Side effects include….

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Disclosure (previous 12 months)

- Consultant – Biogen/IDEC, Lilly, Amgen
- Editorial Boards – UpToDate (editor-in-chief, Dermatology), JAMA Dermatology (Associate Editor), Cutis, emedicine.com, Journal of Drugs in Dermatology, Medicine, Journal of Psoriasis and Psoriatic Arthritis
- Equity holdings (trust accounts) - Celgene; Pfizer; 3M; Johnson and Johnson; Merck; Abbott Laboratories; AbbVie; Procter and Gamble; CVS; Walgreens; Allergen; Amgen
- I will discuss “off-label” uses of some of the currently available agents and will identify which are labeled v. off-labeled uses.
75-year-old woman

- 2 week history of tender, red lesions on the legs
- The eruption was preceded by a “sore throat” for which she was seen in an immediate care center and given doxycycline 100 mg twice daily
- The eruption was first noted on day nine of therapy
- She went back to the ICC and was given triamcinolone 40 mg IM, told to take diphenhydramine, and advised to stop the doxycycline and start amoxicillin
- She did not fill the prescription for amoxicillin and two days later was seen in our offices
75-year-old woman

- PMH included diabetes, hypothyroidism and prior eczema
- Medications at the time of OV: triamcinolone acetonide 0.025 % cream, levothyroxine, pioglitazone, Aspirin 81 mg/d, Calcium 600 + D(3), coQ10 (ubiquinol), Daily Multivitamin, estradiol, metformin, simvastatin, fenofibrate, venlafaxine
What should be done now?

1. Biopsy for routine processing only
2. Biopsy for routine processing and immunofluorescence microscopy
3. Urinalysis
4. Hepatitis C testing
5. Nothing as this is a self-limiting disease
6. No testing is need, but treatment with prednisone should be administered
7. 2, 3, and 4
Course

• **Laboratory results:**
  – Routine biopsy revealed leukocytoclastic vasculitis
  – DIF revealed IgA and fibrinogen deposition in the dermal papillary vessels
  – Urinalysis revealed > 20 hyaline casts per hpf (nl < 5), but no blood or protein
  – CBC was normal
  – CMP revealed an elevated glucose (132) non-fasting
  – Hepatitis panel was negative
  – Rheumatoid factor was negative
What should be done now?

1. Treat with prednisone taper 40 to 0 over 2-3 weeks
2. Treat with dapsone 100 mg twice daily
3. Treat with rituximab 1 gm now and repeat in two weeks
4. Treat with IVIG 1 gm/kg on two consecutive days
5. Treat with mycophenolate mofetil 1 gm twice daily
Course

- The patient was treated with prednisone taper
- The lesions resolved within one month and have not recurred
- Repeat urinalyses have been unremarkable
What caused this patient’s vasculitis?

1. An infection
2. Doxycycline
3. Don’t know
What is the best diagnosis?

1. Henoch-Schönlein purpura
2. Hypersensitivity vasculitis
3. Cryoglobulinemic purpura
4. Cutaneous polyarteritis nodosa
5. Hyperglobulinemic purpura of Waldenström
Does the presence of IgA on DIF confirm a diagnosis of Henoch-Schonlein purpura?

1. Yes
2. No
3. Not certain
Definition of Henoch-Schönlein purpura

• The original descriptions by Henoch and Schönlein were made prior to the development of immunofluorescence and were a clinical tetrad of purpura, abdominal pain, arthritis and nephritis.

• HSP was predominantly seen in children and most when tested were IgA+

• The European Union League Against Rheumatism criteria for HSP include the presence of purpura or petechiae with lower limb predominance and 1 of the following four criteria:
  1. Abdominal pain
  2. Histopathology demonstrating IgA
  3. Arthritis of arthralgia
  4. Renal involvement

• The Chapel Hill Consensus Conference (2012) and a recent Dermatologic Addendum merely note that the presence of predominant IgA is diagnostic of HSP
Discussion

• Biopsy is useful to confirm a diagnosis of vasculitis
• DIF should be performed on the newest (freshest lesion), but it is controversial about the diagnosis of HSP based only on the presence of IgA in the specimen and what the therapeutic or prognostic implications are
• Cutaneous small vessel vasculitis is a finding that serves as a window into a variety of possible scenarios (see next slide with algorithm)
• Acute onset of small vessel vasculitis may not require therapy as the process is often self-limiting
66-year-old woman

- Intermittent blistering on the feet
- Referred by her rheumatologist for possible bullous pemphigoid. When the blisters first developed she was on tofacitinib, it was stopped and she was treated with sarilumab, an IL-6 inhibitor, blisters continued to intermittently appear and sarilumab was stopped and tofacitinib was restarted. She has taken prescription strength naproxen, but stopped this several weeks ago and started celecoxib.
- PMH: RA, asthma
- Medications: celecoxib, triamterene/HCTZ, tofacitinib, potassium, B complex
What is your diagnosis?

1. Friction blistering
2. Bullous pemphigoid
3. Pseudoporphyria
4. Bullous fixed drug eruption
5. Epidermolysis bullosa acquisita
6. Porphyria cutanea tarda
What tests should be performed?

1. Biopsy for immunofluorescence microscopy
2. Urine for porphyrins
3. Serum for porphyrins
4. Antinuclear antibody
5. 1 and 2
6. 1 and 3
7. No testing is needed
# Laboratory results

**RESULTS**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG:</td>
<td>Thick linear basement membrane zone and thick perivascular</td>
</tr>
<tr>
<td>IgG4:</td>
<td>Negative</td>
</tr>
<tr>
<td>IgM:</td>
<td>Weak to 1+ discontinuous granular basement membrane zone and 3+ few scattered and clumped cytoids</td>
</tr>
<tr>
<td>IgA:</td>
<td>Thick linear basement membrane zone and thick perivascular</td>
</tr>
<tr>
<td>C3:</td>
<td>1-2+ discontinuous granular basement membrane and thick perivascular</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>2+ focal patchy deposition on connective tissue fibers</td>
</tr>
</tbody>
</table>
What is your diagnosis now?

1. Friction blistering
2. Bullous pemphigoid
3. Pseudoporphyria
4. Epidermolysis bullosa acquisita
5. Porphyria cutanea tarda
DIAGNOSTIC INTERPRETATION

Positive, nonspecific findings by direct immunofluorescence, typical for pseudoporphyria or porphyria

(See Results and Comments)
75-year-old woman

Patient moved from Florida with 5-month history of blistering on her toes. Was told that she had BP and treated topically.

Medications – naproxen, aspirin, hydrochlorothiazide, isradipine, enalapril, rosuvastatin, atenolol

• Bilateral pedal edema
• Blisters and erosions on the toes
• Mild toenail thickening
• No milia
• Normal pulses
Practical Questions

• How frequent is drug-induced pseudoporphyria?
• Is there a specific patient population at risk for NSAID-induced pseudoporphyria?
• How long does it take to resolve after discontinuation of the drug?
• Can other NSAIDs be used safely?
Pseudoporphyria

- Photodistributed bullous disorder with clinical and histopathological features of PCT

- Causes –
  - Drug-induced
  - Chronic renal failure/hemodialysis
  - UVA radiation (or excessive sun exposure)
    »JAAD 2001; 44: 100-8.
Drug-induced Pseudoporphyria
Some Responsible Agents

- NSAIDs – naproxen, nambumetone, oxaprozin, ketoprofen, diflunisal, celecoxib, diclofenac
- Antibiotics – Tetracycline, nalidixic acid, ciprofloxacin, ampicillin-sulbactam/cefepime, dapsone
- Diuretics – furosemide, HCTZ, bumetanide, torsemide
- Retinoids – isotretinoin, acitretin
- Miscellaneous – cyclosporin, 5-FU, flutamide, pyridoxine, voriconazole, imatinib
- Excessive UV exposure – tanning beds, sunbathing

Pseudoporphyria in Children with JIA

- 1 year prospective study of children attending a rheumatology clinic in Edinburgh
- 10.9% (7/64) had pseudoporphyria
- Naproxen was the leading cause
- Blue-gray eye color was associated with a 3 fold increase in risk of pseudoporphyria
Long-term follow-up in Children with JRA and Naproxen-induced pseudoporphyria

- Cohort of 9 patients followed for up to 5 years
- No therapy, other than cessation of naproxen was used
- Between 1 and 4 months the development of new facial scars ceased
- However, at up to 5 years many patients had subtle facial scarring

Pseudoporphyria in Children with JIA

- Clinical manifestations – facial scarring only - 6, facial and arm lesions – 1
- Other NSAIDs implicated
  - indomethacin 1, piroxicam 2, ibuprofen 2
- Time to resolution – 4 days to 6 weeks (mean 21 days)
- Residual scarring was common
  » Pediatric Dermatol 2000; 17 480-3
NSAID-induced pseudoporphyria

• LaDuca et al reported their observations of 6 patients seen over a 24-month time frame
• Causative agents – oxaprozin (3), nabumetone (2), naproxen (OTC) (1)
• DIF – findings c/w PCT, but neg. studies of the blood, urine and stool
Drug-induced Pseudoporphyria

• Diagnosis
  – Clinical suspicion
  – Absence of hyperpigmentation, hypertrichosis, sclerodermoid features
• Biopsy including DIF
• IIF
• Urinary or plasma porphyrin studies
Drug-induced Pseudoporphyria

• Treatment
  – Discontinuation of the suspected drug or UVA source
  – Hemodialysis-associated – N-acetylcysteine (glutathione precursor)

• Prognosis
  – Blistering/fragility may continue for months
  – Scarring in children may be permanent
Practical Questions - Answers

- How frequent is drug-induced pseudoporphyria? Rare, but may be as high as 10% in patients with JIA Rx’d with naproxen.
- Is there a specific patient population at risk for NSAID-induced pseudoporphyria? Probably not.
- How long does it take to resolve after discontinuation of the drug? 2 weeks to 2 years
- Can other NSAIDs be used safely? Possibly
64-year-old woman

- HPI: March 2017 – patient presented for evaluation of a rash on the chest, back, arms and legs
  - The rash first appeared shortly after her 3rd infusion of gemcitabine and docetaxel for treatment of a uterine sarcoma, and persisted following her 4th infusion
  - Her last chemotherapy was 2 weeks prior to her initial visit
- PMH: Hypertension, Hyperlipidemia, metastatic uterine adenosarcoma treated 6 months earlier with surgery and radiation therapy
- Current Medications – atenolol, atorvastatin
What is the best diagnosis?

1. Pemphigus erythematosus
2. Drug-induced subacute cutaneous lupus erythematosus
3. Phototoxic drug eruption
4. Radiation recall
5. Drug-induced dermatomyositis
What is the most likely causative agent?

1. Atenolol
2. Atorvastatin
3. Gemcitabine
4. Docetaxel
Drug-induced SCLE

- Docetaxol and other taxanes – 17 reported cases
- Gemcitabine and other pyrimidine analogues – 6+ reports
- Statin induced SCLE – 5+ case reports, but none with atorvastatin
- Atenolol – one case reported
What testing is needed?

1. Skin biopsy for routine processing
2. Lesional skin biopsy for direct immunofluorescence microscopy
3. Non-lesional, photoprotected skin biopsy for immunofluorescence microscopy
4. Serum for indirect immunofluorescence
Laboratory Findings

- CBC, ALT 74, AST 146
- ANA 1:2560 Speckled
- Anti-Ro/SS-A 8.0, La/SS-B 0.3
- Anti-nDNA - negative
Drug-induced SCLE

- First reported by Reed et al: Ann Intern Med 1985; 103: 49-51
  - 5 patients with SCLE due to HCTZ, all anti-Ro +, clearing in 2-4 weeks, serology resolved in 1/3, + rechallenge in 1 patient
  - Studied Ro+ patients and found 15/70 had a history of new drug exposure within 6-months of disease onset
  - Clinical improvement or resolution occurred within 2-8 months after d/c of drug. Also, Ro titers decreased.
## Drug induced SCLE

<table>
<thead>
<tr>
<th>Category</th>
<th>% of total cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensives</td>
<td>34</td>
</tr>
<tr>
<td>Antifungals</td>
<td>26</td>
</tr>
<tr>
<td>Chemotherapeutic agents</td>
<td>9</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>8</td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>7</td>
</tr>
<tr>
<td>Others</td>
<td>16</td>
</tr>
</tbody>
</table>

Clinical Course DI-SCLE

• Incubation time
  – Median 6 weeks (range 3 days to 11 years)
    • Longer for calcium channel blockers
    • Shorter for terbinafine

• Not distinguished from idiopathic SCLE
  – Annular and/or papulosquamous plaques in photodistributed locations
  – Histopathologically with an interface dermatitis/lichenoid tissue reaction.
    Eosinophils were a not prominent feature.

• Resolution upon discontinuation
  – Mean 7.3 weeks
  – Median 4 weeks
  – 67% remained Ro/SS-A positive after resolution
DI-SCLE in Sweden

• Population-based, matched, case-control study using ICD-10 diagnosed patients with SCLE (234 patients) compared 1:10
• Use of Prescribed Drug Registry
• Roughly 33% of their SCLE patients had a potential drug associated with the onset of the diagnosis of SCLE
• Terbinafine (OR=38.5), TNF-α inhibitors (OR=8.0), antiepileptics (OR=3.4) and proton pump inhibitors (OR=2.9).

Update on DI-SCLE

Figure 1. Change in incidence of DI-SCLE reports by drug category since August 2009
Figure 2. Proportion of drugs precipitating cutaneous lupus in the first and second decade of our study period.
Doxorubicin was the presumed responsible agent in 3 patients.
Subacute Cutaneous Lupus Erythematosus Induced by Chemotherapy Gemcitabine as a Causative Agent

Figure 1. Timeline of Our Patient’s Exposure to Different Chemotherapeutic Regimens

May 1994 
Intraductal infiltrative ductal breast CA

April 2005 
High-grade malignant mixed mesodermal uterine tumor

June 2008 
Lung metastases

September 2010 
Progression of disease

1 wk Later Skin eruption

Radiation therapy, cyclophosphamide, methotrexate, fluorouracil for 6 cycles

TAH-BSO, carboplatin + paclitaxel for 6 cycles

Doxorubicin × 2 doses; discontinued due to mucositis and HFS

Capcitabine for 5 mo (October 2008 to March 2009)

Capcitabine at reduced dose for 8 mo (August 2009 to April 2010)

November 2010 Gemcitabine

CA indicates carcinoma; TAH-BSO, total abdominal hysterectomy-bilateral salpingo-oophorectomy; and HFS, hand-foot syndrome.

JAMA Dermatol 2013; 149:1071-5
<table>
<thead>
<tr>
<th>Agent</th>
<th>No. of Published Cases of DI-SCLE</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pyrimidine Analogue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>2</td>
<td>Weger et al,¹⁵ 2008 (case 9); Almagro et al,¹⁶ 2011 (case 16)</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2 induced, 1 exacerbated</td>
<td>Fernandes et al,³ 2009 (case 10); Floristan et al,⁴ 2009 (case 12); Weger et al,¹⁵ 2008 (case 9)</td>
</tr>
<tr>
<td>Gemcitabine hydrochloride</td>
<td>1</td>
<td>Present study (case 17)</td>
</tr>
<tr>
<td><strong>Mitosis Inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>3</td>
<td>Chen et al,⁵ 2004 (cases 1-3)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>3 induced, 1 exacerbated</td>
<td>Chen et al,⁵ 2004 (case 4); Adachi and Horikawa,⁶ 2007 (cases 7 and 8); Funke et al,⁷ 2010 (case 13)</td>
</tr>
<tr>
<td><strong>Anthracycline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin hydrochloride with cyclophosphamide</td>
<td>4</td>
<td>Guhl et al,⁸ 2009 (case 11); Funke et al,⁷ 2010 (cases 13-15)</td>
</tr>
<tr>
<td><strong>Antiestrogen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen citrate</td>
<td>2</td>
<td>Fumal et al,⁹ 2005 (cases 5 and 6)</td>
</tr>
</tbody>
</table>

* Total of 17 induced cases (exacerbated cases are not counted toward the total).
What therapy should be given at this time?

1. Sunscreens
2. Topical corticosteroids
3. Oral hydroxychloroquine
4. Two week prednisone taper (40 to 0)
5. No therapy is needed as the process is self-limiting
Should the chemotherapy be stopped?

1. Yes
2. No
3. Not certain
Dermatological adverse events with taxane chemotherapy

Vincent Sibaud¹, Nicole R. Lebœuf², Henri Roche³, Viswanath R. Belum⁴, Laurence Gladieff², Marion Deslandres³, Marion Montastruc³, Audrey Eche³, Emmanuelle Vigarios⁵, Florence Dalenc³, and Mario E. Lacouture⁴

CTCAEv4 Grade 1 or Tolerable Grade 2 Skin AE

Initiate dermatological treatment
AND
continue chemotherapy at current dose

CTCAEv4 Grade ≥3 or Intolerable Grade 2¹ AE

Continue treatment of skin reaction
Interrupt drug dosing for up to 14 days

- Resolves to CTCAEv4 Grade ≤1
- Resolves to CTCAEv4 Grade 2
- Remains at CTCAEv4 Grade ≥3

- Reinstallate drug at initial dose and continue dermatological treatment²
- Reinstallate drug at reduced dose and continue dermatological treatment²
- Consider discontinuing drug treatment
Course

• The chemotherapy was continued, but the patient’s skin disease worsened

• She was hospitalized and our service was consulted
If her chemotherapy is continued, will the use of hydroxychloroquine prevent development of additional skin lesions?

1. Yes
2. No
3. Don’t know
Management of DI-SCLE

- Withdrawal of offending drug – remember to inform the prescribing physician and obtain permission as well as discuss substitute medication(s)
- Topical corticosteroids
- Antimalarial agents
- Short course of systemic steroids
DI-SCLE - Conclusions

• Drugs may induce or exacerbate subacute cutaneous lupus erythematosus

• Somewhere between 20% and 30% of patients with newly diagnosed SCLE have a drug as a trigger, perhaps the incidence is higher in older patients (>50)

• The most common agents are antihypertensives, terbinafine, and PPIs

• None of the drugs that induce/exacerbate cutaneous LE are associated with a high prevalence rate of this reaction
• Drug-induced cutaneous LE differs from drug-induced SLE clinically, serologically and etiologically
• Perhaps the patient with known LE or photosensitivity should avoid some of these agents, or at least be forewarned about the potential for such a reaction
• Management involves drug withdrawal, short courses of corticosteroids and/or antimalarial agents
• Some patient’s disease is ‘awakened’ and does not resolve