Side Effects May Include: Illustrative Cases of Dermatologic Adverse Events

Raegan Hunt, MD, PhD
Chief, Pediatric Dermatology Service
Fellowship Director, Pediatric Dermatology
Assistant Professor of Dermatology & Pediatrics
Baylor College of Medicine
Texas Children’s Hospital

DISCLOSURES
Pfizer, Inc. - consultant

Objectives

- Diagnose cutaneous adverse drug events in pediatric and adolescent patients
- Develop management plans for pediatric drug reactions

Case

- 13-year-old boy with mood disorder (NOS), post-traumatic stress disorder, ADHD
- Violaceous "mapping pattern" on legs x 1 year
- Occasionally affected: trunk, arms, and face
- More prominent in cold conditions
- No pain, burning, itch
- No ulceration
- No nodules

Next best step?

1. Skin biopsy
2. ANA and antiphospholipid antibodies
3. Serum protein electrophoresis (SPEP) and Immuno-Protein Electrophoresis (IPEP)
4. Offer reassurance
5. Take a detailed medication history
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Medication History

**Oral medications:**
- Amantadine 100 mg daily
- Cetirizine 10 mg daily PRN
- Guanfacine 2 mg twice daily
- Hydroxyzine 25 mg daily
- Lamotrigine 25 mg twice daily
- Levothyroxine 50 mcg daily
- Lithium carbonate 150 mg twice daily

**Inhalers:**
- Fluticasone inhaler daily
- Proventil inhaler prn

Which medication likely resulted in his skin findings?

1. Amantadine
2. Guanfacine
3. Lamotrigine
4. Levothyroxine
5. Lithium carbonate

Livedo reticularis

- Lacy, violaceous anastomosing patches
- Caused by changes in cutaneous blood flow

Anatomical Basis for Livedo Reticularis

- Venous plexus is prominent at edges of cutaneous arterial cones (each 1-4 cm)
- Increased deoxygenated blood in venous plexus due to:
  - Decreased blood flow into or through skin
  - Decreased blood drainage out of skin

Bolognia, Jorrizo and Schaffer, Dermatology, 2012.
Livedo reticularis

- Physiological
- Idiopathic/Primary
- Secondary:
  - Vascular occlusion
  - Vasculitis
  - Connective tissue/autoimmune disease
  - Infectious
  - Endocrinological
  - Nutritional
  - Drug

Drugs that can cause livedo reticularis:
- Catecholamines (phenylephrine)
- Intrarterial bismuth
- Amantadine
- Quanidine
- Minocycline
- NSAIDs

Amantadine induced livedo reticularis (LR)

- Best studied in patients treated with Parkinson’s disease:
  - ~30-90% incidence (one outlying study only 2%)
  - More common in women
  - Occurs mostly on the legs
  - Reversible side effect

Amantadine

- Synthetic antiviral agent
- FDA approved to prevent influenza infection (1996)

Recent applications:
- Parkinson’s disease
- Multiple sclerosis (fatigue)
- ADHD

Case

13 year-old-boy with relapsed stage 2 Burkitt’s lymphoma hospitalized for chemotherapy

- Painful groin eruption
- Erythema appeared the morning after patient cleaned genital area with a chlorhexidine gluconate 4% wipe
- No itch
- Worsening despite topical nystatin cream
- Advancing tender border
- Afebrile, absolute neutrophil count 233
Oncology and urology team agreed to start treating patient with IV clindamycin and IV fluconazole

- Fungal/yeast skin culture - negative
- Bacterial skin culture - negative
- Blood cultures - negative
- Skin exposures – Limited to hibiclens wipes, nystatin, zinc oxide

Relapsed Burkitt’s lymphoma: TAT ANHL01P1 group C

- COP-R Day 0
  - cyclophosphamide 537 mg (300 mg/m²) day 0
  - vincristine 1.8 mg (1 mg/m²) day 0
  - prednisone 54 mg BID, day 0

- COMRAP1 Day 8
  - cyclophosphamide 450 mg (250 mg/m²) day 1-3
  - doxorubicin 107 mg (60 mg/m²) day 1
  - prednisone 54 mg BID, day 0-4 with taper over 3 days
  - pegfilgrastim 6 mg day 8

- Intrathecal therapy: methotrexate, cytarabine, hydrocortisone

Toxic Erythema of Chemotherapy

Clinical features
- Erythematous patches or edematous plaques
- Most frequently: hands, feet, intertriginous zones, scrotum
- Less commonly: elbows, knees, neck, and ears
- Dusty hue, petechiae, and/or sterile bullae may be seen in the affected areas of erythema
- Scattered papules may be seen at the periphery of the lesions

- Timing of onset
  - 2 days to 3 weeks after chemotherapy administered

- Symptoms
  - Pain, burning, paresthesia, or tenderness, more often than pruritus
- Heals with desquamation
- Spontaneous resolution without specific therapy
- Possible recurrence if the same or higher dose is administered

Histological findings
- Vascular degeneration of the basal layer
- Necrotic keratinocytes
- Dysmaturation of keratinocytes
- Dermal edema
- Eccrine squamous syringomatous proliferation

Chemotherapeutic agents associated with TEC

More commonly associated:
- Cytarabine (araC)
- Anthracyclines (doxorubicin)
- 5-Fluorouracil
- Cephalosporin (5-FU prodrug)
- Taxanes (docetaxel = paclitaxel)

Less commonly associated:
- Bleomycin
- Busulfan
- Carmustine, lomustine
- Cisplatin, carboplatin
- Cyclophosphamide
- Doxorubicin
- Etoposide
- Gemcitabine
- Hydroxyurea
- Vinorelbine
- Docetaxel
- Ibrutinib
- Mirtazapine
- Mitoxantrone
- Imatinib
- Sunitinib
- Tegafur

GL Anesi, et al. Journal of Clinical Oncology, Vol 30, No 16 (June 1), 2012: p e146
Toxic Erythema of Chemotherapy: Treatment

Supportive
- Cool compresses
- Bland emollients
- Topical corticosteroids
- Topical antibiotics for erosions
- Limited data for:
  - local hypothermia, systemic corticosteroids, oral vitamin B6 (50-150 mg once daily), oral vitamin E (300 mg once daily)

Toxic Erythema of Chemotherapy

- Toxic phenomenon
  - Not immune mediated
  - Self-limited
- Frequently misdiagnosed as
  - Allergic drug reaction
  - Allergic contact dermatitis
  - Graft versus host disease
  - Cutaneous infections

Case

3-year-old boy with Down syndrome
- Spreading erythema x 3 days which seemed at first to be "diaper rash"
- Eye swelling x 1 day
- Afebrile
- Noisy breathing
- O2 saturation 90%
- Hemorrhagic conjunctival injection
- Buccal mucosa and lip erosions
- + Nikolsky sign, large erosions to dermal level

What is your next step?

1. Stop all possible causative medications
2. Observe
3. Run away
4. Hide in the utility closet
5. Call 911
Toxic Epidermal Necrolysis (TEN)

Patient's medication history:
- Trimethoprim–sulfamethoxazole x 3 doses for MRSA external ear infection
- Trimethoprim–sulfamethoxazole discontinued immediately on presentation

Stevens Johnson Syndrome (SJS) - Toxic Epidermal Necrolysis (TEN)

- Clinical findings:
  - Erythematous macules
  - Blister/vesicles
  - Nikolsky sign
  - Detachment of epidermis with lateral pressure
  - Adams-Hansen sign
  - Extension of a blister to adjacent unblistered skin when pressure is put on the top of the bulla
  - Involvement of 3 mucous membranes
  - Skin pain
  - Prodromal symptoms: fever, malaise, vomiting

- SJS-TEN Spectrum:
  - SJS <10% BSA
  - SJS-TEN overlap 10-30% BSA
  - TEN >30% BSA
- Usually occurs 7-21 days after the inciting drug was started
- Mortality: 25-50% in TEN, 5% in SJS

- 1.2 – 6 per million (SJS)
- 0.4 – 1.2 per million (TEN)

- Risk factors
  - HIV
  - Lymphoma
  - Slow acetylator genotypes
  - HLA-B*1502: Asians and East Indians exposed to carbamazepine
  - HLA-B*5801: Han Chinese exposed to allopurinol
  - HLA-A*3101: Europeans exposed to carbamazepine

- Medications most frequently associated with TEN/SJS:
  - Allopurinol
  - Aminopenicillins
  - Antiretroviral drugs, especially NNRTIs
  - Barbiturates
  - Carbamazepine
  - Phenytoin anticonvulsants
  - Lamotrigine
  - Piroxicam
  - Sulfadoxine
  - Sulfasalazine
  - Trimethoprim–sulfamethoxazole

Stevens Johnson Syndrome (SJS) - Toxic Epidermal Necrolysis (TEN)

Treatment

- Stop offending agent quickly!
  - Difference in mortality if stopped at first sign of blister/erosion
  - 11% mortality for early discontinuation vs. 27% for late discontinuation (with short half-life drugs, t1/2 <24 hours)
- Supportive care
  - ICU care; consider transfer to regional burn center
  - Continuous enteral use
  - Avoid manipulation
  - Oral antacids
- Infection prevention
- Ophthalmology consultation
- Urology consultation
- Pulmonary toilet
- Mouth care
- Oral antacids

- Treatment
  - Low prevalence of SJS/TEN limits controlled, prospective clinical trials
  - Treatments reported to be helpful in case series or case reports
    - cyclosporine (3-4 mg/kg/day)
    - cyclophosphamide (100-300 mg/day)
    - Plasmapheresis
    - N-acetylcysteine (2 g 6 h)
    - TNF-α antagonists (e.g. etanercept, infliximab)
  - Controversy: systemic corticosteroids
  - Intravenous immunoglobulins (IVIg): 8 of 11 studies (each with at least 10 patients) suggest that IVIg (at a total dose of >2 g/kg administered over 3-4 days) may reduce TEN associated mortality
    - Our patient treated with IVIg 1gram/kg/day for 3 days (total cumulative dose 3 grams/kg)

**TEN: Follow up**

- Dyschromia frequent
- Scarring possible
- Onychomadesis occurs

**Case**

4-year-old boy with Acute Lymphocytoid Leukemia (ALL) in remission, admitted for concern of possible Stevens Johnson Syndrome

- Crusting of lips
- Mild injection of conjunctiva
- 2 month history of redness and edema dorsal hands
- 2-3 weeks of dry, cracked lips
- 1 week of dry patch on right cheek

- Medications:
  - Voriconazole daily (liver abscesses), 6-mercaptopurine, methotrexate weekly, Vitamin D, ondansetron PRN
  - TMP/SMX prophylaxis (Sat/Sun) - discontinued about 3 weeks prior due to concern of drug reaction
  - Topical exposures: denies

**Physical exam**

- Few round crusted superficial erosions on cheeks and dorsal hands
- Photodistributed erythema

**What are you most concerned about?**

1. Serum-sickness like reaction
2. Drug-induced hypersensitivity syndrome
3. Phototoxicity reaction
4. Photo-allergic contact dermatitis
5. Stevens-Johnson syndrome (SJS)

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Voriconazole

- Antifungal medication
  - Used prophylactically for cancer, transplant, and other immunocompromised patients
- Phototoxic reactions from voriconazole develop in:
  - ~10-20% of treated adults
  - ~20-47% of treated children
- Longer durations of therapy and higher doses appear to increase risk of phototoxicity
- Described phototoxicity reactions:
  - Phototoxicity with erythema and blistering
  - Pseudoporphyria
  - Photo-onycholysis
  - Lentigines
  - Solar elastosis
  - Often severe or fatal

Bolognia, et al. Dermatology, 3rd edition

Voriconazole: cutaneous malignancy

- Increased risk of squamous cell carcinoma of skin (SCC)
  - 73% increased risk for cutaneous squamous cell carcinoma (SCC) developing in lung transplant patients taking voriconazole
  - Often aggressive or multifocal SCC
- Increased risk of melanoma
  - Case reports of melanoma and melanoma in situ reported in context of accelerated photo-aging
- Risk factors for voriconazole-associated cutaneous malignancies:
  - Fitzpatrick skin types I and II
  - Significant UV light exposure
  - Prolonged and/or intense immunosuppression (especially T-cell directed therapy)
  - Tropical sunlight
  - Long-term voriconazole use

Williams and Arron. JAMA Dermatol. 2016 Jun 1;152(6):719-20

16-year-old boy with history of cystic fibrosis, 1 year after lung transplant

- Rapidly growing nodule in conchal bowl
- Moderately-differentiated Squamous Cell Carcinoma (SCC)

- In one study, 4/430 pediatric patients treated with voriconazole developed non-melanoma skin cancer

Voriconazole: summary

- Voriconazole
  - Systemic azole antifungal agent
  - Frequently used as prophylaxis in patients with cancer, post-transplant and other immunocompromised patients
- Associated with:
  - Phototoxic reactions
  - Accelerated photo-damage
  - Increased risk of cutaneous malignancies
- Excellent photo-protection and frequent skin screening is recommended for patients taking voriconazole regularly

What is the mechanism for phototoxicity and increased risk of cutaneous malignancy?

- More research needed
- Voriconazole is metabolized to voriconazole-N-oxide (VNO)
  - VNO is a UVB chromophore
  - Potential role for VNO in DNA damage
THANK YOU