Meet the Professor

Moderator: Eric Warm M.D., F.A.C.P.
Program Director
Vilter Professor of Medicine
University of Cincinnati
Case One

- ID: 53 year old woman
- Chief Complaint: Sore throat, fever
History of Present Illness

- 6 weeks ago
  - Pain in her hands – small joints
  - Pain and decreased vision in her right eye
  - Started sulfasalazine

- 1 week ago
  - Sore throat
  - Fever
  - Swollen glands
  - Started amoxicillin/clavulanic acid
  - Sulfasalazine stopped

Summary

- 53 year old female
- Sore throat, fever,
History of Present Illness

- 3 days ago developed rash
  - Itchy
  - Diffuse
  - Bleeding in mouth
  - Swollen face (couldn’t easily open her eyes)

Summary
- 53 year old female
- Sore throat, fever,
- Joint/eye pain
- Sulfasalazine
- Amox/clav acid
Review of Systems

- General
  - Weight loss of 20 pounds over the past 6 weeks
  - Fatigue (6 weeks)
  - No hot or cold intolerance

- HEENT
  - No headache or neck pain
  - Eyes swollen (can open with effort)
  - Pain, bleeding in mouth

Summary

- 53 year old female
- Sore throat, fever,
- Joint/eye pain
- Sulfasalazine
- Amox/clav acid
- Rash, bleeding
- Facial edema
Review of Systems

- Heart
  - No chest pain

- Lungs
  - No shortness of breath
Review of Systems

- Abdomen
  - No melena
  - No change in bowel habits
Review of Systems

- Genitourinary
  - No dysuria

- Extremities
  - No edema
  - No current joint pain or stiffness
  - No swollen joints

Summary
- 53 year old female
- Sore throat, fever,
- Joint/eye pain
- Sulfasalazine
- Amox/clav acid
- Rash, bleeding
- Facial edema
- Wt. loss, fatigue
Review of Systems

- Skin – diffuse itchy rash
- Mental Status – no confusion; just tired

Summary

- 53 year old female
- Sore throat, fever,
- Joint/eye pain
- Sulfasalazine
- Amox/clav acid
- Rash, bleeding
- Facial edema
- Wt. loss, fatigue
Past Medical History

- Lyme disease (treatment status unknown)
- GERD (15 years)
- Ovarian cyst removal

Summary

- 53 year old female
- Sore throat, fever
- Joint/eye pain
- Sulfasalazine
- Amox/clav acid
- Rash, bleeding
- Facial edema
- Wt. loss, fatigue
Allergies

- None

Summary

- 53 year old female
- Sore throat, fever,
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- Rash, bleeding
- Facial edema
- Wt. loss, fatigue
- Hx of Lyme disease
- Ovarian cyst
- GERD
Medications

- Sulfasalazine 2 grams per day (stopped 7 days prior to admission)
- Amoxicillin/clavulanic acid 875/125 mg bid
- Omeprazole 40 mg qd
- Aspirin 81 mg qd

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- GERD
Social History

- Alcohol - none
- Tobacco – 2 packs per day for 40 years
- Drugs - none
- Single – not sexually active; 1 prior partner
- No recent travel history

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- GERD
Family History

Father

- DM II, CAD, HTN, MGUS

Mother

- HTN, depression

Sister

- Discoid lupus

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- Rash, bleeding
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- Wt. loss, fatigue
- Hx of Lyme disease
- Ovarian cyst
- GERD
- Smoker
Physical Exam

- Temperature: 102.5 Fahrenheit
- Blood Pressure 130/80
- Pulse 115
- Respirations 22
- BMI = 24

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- Hx of Lyme disease
- Ovarian cyst
- GERD
- Smoker
- Fam Hx of Lupus
Physical Exam

• General
  • Appears unwell
  • Not cachectic

• HEENT
  • Facial edema
  • Hemorrhagic vesicles in oral cavity

Summary

• 53 year old female
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• Wt. loss, fatigue
• Hx of Lyme disease
• Ovarian cyst
• GERD
• Smoker
• Fam Hx of Lupus
• Febrile
• Tachycardic
• Tachypneic
Physical Exam

- Neck
  - Tender lymphadenopathy

- Heart
  - Normal

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- Tachypneic
Physical Exam

- **Lungs**
  - Clear

- **Abdomen**
  - Diffuse tenderness, more in RUQ
  - Hepatomegaly
  - Possible splenomegaly
  - No additional masses

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- Tachypneic
Physical Exam

- Extremities

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- HSM
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Initial Laboratory Exam

A.  
1. CBC
2. Renal
3. LFT’s
4. TFT’s
5. UA
6. EKG
7. Drug Screen

B.  
1. CXR
2. INR
3. CK, troponin
4. ABG
5. CRP
6. ESR
7. HIV
8. B12 level

To Secondary Tests
**CBC**

- **WBC** 12.2 K/UL
- **RBC** 4.41 M/UL
- **HGB** 14.8 G/DL
- **HCT** 39.2%
- **MCV** 84.7 FL
- **MCH** 25.5 PG
- **MCHC** 33.1 G/DL
- **RDW** 14.5%
- **PLT** 332 K/UL

- **PMN** 70%
- **LYMPH** 23%
- **MONO** 1%
- **EOS** 6%
- **BASO** 0%

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To initial labs
Renal

- Sodium: 142 MEQ/L
- Potassium: 3.8 MEQ/L
- Chloride: 100 MEQ/L
- CO2: 24 MEQ/L
- BUN: 8 MG/DL
- Creatinine: 1.0 MG/DL
- Glucose: 89 MG/DL

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To initial labs
**LFT’s**

- AST = 106 U/L (11-35)
- ALT = 350 U/L (7-46)
- Alkaline Phosphatase = 2959 U/L (46-240)
- Bilirubin, total = 2.70 MG/DL (0.0-1.0)
- Albumin 3.2 GM/DL (3.5-5.0)

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To initial labs

**TFT’s**

- TSH = 3.6 uIU/ml (0.47-6.90)
Urinalysis

- Specific Gravity = 1.025
- Dark Yellow
- pH = 5.0
- Protein = 0
- RBC = 0 per hpf
- WBC = 0 per hpf
- No casts
- Nitrite negative
- Leukocyte esterase negative

To initial labs
ABG

- Not done

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To initial labs
INR

• 1.3 INR

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To initial labs
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**HIV**

- Negative

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- To initial labs
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To initial labs
CRP

- 112 mg/dl

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To initial labs
B12 level

- Normal

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CK, Troponins

- CK = 43 mg/dl
- Troponin 0.00 mcg/L

To initial labs

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Toxicology

• Negative

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Secondary Laboratory Exam

- 1. Blood cultures
- 2. CT Abdomen
- 3. ECHO (TTE)
- 4. Bone marrow Bx
- 5. Skin biopsy
- 6. Liver biopsy
- 7. Iron Studies
- 8. SPEP
- 9. RF
- 10. ANA

- 11. EBV titers
- 12. Parvo B12 titers
- 13. CMV titers
- 14. Lyme titers
- 15. Leptospirosis
- 16. Bartonella
- 17. HSV titers
- 18. Adenovirus titers
- 19. ANCA
- 20. Anticardiolipin
- 21. Lupus Anticoagulant

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To initial tests

To next steps
Blood Cultures

- No growth

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To Secondary Tests
CT Abdomen

- right pleural effusion
- diffuse thoracic and abdominal lymph nodes enlargement (maximum diameter 26 mm)
- severe hepatomegaly
- mild splenomegaly
- no sign of pneumonia

To Secondary Tests

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ECHO

- No cardiac vegetations or pericardial effusion
Bone Marrow Biopsy

- No lymphoma or hematologic malignancy,
- Mild eosinophilic hyperplasia.

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Skin Biopsy

- chronic perivascular infiltration, made mostly by lymphocytes with very rare eosinophils

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To Secondary Tests
Liver Biopsy

- Portal tracts infiltration of lymphohistiocytosis, neutrophils and eosinophils with intralobular foci of necrosis
Iron Studies

- Not done
SPEP

- Total gamma globulins, IgG/A/M, K/Lambda chain ratio all normal

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**EBV titers**

- Negative

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To Secondary Tests
Parvovirus B19

- Negative

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To Secondary Tests
CMV titers

- Negative

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To Secondary Tests
Lyme titers

- Negative

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To Secondary Tests
Leptospirosis titers

- Negative

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- HSM
Bartonella Titers

- Negative

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To Secondary Tests
HSV titers

- Negative
### Adenovirus titers

- Negative

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To Secondary Tests
Rheumatoid Factor

- Negative

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Negative

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To Secondary Tests
Anticardiolipin

- Negative

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To Secondary Tests
**Lupus anticoagulant**

- Negative

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Next Steps

- Add Vancomycin
- Add Doxycycline
- Add Antifungals
- Add Gram Negative Coverage
- Add Steroids
- Add Chemotherapy
- Thick and Thin Smear
- Hepatitis Studies
- Continue to Observe

To Secondary Tests
To Answer

Summary

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Next Steps

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No.

To Secondary Tests
To Next Steps
Next Steps

Yes!
What is the diagnosis?

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To Secondary Tests
To Answer
Fever, rash, lymphadeopathy and systemic illness all due to:

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**DRESS**

Drug Rash Eosinophilia Systemic Symptoms
## DRESS

<table>
<thead>
<tr>
<th>RegiSCAR inclusion criteria for DRESS syndrome. Three of the four starred criteria required for diagnosis</th>
<th>Japanese consensus group diagnostic criteria for DIHS. Seven criteria needed for diagnosis of DIHS or the first five criteria required for diagnosis of atypical DIHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>Maculopapular rash developing &gt; 3 weeks after starting the suspected drug</td>
</tr>
<tr>
<td>Reaction suspected to be drug-related</td>
<td>Prolonged clinical symptoms 2 weeks after discontinuation of the suspected drug</td>
</tr>
<tr>
<td>Acute Rash*</td>
<td>Fever &gt; 38 °C</td>
</tr>
<tr>
<td>Fever &gt; 38 °C*</td>
<td>Liver abnormalities (ALT &gt; 100 U/L) or other organ involvement</td>
</tr>
<tr>
<td>Lymphadenopathy in at least two sites*</td>
<td>Leukocyte abnormalities</td>
</tr>
<tr>
<td>Involvement of at least one internal organ*</td>
<td>Leukocytosis ( &gt; 11 x 10^9/L)</td>
</tr>
<tr>
<td>Blood count abnormalities (lymphopenia or lymphocytosis*, eosinophilia*, thrombocytopenia*)</td>
<td>Atypical lymphocytosis (&gt;5%)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Human herpesvirus 6 reactivation</td>
</tr>
<tr>
<td>Drug</td>
<td>Cases related to the Drug</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Abacavir</td>
<td>5</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>19</td>
</tr>
<tr>
<td>Amoxicillin plus clavulanic acid</td>
<td>1</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>2</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>1</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1</td>
</tr>
<tr>
<td>Captopril</td>
<td>1</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>47</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>1</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>1</td>
</tr>
<tr>
<td>Clonipramine</td>
<td>1</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1</td>
</tr>
<tr>
<td>Codein phosphate</td>
<td>1</td>
</tr>
<tr>
<td>Cotrimoxazole / Cefixime</td>
<td>1</td>
</tr>
<tr>
<td>Cyaramide</td>
<td>1</td>
</tr>
<tr>
<td>Dapsone</td>
<td>4</td>
</tr>
<tr>
<td>Diaphenylsulfone</td>
<td>1</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>1</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>1</td>
</tr>
<tr>
<td>Hydroxichloroquine</td>
<td>2</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>2</td>
</tr>
<tr>
<td>Imatinib</td>
<td>1</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>10</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>5</td>
</tr>
<tr>
<td>Minocycline</td>
<td>3</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>8</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1</td>
</tr>
<tr>
<td>Oxacarbazepine</td>
<td>3</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>10</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>1</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>7</td>
</tr>
<tr>
<td>Quinine and thiamine</td>
<td>1</td>
</tr>
<tr>
<td>Salazosulfapyridine</td>
<td>2</td>
</tr>
<tr>
<td>Sodium meglumine ioxitalamate</td>
<td>1</td>
</tr>
<tr>
<td>Sodium valproate/ethosuximide</td>
<td>1</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>1</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>1</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>2</td>
</tr>
<tr>
<td>Sulfaazine</td>
<td>10</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>2</td>
</tr>
<tr>
<td>Tribenoside</td>
<td>1</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>4</td>
</tr>
<tr>
<td>Zanosamide</td>
<td>1</td>
</tr>
</tbody>
</table>

Font adapted: Cacoub P et al
DRESS

- Starts within 2–6 weeks after taking a drug
- An incidence that ranges from 1/1000 to 1/10000 exposures
- Antiepileptics first described (now many drugs)
- Pathogenesis not completely understood
- Amoxicillin shown to trigger it in patients who are taking allopurinol, sulfasalazine, NSAIDs, carbamazepine, strontium, lisinopril, lansoprazole, and minocycline

DRESS

- How amoxicillin triggers DRESS syndrome is matter of debate
- Amoxicillin can induce reactivation of HHV 6 and EBV even in patients taking sulfasalazine
- With amoxicillin:
  - DRESS syndrome does not flare immediately after the introduction of the antibiotic
  - The reason the antibiotic is prescribed may not be URI, but the start of DRESS

Figure 3: Sequence of events of drug-virus-immune system interaction in patients with DRESS/DIHS triggered by aromatic anticonvulsants. Aromatic anticonvulsants are metabolized by the oxidation system of cytochrome P450 (CYP) in arene oxide radicals (intermediate reactive metabolite) (1a). These arene oxides are detoxified by glutathione transferase and epoxide hydrolase in non-toxic metabolites 2. In genetically predisposed individuals or by additional factors, occurs an impaired detoxification and accumulation of these metabolites 3, which can cause cellular damage generating Danger Signs that can stimulate resting T cells, inducing co-stimulatory pathways 4. In addition, ethnic predisposition to certain HLA types may contribute to the formation of neoantigens from the combination of these intermediary reactive metabolites with tissue macromolecules and formation of haptens (5a), which can be presented via the human histocompatibility complex class I (HLA-DR) or class II (HLA A, B or C), to CD4 or CD8 T cells 6. It was demonstrated that carbamazepine, valproic acid and amoxicillin are able to exert immunomodulatory actions by inhibiting histone deacetylase on B lymphocytes, producing a hypogammaglobulinemia that precedes the clinical onset of DRESS/DIHS. The clonal expansion of T cells requires sequential reactivation of latent herpesvirus, and at the same time, CD8 + CLA + T cells are produced, which are directed towards skin, CD8 + CCR4 + T cells addressed to the lungs (7b) and CD4 + IL4, IL5 producer and IL17 CD4Th17 + producer that cause tissue and peripheral eosinophilia.
### Table 1

Results of *in vitro INF-gamma release test* in the patient with DRESS syndrome (during corticosteroid therapy).

<table>
<thead>
<tr>
<th>Drug</th>
<th>INF-gamma without drug (pg/ml)</th>
<th>INF-gamma with drug (pg/ml)</th>
<th>% INF-gamma increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>590</td>
<td>766</td>
<td>30</td>
</tr>
<tr>
<td>Dypirone</td>
<td>590</td>
<td>822</td>
<td>39</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>590</td>
<td>766</td>
<td>30</td>
</tr>
<tr>
<td>Clozapine</td>
<td>590</td>
<td>550</td>
<td>No increase</td>
</tr>
<tr>
<td>Solian</td>
<td>590</td>
<td>567</td>
<td>No increase</td>
</tr>
<tr>
<td>Dekinet</td>
<td>590</td>
<td>580</td>
<td>No increase</td>
</tr>
<tr>
<td>Seroquel</td>
<td>590</td>
<td>420</td>
<td>No increase</td>
</tr>
<tr>
<td>Nozinan</td>
<td>590</td>
<td>440</td>
<td>No increase</td>
</tr>
<tr>
<td>Valproate</td>
<td>590</td>
<td>450</td>
<td>No increase</td>
</tr>
</tbody>
</table>

DRESS

- French Society of Dermatology (2010)
  - systemic corticosteroids (prednisone) at 1 mg/kg/day of prednisone in patients with:
    - transaminases greater than five times normal
    - renal involvement
    - pneumonia
    - hemophagocytosis
    - cardiac involvement.
  - IVIG at a dose of two g/kg over five days for patients with life-threatening signs such as renal failure or respiratory failure
  - propose the use of steroids with ganciclovir in patients with signs of severity and confirmation of a major viral reactivation of HHV-6.

On the third hospital day the clinical status quickly worsened

- severe deterioration of skin rash
- heart and respiratory rates higher
- after labs returned negative, antibiotics were stopped
- Methylprednisone 1 mg/Kg/day was started
- Prompt recovery of fever, rash, lymph nodes enlargement, and laboratory abnormalities