Erythema Multiforme, Stevens-Johnson Syndrome & Toxic Epidermal Necrolysis

Scott Worswick
Associate Professor
Residency Co-Program Director
Director: Inpatient Dermatology
3-11-2022

Objectives

- Expand your Ddx for patients with:
  a.) targets or targetoid lesions
  b.) a dusky erythema and skin pain (SJS/TEN)
     (expand your potential work-up for a patient who presents in either above scenario)
- Review of current literature involving treatment and prognosis for EM/SJS/TEN
Part 1: What can cause mucosal erosions?

- EM Major
- FDE, SJS, TEN
- MIRM
- RIME
- PNP or PV or CP
- HSV stomatitis
- CMV
- HFMD
- acute GVHD
- chemotherapy
- candida
- Behcet’s/SLE/Crohn’s/apthae/LP/GPA/SCC

---

Table 1. A summary of the well-documented trigger factors for Erythema multiforme identified in Sokumbi et al. and Huff et al. [1,4].

<table>
<thead>
<tr>
<th>Trigger Factors for EM</th>
<th>Mycoplasma pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial infections</td>
<td>Yersinia enterocolitica</td>
</tr>
<tr>
<td></td>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>Viral infections</td>
<td>HSV (types 1 and 2)</td>
</tr>
<tr>
<td></td>
<td>Hepatitis C Virus</td>
</tr>
<tr>
<td></td>
<td>Epstein-Barr Virus</td>
</tr>
<tr>
<td></td>
<td>Influenza Virus</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>Histoplasma</td>
</tr>
<tr>
<td></td>
<td>Candida (vulvovaginal candidiasis)</td>
</tr>
<tr>
<td>Medications</td>
<td>NSAIDs</td>
</tr>
<tr>
<td></td>
<td>Antiepileptics</td>
</tr>
<tr>
<td></td>
<td>Sulfonamides</td>
</tr>
<tr>
<td></td>
<td>Antibiotics</td>
</tr>
<tr>
<td></td>
<td>Penicillins</td>
</tr>
<tr>
<td>Other conditions</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td>Complex aphthosis</td>
</tr>
<tr>
<td></td>
<td>Malignancies</td>
</tr>
<tr>
<td></td>
<td>Menstruation</td>
</tr>
<tr>
<td></td>
<td>Benzoic acid consumption</td>
</tr>
<tr>
<td></td>
<td>Polymorphous light eruption</td>
</tr>
</tbody>
</table>
Part 1: What can cause dusky erythema?
*SJS/TEN (sometimes DRESS and AGEP too)
Fixed Drug
*Linear IgA
*SSSS or Toxic Shock
*Disseminated CMV (and other viruses)
Lichen planus/Lichenoid Drug
*CTD
*aGVHD
*PNP
*Vasculitis
Burn

*possible dermatologic emergency

Your Ddx options for the next 6 patients:

A.) TEN
B.) Graft versus Host Disease
C.) Paraneoplastic Pemphigus
D.) DRESS
E.) Generalized Fixed Drug
F.) TSS
G.) Disseminated CMV
H.) Mercury poisoning
I.) Scalding burn
J.) Chemical burn
K.) Linear IgA Disease
L.) Chikungunya
M.) Bullous Lupus
N.) Vasculitis
Patient #1: 62 y/o F with HepB & DLBCL [s/p peripheral allograft transplant 5 weeks prior] with BSA 90% dusky erythema
BP103/63   HR113   Tmax36   RR28

Patient #2: 25 y/o M with schizophrenia has painful blisters & dusky erythema first on buttocks and nose, then generalizing over 2 days
BP 111/79   HR 67   Tmax 36   RR13

Patient #3: 71 y/o M with HTN has a 2 month h/o painful blisters in mouth then increasing peeling of skin as well as
BP 119/83   HR 102   Tmax36   RR 24

Patient #1: CMV
Patient #2: Hot water burn
Patient #3: PNP
Again, your Ddx options for the next 6 patients:

A.) TEN
B.) Graft versus Host Disease
C.) Paraneoplastic Pemphigus
D.) DRESS
E.) Generalized Fixed Drug
F.) TSS
G.) Disseminated CMV
H.) Mercury poisoning
I.) Scalding burn
J.) Chemical burn
K.) Linear IgA Disease
L.) Chikungunya
M.) Bullous Lupus
N.) Vasculitis

Patient #4: 27 year-old Female with SLE (on HCQ and AZA) and recent dental abscess (given clindamycin 2 weeks prior) presents with a 2 day h/o skin pain followed by red-purple “splotches” (BSA 12%), fevers, and joint pains. LFTs in the 100s other labs wnl.
HR 105 RR 16 Tmax 100.8 BP 113/76

Patient #5: 6 month old male with malaise then vesicobullous lesions on the skin (BSA ~30%) then desquamation. No prior meds.
HR 110 RR 18 Tmax 101.3 BP 110/71

Patient #6: 91 y/o Female admitted with septic shock and given pip-tazo and vancomycin for 7 days then develops bullae and sloughing (BSA 75%).
HR 99 RR 16 Tmax 99.6 BP 99/69
Erythema Multiforme: Treatment

- Acyclovir 400mg PO bid prophylaxis
- Levamisole 150mg/d for 3 days for attacks
- Systemic steroids
- dapsone
- Thalidomide
- Apremilast, adalimumab, mycophenolate, rituximab

TEN: What do you do for management?

- a. Systemic steroids
- b. Start cyclosporine 3mg/kg/d
- c. Etanercept 50mg SC once
- d. Initiate IVIG daily for 4 days at 1g/kg/d
- e. Supportive care in medical ICU or burn unit

Cyclosporine

- SCORTEN vs ABCD-10
- Corticosteroids: -0.13 (95% CI: -0.42 - 0.16)
- IVIG: -0.39 (-0.87 - 0.09)
- supportive care: 0.13 (-0.15 - 0.40)
- cyclosporine: **-0.88 (-1.47 - -0.29)**
- etanercept: -0.95 (-1.81 - -0.07)
- IVIG + steroids: -0.56 (-0.94 - -0.19)

What about Etanercept?
Important Case Series in 2014

- 10 patients
- 50mg etanercept SC once (within 6 hours of arrival)
- Complete re-epithelialization in 8.5 days
- No complications or side effects (0% death rate)
- Expected SCORTEN mortality of: 47%

Table I. Detail of the SCORTEN components and SCORTEN scores in 10 patients with toxic epidermal necrolysis treated with etanercept

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>SCORTEN components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;40 y</td>
<td>1 1 0 1 1 1 1 1 1 1</td>
</tr>
<tr>
<td>Heart rate &gt;120 beats/min</td>
<td>0 0 1 1 1 1 0 0 0 0</td>
</tr>
<tr>
<td>Cancer or hematologic malignancy</td>
<td>1 0 0 0 0 1 0 1 0 0</td>
</tr>
<tr>
<td>&gt;10% body surface area involvement</td>
<td>1 1 1 1 1 1 1 1 1 1</td>
</tr>
<tr>
<td>Serum urea level</td>
<td>1 1 0 0 0 0 0 1 0 0</td>
</tr>
<tr>
<td>Serum bicarbonate level &lt;20 mmol/L</td>
<td>1 0 0 0 0 0 0 1 0 0</td>
</tr>
<tr>
<td>Serum glucose level &gt;14 mmol/L</td>
<td>0 0 0 0 1 1 0 1 0 1</td>
</tr>
<tr>
<td>SCORTEN score</td>
<td>6 3 2 3 4 5 2 6 2 3</td>
</tr>
</tbody>
</table>


- 13 patients at UCLA-WLAVA
- 13 patients at USC
- All seemed to have had arrest of progression after one 50mg dose of etanercept
- Variable rates of re-epithelialization and desquamation
- Mortality in 17 etanercept patients: 0% (average BSA was 34%; predicted SCORTEN was 28%)
- Mortality in 9 non-etanercept patients: 33% (average BSA was 23%; predicted SCORTEN was 27%)
Basic Science Data:
**Etanercept vs Corticosteroids**

- Pre-clinical testing of etanercept
  - Obtained blister cells from 10 pts with SJS/TEN
  - Most cells $\rightarrow$ cytotoxic T cells or NK T cells
  - Treated w/ etanercept $\rightarrow$ secretion of granulysin and TNF-α after 48 hrs

2018: First RCT for **Etanercept vs Corticosteroids**

- Prospective, RCT of etanercept vs corticosteroids for SJS/TEN
  - Dose of etanercept: 25-50mg SC twice weekly
  - 71 patients completed the study
    - 38 etanercept (predicted mortality of 17.7%)
      - Observed: 4 died (8.3%)
      - Median time for skin healing in pts with >10% BSA was **14 days**
    - 33 steroids (predicted mortality of 20.3%)
      - Observed: 7 died (16.3%)
      - Median time for skin healing in pts with >10% BSA was **19 days**
  - Mortality for supportive care: 26.3%
  - Mortality for etanercept: 8.3%

Clinical Trial: CsA vs Etanercept for SJS/TEN

- Phase III Randomized Trial of the Treatment of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Comparing Supportive Care, Cyclosporine, and Biologic Therapy (Etanercept) in Adults
- Multi-centered, double-blind, RCT
- 20 sites within North America, 267 patients
- Not yet enrolling patients

https://clinicaltrials.gov/ct2/show/NCT02987257

Take Home Points: EM & SJS/TEN

- Expand your oral erosions differential diagnosis for patients with EM Major or SJS/TEN
- Expand your Ddx for dusky erythema for SJS/TEN patients
- Remember commons EM triggers: HSV, drugs (NSAIDs, anti-epileptics, antibiotics), mycoplasma, EBV, CMV, influenza, IBD
- Good treatments for EM flare: steroids, levamisole
- Good treatments for EM control: acyclovir prophylaxis, dapsone, thalidomide, apremilast, rituximab
- Think about treating SJS/TEN with: etanercept or cyclosporine