Clinical Pathophysiology Conference

Red, White, Blue and Yellow: A Fatal Combination of Raynaud’s and Jaundice

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Chief Resident Medical Service I
Montefiore Medical Center

November 3, 2005
Chief Complaint

- 25 year-old African-American woman with a history of Raynaud’s phenomenon complained of shortness of breath, nausea, vomiting and jaundice over the course of one week.
Case History

She had been feeling well until

- One week prior to admission when she began experiencing shortness of breath. This progressed over one week and she complained of dyspnea with minimal exertion. Denied chest pain, diaphoresis or leg swelling.

- Two days PTA, mother noted her eyes and skin to be yellow.

- The day of admission she went to work and had nausea and vomiting associated with dizziness and went to Montefiore ED.
Case History

- **PMH:**
  - Raynaud’s phenomenon for 2 yrs
  - Followed by a rheumatologist for 2 yrs for Raynaud’s and abnormal serologies
  - No prior surgeries

- **Meds:** Nifedipine QD

- **Allergies:** NKDA

- **Family History:** No family history of connective tissue disease, cancer, cardiac or liver disease

- **Social History:** Denied tobacco, alcohol or drug use. Not sexually active. Lives with parents. Works at Lincoln hospital. Denied recent travel.
History summary

25yo AA female with history of Raynaud’s

- Dyspnea x 1 week
- Jaundice x 2 days
- Nausea/vomiting x 1 day

Differential diagnosis?

- **Liver/GI:**
  - Autoimmune hepatitis
  - Primary biliary cirrhosis
  - Acute hepatitis: viral, toxic, fulminant
  - Portal vein thrombosis

- **Hematologic:**
  - Hemolytic anemia
    - Autoimmune, G-6PD, sickle cell
  - Prothrombotic (APLA) state with
    - PE’s and hepatic vein thrombosis
  - Severe symptomatic anemia

- **Infectious:**
  - Pneumonia/Sepsis/DIC
  - Acute Viral Hepatitis
  - HIV + opportunistic infections/Hepatitis

- **Rheumatologic:**
  - SLE with autoimmune hemolytic anemia
  - SLE with visceral vasculitis
Physical Exam

- **ED Triage Vitals**
  - Temp = 98.1° orally
  - BP 123/92
  - Pulse 140
  - RR 20
  - Pulse ox = 98% on room air
Physical Exam

- ED exam noted tachycardia and jaundice
- While in the ED, patient was noted by nurse and mother to have a seizure that lasted one minute: tonic-clonic movements, eyes rolled back, and unresponsive; Fingerstick was 161

- 2nd set of vitals
  - Tmax 102.8° rectally
  - BP 124/87
  - Pulse 136
  - RR 30
  - Pulse ox 98% on room air, 100% on NRB

- Ativan 2mg IV given, Tylenol given, and 2L NS infused
Physical Exam

- Detailed Physical Exam
  - General appearance: Drowsy, lethargic but AAO x 3
  - Skin: pale, cool, dry, jaundiced
  - HEENT: icteric conjunctiva, PERRL, MMM
  - Neck: no lymphadenopathy, no JVD
  - Chest: CTA B/L
  - Heart: tachycardic, regular rhythm, no murmurs
  - Abdomen: soft, mild tenderness, + BS, liver 9cm, no splenomegaly
  - Extremities: cool extremities (U + L), “petechiae” lower legs B/L
  - Pulses: noted to be “decreased”
History and Physical Summary

25yo AA female with history of Raynaud’s

- Dyspnea x 1 week
- Jaundice x 2 days
- Nausea/vomiting x 1 day
- Seizure
- Fever
- Tachycardia
- “Petechiae”

Differential diagnosis?

- Liver/GI:
  - Autoimmune hepatitis
  - Primary biliary cirrhosis
  - Acute hepatitis: viral, toxic, fulminant
  - Portal vein thrombosis
- Hematologic:
  - Hemolytic anemia
  - Prothrombotic (APLA) state with PE’s and hepatic vein thrombosis
  - Severe symptomatic anemia
- TTP (Thrombotic Thrombocytopenic Purpura)
  - Catastrophic anti-phospholipid syndrome
- SLE with vasculitis
  - Infectious:
    - Pneumonia/Sepsis/DIC
    - Acute Viral Hepatitis
    - HIV + opportunistic infections/Hepatitis
- Rheumatologic:
  - SLE with autoimmune hemolytic anemia
  - SLE with visceral vasculitis
# Initial Laboratory Data

<table>
<thead>
<tr>
<th>CBC</th>
<th>Chem 7</th>
<th>LFTs</th>
</tr>
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<tbody>
<tr>
<td>WBC</td>
<td>Na</td>
<td>TP</td>
</tr>
<tr>
<td>H/H</td>
<td>K</td>
<td>Alb</td>
</tr>
<tr>
<td>Plts</td>
<td>Cl</td>
<td>AST</td>
</tr>
<tr>
<td></td>
<td>HCO3</td>
<td>ALT</td>
</tr>
<tr>
<td></td>
<td>BUN</td>
<td>T.Bili</td>
</tr>
<tr>
<td></td>
<td>Cr</td>
<td>D.Bili</td>
</tr>
<tr>
<td></td>
<td>Glu</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>Ca</td>
<td>LDH</td>
</tr>
</tbody>
</table>

(normal CBC 2 years prior)

<table>
<thead>
<tr>
<th>Coags</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
</tr>
<tr>
<td>PTT</td>
</tr>
</tbody>
</table>

UA: dark yellow, clear, pH 6.0, SG 1.019, **prot >1000**, gluc neg, ketone neg, **blood large**, LE trace, nitrate neg, small bili

**RBC 56**, **WBC 8.2**, **TP = 256/Cr 106 = ~2.5g/day proteinuria**
Peripheral Smear
H & P and Lab Summary

25yo AA female with history of Raynaud’s

- Dyspnea x 1 week
- Jaundice x 2 days
- Nausea/vomiting x 1 day

- Seizure
- Fever
- Tachycardia
- "Petechiae"
- Thrombocytopenia
- Hemolytic anemia
- Schistocytes on peripheral smear
- Proteinuria and hematuria

Differential diagnosis?

- TTP
  - Catastrophic APL syndrome
  - SLE with autoimmune hemolytic anemia and vasculitis
  - Pneumonia/Meningitis/Sepsis/DIC
Hematology Consult

- Hematology was consulted and agreed the diagnosis was consistent with TTP
  - Fever, hemolytic anemia and thrombocytopenia
  - Hx auto-immune disease
  - *Recommended:*
    - **ACT**
      - Admit to ICU, Transfusion services to be made aware
      - Bilateral single or Shiley catheter for initiation of plasma exchange
      - Additional blood tests or at least plasma samples frozen
        - Coombs (Direct AHG), APLA work-up, TTP work-up
    - **PRIOR TO:**
      - 2-4 units of FFP in the meantime prior to catheter
Thrombotic Thrombocytopenic Purpura

- A *thrombotic, not a bleeding* clinical syndrome
  - Diagnostic criteria
- Acquired (inhibitor) or inherited (deficiency)
- Pathophysiology
  - ULvWF → vWF multimers
  - vWF cleaving protease
  - ADAMTS-13
  - *(a disintegrin and metalloprotease with thrombospondin type-1 motifs)*
- Treatment:
  - Plasma Infusion
  - Plasma Exchange
Rheumatology Consult

- Rheumatology was called to review her prior rheumatologic history and serologies.
- According to her private rheumatologist, the patient had a history of:
  - Raynaud’s phenomenon for 2-3 years
  - Mild intermittent arthralgias
  - Denied morning stiffness, rash, skin changes, or alopecia
  - “Undifferentiated” connective tissue disease
<table>
<thead>
<tr>
<th>Two years ago</th>
<th>One year ago (Quest)</th>
<th>One year ago (Monte)</th>
<th>This admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA 1:640 speckled, ESR 40</td>
<td>Anti DNA &lt;30….(negative)</td>
<td>2.5 ……. (negative)</td>
<td>Anti DNA 1.8 …(negative)</td>
</tr>
<tr>
<td></td>
<td>Anti Smith &gt;6……..(positive)</td>
<td>&gt;100 …..(positive)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti RNP &gt;6……..(positive)</td>
<td>&gt;100 …..(positive)</td>
<td></td>
</tr>
<tr>
<td>RF 205…………..(positive)</td>
<td>CRP 0.5 ……..(normal)</td>
<td>C3 91 ………….(normal)</td>
<td></td>
</tr>
<tr>
<td>C3 152 ………..(normal)</td>
<td>C4 40 ……..(normal)</td>
<td>C4 22 ………….(normal)</td>
<td></td>
</tr>
<tr>
<td>Anti Ro ………(negative)</td>
<td>Anti Ro 0.6 ……..(negative)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti La ………(negative)</td>
<td>Anti La 0.7 ………(negative)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2 glycoprotein &lt;20 ..(negative)</td>
<td>B2 glycoprotein 5.7 (negative)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti CL IgM, IgG &lt;6 ..(negative)</td>
<td>Anti CL IgM, IgG (negative)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti SCL ……….(negative)</td>
<td></td>
<td></td>
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</tbody>
</table>
Connective Tissue Disease

- Unclassified CTD
  - Does not differentiate or belong to any particular pattern
- Atypical CTD
  - E.g. related to silicone breast implants
- Overlap Syndrome
- MCTD
- Defined CTD
Connective Tissue Disease

- Defined CTD
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Sjögren’s syndrome
  - Scleroderma
  - Polymyositis/Dermatomyositis
Connective Tissue Disease

Classification relies on:
- Well-defined patterns of disease presentation
- Autoantibody profiles
- No definite diagnostic criteria
Undifferentiated Connective Tissue Disease

- Predictors of evolution to SLE in UCTD at 5 years*
  - African American ancestry
  - Alopecia
  - Serositis (4.1)
  - Discoid lupus (15.8)
  - Positive Coombs test
  - Positive ANA (4.8)
  - Positive anti-Smith antibodies (28.2)
  - Positive anti-dsDNA antibodies

( ) Relative risk
* Cox multivariate regression analysis of 118 patients

J Rheumatol 1996;23:469-75
Undifferentiated Connective Tissue Disease

- Autoantibodies in descending frequency
  - ANA 55 – 98%
  - Anti-Ro/SSA 8 – 64%
  - Anti-dsDNA 4 – 21%
  - Anti-La/SSB ~5%
  - Anti-Sm ~1%

Clin Exp Rheumatol 2004;22:S14-S18
## Undifferentiated Connective Tissue Disease

### Predictors of evolution using autoantibodies at 10 years*

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Disease</th>
<th>Predictive value</th>
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<tbody>
<tr>
<td>Jo-1</td>
<td>Poly/Dermatomyositis (ND)</td>
<td></td>
</tr>
<tr>
<td>Scl-70</td>
<td>Scleroderma (ND)</td>
<td></td>
</tr>
<tr>
<td>Sm</td>
<td>SLE (89)</td>
<td></td>
</tr>
<tr>
<td>dsDNA</td>
<td>SLE (64)</td>
<td></td>
</tr>
</tbody>
</table>

ND – no data

*186 patients:

17.2% evolved to definite CTD

Arth & Rheumat 1999;42:S320
Undifferentiated Connective Tissue Disease

- Predictors of evolution using anti-Ro/SSA over 5 years in 148 patients
  - Well-defined (24.3%)
    - 50% - Sjögren’s
    - 30.5% - SLE
    - RA (2*), SSc (2), PM/SSc (1), MCTD (1), Wegener’s granulomatosis (1)
  - Stable (76%)

* Individual patients

Clin Exp Rheumatol 2001;19:403-9
Undifferentiated Connective Tissue Disease

- Autoantibody profiles can evolve and accumulate over time
- Individual autoantibodies are not totally predictive
  - SLE seems to be preceded by evolution from anti-Ro through ANA or Sm and then dsDNA

NEJM 2003;349;1526-33
Mixed Connective Tissue Disease

- SLE
- Scleroderma
- Myositis
- U1-snRNP antibodies

Mixed Connective Tissue Disease

- Sharp (1972) criteria
- Definite diagnosis requires 4 major criteria with positive anti-U1 RNP greater than 1:4000 and a negative anti-Sm Ab. U1 RNP is the specific RNP protein associated with this syndrome.
- Probable diagnosis requires either 3 major criteria or 2 major criteria (which must come from the first 3 major criteria listed) and 2 minor criteria plus an anti-U1 RNP greater than 1:1000.
- Possible diagnosis requires 3 major criteria without serologic evidence of disease or, if anti-U1 RNP is greater than 1:100, 2 major criteria or 1 major and 3 minor criteria.

  - Major criteria are severe myositis, pulmonary involvement (diffusing capacity of lung for carbon monoxide 70% of normal pulmonary hypertension proliferating vascular lesions on lung biopsy), Raynaud phenomenon or esophageal hypomotility, swollen hands observed or sclerodactyly, and highest observed anti-U1 RNP (>1:10,000) with negative anti-Sm Ab.

  - Minor criteria are alopecia, leukopenia (4000 WBC/cc), anemia (<10 g/dL for females, <12 g/dL for males), pleuritis, pericarditis, arthritis, trigeminal neuralgia, malar rash, thrombocytopenia (<100,000/cc), mild myositis, and history of swollen hands.
Mixed Connective Tissue Disease: Long term outcome over 15 years

- 62% had favorable outcome
- 38% had active disease or death
- 11 of 47 patients died (22%)
  - Cause of death mostly pulmonary hypertension

Diagnosis

UCTD
TTP and UCTD/MCTD

- Classic TTP: ~3.7 cases* per 1 million residents
- No association with UCTD
- Few reported cases of MCTD and TTP
  - 7 in literature

Using Clinical Looking Glass
# TTP (ICD9) Demographics

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Age avg, range</td>
<td>41 (9-86)</td>
<td>47.1 (21-70)</td>
</tr>
<tr>
<td>Female</td>
<td>75%</td>
<td>64.1%</td>
</tr>
<tr>
<td>Male</td>
<td>25%</td>
<td>35.9%</td>
</tr>
<tr>
<td>Black</td>
<td>61%</td>
<td>33.2%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>33%</td>
<td>38.0%</td>
</tr>
<tr>
<td>White</td>
<td>6%</td>
<td>15.0%</td>
</tr>
<tr>
<td>Asian</td>
<td>1.0%</td>
<td></td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>12.6%</td>
<td>80.6%</td>
</tr>
</tbody>
</table>

n=36  n=24131  n=206

*CLG data (Cohen, Lansigan, Weiss)
TTP (ICD9) Cases 2000-2005 at Montefiore

DISEASE ASSOCIATIONS

- **ANA**: 14%
- **HIV**: 36%
- **UNKNOWN**: 50%

*CLG data (Cohen, Lansigan, Weiss)*
TTP Lab Data by ICD9

% of patients

Lab data within 5 year period

- PLT<10
- LDH>1000
- BILI>2
- HGB<7
- Cr>2
- AST>200

*CLG data (Cohen, Lansigan, Weiss)
TTP (ICD9) Mortality at Montefiore*

*Mortality Analysis - TTP mortality

*CLG data (Cohen, Lansigan, Weiss)
ICU Course: Day 1 thru 3

25yo woman with Raynaud’s, UCTD, TTP

- Fever
- Intubation for “airway protection”
- Hypotension, briefly on pressors
- Pulmonary edema
- Acute ↓ Hb to 6.1
- ↑ WBC to 37
- ↑ transaminases and bilirubin
- Metabolic acidosis
ICU Course: Day 1 thru 3

- Plasma exchange was begun 12hrs into the admission and continued daily
- Support with PRBCs
- Vanco and Zosyn started for presumed sepsis
- Lasix was started for pulmonary edema
# Labs Day 1 thru 3

<table>
<thead>
<tr>
<th>Time</th>
<th>0hrs</th>
<th>6hrs</th>
<th>14hrs</th>
<th>30hrs</th>
<th>42hrs</th>
<th>54hrs</th>
<th>64hrs</th>
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<tbody>
<tr>
<td><strong>Interventions</strong></td>
<td>Admission</td>
<td>FFPs</td>
<td>TPE x 1</td>
<td>TPE x 2</td>
<td>CAC</td>
<td></td>
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<tr>
<td><strong>WBC</strong></td>
<td>6.6</td>
<td>6.2</td>
<td>17.9</td>
<td>18.4</td>
<td>36.7</td>
<td>23.0</td>
<td>42.3</td>
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<tr>
<td><strong>HEMOGLOBIN</strong></td>
<td>8.3</td>
<td>6.1</td>
<td>10.6</td>
<td>8.8</td>
<td>11.6</td>
<td>8.8</td>
<td>8.3</td>
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<tr>
<td><strong>HEMATOCRIT</strong></td>
<td>26.0</td>
<td>18.7</td>
<td>30.9</td>
<td>26.0</td>
<td>34.7</td>
<td>26.0</td>
<td>23.8</td>
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<tr>
<td><strong>PLATELET</strong></td>
<td>7.0</td>
<td>6.0</td>
<td>19.0</td>
<td>10.0</td>
<td>15.0</td>
<td>11.0</td>
<td>14.0</td>
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<tr>
<td><strong>LDH</strong></td>
<td>1301</td>
<td>2200</td>
<td>2620</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>UREA</strong></td>
<td>15</td>
<td>17</td>
<td>21</td>
<td>25</td>
<td>25</td>
<td>31</td>
<td>36</td>
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<tr>
<td><strong>CREATININE</strong></td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0.9</td>
<td>1.0</td>
<td>1.0</td>
<td>1.6</td>
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<tr>
<td><strong>AST</strong></td>
<td>81</td>
<td>65</td>
<td>713</td>
<td>526</td>
<td>663</td>
<td></td>
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<tr>
<td><strong>ALT</strong></td>
<td>46</td>
<td>35</td>
<td>390</td>
<td>342</td>
<td>439</td>
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<td><strong>ALKALINE PHOS</strong></td>
<td>55</td>
<td>53</td>
<td>51</td>
<td>57</td>
<td>54</td>
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<tr>
<td><strong>BILIRUBIN TOTAL</strong></td>
<td>6.6</td>
<td>4.8</td>
<td>11.4</td>
<td>12.6</td>
<td>12.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BILIRUBIN DIRECT</strong></td>
<td>0.4</td>
<td>1.4</td>
<td>4.5</td>
<td>4.8</td>
<td>5.8</td>
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<tr>
<td><strong>pH</strong></td>
<td>7.20</td>
<td></td>
<td></td>
<td>7.448</td>
<td>7.133</td>
<td></td>
<td></td>
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<tr>
<td><strong>PCO2</strong></td>
<td>29.0</td>
<td></td>
<td></td>
<td>21.6</td>
<td>16.4</td>
<td></td>
<td></td>
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<tr>
<td><strong>PO2</strong></td>
<td>131.0</td>
<td></td>
<td></td>
<td>151.0</td>
<td>138.0</td>
<td></td>
<td></td>
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<tr>
<td><strong>LACTIC ACID</strong></td>
<td>6.6</td>
<td></td>
<td></td>
<td>2.6</td>
<td>13.8</td>
<td></td>
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</tbody>
</table>
### ICU: Day 2 and 3 Labs

- **Haptoglobin**: 8 L
- **Coombs (DAT)**: negative
- **APLA workup**: negative
- **Fibrinogen**: 331
- **D-Dimer**: 3.0 H
- **Urine toxicology**: negative
- **Hepatitis B&C**: negative

**Respiratory culture**: Many staph aureus, few streptococcus pneumoniae

**Blood and urine cultures**: no growth to date
ICU: Day 2 and 3 – Labs and Tests

- **CPK**
  - #1: 520
  - #2: 540

- **CK-MB%**
  - #1: 1.3
  - #2: 0.9

- **Trop-T**
  - #1: 0.15
  - #2: 0.18
  - #3: 0.12

- **EKG:** sinus tach 144, low voltage compared to initial EKG

- **ECHO:** diffuse hypokinesis, small pericardial effusion, EF = 30%
  - Started low-dose dobutamine 2.5mcg/kg/min
  - Continued Lasix for diuresis
Chest X-ray: 12 hrs
Chest X-Ray: Day 3
CACCAC

- On Day 3, during the 3\textsuperscript{rd} round of plasma exchange, the patient went into cardiac arrest.
- Bedside ECHO showed a small pericardial effusion “not sizeable enough to tap”.
- She was pronounced dead after 40 minutes of ACLS.
- ADAMTS-13 activity assay: $< 0.1\text{u/ml}$ (reference range $> 0.56$).
Heart
Anti-human vWF
Phosphotungstic acid hematoxylin (PTAH)
Heart

Hyaline thrombi rich in platelets and von Willebrand factor with minimal fibrin deposits

Petechial hemorrhage

Acute ischemic myocardial injury
Lung
Lung, Right Lower Lobe: Diffuse hemorrhage
Lung

Platelet-rich microthrombi
Bilateral acute inflammation and diffuse hemorrhage

No evidence of vasculitis
Kidney
Anti-human vWF
Kidney

Microthrombi in the glomerular capillaries and arterioles

No evidence of lupus nephritis
Liver
Liver

Microthrombi
Focal necrosis
Centrilobular congestion
Pancreas: numerous microthrombi (\(\alpha h-vWF\))
Adrenal gland: numerous microthrombi (ah-vWF)
Brain and spinal cord
Brain and spinal cord

Hyaline thrombi in the gray matter of the brainstem, hippocampus, neocortex and the cerebellum

Anoxic changes seen within the CNS were consistent with capillary thrombi and with clinical events which included a low cardiac output (EF 30%), seizures, acute myocardial infarction and repeated episodes of hypotension.
Microvascular platelet and von Willebrand factor-rich thrombi devoid of fibrin are found in the brain, heart, kidney, pancreas, adrenal glands, spleen and other organs.

Diffuse multiorgan petechial hemorrhages and ischemia.

Acute Ischemic Myocardial Injury
Lung, bilateral, acute inflammation, diffuse hemorrhage
Differential Diagnosis:

Thrombotic Thrombocytopenic Purpura (TTP)
Hemolytic Uremic Syndrome (HUS)
Disseminated intravascular coagulation (DIC)
Systemic Lupus Erythematosus (SLE)
Thrombotic Thrombocytopenic Purpura (TTP)
Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome Are Distinct Pathologic Entities, A Review of 56 Autopsy Cases
Gregory A. Hosler, MD, PhD; Ana M. Cusumano, MD; Grover M. Hutchins, MD
From the Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Md
Archives of Pathology and Laboratory Medicine: 2003 Vol. 127, No. 7,

Table 3. Summary and Statistical Comparison of Features of Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS)

<table>
<thead>
<tr>
<th>Feature</th>
<th>TTP</th>
<th>HUS</th>
<th>P Value</th>
<th>t Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>25</td>
<td>31</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>6/19</td>
<td>16/15</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Age, y ± SD</td>
<td>37.4 ± 15.2</td>
<td>33.6 ± 23.5</td>
<td>...</td>
<td>0.49</td>
</tr>
<tr>
<td>Survival, d ± SD</td>
<td>28.6 ± 32.9</td>
<td>40.5 ± 38.3</td>
<td>...</td>
<td>0.26</td>
</tr>
<tr>
<td>Kidney</td>
<td>24/25</td>
<td>31/31</td>
<td>&gt;.99</td>
<td>...</td>
</tr>
<tr>
<td>Pancreas</td>
<td>24/25</td>
<td>6/26</td>
<td>.001*</td>
<td>...</td>
</tr>
<tr>
<td>Brain</td>
<td>15/20</td>
<td>2/23</td>
<td>.001*</td>
<td>...</td>
</tr>
<tr>
<td>Adrenal glands</td>
<td>24/25</td>
<td>4/29</td>
<td>.001*</td>
<td>...</td>
</tr>
<tr>
<td>Heart</td>
<td>25/25</td>
<td>1/29</td>
<td>.001*</td>
<td>...</td>
</tr>
<tr>
<td>Purpura</td>
<td>19/25</td>
<td>16/31</td>
<td>0.1</td>
<td>...</td>
</tr>
<tr>
<td>Fever</td>
<td>24/25</td>
<td>7/31</td>
<td>.001*</td>
<td>...</td>
</tr>
<tr>
<td>Hemolytic anemia/thrombocytopenia</td>
<td>25/25</td>
<td>31/31</td>
<td>&gt;.99</td>
<td>...</td>
</tr>
<tr>
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<td>5/25</td>
<td>28/31</td>
<td>.001*</td>
<td>...</td>
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<tr>
<td>Neurologic dysfunction</td>
<td>22/25</td>
<td>17/31</td>
<td>.01*</td>
<td>...</td>
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</table>

* Statistically significant using χ² analysis; degrees of freedom = 1.
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