Hospital Dermatology: Pearls and Pitfalls

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Disclosures

• Relevant Financial Relationships
  – None

• Off Label Usage
  – Yes
What is Hospital Dermatology?

• Long-standing unique tradition at Mayo, a tertiary care center with a large referral service

• We preserved and improved on the quality of care rendered our patients with difficult skin diseases in our hospital program

• Hospital core group
  – Clinical Division
    • MDP Davis, R El Azhary, D. Wetter, M McEvoy, J Sartori
  – Laboratory Division
    • AG Bridges, MC Camilleri
Role of Dermatology Hospitalist

Hospitalist

Inpatient Dermatology
- Lymphoma
- Autoimmune bullous disorders
- Ulcers
- PG, Calciphylaxis
- Vasculitis
- CTD
- Erythroderma
- Generalized dermatitis
- Hypersensitivity reactions
- Cellulitis
- Psoriasis

Outpatient - Hospital based
- Psoriasis
  - Goeckerman
  - Phototherapy

Consult Service
- Pediatrics/Neonatal medicine
- Drug eruptions
- GVHD
- Dermatitis
- Lesions
- Vasculitis/vasculopathy
- Infection
- Ulcers
- Lymphoma
Pearls and Pitfalls of Hospital Dermatology

Goals of this lecture

• Review clinical and histopathological presentations, differential diagnosis, evaluation and management of major categories of dermatologic diseases in hospitalized patients

1. “Help!” Red and Scaly All Over
2. I itch and nothing helps!
3. I think it’s a drug eruption. Now what do I do?
4. Bugs – What “bugs” you?
5. Oh no! The patient has purpura
6. Yikes! The flesh eating ulcer
“HELP!”
Red and Scaly All Over
• 91 year old woman admitted to Ortho for left hip replacement
• HTN, hyperlipidemia, GERD and dermatitis
• Worsening dermatitis for 3 months
• Hip replacement cancelled
• Admitted to Derm service
What is your diagnosis?

A. Dermatitis
B. Pityriasis Rubra Pilaris (PRP)
C. Psoriasis
D. Drug reaction
E. Lymphoma
Sézary syndrome

- Clonal T-cell receptor gene rearrangement detected in skin biopsy
- Lymphadenopathy
- Convoluted lymphocytes on peripheral smear
- Patient declined aggressive management and methotrexate initiated up to 25mg weekly
Erythroderma

- Psoriasis
- Pityriasis rubra pilaris
- Dermatitis
- Drug eruption
- Lymphoma
- Infection
- Autoimmune bullous disorder
“I itch and nothing helps!!”
• 54 y/o F with severe pruritic eruption x 1.5 years
• Admitted to Dermatology inpatient service for wet dressings
• Outside skin biopsies non-specific dermatitis
• DIF ? DH (negative anti-gliadin and TTG antibodies, duodenum biopsy negative for celiac disease)
• Prior treatments:
  - Topical corticosteroids (poor response)
  - Dapsone gel (poor response)
  - UVB (some benefit)
  - Dapsone 50 mg QD x 8 months (initially helpful)
  - Systemic corticosteroids (30 day course w/ taper)
  - Hydroxyzine and doxepin (some benefit)
What is your diagnosis?

A. Scabies
B. Prurigo Nodularis
C. Dermatitis Herpetiformis
D. Bullous Pemphigoid
E. Lymphoma
**Pruritus Evaluation**

- Normal or negative: CBC, peripheral smear, ESR, SPEP, IgA, IgM, IgG, TSH, ANA, gliadin Ab, endomysial Ab, TTG, Hep B/C, HIV, CXR
- AST 51 and ALT 111: known steatohepatitis
- Skin swab: Methicillin sensitive Staph aureus
- Biopsies for H&E and DIF obtained
• Elevated BP180 (90) and BP230 (90)
• Final diagnosis: **Bullous pemphigoid (pemphigoid nodularis)**

DIF: Linear deposition of IgG along BMZ

IIF: 1:640 BMZ titer on monkey esophagus with epidermal pattern on salt-split skin
Pearl: Atypical presentations of bullous pemphigoid

- 20% non-bullous
- Eczematous, dyshidrosiform, urticarial, erythrodermic, nodular, lichenoid, or targetoid
- Include evaluation for autoimmune bullous disorders in erythroderma and pruritus work-up
Pruritus

- Xerosis
- Dermatitis
- Hypersensitivity reaction
- Dermatophytosis
- Folliculitis
- Scabies

- Autoimmune bullous disease
- Liver disease
- Renal disease
- Thyroid disease
- Anemia
- Lymphoproliferative disorders
I think it’s a drug eruption. Now what do I do?
Drug Eruptions

Simple
- No systemic symptoms
  - Morbilliform
  - Urticarial

Complex
- Systemic involvement
  - Life threatening
  - Drug hypersensitivity reaction
    - Stevens-Johnson syndrome (SJS)
    - Toxic epidermal necrolysis (TEN)

Other
Drug Reactions

3 things you need to know

1. Type of drug reaction
2. Statistics
   - What drugs are most likely to cause that type of reaction?
3. Timing
   - How long after the drug was started did the reaction begin?
<table>
<thead>
<tr>
<th>Reaction Type</th>
<th>Drug</th>
<th>% Rxn for Drug</th>
<th>DATES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbilliform</td>
<td>ASA</td>
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<tr>
<td>Urticarial</td>
<td>Colace</td>
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<td>Fixed Drug</td>
<td>Bactrim</td>
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<td>Erythroderma</td>
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<td>EM</td>
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<tr>
<td>SJS</td>
<td>Vancomycin</td>
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<td>TEN</td>
<td>HCTZ</td>
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<tr>
<td>AGEP</td>
<td>Dilantin</td>
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- Vasculitis
  - LCV
  - HSP
  - Other
- Lupus-like
- Blistering
  - Pemphigus
  - LABD
  - PseudoPCT
- Pseudolymphoma
- Cytotoxic

**DATES**

**% Rxn for Drug**

**http://www.drugeruptiondata.com**

**UserName = Mayo1**

**Password = Physicians**

**MR = Many Reports**

**R = Reported**

**NR = Not Reported**
This patient is hospitalized for a pneumonia and has developed this pruritic eruption. What is the most important intervention that will lead to resolution of the rash?

A. Topical corticosteroids
B. Systemic Corticosteroids (prednisone 0.5-1 mg/kg/day)
C. Find out what drug was recently started and stop that drug
D. Arrange for an urgent skin biopsy to find out what the rash is due to
E. Oral antihistamines
Clinical Pearls

- Drug eruptions are extremely common
- Tend to be generalized
- Maculopapular/morbilliform most common
- Best intervention: Stop the offending drug
- How to spot the culprit?
  - Drug started within days to a week prior to rash
  - Can be difficult!
  - Tip: can generally exclude all drugs started after onset of rash!
- Drug eruptions can continue for 1-2 weeks even after stopping culprit drug
Patient just admitted
BP 80/50 mmHg
Your diagnosis?
• ↑↑ epidermal necrosis & ↓↓ dermal infiltrate compared to SJS
TEN

• Most severe presentation in spectrum which includes EM & SJS
• Generalized erythema, purpura & flaccid bullae
• Widespread epidermal detachment >10% of BSA
• Extensive mucous membrane involvement
• No target lesions
TEN/SJS

- Drug-related
- Extracutaneous involvement
  - Fever
  - Leukopenia
    - Poor prognostic factor
  - Involvement of GI, renal & respiratory mucosa
TEN/SJS

• Drug-related
  – Sulfonamides
    • Slow acetylator phenotype
  – Anticonvulsants
    • Dilantin, phenobarbital, carbamazepine, lamotrigine
  – Penicillin derivatives
  – NSAIDS
  – Allopurinol
SJS

- Target lesions
SJS

- Generalized erythema or purpura
- <10% epidermal detachment
SJS

- Extensive ulceration of oral, genital, &/or ocular mucous membranes ($\geq 2$ surfaces)
TEN/SJS Bottom Line
(Personal View)

- TEN/SJS are both associated with high mortality rates (up to 25%) from sepsis and multiorgan failure
- Require intensive supportive management in ICU/Burn unit
- Discontinue the causative drug or treat underlying infection
  - Mycoplasma in 25% of pediatric patients with SJS
- Bulk of evidence
  - Supports use of intravenous immunoglobulin
    - 0.5-1gm/kg/d X 4 days
    - IVIG blocks Fas mediated apoptosis in vitro and arrests development of TEN in vivo
  - Does not support use of systemic corticosteroids
  - Cyclosporine
    - 3mg/kg X 10days, then 1 mg/kg X 10 days; go back up if you taper too quickly & the patient flares
CASE
• 33 yo F G1P1, 2 weeks postpartum
• Persistent, painful generalized eruption X 3 months
• Severe head, ear and mouth pain with dysphagia
• Reported NO medications
• Received systemic and topical steroids
What is your diagnosis?

A. Scabies
B. Drug reaction with eosinophilia and systemic disease (DRESS)
C. Polymorphic eruption of pregnancy
D. Connective tissue disease (CTD)
E. Psoriasis
F. Autoimmune bullous disorder
Laboratory evaluation

- Oral swab: + HSV-1 & Candida
- Cutaneous swab: MSSA
- Leukocytosis (18.9) with eosinophilia (4.47)
- ↑ aldolase, LDH, ALT, AST
- PCR HHV-6 negative

- CT chest/ abdomen/ pelvis
  - B/L axillary & inguinal lymphadenopathy
- ↓ zinc
- TSH wnl
- EKG normal
• Latent TB
  – + PPD 7 months ago – INH initiated
  – Onset of rash 4 months later
  – Rash persisted and 1 month later INH discontinued
Hospital course

• 3 consecutive days high dose methylprednisolone (1.5 gm/day) followed by transition to prednisone
• Mycophenolate mofetil and IVIG
• ↓ aldolase, LDH, LFTs, eosinophils
• Improvement in skin, symptoms
DRESS Syndrome

Drug Reaction with Eosinophilia and Systemic Symptoms
DRESS Syndrome

• AKA:
  • Anticonvulsant Hypersensitivity Syndrome
  • Drug-induced Pseudolymphoma
  • Drug-induced Hypersensitivity Syndrome
  • Hypersensitivity syndrome
  • Drug-induced Delayed Multiorgan Hypersensitivity Syndrome
DRESS Syndrome

• Severe, idiosyncratic drug reaction
• Commonly implicated drugs: anticonvulsants, sulfonamides, allopurinol, NSAIDS, azithromycin, azathioprine, and anti-retrovirals
• Most cases present after delay of 2-8 weeks, but onset has been reported from 3-105 days after drug initiation
  – Time to abnormally metabolize the drug leading to toxic drug metabolites
• Reactivation of HHV-6 has been observed
Clinical Features of DRESS

• Fever, leukocytosis, eosinophilia
• Huge variability in presentation
  – Each class of drug causes a slightly different clinical picture
• Facial edema mimicking angioedema
• Generalized eruption: erythematous edematous papules, vesicles, bullae, pustules, purpura, target lesions and erythroderma
Clinical Features of DRESS

• Lymphadenopathy
• Myositis
• Liver function test abnormalities
• May result in severe hepatocellular or cholestatic damage, necessitating transplant
  – 10% mortality typically from liver failure
• Variable lung, kidney, heart, thyroid involvement
Treatment of DRESS

- Withdrawal of offending medication
- Avoid cross-reacting medications
- High-dose systemic steroids
  - 1.5-2 mg/kg tapering dose over 1-3 months
- LFTs should be followed until resolved
- Supportive care
- ICU/Burn unit care is not required
Miscellaneous Drug Eruptions You Should Know About

• Acute generalized exanthematous pustulosis (AGEP)
• Linear IgA bullous dermatosis (LABD)
• Symmetric drug-related intertriginous and flexural exanthema (SDRIFE)
• TNF-alpha antagonist-induced lupus-like drug eruption/syndrome (TAILS)
CASE
• 31 year old woman admitted to Medicine
• 1 week history of generalized erythema and edema
• Following uncomplicated Caesarian delivery
• Given Clindamycin
• Tachycardia, leukocytosis, elevated ESR and CRP
• Systemic steroids given
Acute Generalized Exanthematous Pustulosis (AGEP)

- Also known as a pustular drug eruption
- Fever and leukocytosis with neutrophilia and eosinophilia are often present
- Many implicated drugs: macrolide & beta-lactam antibiotics, cephalosporins, tetracyclines, vancomycin, sulfonamides, carbamazepine, allopurinol, furosemide, antifungals, calcium channel blockers, ACE inhibitors, acetaminophen
- Sudden onset 2-5 days after drug started
- Begins on the face and intertriginous areas
- Disseminates in a few hours
Treatment of AGEP

• Discontinuation of drug
• Topical care
• Eruption usually resolves rapidly in 3-5 days with desquamation
• May be due to a specific T-cell reaction
• Neutrophils may be recruited by local cytokines
CASE
• 19-yo man with pruritic eruption
• Began shortly after starting vancomycin
DIF- Linear deposition of IgA along the BMZ
Drug-induced LABD

- Various clinical presentations
- Vesiculobullous eruption on trunk/extremities
  - Herpetiform or rosette-like bullae
- Morbilliform, urticarial
- Can resemble DH, BP, CP, PV, LP, EM or TEN
- 40% with mucosal involvement
Drug-induced LABD

- Drug-induced
  - Vancomycin – most common drug
  - Others: Penicillins, cephalosporins, captopril, trimethoprim/sulfamethoxazole, phenytoin, furosemide, glyburide, diclofenac

- Onset: 3-14 days after exposure

- Target Ag- BPAG2 (BP180)
Drug-induced LABD

Treatment

• Removal of the offending agent
• Dapsone, Sulfapyridine, Corticosteroids
• Dialysis
CASE
• 84 yo male
• 2 day intertriginous eruption
• On Levaquin, Cefepime, and Hydroxyzine
What is Your Diagnosis?

A. Acute generalized exanthematous pustulosis (AGEP)
B. Intertrigo
C. Hailey-Hailey disease
D. Cellulitis
E. Symmetric drug-related intertriginous and flexural exanthema (SDRIFE)
Symmetric Drug-Related Intertriginous and Flexural Exanthema (SDRIFE)

• Diagnostic criteria
  – Exposure to systemic drug predominantly aminopenicillins and B-lactams at first or repeated dose (contact allergens excluded)
  – Erythema of the gluteal/perineal area
  – Involvement of at least one other intertriginous/flexural localization
  – Symmetry of the affected areas
  – Absence of systemic symptoms and signs
CASE
• 18 year old female with juvenile RA in the MICU
• Fever, chills, hypotension, headache, N/V, fatigue, weakness
  • Etanercept 0.98mL of 50 mg/mL SC weekly
    • Started 1 year ago and last injection 4 wks ago
  • Methotrexate 2.5 mg weekly
    • Discontinued 8 wks ago
  • Prednisone 5 mg qAM
    • Increased to 20 mg
  • Started on amoxicillin 2 days after rash
The most likely diagnosis for this patient’s skin eruption is:

A. Stevens Johnson syndrome (SJS)
B. Infectious mononucleosis from EBV
C. Lupus erythematosus or lupus-like reaction secondary to etanercept
D. Secondary syphilis
E. DRESS (drug reaction with eosinophilia and systemic symptoms)
Laboratory Evaluation

• Pancytopenia
  • Anemia and thrombocytopenia (3 months prior); leukopenia; normal peripheral smear; no eosinophilia
• Elevated ANA (>12)
• Elevated ds-DNA (>1000)
• ENA: Elevated Scl70 Ab (1.8)
• Decreased Complement
  • Total C (8), C4 (9)
• SPEP: Polyclonal hypergammaglobulinemia
Vacuolar interface dermatitis consistent with lupus-like reaction secondary to etanercept or LE
TNF-alpha Inhibitors

- Using more of these agents to treat chronic inflammatory diseases
  - RA, AS, psoriasis, PsA, and IBD
- Infliximab
  - Chimeric monoclonal Ab (IV)
- Etanercept
  - Recombinant TNF-alpha soluble receptor fused to the Fc fragment of IgG2 (SC)
- Adalimumab
  - Recombinant human IgG1 monoclonal Ab (SC)
- Golimumab
  - Human IgG1 monoclonal Ab (SC)
- Certolizumab
  - Recombinant humanized monoclonal Ab Fab fragment (SC)
TAILS

- Incidence 0.2-0.4%
  - Difficult to establish
  - Based on post-marketing studies
- As use of these agents increases, incidence of cutaneous reactions will increase
- Most cases caused by the agents that have been more widely used
- Onset: <1 month – 4 years
- Diagnostic and therapeutic challenge
TAILS: Pathogenesis

• TNF-alpha inhibitor leads to production of autoantibodies
  • Disruption in cytokine balance
    • Suppression in production of Th1 cytokines, driving the immune response to Th2 cytokine production
  • Interference with apoptosis by decreasing CD44 expression
  • Inhibition of cytotoxic T-cells
Drug-induced autoimmunity

• Patients treated with TNF-alpha inhibitors develop antibodies found in patients with SLE (ANA, ds-DNA, ENA) in the absence of clinical features of SLE

• Not an indication to stop drug
Drug-induced autoimmunity

Use of these agents may trigger or unmask SLE in some patients.
TNF-alpha Inhibitor Induced SLE: Diagnosis

- In the setting of ongoing treatment with TNF-alpha inhibitor
- No prior history of SLE
- Cutaneous findings of SLE
  - Malar rash, photosensitive rash, mucosal ulcers, alopecia
- Systemic findings of SLE
  - Constitutional symptoms – fever, malaise, weight loss
  - Arthralgias, arthritis
- + Serology – ANA, ds-DNA
- Low complement
- Negative anti-histone antibodies
- Resolution of symptoms when drug is discontinued
TNF-alpha Inhibitor Induced SLE: Management

• Stop the drug
• Resolution of symptoms in 3 weeks to 6 months
• Patients may require systemic therapy
  • Corticosteroids and steroid sparing immunosuppressive agents (methotrexate, azathioprine, mycophenolate mofetil)
Regarding TNF-alpha Inhibitors which statement is INCORRECT:

A. It is contraindicated to use these drugs in patients with SLE
B. Re-challenging patients who develop anti-TNF alpha induced SLE with alternative TNF-alpha inhibitor agents is safe.
C. It is recommended to perform baseline serologic testing for CTD prior to starting therapy
D. It is recommended to perform baseline CXR and TB testing prior to starting therapy.
E. Patients should be followed closely after initiation of therapy to assess for development of lupus-like reactions and other cutaneous reactions
TNF-alpha inhibitors can cause the following cutaneous reaction:

A. Psoriasiform dermatitis
B. Granulomatous dermatitis
C. Vasculitis
D. Alopecia areata
E. All of the above
Psoriasiform dermatitis and palmoplantar pustulosis indistinguishable from psoriasis
Cutaneous Reactions to TNF-alpha Inhibitors

- Injection site reaction
- Urticaria
- Cellulitis
- Psoriasiform dermatitis
- Granulomatous dermatitis
- LE-like syndrome
- Vasculitis
- Alopecia areata
- Erythema nodosum
- SJS
- Morphea
- Erythroderma
CASE
70 yo F, 2 month h/o recurrent follicular lymphoma, treated 2 yrs ago

Transferred from outside hospital for worsening desquamating eruption and severe mucositis for 1 month

Skin and mucosal biopsies showed lichenoid dermatitis and mucositis c/w SJS/TEN

1 month prior to the eruption developing, she received 1 dose of a cefazolin as well a course of trimethoprim/sulfa and levofloxacin for URI

She has not responded to systemic steroids and IVIG
What is the likely diagnosis?

A. Stevens Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN)
B. Drug reaction with eosinophilia and systemic symptoms (DRESS)
C. Lymphoma
D. Infection
E. Paraneoplastic pemphigus
Paraneoplastic pemphigus

DIF- Cell surface staining along with linear to granular deposition along the BMZ with IgG and C3

• IIF - + ICS titer 1:80
• Dsg 3 +
• Dsg 1 -
Pitfall

• Not considering other diseases associated with mucosal lesions, blisters, and sloughing when evaluating a patient for possible SJS/TEN
BUGS: What “bugs” you?

YOU’VE GOT THE WORST CASE OF WHATEVER THIS IS, I’VE EVER SEEN.
• 77 yo male with CLL most recently treated with ibrutinib (EGFR inhibitor)

• Abdominal pain secondary to acute pancreatitis

• Worsening skin eruption involving head, neck, chest, and back 2-3 weeks after ibrutinib started
What is your diagnosis?

A. Ibrutinib drug eruption
B. Scabies
C. Varicella-Zoster infection
D. Deep fungal infection
E. Impetigo
Disseminated VZV

- Lesion swab
  - Bacterial culture: Staph aureus 4+
  - HSV1/HSV2 PCR: negative
  - PCR VZV: Positive

- Reactivation of VZV infection: started on IV Acyclovir 10mg/kg Q8H until lesions have crusted. Negative pressure room. Mupirocin 2% oint TID

- Ophthalmology: no ocular involvement
- Pancreatitis due to visceral involvement
- Cholecystectomy deferred
Disseminated Zoster Pearls

- **Definition**
  - > 20 lesions outside of 2 contiguous dermatomes
- **At risk group**
  - Elderly, immunosuppressed
- **Viscera can be affected**
- **Hutchinson’s sign** – Call ophthalmology
- **Contact and airborne precautions**
- **Treatment**
  - IV Acyclovir until lesions healed over or clear
Cutaneous adverse effects of targeted therapies

• Epidermal growth factor (EGFR) inhibitors
  – Papulopustular eruption in a seborrheic distribution
    • Most common cutaneous side effect
    • Dose-dependent
    • 1-2 weeks after therapy
  – Pruritus, xerosis
  – Paronychia
  – Mucositis
  – Pattern or cicatricial alopecia
What is the best management for papulopustular eruption from an EGFR inhibitor?

A. Systemic steroids  
B. Topical retinoids  
C. Low potent topical steroids and topical clindamycin  
D. Systemic antihistamines for pruritus and systemic antibiotics (tetracyclines) for severe eruptions  
E. C and D
Pearl

• Dermatologists need to be familiar with the skin-related toxicities associated with targeted therapies
CASE
• 72 yo F with psoriasis and psoriatic arthritis
  – Worsening skin eruption on extremities x 1 month
    • Infliximab
    • Methotrexate
    • Prednisone \(\rightarrow\) Methylprednisolone
  – Fever, tachypnea, tachycardia
  – Admitted for possible sepsis
    • Started on Vancomycin and Cefepime
What is your diagnosis?

A. Occlusive vasculopathy
B. Infection
C. Lupus-like reaction to TNF inhibitors
D. Psoriasis
E. Lymphoma
Which organism is this?

A. Blastomycosis
B. Coccidiomycosis
C. Cryptococcus
D. Histoplasmosis
Disseminated Histoplasmosis

- Cutaneous, pulmonary, and intestinal involvement
- Histoplasma antibody and urine antigen positive
- Fungal blood cultures positive
- All immunosuppressants discontinued
- Responded to treatment with amphotericin X 2 weeks, followed by itraconazole
- Monitor itraconazole levels and Histoplasma urine antigen
Disseminated Histoplasmosis

• Histoplasma capsulatum
  – Grows in soil which contains bird and bat feces
  – Endemic in Mississippi and Ohio river basins; Central and South America; Southern Europe; Africa; South and Southeast Asia

• Hematogenous dissemination in patients with suppressed immune systems
Disseminated Histoplasmosis

• Patients may present with ill-defined symptoms
  – Fevers, weight loss
• Up to 20% may present in septic shock and multisystem organ failure
• Variable clinical presentation
  – Papules & nodules with necrosis & hyperkeratosis; ulcers; bullous EM-like; erysipelas-like; petechiae/purpura; acneiform & folliculopustular papules; vesicles, herpetiform; exfoliative, nummular or psoriasiform dermatitis; morbilliform eruption
• Gold standard for diagnosis
  – Tissue cultures
Pearls

• Infection MUST be excluded in an immunocompromised patient!!!

• Recently described *phenomenon of immune reconstitution syndrome*
  – In the setting of disseminated histoplasmosis in patients who have been on a biologic agent or had reduced cellular immunity
  – Patients do well clinically and have therapeutic itraconazole levels with decrease in histoplasma urine antigens
  – Develop new skin or LN lesions with negative cultures but organisms still present on biopsy
  – Tx with prednisone taper and continue itraconazole
CASE
• 3 month boy with fever, irritability & rapidly progressing generalized blisters over past 24 hours
What is your diagnosis?

A. Erythema multiforme (EM)
B. Herpes infection
C. Stevens Johnson syndrome/ Toxic epidermal necrolysis (SJS/TEN)
D. Staphylococcal scalded skin syndrome (SSSS)
E. Toxic shock syndrome (TSS)
Staphylococcal Scalded Skin Syndrome (SSSS)

- Common in infants and children
- Secondary to extracutaneous S. aureus, phage grp II, infection
  - Produce exfoliative toxins, bind to dsg 1 leading to acantholysis of the upper epidermis
- Fever, irritability, purulent rhinorrhea and conjunctivitis, painful, tender skin
  - Periorificial edema and scale crusts
  - Confluent erythema, superficial erosions and flaccid bullae, esp. in intertriginous sites
Treatment

• Throat culture positive for MSSA
• IV antibiotics
  – Vancomycin (per ID) – stopped after 5 days,
    Clindamycin 80 mg IV q8h and Oxacillin 300 mg
    IV q6h
• Plastibase ointment
• Zinc oxide ointment to groin and neck
• Mupirocin ointment to nares and severe areas
CASE
• 7 month male
  – Atopic dermatitis
  – 24 hours of explosive worsening of AD
    • VSS
    • Non-toxic, happy, no change in temperament
What is your diagnosis?

A. Eczema Coxsackium
B. Eczema Herpeticum
C. Gianotti Crosti syndrome
D. Secondary bacterial infection in setting of atopic dermatitis
Eczema Coxsackium

- Enterovirus PCR swabs from both tongue and skin positive
- HSV/VZV PCR swab negative
- Bacterial swab culture grew 2+ Staph aureus
- After 30 hrs of wet dressings, he had 75% improvement
Eczema Coxsackium

- Coxsackievirus A6 infection
- Widespread vesiculobulvous exanthem favoring the perioral area, trunk and areas of previous dermatitis or injury as well as classic sites of hand, foot and mouth disease
- Young children
- Summer and Fall
- Spread via fecal-oral and respiratory routes
Anticipating and preventing infection in patients treated with immunosuppressive medications for dermatologic indications: A dermatologist’s checklist

Julia S. Lehman, MD, David A. Wetter, MD, Mark D. P. Davis, MD, Rokea A. el-Azhary, MD, PhD, Lawrence E. Gibson, MD, and Amer N. Kalaaji MD

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Infection and Infection Prevention in Patients Treated with Immunosuppressive Medications for Autoimmune Bullous Disorders

Julia S. Lehman MD, Dédée F. Murrell MA, BMBCh, FAAD, MD, FACD, Michael J. Camilleri MD and Amer N. Kalaaji MD

Infection and Infection Prevention in Patients Treated with Immunosuppressive Medications for Autoimmune Bullous Disorders, 2011-10-01Z, Volume 29, Issue 4, Pages 591-598, Copyright © 2011 Elsevier Inc.
• 66 y/o male with no prior medical history
• Blisters of mouth and skin for 1.5 months
• Seen by outside derm: biopsies pemphigus vulgaris
• Prednisone 60 mg x 2 wks, worsening
• Prednisone 80 mg
• Mayo referral
• Admitted for wet dressings/wound care
• Plan for therapy with Rituximab
DIF: Cell surface staining with IgG and C3;
IIF: 1:1280 ICS;  DSG1 131 DSG3 203
Table I. Infection prevention checklist for dermatologists when caring for patients with immune-mediated dermatoses requiring iatrogenic immunosuppression

<table>
<thead>
<tr>
<th>Screen patient for infectious risk factors¹, such as:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppressive medications</td>
</tr>
<tr>
<td>Comorbid immunosuppressing illnesses (such as diabetes mellitus, organ transplantation, cancer requiring chemotherapy, hematologic malignancy, HIV, chronic kidney disease requiring dialysis, history of liver failure, and autoimmune diseases requiring immunosuppression)</td>
</tr>
<tr>
<td>History of blood transfusion</td>
</tr>
<tr>
<td>History of high-risk sexual activity</td>
</tr>
<tr>
<td>History of travel to remote or rural areas, or areas with endemic disease</td>
</tr>
<tr>
<td>History of positive PPD test or exposure to tuberculosis</td>
</tr>
<tr>
<td>Nutritional deficiency or malabsorption</td>
</tr>
</tbody>
</table>

Consider laboratory screening and/or chest radiography for patients with pertinent risk factors (specific tests to consider in parentheses):

- Hepatitis B (HBsAg, anti-HBc, IgM anti-HBc, anti-HBs)
- Hepatitis C (HCV enzyme immunoassay)
- HIV (HIV ELISA)
- Strongyloides (stool ova and parasites; Strongyloides ELISA)
- Tuberculosis (PPD tests; interferon-gamma release assay; chest radiograph, including patients with a positive PPD test from previous Bacillus Calmette–Guérin vaccination)
- Systemic fungal infections, such as cryptococcosis, histoplasmosis, coccidioidomycosis, blastomycosis, and paracoccidioidomycosis (serum and/or urine studies; chest radiograph)

Consider pneumocystis pneumonia prophylaxis, particularly in patients of advanced age, multiple medical comorbidities (especially pulmonary), in whom prolonged or intense immunosuppressive therapy is anticipated⁷

Ensure that the patient's immunization schedule is up to date,² according to the latest recommendations:

- Seasonal influenza vaccination (non-live vaccine available; live vaccine to be avoided after immunosuppressive therapies have been begun)
- Pneumococcus vaccination (non-live vaccine)
- Herpes zoster vaccination (live vaccine; to be given ≥ 30 days before initiation of immunosuppressive therapies; to be avoided after immunosuppressive therapies have been begun)
- Tetanus/diphtheria vaccination (non-live vaccine)

Educate patients¹ regarding:

- Importance of hand washing
- Avoidance of high-risk infectious exposures where possible (ie, crowded areas, farms, compost, nursing homes, and daycare centers)
- Early signs and symptoms of infections (such as pneumonia, urinary tract infection, influenza, herpes zoster, etc.)

Assess possibility of—and treat patients for—impetiginization and colonization (particularly herpetic simplex virus, Candida, and Staphylococcus) at each clinical encounter
Evaluation

• CBC, chem 20 panel

• Negative CXR, Hepatitis screen, HIV, syphilis serologies

• QuantiFERON-TB POSITIVE!!!

• Vaccination status
  – Influenza and Pneumococcal vaccine: past fall
  – Herpes zoster: no
  – DTaP: unknown
What would you do next?

A. Continue steroids alone
B. Continue steroids, vaccinate, and wait 4 weeks to give Rituximab
C. Continue steroids, vaccinate and wait 2 weeks to give Rituximab
D. Continue steroids, hold vaccination, and give Rituximab
E. Continue steroids, start mycophenolate mofetil
Infectious Disease Consult

• No signs/symptoms of active disease → latent TB
• Started on isoniazid and pyridoxine x 9 months
• QFT +: likely because of systemic steroids
• Delay Rituximab for at least 2 wks (ideally 4wks)
• Give DTaP
Inactivated vaccines are safe; effectiveness might be lower.

If vaccination within 2 wks of therapy or while on therapy, should revaccinate (at least 3 months post-therapy if immunity restored).

<table>
<thead>
<tr>
<th>YES</th>
<th>MAYBE</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza (inactivated) yearly</td>
<td>Meningococcal</td>
<td>Varicella</td>
</tr>
<tr>
<td>Tdap once, Td booster every 10 years</td>
<td>Hepatitis A</td>
<td>Zoster</td>
</tr>
<tr>
<td>Pneumococcal (PCV13 or PPSV23)</td>
<td>Hepatitis B</td>
<td>MMR</td>
</tr>
<tr>
<td>HPV, if &lt; 26 y/o</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Anticipated treatment: Prednisone ≥20mg/day OR prednisone + cytotoxic agent (e.g. methotrexate, cyclophosphamide)/TNF-alpha inhibitor?

Yes

Defer PJP prophylaxis

No

Estimated Duration of Immunosuppressive Therapy

≥ 4 weeks or unknown

Evaluate for:
- Advanced age
- Preexisting T- or B-cell immunodeficiency
- Human immunodeficiency virus positive status
- Comorbid interstitial pulmonary fibrosis
- Prior organ transplant
- Comorbid hematologic malignancy
- Depressed CD 4 count (<250/microliter)
- Lymphopenia (total lymphocyte count <800/microliter)

Risk factors present

Consider PJP prophylaxis during treatment

No risk factors present

Consider re-evaluation (especially CD4 counts, serum albumin, lymphocyte count) 1-2 months after initiation of therapy

< 4 weeks

Defer PJP prophylaxis

Reassess the need for continuation of immunosuppressive medications

Treatment prolongation is required
The Patient has Purpura!
<table>
<thead>
<tr>
<th>Clinical</th>
<th>Histologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>Inflammation of blood vessel walls</td>
</tr>
<tr>
<td>Purpura</td>
<td>RBC extravasation</td>
</tr>
<tr>
<td>Subepidermal vesicles/bullae, ulcers</td>
<td>Necrosis, occlusion or destruction of blood vessel walls</td>
</tr>
</tbody>
</table>

- **Nonpalpable and palpable purpura**
  - Petechiae – purpuric macules
  - Ecchymoses – purpuric patches

- **Retiform purpura** – livedo reticularis (lace-like) or racemosa (net-like)
Purpura – Etiopathogenesis guides the differential diagnosis

- Immunologic or Allergic
- Infectious or Septic
- Occlusive
- Bleeding diathesis thrombocytopenia
CASE
22 year old male developed leg ulcers associated with a rash. Intensive wound care has been initiated. Which of the following would you recommend in addition?

A. Observation  
B. Topical corticosteroids  
C. Systemic corticosteroids  
D. ACE wraps  
E. Surgical consultation for possible revascularization procedure
LCV

Immunofluorescence Findings

- IgM > IgG, C3, & fibrinogen in blood vessels in the superficial dermis
Immune or Allergic

- Palpable purpura
  - LCV and its Variants
- ANCA-associated vasculitis
  - HSP or IgA vasculitis
  - Mixed cryoglobulinemia Types II and III
  - Urticarial vasculitis
LCV: Etiology

Vasculitis is a clinical sign
Ask what underlies the diagnosis

• Idiopathic (45-55%)
• Infection (15-20%)
• Inflammatory diseases/Systemic diseases (15-20%)
  – Connective tissue diseases: Lupus erythematosus, rheumatoid arthritis, Sjögren’s syndrome
• Drugs (10-15%)
  – PCN, sulfas, PTU, allopurinol, thiazides
• Malignancy (<5%)
Evaluation

• Possible **causes & extent of involvement**
  – H & P, hemoccult, CBC, UA, ESR, CRP, ANA, ENA, ANCA, complement studies, RF, SPEP, TSH, cryoproteins, hepatitis serologies, thrombophilia workup, pan cx, CXR

• **Skin biopsies**
  – 1 – 2 day old lesion for routine histology
  – < 24 hour old macule for DIF
  – Do **not** biopsy ulcers
HSP, Types II & III cryoglobulinemia, ACNA-associate vasculitis

Clinical Features

- Similar to LCV
- Involvement above waist
HSP, Types II & III cryoglobulinemia, ACNA-associated vasculitis
Clinical Features

- Larger lesions with figurate, retiform, or stellate shapes
HSP

- **Histologic Findings**
  - Similar to LCV

- **Immunofluorescence Findings**
  - IgA in blood vessel walls in the superficial dermis in >90%
Clinical Pearl
When to treat?

• If mild and nonprogressive
  – Many do not treat
  – Supportive tx, compression

• If painful, severe or rapidly progressive
  – Treat!
    • Associated with systemic disease
    • Associated with ulcerations
Pitfall

• Treating the ulcer as something other than vasculitis
CASE
The college student was well earlier today. 6 hours ago she developed a bad sore throat and muscle pains ‘I feel awful’
Now prostrate, febrile, hypotensive, & tachycardic
The most important & lifesaving measure initiated was

A. Supportive management alone
B. Intravenous ceftriaxone
C. Systemic corticosteroids (dexamethasone)
D. Activated Protein C
E. Lumbar puncture
Clinical Pearl

• Purpura fulminans
  – Due to DIC
  – Induced by meningococcemia

• Emergency!
  – No more than 30 minutes should elapse before the administration of appropriate antibiotics
  – Treat empirically, don’t wait for the results of tests
Pearl

• Purpura fulminans? Identify cause of DIC, manage cause
  – Think meningococcus or other underlying infection
• Medical emergency requiring intensive supportive management in an ICU
• Dermatologists can be valuable in guiding appropriate diagnosis and management
• Pitfall: Thinking this is LCV and starting systemic corticosteroids
• Purpura fulminans with symmetrical peripheral gangrene is an ominous clinical presentation affecting all age groups
  – Outcome: Death/Amputation
Occlusive Intraluminal

- Thrombosis Embolism
- Coagulation disorders Fibrin
- Cryoprotein- Type I cryoglobulinemia

Vessel Wall

- Degos’ disease or malignant atrophic papulosis
- Livedoid vasculopathy
Occlusive Vasculitis
Intraluminal

- Thrombosis-Emboli
  - Atherosclerosis
  - Cholesterol emboli
  - Thrombotic thrombocytopenic purpura (TTP)
Occlusive Vasculitis
Intraluminal Coagulation Disorder - Fibrin

- DIC/purpura fulminans
- Coumadin necrosis
- Heparin necrosis
- Protein C deficiency
- Protein S deficiency
- Antithrombin III deficiency
- Antiphospholipid antibody syndrome
- Mutation in factor V Leiden
- G20210A mutation in prothrombin gene
Occlusive Vasculitis
Intraluminal
Coagulation Disorder - Fibrin
Occlusive Vasculitis
Intraluminal
Coagulation Disorder - Fibrin
Occlusive Vasculitis
Intraluminal

- **Cryoproteins**
  - Cryoglobulins
  - Cryofibrinogen

- **Type I cryoglobulinemia**
  - Monoclonal Ig, most commonly IgM
  - Associated with lymphoproliferative disorders
Type I Cryoglobulinemia
Clinical Features

- Purpuric macules & papules
- Small, punched-out ulcers on acral sites
Type I Cryoglobulinemia

Histologic Features

- Deeply eosinophilic, homogeneous, hyalin, amorphous, PAS+ material in lumina of vessels
Infectious or Septic Vasculitis
Pathogenesis

• Direct infection of blood vessel wall

• Interaction of the host immune response with microorganism in the blood vessel wall
Infectious Vasculitis
Clinical Variants

- Ecthyma gangrenosum (*Pseudomonas*)
- Gonococcemia (*Neisseria gonorrhoeae*)
- Bacterial endocarditis
- Rocky Mountain Spotted Fever (*Rickettsia rickettsii*)
- Fungal sepsis (*Candida, Aspergillus*)
Infectious Vasculitis
Histologic Features

• Involvement of deeper vessels
• Prominent thrombosis
• Usually cell-poor infiltrate
• Organisms may be visualized in & around blood vessel walls in acute but not chronic septic vasculitis
Infectious Vasculitis
Histologic Features
CASE
A patient on hemodialysis
A patient on dialysis for chronic renal failure suddenly develops extraordinarily tender ulcerations involving legs, thighs and abdominal pannus.

Which of the following statements are most accurate about this condition?

A. Corticosteroids are the treatment of choice.
B. Surgical excision of the affected areas should be immediately performed.
C. The prognosis of this condition is dismal, and there is no treatment that consistently works.
D. Sodium thiosulfate leads to a predictable improvement in this condition.
E. Parathyroidectomy will usually be curative.
Occlusive

Intraluminal

Thrombosis Embolism
Coagulation disorders Fibrin
Cryoprotein- Type I cryoglobulinemia
Calciphylaxis
Soft tissue X-ray

- Net-like pattern of calcification
- 90% specificity
Clinical Pearls

- Calciphylaxis is multifactorial and usually fatal
- The prognosis is dismal
- 1-year survival: 46%
- 2-year survival: 20%
‘One of the worst ways to die’
Clinical Pearls

• Under-recognized syndrome
  – Occurs in 4% of hemodialysis patients
  – Non uremic cases associated with
    • Warfarin therapy, CTD, hematologic malignancies, DM, primary hyperparathyroidism, vitamin D deficiency, protein C and S deficiency, factor V Leiden deficiency, Crohn disease, and liver disease

• No clearly effective treatments
Calciphylaxis treatment strategies

Correct calcium-phosphate balance
- Sodium thiosulfate
- Cinacalcet
- Low calcium dialysate

Improve tissue perfusion & oxygenation
- TPA
- Hyperbaric oxygen
- Avoid warfarin for anticoagulation

Wound Care
- Debridement
- Surgical
- Whirlpool
- Maggot

Pain control
- Palliative care

- Multidisciplinary approach
- Mechanism - Thrombotic tissue ischemia; Must address the clot & prevent more
Calciphylaxis

ESRD from focal segmental GN on HD

Before low dose TPA X 14 days

One month later

6 months later
CASE
70 yo M with DM, HTN, hyperlipidemia, peripheral neuropathy, *pancytopenia*, CAD s/p CABG and MI

Transfemoral, endovascular aortic valve insertion for CHF secondary to aortic stenosis

- Complicated *intraoperatively* by *cardiac arrest*, requiring transcatheter placement of another aortic valve

- *Postoperatively*, he developed fever, leukocytosis, anemia, and *thrombocytopenia* (43) followed 4 days later by *cerebral infarction*

Consulted for LLE *nonpalpable purpura* that developed 9 days after the procedure
What is your diagnosis?

A. Cholesterol emboli
B. Thrombocytopenia
C. Infectious emboli
D. Polymer gel emboli
E. Vasculitis
What is this material?

• Colloidal iron stain established this was hydrophilic material

• X-ray probe microanalysis of the material
  • Phosphorus, sulfur and iron
Hydrophilic Polymer Coating

• Purpose:
  – Decrease friction
  – Reduce arterial spasm & pain
  – Reduce thrombosis

• Must be meticulously cleaned and moistened in order to avoid drying out and becoming tacky

• Not to be used for initial vascular access, because passage through entry needles can shear off the hydrophilic coating
“Clinical sequelae ranged from undetectable (no symptoms) to renal failure, myocardial infarction, pulmonary infarction, stroke, ongoing gangrene, and/or death occurring within days to weeks of suspected embolization of foreign material.”
Polymer coating embolism from intravascular medical devices — a clinical literature review

Highlights

- Recent literature associates polymer coating embolism with a range of adverse clinical sequelae.
- The elusive, microscopic phenomenon has been difficult to detect for almost three decades.
- Major polymer-emboli-related conditions include obstructions of blood flow in small vessels.
- Polymer emboli incidence is dependent on device coating integrity measured by particulate release.
- Regulators may default to controlling particulate release from intravascular devices.
- Research highlights the potential of using low-particulate-release coatings on intravascular devices.

https://www.sciencedirect.com/science/journal/10548807
Hydrophilic Polymer Gel Emboli: An Epidemic
Pearls:
Hydrophilic Polymer Gel Emboli

• Can embolize to the skin and cause microvascular occlusion presenting as purpura, livedo racemosa, livedo reticularis, hemorrhagic panniculitis, or ulceration
• Recent interventional procedure
• Treatment is supportive
• Lesions gradually improve
• Be aware of internal organ involvement of emboli
Yikes!
The flesh eating ulcer
58-year-old woman with multiple ulcerations and abscesses involving both breasts x 5 months

- Started after breast reduction surgery for pendulous breasts
- Ulcerations began at the incision sites 3 weeks postoperatively
- Multiple admissions to plastic surgery for incision and drainage of breast abscesses
- Several admissions to infectious diseases service for intravenous antibiotics
- Ulcerations have progressed
The treatment that led to resolution of these abscesses was:

A. Readmission of patient for incision and drainage of abscesses
B. Bilateral mastectomy
C. Long-term suppressive oral antibiotic treatment depending on antimicrobial susceptibilities
D. Oral prednisone
E. Skin grafting of ulcerations
Discussion
Pyoderma Gangrenosum

• There are many weird causes of ulcerations
• Weirdest of all: pyoderma gangrenosum
• Clues in this patient:
  – Irregular, violaceous undermined border
  – Pathergy (triggered by trauma, surgical debridement, and attempts to graft)
Clinical Pearls

• Pyoderma gangrenosum can occur anywhere on body including the breasts

• Characteristic clinical presentation
  – Rapidly progressive ulcerative process
  – Begins as a small pustule which breaks down forming an ulcer
  – Satellite papules may appear at the border, break down, and then fuse with the central ulcer
  – Fully developed: painful, undermined ulcer with blue/purple border
  – Heals with atrophic scar
Associated conditions

• 50% have no underlying cause

• Associations (50%)
  – IBD - Most common (1.5%-5% of IBD patients get PG)
  – RA, seronegative arthritis (>1/3 PG pts have arthritis)
  – Hematologic abnormalities, malignancies
Edge of the ulcer, dense infiltrate of PMN undermining the epidermis.
All special stains and tissue cultures fail to reveal infection… c/w pyoderma gangrenosum.
CASE
• 59 yo woman admitted with 1 yr. history of expanding leg ulcers
• On prednisone, cyclosporine and azathioprine for presumed diagnosis of pyoderma gangrenosum
• No biopsy
What is your diagnosis?

A. Pyoderma gangrenosum
B. Lymphoma
C. Infection
D. Occlusive vasculopathy
E. Calciphylaxis
Sporotrichosis

Admission

4 months

1 year
Bottom Line with PG

• Diagnosis of exclusion

• BUT! It’s important to do our best since treating a patient for PG when they DON’T have it with steroids and/or immunosuppression has it’s own set of associated risks, and can certainly aggravate the actual condition
Common diseases misdiagnosed as PG

- Vascular occlusive disease
- Chronic venous disease
- Vasculitis
- Neoplasm
- Exogenous tissue injury/Factitial Disease
- Spider bite
- Infection
Lessons learned

• Pyoderma gangrenosum can be underdiagnosed
• Pyoderma gangrenosum can be overdiagnosed
Summary: Pearls and Pitfalls in Hospital Dermatology

- Erythroderma
- Pruritus
- Drugs – Simple, Complex, Misc
- BUGS: Infection and infection prevention
- Purpura
- Neutrophilic dermatoses – PG
- Handout
Thank you!

Bridges.Alina@mayo.edu
Comments/questions?