrolimus and methotrexate
- **Post-transplant course:**
  - **D+100** - No morphologic disease, 97% T cell donor chimerism.
  - **1 year** - No morphologic evidence of MDS. FISH/KT and donor chimerism 100%. NGS absent for original Tier 1 *TP53*, *DNMT3A*, *RUNX1*.

- One year post-HSCT, patient presented with diffuse hyperpigmentation on the chest, abdomen, extremities and lichen-planus changes characterized by flat violaceous lesions on bilateral legs and arms with morphea-like lesion around the left elbow (total BSA 35%): skin bx consistent with GVHD.
- Patient was started on the FLIGHT Study with itacitinib 200mg in combination with ECP (twice weekly)
- One month later, signs of flare of skin cGVHD so was started on prednisone 0.5mg/kg but was unable to tolerate steroids due to GI AE's. He decreased itacitinib to 100mg while being on voriconazole

What would you do next?

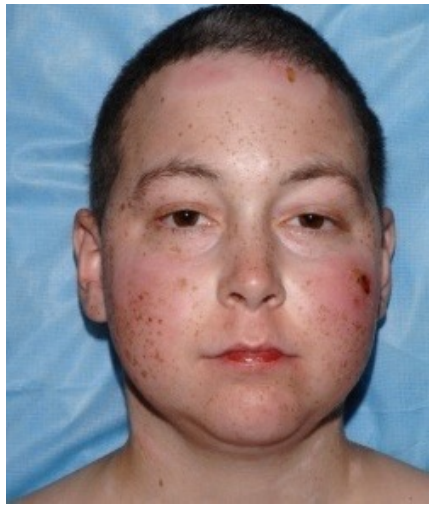


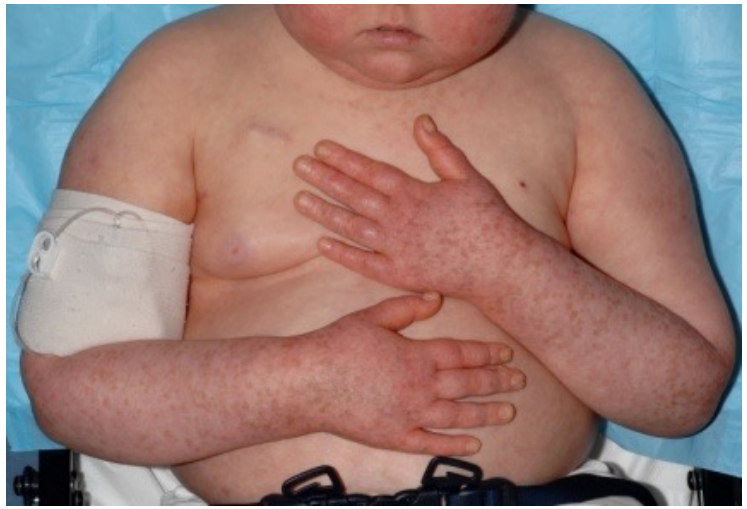
Voriconazole-Induced Phototoxicity Masquerading as Chronic Graft-versus-Host Disease of the Skin in Allogeneic Hematopoietic Cell Transplant Recipients

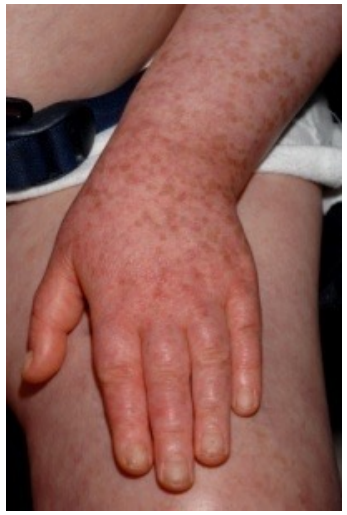
Asha R. Patel,[1] Maria L. Turner,[1] Kristin Baird,[2] Juan Gea-Banacloche,[3] Sandra Mitchell,[4] Steven Z. Pavletic,[3] Barbara Wise,[2] Edward W. Cowen[1]

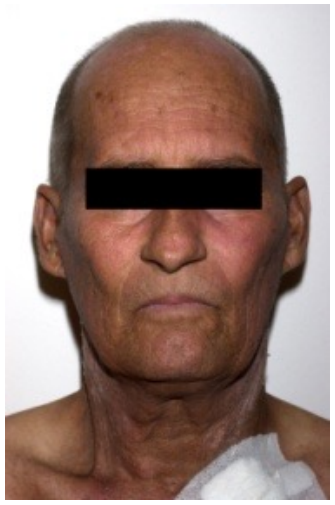
Systemic fungal infections pose a significant risk to patients following allogeneic hematopoietic cell transplantation (alloHCT). Voriconazole (Vfend®, Pfizer) is an oral second-generation triazole antifungal agent that offers a broad spectrum of coverage against fungal species and is frequently utilized in the post-HCT setting. Herein, we describe 5 patients who were initially believed to be experiencing a flare of cutaneous chronic graft-versus-host disease (cGVHD), but who were actually exhibiting phototoxicity caused by voriconazole. A high index of suspicion for this adverse reaction in the post-alloHCT setting will prevent misdiagnosis and avoid inappropriate therapy for cGVHD.

Biol Blood Marrow Transplant 15: 370-376 (2009)









Photodermatol Photoimmunol Photomed 2007; 23: 29–31
Blackwell Munksgaard

Photodermatology
Photoimmunology
& Photomedicine

Brief communication

Voriconazole-induced pseudoporphyria

J P Tolland[1], P P McKeown[2], J R Corbett[3]

[1]*Departments of Dermatology, Belfast City Hospital Trust, Royal Hospitals Trust Belfast,* [2]*Department of Cardiology, Royal Hospitals Trust Belfast, and* [3]*Department of Dermatology, Royal Hospitals Trust Belfast*

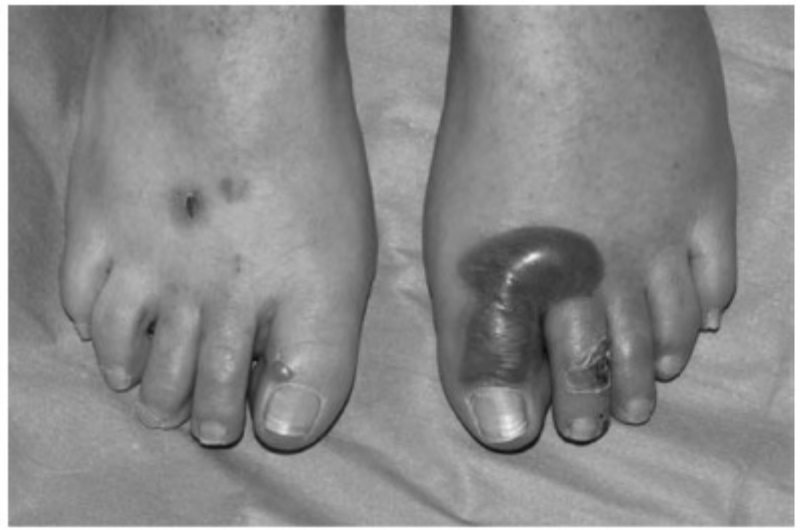


Fig. 1. Bullae and erosions on the dorsal aspects of the feet.

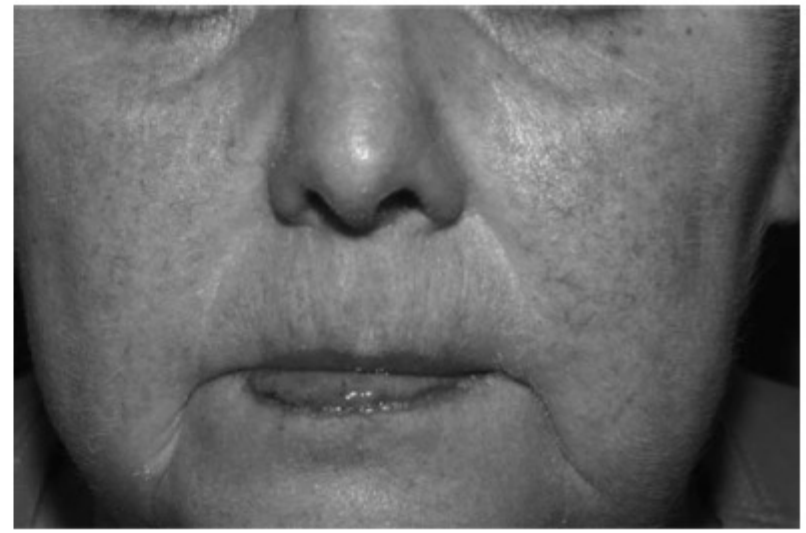
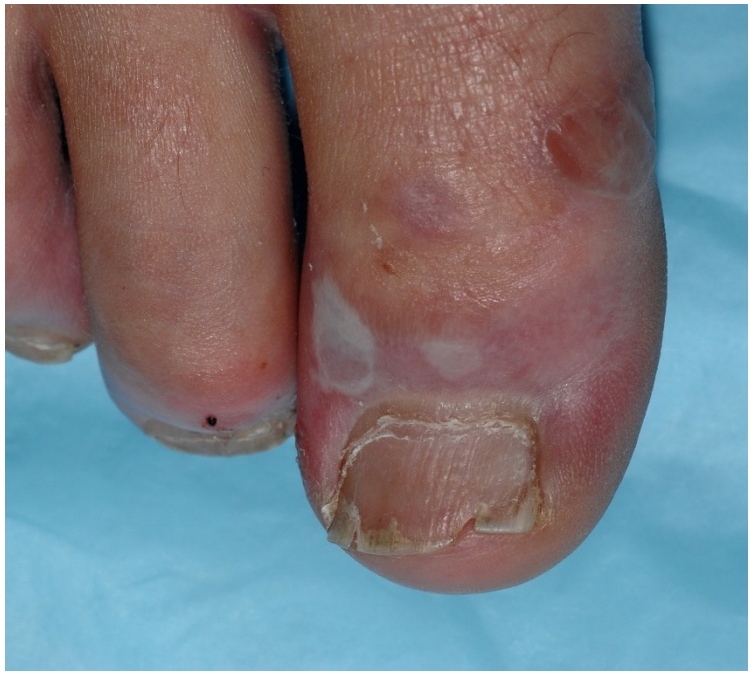
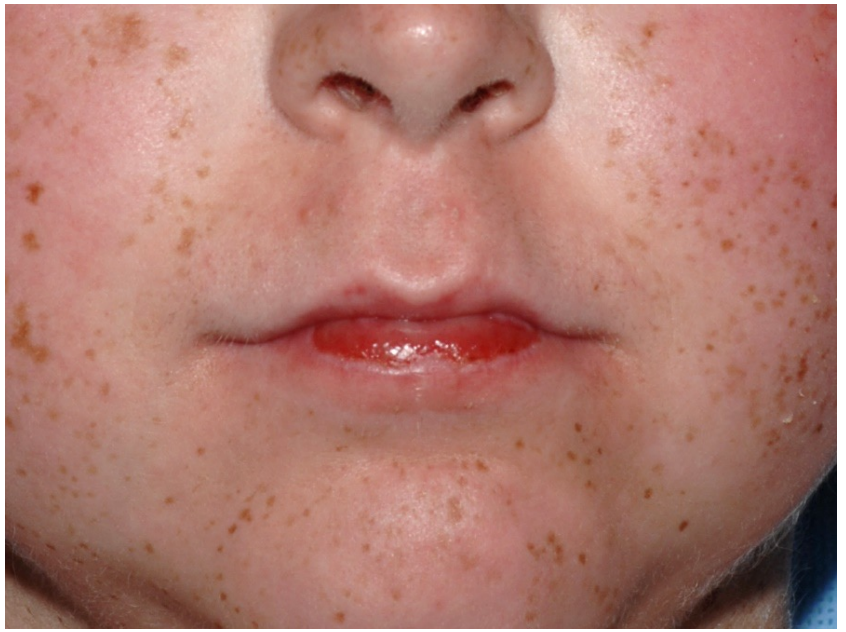
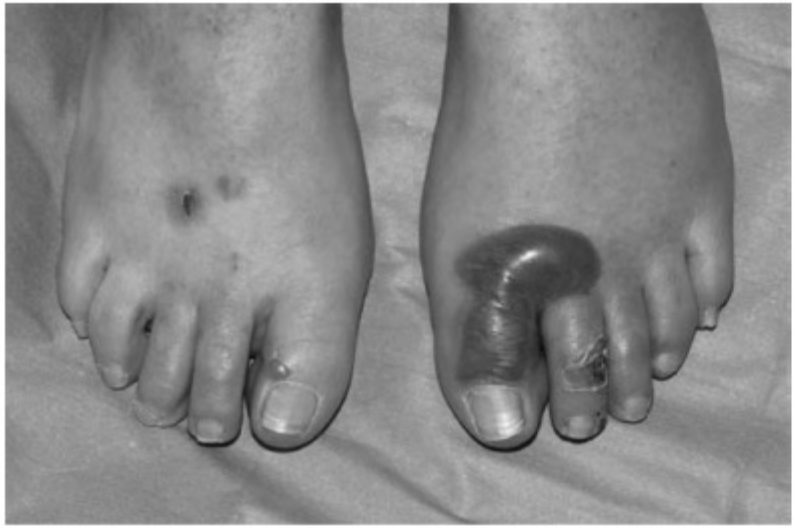


Fig. 2. Erosive lesions on lips.







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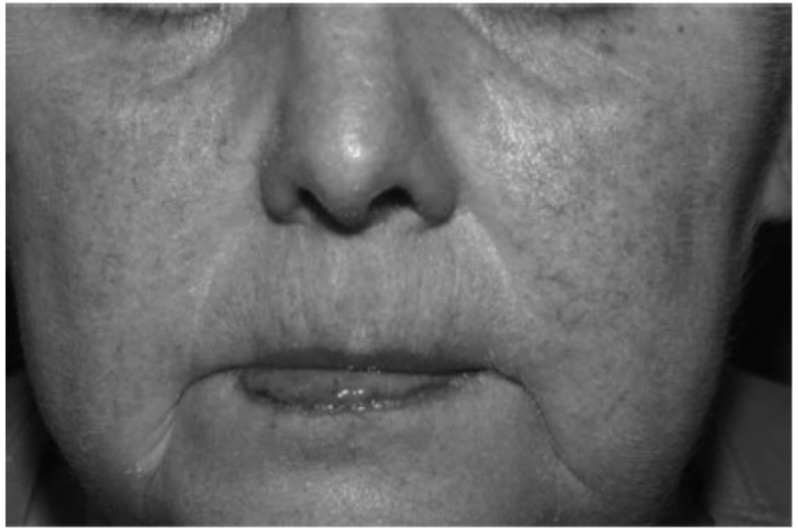


Fig. 2. Erosive lesions on lips.

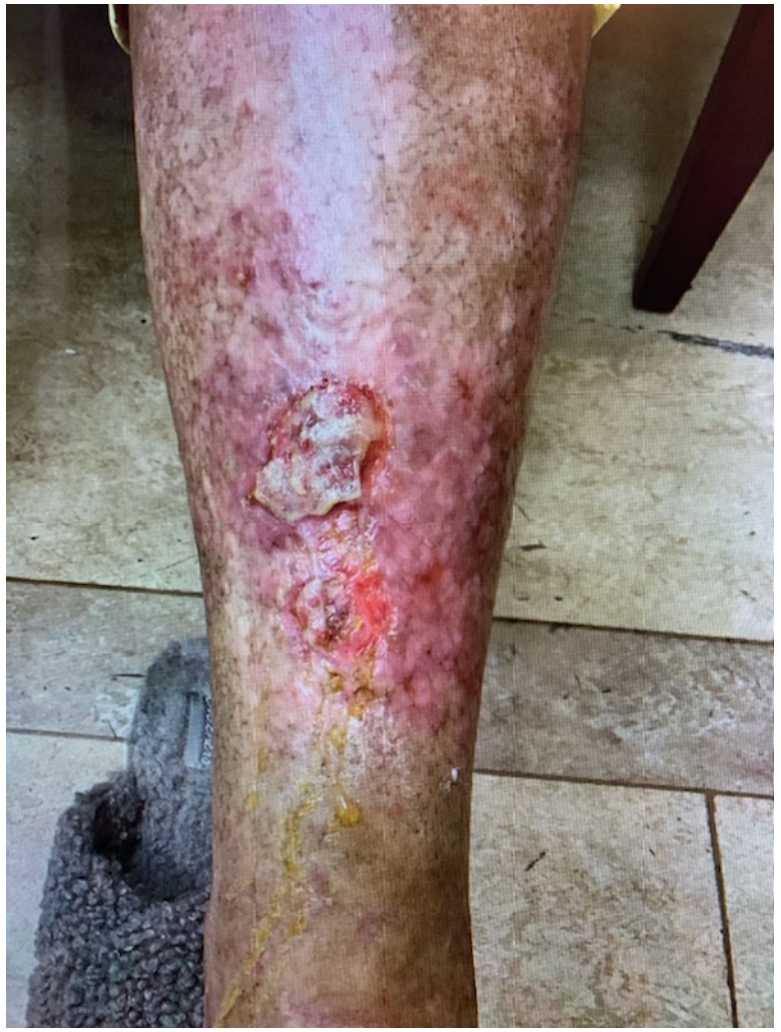
Case Presentation (2)

- Increased itacitinib back to 200mg as voriconazole stopped
- One month later : New onset of open ulcers on bilateral shins with one open wound (not oozing) on the ankle. Increased skin tightening in bilateral shins and calves

What would you do next?

- Belumosudil 200mg daily with ECP
- After one month, sclerotic lesions improved but no further improvement after 6 months

What would you do next?

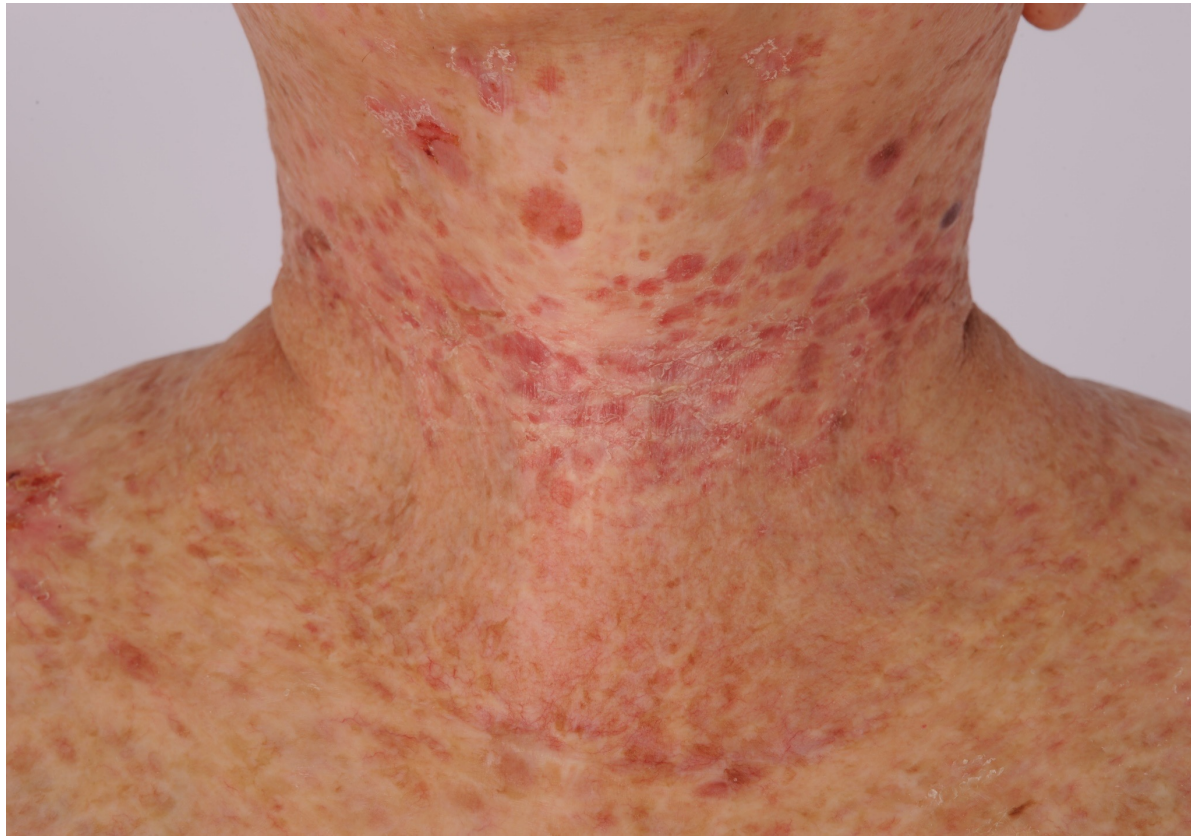


Case Presentation (3)

- A 66-year-old man with a *Jak-2* negative myelofibrosis underwent allogeneic HSCT in June 2013:
  - ***Donor***: HLA mismatched unrelated donor
  - ***Conditioning regimen:*** RIC (fludarabine/melphalan)
  - ***Graft source***: PBSC
  - ***GVHD prophylaxis***: tacrolimus and methotrexate
  - **Maintenance:** Ruxolitinib 2018-2021
- **Early post-transplant course:**
  - **3 months**: ITP treated with IVIG (NR) so was given rituximab and prednisone 1mg/kg
  - **9 months:** hospitalized for pneumonia, biopsy consistent with COP and possible GVHD for which he was treated with prednisone 1mg/kg

Case Presentation (3)

- **2 years post-HSCT:** mild macular rash located at part of the abdomen and upper back (BSA 5%) managed with topical steroids
- **3 months later:** after IVIG infusion, developed a new diffuse moderate erythema on the back, mild hyperemia on the anterior chest, in addition to thick dry skin on the face. Skin biopsy consistent with grade I GVHD so started prednisone 0.5 mg/kg with no response.
- Increased prednisone to 1 mg/kg and resumed Tacrolimus with good response (erythema completely resolved)
- Tapered prednisone but once down to 0.5 mg/kg, he developed scleroderma features around front/sides of the neck from the chin toward mid abdomen in a band like pattern so prednisone was increased to 1 mg/kg and Tacrolimus increased

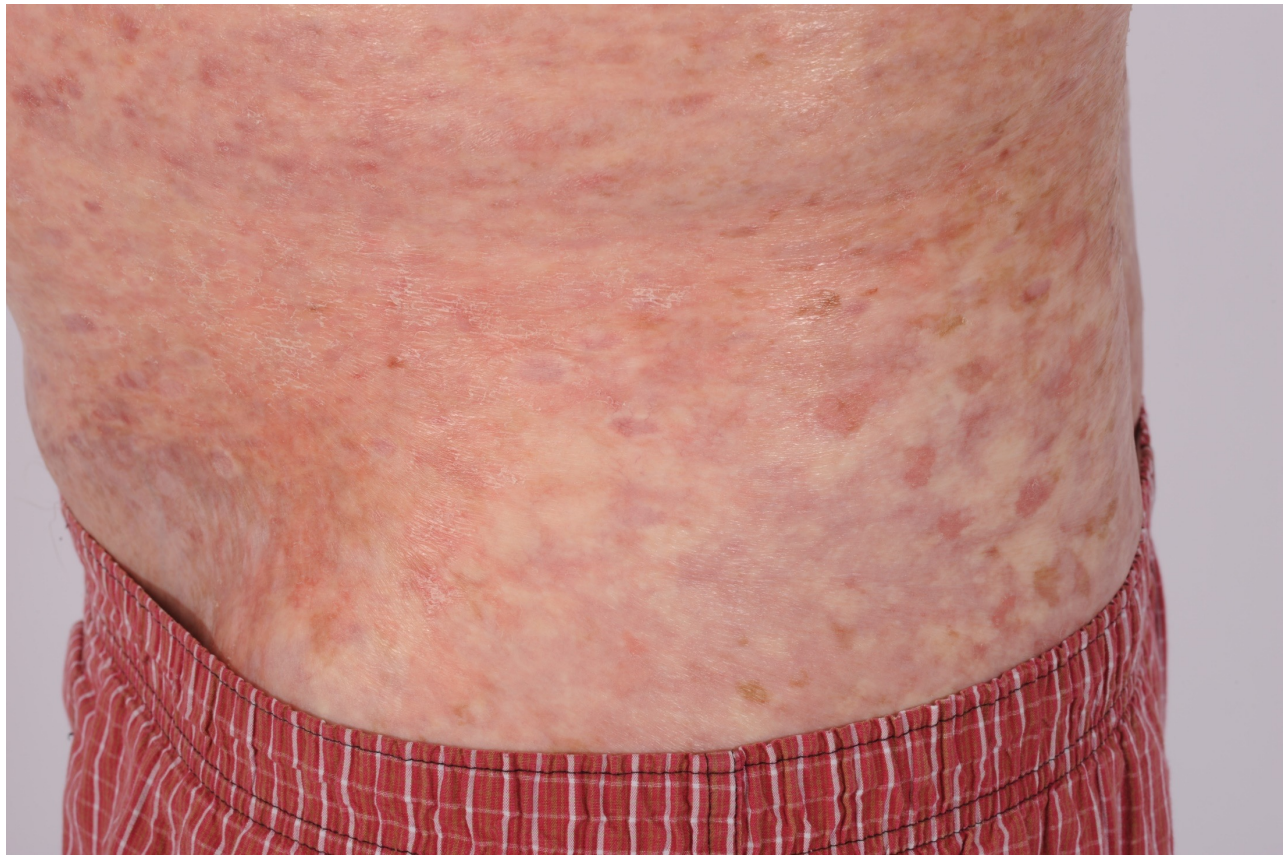


What would you do next?

Case Presentation (3)

- Started on ibrutinib in 8/2017 (in addition to ECP) but developed pericarditis so was discontinued

What would you do next?



Case Presentation (3)

- Ruxolitinib started in 2018 – 2021; given primarily for maintenance myelofibrosis treatment, skin GVHD is worse with worsening erythema on the chest/abdomen in addition to scleroderma features in the trunk/lower extremities

What would you do next?

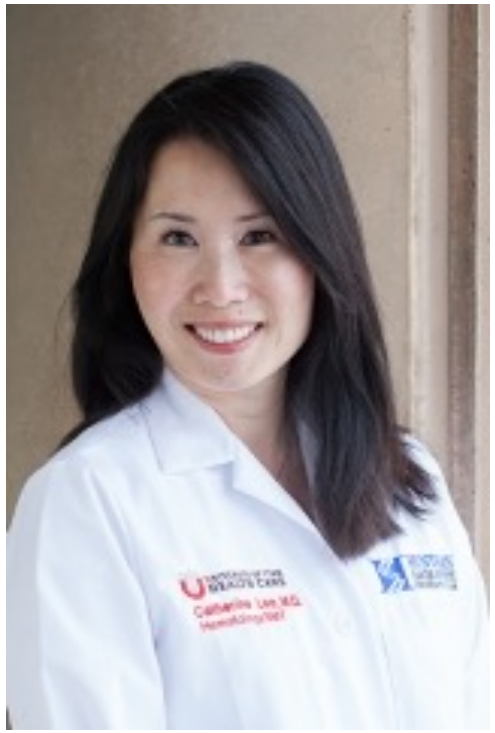
- Belumosudil in 2021 => AE's altered cognition, fatigue

What would you do next?

- Transitioned to prednisone 1 mg/kg and then screened for clinical trial (Axatilimab trial)

Thank you

- Special thanks to Catherine Lee from Huntsman Cancer Hospital for sharing the clinical vignettes



Questions?