Cases from the Cornfields!

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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F050 - Cases from the Cornfields: Pearls from the Midwest!

DISCLOSURES

No relevant relationships with industry.
Off-label use of FDA-approved medications will be discussed.
Speakers

- **Nkanyezi (Kanya) Ferguson, MD**
  medical dermatology, Mohs surgery, clinic director, global dermatology, skin of color

- **Megan Noe, MD, MPH, MSCE**
  medical dermatology, dermatoepidemiology

- **Jennifer Powers, MD**
  medical dermatology, surgical dermatology pigmented lesions, wound healing

- **John Selby, MD, PhD**
  medical dermatology, VA service chief, phototherapy director mechanobiology basic science lab

- **Mary Stone, MD**
  medical dermatology, dermatopathology, residency program director
Objectives

• Identify clinical pearls from challenging medical dermatology, dermatopathology, and surgical cases.

• Recognize appropriate multidisciplinary approach to treating patients with complex cutaneous disease.

• Appreciate the importance of clinicopathologic correlation in approaching dermatology patients.
Case #1

• 68 year-old white male

• **Chief Complaint**
  – Acute generalized itchy skin rash

• **Past Medical History**
  – Dyslipidemia
  – Diabetes mellitus type II
  – Hypertension
  – GERD
  – Nummular dermatitis
  – Metastatic Merkel cell carcinoma
    • Left wrist primary
    • Excision with positive SNL (2/2)
    • Nodal metastases to left supraclavicular lymph nodes
    • Pembrolizumab (3 doses)
Case #1

- **Social History**
  - University clerk
  - No active tobacco use; former cigarette smoker (35 pack-years)
  - No alcohol use

- **Medications**
  - Acetaminophen
  - Amlodipine
  - Atorvastatin
  - Colesevelam
  - Furosemide
  - Glipizide
  - Metformin
  - Pantoprazole
  - Omeprazole
  - Pioglitazone
  - Potassium chloride
  - Triamcinolone 0.5% ointment
  - Trimethoprim-polymyxin B solution
What is the most likely diagnosis?

A. Pembrolizumab-induced *pustular psoriasis*

B. Pembrolizumab-induced *lichenoid dermatitis*

C. Amlodipine-induced *eczematous dermatitis*

D. Pioglitazone-induced *lichenoid dermatitis*

E. Omeprazole-induced *subacute cutaneous lupus (SCLE)*
What is the most likely diagnosis?

A. Pembrolizumab-induced *pustular psoriasis*
B. Pembrolizumab-induced *lichenoid dermatitis*
C. Amlodipine-induced *eczematous dermatitis*
D. Pioglitazone-induced *lichenoid dermatitis*
E. Omeprazole-induced *subacute cutaneous lupus (SCLE)*
Pembrolizumab

FDA-approved for numerous recurrent, relapsed, metastatic malignancies:

- Cervical cancer
- Gastric cancer
- Squamous cell carcinoma (head & neck)
- Hepatocellular carcinoma
- Hodgkin lymphoma
- Melanoma (approved 9/2014)
- Merkel cell carcinoma
- Non-small cell lung cancer
- Primary mediastinal B-cell lymphoma
- Urothelial cell carcinoma

Dosing: 200 mg IV every 3 weeks until disease progression, unacceptable toxicity, or 24 months
Nivolumab

FDA-approved for numerous recurrent, relapsed, metastatic malignancies:

- Colorectal cancer
- Renal cell cancer
- Squamous cell carcinoma (head & neck)
- Hepatocellular carcinoma
- Hodgkin lymphoma
- Melanoma (approved 12/2014)
- Small cell carcinoma
- Non-small cell lung cancer
- Urothelial cell carcinoma

Dosing: 3 mg/kg IV every 2 weeks until disease progression, or unacceptable toxicity
Cutaneous adverse reactions to anti-PD1 therapies (pembrolizumab/nivolumab)

• COMMON
  – Maculopapular eruption
  – Lichenoid dermatitis
  – Eczematous dermatitis
  – Vitiligo
  – Pruritus
  – Psoriasis/psoriasiform dermatitis
  – Alopecia

• RARE
  – Bullous pemphigoid
  – Erythema multiforme
  – Dermatitis herpetiformis
  – SJS/TEN
  – Lupus erythematosus
  – Sweet’s syndrome
  – Others
Cutaneous adverse reactions to anti-PD1 therapies (pembrolizumab/nivolumab)

- Dermatologic toxicities are the most prevalent overall
- Approximately **10-50% patients** will have a cutaneous toxicity, most **grade 1** (<10% BSA) or **grade 2** (10-30% BSA)
- Onset ~5 weeks after initiation of therapy (1-2 doses)
- Some studies suggest increasing incidence of skin toxicity that is proportional to increasing drug exposure
Cutaneous adverse reactions to anti-PD1 therapies (pembrolizumab/nivolumab)

- **Relationship between Adverse Reactions and Overall Survival (OS)?**
  - Melanoma patients on nivolumab
    - Rash and vitiligo associated with increased OS
      - *Clin Cancer Res* 2016; 22(4):886-894
    - Objective response rates higher in patients with any adverse reaction
Cutaneous adverse reactions to anti-PD1 therapies (pembrolizumab/nivolumab)

- Relationship between Adverse Reactions and Overall Survival (OS)?
  - Trial cohort of melanoma, merkel cell carcinoma, lung cancer, prostate cancer patients on pembrolizumab
- Cutaneous adverse reactions associated with increased progression-free intervals

*JAMA Dermatol* 2015; 151(11):1206-1212
Cutaneous adverse reactions to anti-PD1 therapies (pembrolizumab/nivolumab)

- MANAGEMENT of Grade 1 and 2 Reactions?
  - Continue anti-PD1 therapy
  - Sun protection
  - Emollients
  - Topical steroids
  - Antihistamines
Cutaneous adverse reactions to anti-PD1 therapies (pembrolizumab/nivolumab)

- **MANAGEMENT of Severe Grade 2 or 3 Reactions?**
  - Hold anti-PD1 therapy
  - Systemic steroids 1.0 to 0.5 mg/kg/day; then taper
  - Resume immunotherapy with steroid dose equivalent to prednisone <10 mg/day

- **Role for non-immunosuppressive therapies?**
  - Narrowband UVB phototherapy
  - Acitretin — Apremilast
Cutaneous adverse reactions to anti-PD1 therapies (pembrolizumab/nivolumab)

- Does the use of systemic steroids affect survival in a patient on anti-PD1 therapy?
  - Objective response rates were similar in patients who did and did not receive systemic steroids

*J Clin Oncol* 2016; 35:785-792
Cutaneous adverse reactions to anti-PD1 therapies (pembrolizumab/nivolumab)

• Would the use of any other immunosuppressive medication affect survival in a patient on anti-PD1 therapy?
  – Methotrexate?
  – Cyclosporine?
  – TNF-α inhibitors?
  – IL12/23 inhibitors?
  – IL 17 inhibitors?

Lots of unanswered questions with regards to the use of these medications in our patients, especially those with pre-existing dermatologic conditions.
Anti-PD1 therapies and pre-existing skin disease

• A patient with pre-existing *psoriasis vulgaris* treated with ustekinumab >5 years is found to have metastatic colorectal cancer...
  
  – Did psoriasis contribute to risk for this malignancy?
    
    • *Maybe*...
  
  – Did ustekinumab contribute to cancer development?
    
    • *Probably not*...
  
  – Should ustekinumab be *stopped* prior to proceeding with anti-PD1 therapy?
    
    • *Uncertain*...
  
  – Can ustekinumab be safely re-started at some point during anti-PD1 therapy without affecting the patient’s overall survival?
    
    • *Uncertain*...
How would you manage our patient?

After holding his pembrolizumab infusion, which of the following systemic medications would you start?

A. Prednisone
B. Cyclosporine
C. Acitretin
D. Methotrexate
E. Narrowband UVB phototherapy
How would you manage our patient?

After holding his pembrolizumab infusion, which of the following systemic medications would you start?

A. Prednisone
B. Cyclosporine
C. Acitretin
D. Methotrexate
E. Narrowband UVB phototherapy
Case #1 Outcome

- **Week 0**: Pembrolizumab held
- **Weeks 1 - 2**: Potent topical steroids without benefit
- **Weeks 3 - 7**: Prednisone burst & taper, topical steroids, and acitretin 25 mg daily
- **Week 6**: PET/CT demonstrates complete response, pembrolizumab resumed
- **Weeks 8 - 18**: Acitretin 25 mg daily and topical steroids
- **Weeks 19 - 28**: Acitretin 25 mg alternating with 50 mg daily Pembrolizumab *discontinued* (11 total doses) due to hospitalizations for pneumonitis and NSTEMI
Our patient also had a nodular basal cell carcinoma (BCC) present on his nose, *clinically diagnosed* during his initial visit for evaluation of pembrolizumab-induced lichenoid dermatitis.

The BCC was *not biopsied*, but it was monitored throughout the duration of his anti-PD1 treatment.
Did 11 doses of pembrolizumab cure his BCC?

A. Yes
B. No
Did 11 doses of pembrolizumab cure his BCC?

A. Yes

B. No
Case #1 Pearls

• Increasing numbers of patients will be treated with anti-PD1 therapies, and many (10-50%) will experience cutaneous adverse events.

• Lichenoid dermatitis, eczematous dermatitis, vitiligo, pruritus, and psoriasis/psoriasiform dermatitis are most common.

• Topical steroids and other non-immunosuppressive therapies can be used while continuing immunotherapy.

• Impact of concomitant use of immunosuppressive medications on the survival of patients treated with anti-PD1 therapies is uncertain.
Case #2

• 44 year-old African-American male

• **Chief Complaint**
  – Itchy skin rash on the trunk & upper/lower extremities
  – Onset ~1 year ago
  – Failed treatments
    • Triamcinolone 0.1% ointment
    • Doxycycline
What other systemic disorders should you look for in this patient?

A. Hypertension
B. Chronic kidney disease
C. Diabetes mellitus
D. Chronic venous insufficiency
E. Hypothyroidism
What other systemic disorders should you look for in this patient?

A. Hypertension
B. Chronic kidney disease
C. Diabetes mellitus
D. Chronic venous insufficiency
E. Hypothyroidism
Acquired reactive perforating collagenosis (RPC): Associated systemic disorders

• COMMON
  – Diabetes mellitus
    • Fasting plasma glucose ≥126 mg/dL
    • Oral glucose tolerance test with two-hour glucose ≥200 mg/dL
    • Hemoglobin A1C ≥6.5%
  – Chronic kidney disease
    • Serum creatinine
eGFR <60 mL/min/1.73 m² persistent for >3 months
Acquired reactive perforating collagenosis (RPC): Associated systemic disorders

- **COMMON**
  - **Hypertension (Stage 1)**
    - *systolic* 130-139 mmHg
    - *diastolic* 80-89 mmHg
    - Both *in-office* and *out-of-office* measurements required

- **Chronic venous insufficiency**
  - Duplex venous ultrasound evaluating for retrograde flow
    - >500 ms for superficial or perforating veins, >1000 ms for deep veins
Acquired reactive perforating collagenosis (RPC): Associated systemic disorders

- RARE
  - Steatohepatitis
  - Sclerosing cholangitis
  - Hepatocellular carcinoma
  - Pancreatic carcinoma
  - Prostate carcinoma
  - Hodgkin’s disease
  - Myelodysplastic syndrome
  - Hepatitis B/C
  - Pulmonary aspergillosis
  - Lupus vulgaris
  - Scabies
  - HIV
  - Drug-induced sorafenib, indinavir, others
Case #2

• 44 year-old African American male

• Chief Complaint
  – Itchy skin rash on the trunk & upper/lower extremities

• Past Medical History
  – Dyslipidemia
  – Diabetes mellitus type II
Case #2

- **Social History**
  - Born in Nigeria
  - Relocated to the U.S. in 2013
  - Catholic priest
  - No alcohol or tobacco use

- **Medications**
  - Atorvastatin
  - Canagliflozin
    *Inhibitor of sodium-glucose transport proteins (SGLT2)*
  - Linagliptin
    *Dipeptidyl peptidase-4 inhibitor*
Case #2

• **Outside Records**
  – Hemoglobin A1c 9.1%
  – eGFR 121 ml/min/1.73m² (normal)
  – TSH 1.85 mclU/mL (normal)
  – Normotensive
In addition to *topical* steroids and antihistamines, how would you manage this patient?

A. Acitretin  
B. Allopurinol  
C. Narrowband UVB phototherapy  
D. Prednisone  
E. Dapsone
In addition to *topical* steroids and antihistamines, how would *you* manage this patient?

A. Acitretin

B. Allopurinol

C. Narrowband UVB phototherapy

D. Prednisone

E. Dapsone
Case #2

- **Months 1-2:** narrowband UVB phototherapy; no perceived benefit
  Patient wants to try allopurinol...
Is there any specific lab that needs to be checked before starting allopurinol?

A. Yes
B. No
Is there any specific lab that needs to be checked before starting allopurinol?

A. Yes

B. No
Given the risk for severe cutaneous adverse reactions, consider genetic testing for the HLA-B*5801 allele in

- Korean patients with CKD ≥ stage 3
- Han Chinese patients
- Patients of Thai descent

CBC, uric acid, ALT/AST, Cr/eGFR periodically checked after initiation of allopurinol
Case #2

- **Months 1-2:** narrowband UVB phototherapy; no perceived benefit
- **Months 3-4:** Allopurinol with benefit
- **Months 5-8:** Allopurinol continued with benefit
- **Month 9:** *Salmonella* enteritis and new rash?
What is the most likely diagnosis?

A. Pityriasis rosea
B. Allopurinol-induced pityriasis rosea-like eruption
C. Secondary syphilis
D. Psoriasis vulgaris
E. Evolving cutaneous T cell lymphoma
What is the most likely diagnosis?

A. Pityriasis rosea
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Pityriasis rosea (PR) and PR-like eruptions

- **Infectious etiology**
  - HHV7, HHV6
  - CMV, EBV
  - Influenza, parainfluenza
  - parvovirus B19
  - *Legionella*
  - *Mycoplasma*
  - *Chlamydia*
  - others...

- **Drug-induced**
  - barbiturates
  - captopril
  - metronidazole
  - allopurinol
  - terbinafine
  - others...
  - clonidine
  - imatinib
  - TBF-α inhibitors
  - omeprazole
  - vaccines
Case #2

- **Months 1-2**: narrowband UVB phototherapy; no perceived benefit
- ** Months 3-4**: Allopurinol 100 mg daily with benefit
- **Months 5-8**: Allopurinol 100 mg daily continued with benefit
- **Month 9**: *Salmonella* enteritis and new rash?
  - Biopsy: Parakeratotic superficial perivascular & spongiotic dermatitis
  - **Subjective** history of *salmonella* enteritis
  - Allopurinol 100 mg daily continued
  - TAC 0.1% soak & smear with benefit
Case #2

• **Months 9-11**: Review of outside electronic medical records
  – Enteric pathogen PCR test positive for Salmonella
  – No vaccinations 2-3 months prior to onset of new skin rash
  – WBC counts 2k to 3k with lymphopenia for >2.5 years
  – Hematology evaluation:
    “Secondary to racial differences in WBC counts; no further work-up recommended.”

• **Month 12**: Significant worsening of rash?
Case #2

- **Months 9-11**: Allopurinol continued; TAC 0.1% soak & smear with benefit
- **Month 12**: Significant worsening of rash?
  - Biopsy: Psoriasiform dermatitis
  - Syphilis, Hepatitis B, and Hepatitis C serologies negative
  - Quantiferon gold testing negative
  - HIV screen positive
  - HIV-1, CD4 count **undetectable**
  - ART: elvitegravir, cobicistat, emtricitabine, and tenofovir
  - Sulfamethoxazole/trimethoprim prophylaxis
  - Halobetasol 0.05% ointment, narrowband UVB phototherapy, allopurinol
Case #2 Pearls

• A new diagnosis of a reactive perforating collagenosis (RPC) should trigger screenings for hypertension, diabetes mellitus, chronic kidney disease, and venous insufficiency.

• Treatment of RPC can be challenging, with nbUVB phototherapy and allopurinol demonstrating some clinical efficacy in this case.

• Eruptive psoriasis/psoriasiform dermatitis is a potential clue to an underlying HIV infection.

• As a physician, it is important to recognize potential implicit biases that might otherwise affect your management decisions.
The Dermatology Foundation has supported & advanced our careers.