Drug induced severe mucocutaneous reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis, and mimickers

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I will be discussing off-label use of medications during this lecture.
Disclosure of Relationships with Industry

Research/Grants: Eli Lilly, Soligenix, Helsinn, Eisai, Boehringer Ingelheim, Corrona, Akros, Novartis, AbbVie, BMS, Celgene, Glenmark

Advisory boards: Novartis, Boehringer Ingelheim, Helsinn

Speaker: Helsinn, Celgene, Kyowa Kirin
Learning Objectives

1. Discuss the role of inpatient dermatology consultation in the identification of SJS/TEN
2. Work through an algorithmic approach to patients with drug-induced severe mucocutaneous reactions
3. Use cases to highlight diagnostic clues of SJS/TEN mimickers
In 4 academic hospitals in the US, ~72% patients with suspected SJS/TEN were given an alternate diagnosis after evaluation by dermatology.

SJS/TEN diagnosis – role of dermatology consultation

SJS/TEN diagnosis – role of dermatology consultation

- Known risk factors for SJS/TEN (e.g., drug exposure, malignancy, HIV/AIDS) are not helpful to differentiate it from its mimickers
- The clinical presentation (fever, painful skin, Nikolsky, mucosal involvement) is helpful to differentiate SJS/TEN from its mimickers
- The most common “mimickers” are SCARs and EM
- Common “mimickers” include disease with severe mucocutaneous involvement

<table>
<thead>
<tr>
<th></th>
<th>FREQUENCY</th>
<th>PERCENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>SJS/TEN</td>
<td>59</td>
<td>28.4%</td>
</tr>
<tr>
<td>DRESS</td>
<td>21</td>
<td>10.1%</td>
</tr>
<tr>
<td>MORBILLIFORM</td>
<td>18</td>
<td>8.7%</td>
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<tr>
<td>EM</td>
<td>15</td>
<td>7.2%</td>
</tr>
<tr>
<td>AGEP</td>
<td>13</td>
<td>6.2%</td>
</tr>
<tr>
<td>BULLOUS PEMPHIGOID</td>
<td>8</td>
<td>3.8%</td>
</tr>
<tr>
<td>STAPHYLOCOCCAL SCALDED SKIN SYNDROME</td>
<td>6</td>
<td>2.9%</td>
</tr>
<tr>
<td>PEMPHIGUS</td>
<td>5</td>
<td>2.4%</td>
</tr>
<tr>
<td>FIXED DRUG ERUPTION</td>
<td>5</td>
<td>2.4%</td>
</tr>
<tr>
<td>SMALL VESSEL VASCULITIS</td>
<td>5</td>
<td>2.4%</td>
</tr>
<tr>
<td>CONTACT DERMATITIS</td>
<td>5</td>
<td>2.4%</td>
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<tr>
<td>VIRAL EXANTHEM</td>
<td>5</td>
<td>2.4%</td>
</tr>
<tr>
<td>SERUM SICKNESS-LIKE REACTION</td>
<td>4</td>
<td>1.9%</td>
</tr>
<tr>
<td>ATOPIC DERMATITIS</td>
<td>3</td>
<td>1.4%</td>
</tr>
<tr>
<td>LINEAR IGA BULLOUS DERMATOSIS</td>
<td>3</td>
<td>1.4%</td>
</tr>
<tr>
<td>PUSTULAR PSORIASIS</td>
<td>3</td>
<td>1.4%</td>
</tr>
<tr>
<td>MYCOPLASMA INDUCED MUCOSITIS AND RASH</td>
<td>3</td>
<td>1.4%</td>
</tr>
<tr>
<td>URTICARIA MULTIFORME</td>
<td>3</td>
<td>1.4%</td>
</tr>
<tr>
<td>OTHER</td>
<td>24</td>
<td>11.5%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>208</td>
<td>100%</td>
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</tbody>
</table>

Case 1 – Consult for “SJS”

- 43 yo female with a 2 month history of progressive bullous rash
- ROS:
  - Positive: pruritus
  - Negative: fever, chills, fatigue, sore throat, dysphagia, photophobia, unexplained weight loss or shortness of breath.
- Meds: famotidine, ibuprofen, lisinopril, furosemide
Case 2 – Consult for “SJS”

- 64 yo male with h/o perforated appendicitis s/p percutaneous tube placement, and antibiotic coverage was transferred from OSH with a 10 day history of a progressive bullous rash

- **ROS:**
  - Positive: fever, chills, fatigue
  - Negative: sore throat, dysphagia, unexplained weight loss or shortness of breath.

- **Meds:**
  - vancomycin, piperacillin/tazobactam, ceftriaxone
Case 3 – Consult for “SJS/TEN”

- 42 yo Hispanic male with h/o HTN
- ROS:
  - Positive: photophobia
  - Negative: sore throat, dysphagia, odynophagia, shortness of breath
- Meds: captopril
Case 4 – Consult for “SJS”

- 23yo female previously healthy presented with a painful bullous eruption of 2 days duration after taking TMP-SMX for a urinary tract infection. She had history of “cold sores as a child” and a prior episode of a similar rash in the same affected areas.
- ROS:
  - Negative for fever, chills, sore throat, dysphagia, unexplained weight loss or shortness of breath.
- Meds: TMP-SMX
Bullous pemphigoid

• Clinical:
  – Polymorphic eruption:
    • non-bullous phase (papules, wheals)
    • bullous phase (tense bullae of 1-4 cm on normal or erythematous skin)
  – Trunk and intertriginous regions, symmetric distribution
  – Occasional involvement of oral cavity (10-30%)
  – Severe pruritus

• Laboratory abnormalities:
  – Eosinophilia in 50%
  – Positive BP180 and/or BP230 antibodies (60-100%)

• Histopathological studies are diagnostic
Drug-induced BP

• Diuretics:
  – Furosemide
  – Bumetanide

• Analgesics

• Antibiotics
  – Amoxicillin
  – Ciprofloxacin

• Other:
  – Potassium iodide
  – Captopril > other ACE inhibitors
Linear IgA bullous dermatosis

- Can be divided as drug-induced (1-30 d) or idiopathic
- Clinical:
  - Vesiculobullae following herpetiform arrangement or annular polycyclic plaques, “string of pearls” sign
  - Face, upper trunk, intertriginous
  - Koebnerization
  - May present oral, nasal, pharyngeal lesions
  - Nikolsky sign positive
- Laboratory abnormalities: uncommon
- Histopathological studies are diagnostic
Drug-induced LABD

- Vancomycin
- Antibiotics
  - Penicillins
  - Cephalosporines
- NSAIDs
- Captopril > ACE inhibitors
- Rare: phenytoin, sulfonamides
Pemphigus foliaceus

• Rarely drug-induced
• Clinical:
  – Vesiculobullae that rupture easily and form crust
  – Face, scalp, upper trunk, and extremities
  – Scalp involvement can result in alopecia
  – Does not present mucosal lesions, but occasionally if drug-induced
  – Positive Nikolsky’s sign
• Laboratory abnormalities: uncommon
• Histopathological studies are diagnostic
Drug-induced pemphigus foliaceus

• Drugs with thiol (-SH) functional group
  – ACE inhibitors (captopril, lisinopril, enalapril, fosinopril)
  – DMARs (*penicillamine [50% of all cases], bucillamine*)
  – Tiopronin

• Drugs with sulfur groups (that are cleaved or metabolized to thiol groups)
  – ARBs (candesartan)
  – Penicillins, cephalosporins
  – Piroxicam
Fixed drug eruption

• Type IV hypersensitivity reaction via CD8\(^+\) T cells, IFN-gamma and Fas-Fas ligand.
• 1-2 weeks after first ingestion and then 30min - 8h
• Clinical:
  – Sharply localized, circumscribed round or oval lesion that recurs at the same site or sites each time the offending drug is administered.
  – Commonly perioral, genital and/or on hands and feet.
  – Residual hyperpigmentation between flares.
• Laboratory abnormalities: uncommon
• Histopathological studies are diagnostic
Fixed drug eruption

- Antibiotics: Sulfonamides (up to 75% in some series), tetracyclines, ciprofloxacin
- Analgesics: NSAIDs, acetaminophen
- Loratadine
- Pseudoephedrine
- Barbiturates
- Allopurinol
- Carbamazepine
Algorithm for drug-induced severe mucocutaneous reactions

Primary lesion

Tense bullae
- Photo distribution
- BSLE

Non specific distribution, pruritic
- BP

“String of pearls”, intertriginous
- LABD

Seborrheic distribution
- PF

Flexural & perioral
- SSSS

Mucosal
- MIRM

Small & confluent macules
- SJS/TEN

Large patches
- Fixed drug

Papules
- EM

Typical targets

Atypical targets

Facial, hand edema
- DRESS

Intertriginous pinpoint pustules, coalescence → desquamation
- AGEP

Macules/papules

Seborrheic distribution
- Small & confluent macules

Large patches
- Papules

Mucosal

Fixed drug
- MIRM

SJS/TEN
- SSSS

Papules
- EM

Non specific distribution, pruritic
- BP

LABD
- BSLE

PF
- SSSS

MIRM
- SJS/TEN

Fixed drug
- MIRM

SJS/TEN
- SSSS

Papules
- EM

DRESS
- AGEP

AGEP

Mucocutaneous reactions that are not usually caused by drugs but can mimic drug-induced mucocutaneous reactions
# Drug induced severe mucocutaneous reactions

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<td>Generalized fixed drug eruption</td>
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