Stevens-Johnson syndrome and toxic epidermal necrolysis mimickers

Lucia Seminario-Vidal, MD, PhD
University of South Florida

July 26th, 2018

I will be discussing off-label use of medications during this lecture.
Learning Objectives

1. Review the clinical presentation of SJS/TEN
2. Discuss the role of inpatient dermatology consultation in identification of SJS/TEN mimickers
3. Recognize common mimickers and identify diagnostic clues to differentiate them from SJS/TEN
Disclosure of Relationships with Industry

Lucia Seminario-Vidal, MD, PhD

Research/Grants: Regeneron-Sanofi, Eli Lilly, Soligenix, Actelion, Eisai, Boehringer Ingelheim, Corrona, Akros, Novartis, AbbVie
Consultant: Navigant Life Sciences
Advisory boards: Novartis, Boehringer Ingelheim
Speaker: Actelion, Celgene
Background

- SJS/TEN characterizes by a severe mucocutaneous reaction most commonly triggered by a medication, with a 10-50% mortality.
- SJS/TEN is associated with a prolonged length of stay and higher costs of care (16.5 days, $58,954)
- Distinguishing SJS/TEN from other dermatological conditions maybe be challenging, as they may present with desquamation, mucosal involvement, and systemic symptoms.
- The misdiagnosis of SJS/TEN may result in unnecessary hospital admissions to the ICU, increased costs, and may expose patients to unnecessary treatments.

SJS/TEN diagnosis

- History of a new medication (7-21 days prior)
- Prodromal symptoms including fever, myalgia, and headache; occasional photophobia, dysphagia
SJS/TEN diagnosis

- Risk factors:
  - HIV infection
  - Autoimmune disease
  - Active malignancy (particularly hematologic)

- Medication exposure:
  - Allopurinol
  - Antibiotics
  - Anticonvulsants
  - Nevirapine
  - NSAIDs


SJS/TEN diagnosis

• Clinical:
  – Erythematous to dusky macules that show evidence of coalescing AND/OR denuding skin or blistering in a predominantly truncal distribution. Nikolsky sign (sloughing with direct lateral pressure on non-blistered, but involved, skin) should be considered as a supportive feature.
  – Mucous membrane involvement
  – Increasing number of skin lesions

• Confirmation by histopathological studies

• Rule out mimickers


SJS/TEN classification

- SJS: <10%
- SJS-TEN: 10-30%
- TEN: >30%
SJS/TEN diagnosis

SJS – Dusky macules and atypical macular targets
SJS/TEN diagnosis

SJS-TEN – Dusky macules coalescing into bullae and denuded skin
SJS/TEN diagnosis

Histological findings:

• interface dermatitis +/- necrotic keratinocytes +/- eosinophils AND negative direct immunofluorescence for features that alter the diagnosis

SJS/TEN diagnosis – role of dermatology consultation

- A survey among directors of accredited burn units in the US indicated that admission to the burn ICU is based on clinical suspicion of SJS/TEN (74%), and biopsy or dermatological evaluation are NOT required for admission (67% and 87%, respectively)
- Two surveys of burn centers indicated that ~50% of the burn centers consult dermatology for the evaluation of patients with suspected SJS/TEN
- In one large burn center, 53.2% of the patients with suspected SJS/TEN (n = 50) were evaluated by dermatology and 36% of those received an alternate diagnosis.

SJS/TEN diagnosis – role of dermatology consultation

- In 4 academic hospitals in the US, ~72% patients with suspected SJS/TEN were given an alternate diagnosis after evaluation by dermatology.

- The most common “mimickers” are DRESS, morbilliform drug eruptions, EM, and AGEP
SJS/TEN mimickers

- Known risk factors for SJS/TEN are not helpful to differentiate it from its mimickers

<table>
<thead>
<tr>
<th></th>
<th>TOTAL (N=208)</th>
<th>SJS/TEN (N=59)</th>
<th>MIMICER (N=149)</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE, MEAN(SD)</td>
<td>49.2(20.2)</td>
<td>48.0 (20.4)</td>
<td>49.7(20.1)</td>
<td>0.595</td>
</tr>
<tr>
<td>GENDER, NO. OF MALES(%)</td>
<td>102(49.0%)</td>
<td>37(62.7%)</td>
<td>65(43.6%)</td>
<td>0.013</td>
</tr>
<tr>
<td>HIGH RISK PRE-EXISTING CONDITIONS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALIGNANCY, NO. (%)</td>
<td>32(15.4%)</td>
<td>13(22.0%)</td>
<td>19(12.8%)</td>
<td>0.094</td>
</tr>
<tr>
<td>KIDNEY DISEASE, NO. (%)</td>
<td>22(10.6%)</td>
<td>7(11.9%)</td>
<td>15(10.1%)</td>
<td>0.704</td>
</tr>
<tr>
<td>HIV/AIDS, NO. (%)</td>
<td>5(2.4%)</td>
<td>3(5.1%)</td>
<td>2(1.3%)</td>
<td>0.136</td>
</tr>
<tr>
<td>MORE THAN 1, NO. (%)</td>
<td>4(1.9%)</td>
<td>0(0.0%)</td>
<td>4(2.7%)</td>
<td>0.1004</td>
</tr>
<tr>
<td>NONE, NO. (%)</td>
<td>145(69.7%)</td>
<td>36(61.0%)</td>
<td>109(73.2%)</td>
<td>0.086</td>
</tr>
<tr>
<td>USE OF HIGH RISK MEDICATIONS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANTIBIOTICS, NO. (%)</td>
<td>74(35.6%)</td>
<td>20(33.9%)</td>
<td>54(36.2%)</td>
<td>0.750</td>
</tr>
<tr>
<td>ANTIVIRALS, NO. (%)</td>
<td>4(1.9%)</td>
<td>2(3.4%)</td>
<td>2(1.3%)</td>
<td>0.319</td>
</tr>
<tr>
<td>ALLOPURINOL, NO. (%)</td>
<td>1(0.5%)</td>
<td>1(1.7%)</td>
<td>0(0.0%)</td>
<td>0.287</td>
</tr>
<tr>
<td>ANTICONVULSANTS, NO. (%)</td>
<td>18(8.7%)</td>
<td>5(8.5%)</td>
<td>13(8.7%)</td>
<td>0.954</td>
</tr>
<tr>
<td>NSAIDS, NO. (%)</td>
<td>5(2.4%)</td>
<td>4(6.8%)</td>
<td>1(0.7%)</td>
<td>0.024</td>
</tr>
<tr>
<td>MORE THAN 1, NO. (%)</td>
<td>61(29.3%)</td>
<td>24(40.7%)</td>
<td>37(24.8%)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

SJS/TEN mimickers

OHSU, OSU, UAB & USF collaboration
Seminario-Vidal L et al [unpublished]
The clinical presentation is helpful to differentiate SJS/TEN from its mimickers

<table>
<thead>
<tr>
<th></th>
<th>SJS/TEN (N=59)</th>
<th>MIMICKER (N=149)</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEVER</td>
<td>37 (62.7%)</td>
<td>28 (18.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAINFUL SKIN</td>
<td>53 (89.8%)</td>
<td>62 (41.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>POSITIVE NIKOLSKY SIGN</td>
<td>47 (79.7%)</td>
<td>12 (8.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRIMARY LESION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACULE/PATCH</td>
<td>0(0.0%)</td>
<td>20(13.4%)</td>
<td>0.003</td>
</tr>
<tr>
<td>PAPULE/PLAQUE</td>
<td>0(0.0%)</td>
<td>34(22.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VESICLE/BULLAE</td>
<td>20 (33.9%)</td>
<td>40(26.8%)</td>
<td>0.312</td>
</tr>
<tr>
<td>ERYTHRODERMA</td>
<td>0(0.0%)</td>
<td>21(14.1%)</td>
<td>0.002</td>
</tr>
<tr>
<td>TYPICAL TARGETS</td>
<td>1(1.7%)</td>
<td>25(16.8%)</td>
<td>0.003</td>
</tr>
<tr>
<td>ATYPICAL TARGETS</td>
<td>38(64.4%)</td>
<td>9(6.0%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
SJS/TEN mimickers & clues to diagnosis
DRESS/DIH

*(Drug Reaction with Eosinophilia and Systemic Symptoms/ Drug-induced hypersensitivity syndrome)*

DRESS – Follicular accentuation
Diagnosis – DRESS

- History of a new medication (15-40 days prior)
- Clinical:
  - Fever
  - Morbilliform eruption, with follicular accentuation
  - Rarely vesicles, tense bullae induced by edema
  - Face, upper trunk, and extremities
  - Facial edema
  - Lymphadenopathy

- Laboratory abnormalities:
  - Eosinophilia (NOT always), atypical lymphocytes
  - Common: hepatitis, nephritis
  - Rare: myocarditis, pneumonitis, thyroiditis, pancreatitis, encephalitis
  - Viral reactivation: HHV6/7, CMV, EBV

- Histopathological studies could be supportive
- Rule out other causes
- RegiSCAR score
Diagnosis - Erythema multiforme

Criteria to differentiate from SJS/TEN:

• Type of elementary lesion: typical targets +/- atypical targets
  • Typical: <3 cm in diameter, round with well-defined border, and at least 3 distinct zones, e.g. 2 concentric rings of color change surrounding a central circular zone that has evidence of damage to the epidermis in the form of bulla or crust
  • Atypical: elevated/edematous (papule) target with 2 zones or poorly defined borders

Diagnosis - Erythema multiforme

Criteria to differentiate from SJS/TEN:
• Distribution of lesions: upper extremities AND face, also trunk; most commonly dorsal hands, grouped on elbows.
• Koebnerization on prior sites of trauma
• Mucosal lesions: vesiculobullous and rapidly develop into painful erosions that involve the buccal mucosa and lips
• Renal, hepatic and hematologic abnormalities are extremely rare.
• Lack of association with HIV, autoimmune conditions, or cancer

The SCAR study that determined the difference between SJS/TEN and EM major (n = 552) could not distinguish between the two entities in 16.6 % of the cases

Etiology - Erythema multiforme

Risk factors:

- Infections (~90%)
  - Viral: HSV (majority trigger in adults/children), VZV, EBV, CMV, parapoxvirus (orf), others
  - Bacterial: M. pneumoniae, Chlamydiae, Salmonella, MTB
  - Fungal: Histoplasma capsulatum, dermatophytes

- Medications
  - NSAIDs, sulfonamides, other antibiotics, antiepileptics, allopurinol
AGEP
(Acute generalized exanthematous pustulosis)
Diagnosis - AGEP

• History of a new medication (~2 days prior)

• Clinical:
  – Morbilliform eruption
  – Trunk and intertriginous regions
  – Occasional facial edema
  – Pinpoint non-follicular pustules
  – Rarely vesicles, bullae, or TEN-like dermatosis induced by coalescence of pustules

• Pruritus +/- fever

• Laboratory abnormalities:
  – Eosinophilia

• Histopathological studies are supportive: Intraepidermal and subcorneal pustules.
Etiology AGEP

• Drugs:
  – Aminopenicillins
  – Quinolones
  – Hydroxychloroquine
  – Sulfonamides
  – Antifungals: terbinafine, ketoconazole, fluconazole
  – Diltiazem

• Infections:
  – Parvovirus B19, CMV
  – *Chlamydia pneumonia*
<table>
<thead>
<tr>
<th></th>
<th>Clinical clues</th>
<th>Time course</th>
<th>Fever</th>
<th>Pruritus Pain</th>
<th>Edema</th>
<th>Mucosa</th>
<th>Enlarged lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRESS</strong></td>
<td>Polymorphic follicular accentuation</td>
<td>2-6 weeks</td>
<td>+/-</td>
<td>pruritus</td>
<td>face, hands</td>
<td>rare</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Erythema multiforme</strong></td>
<td>Typical or papular atypical targets, koebnerization</td>
<td>varies</td>
<td>rare</td>
<td>pruritus pain</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>AGEP</strong></td>
<td>Pinpoint pustules, first intertriginous</td>
<td>1-3 days</td>
<td>rare</td>
<td>pruritus</td>
<td>face, hands</td>
<td>no</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Morbilliform drug eruption</strong></td>
<td>Monomorphic centrifugal</td>
<td>4-14 days</td>
<td>N</td>
<td>pruritus</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td><strong>SJS/TEN</strong></td>
<td>Atypical targets, + Nikolsky</td>
<td>7-21 days</td>
<td>+/-</td>
<td>pain</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>