Welcome to Derm Clinic in the Bronx

Charles Gropper, MD
Chair of Dermatology
Saint Barnabas Hospital
Bronx, NY
Disclosures

• No Conflicts of Interest
Day 2 of Admission
Day 2 of Admission
Day 4 of Admission
History of Present Illness

• CC: 41 year old Hispanic male presented with **left-sided abdominal, chest, and arm pain.** Onset approximately 1 month ago after being **assaulted with a lead pipe** to his left flank. He received medical attention at the time, but has been increasingly sedentary and with poor appetite. Patient **reports falling 2 days ago after which pain worsened.** He noted **purplish discoloration and swelling to his left chest.** He also reports **lying down on his left side for 16 hours.** Also admits he has been using **cocaine and heroin** in the morning.

• ROS: **+ left chest pain, +left flank pain, +left arm pain**
• -headache –cough –sore throat – shortness of breath --
  diarrhea –palpitations –numbness –weakness –dizziness --
  urinary complaints –eye/ear
HPI

- **Past Medical History**: multiple hospital admissions for substance abuse detoxification
- **Past Surgical History**: none
- **Allergies**: NKDA
- **Medications**: none
- **Social History**:
  - *polysubstance abuse* (3-5 bags daily of inhaled heroine, crack cocaine, marijuana, 4 pints EtOH daily, cigarette smoker) with multiple prior detox.
  - Lives at home alone.
  - Has a girlfriend.
HPI

• Vitals: T 98.3, HR 88, RR 20, BP 129/89, Sat 96% on RA

• Physical per ED:
  – General: alert and oriented x3, acutely distressed, appears ill, restless, writhing around in pain
  – Skin: “mottled skin on chest, abdomen, and extremities”
**HPI**

Calcium 8.5  
Albumin 2.5  
Total Protein 5.3  
ALT 31  
AST 77  
Total Bilirubin 1.1  
Alkaline Phosphatase 48

CPK 2798  
Lactic Acid 7.6  
Anti-HCV nonreactive  
HBsAB reactive  
HBsAG nonreactive  
HIV AG/AB nonreactive
HPI

• **Urinalysis**
  – WBC 21
  – RBC 7
  – Bacteria – few
  – Moderate budding yeast

• **Coagulation Studies**
  – PT 13.8 (H)
  – PTT 32.1 (H)
  – INR 1.3
  – Fibrinogen 552 (H)

• Blood culture - pending
• Urine culture – pending
• Fungal future – pending
HPI

• **Urine Drug Screen**
  – Barbiturate – negative
  – THC – positive
  – Cocaine – positive
  – Benzodiazepine – negative
  – Opiates – positive

• **Blood alcohol** – none detected
Imaging Studies:

- **CXR**: wnl
- **CT Abdomen/Pelvis without contrast**: wnl
- **CTA Chest/Abdomen/Pelvis with contrast**:
  - “heart is at upper limits of normal.... No acute pulmonary process seen... “
  - **liver** shows heterogeneous enhancement with multiple wedge-shaped perfusion defects suspicious of multifocal infarction...
  - **kidney** shows multiple cortical filling defects...
  - **main superior mesenteric artery** shows enhancement and there is decreased enhancement in the distal vessels...”
Events...

- **Severe sepsis:**
  - Empiric antibiotics (vancomycin and zosyn)
  - IVF with NS $\rightarrow$ hypothermic at 92.7 $\rightarrow$ warming protocol
  - Hypotensive $\rightarrow$ required vasopressors
- **Embolic infarct to liver, kidneys**
  - Suspect endocarditis $\rightarrow$ plan for ECHO
- **Acute abdomen and ischemic bowel disease**
  - General surgery consulted
  - NPO
  - No surgical intervention
- **Acute Kidney Injury**
  - Nephrology consulted
  - Suspect dehydration and 2/2 rhabdomyolysis
Events...

- **Tachypnea** → sustained respiratory distressed → **intubation**
- Over the course of a few hours... skin eruption becomes much more prominent with reports of “bullae”... **Dermatology was consulted**
Differential Diagnosis

• Necrotizing Fasciitis
• Levamisole-Induced Vasculitis
• Purpura Fulminans
• Staphylococcal Scalded Skin Syndrome
• Streptococcal Toxic Shock Syndrome
• Toxic Epidermolytic Necrosis
• Pemphigus Disorder
• Calciphylaxis
Patient RL

• A. Skin, Left Upper Thigh, Punch Biopsy
• B. Left Hip
A. Skin, Left Hip, Punch Biopsy
Diagnosis:

A. Skin, Left Upper Thigh, Punch Biopsy
- Epidermis without stratum corneum.
- No thrombi or vasculitis seen in the submitted sections.

B. Left Hip
- Epidermis without stratum corneum and with mixed dermal infiltrate.
- No thrombi or vasculitis seen in the submitted sections.

Comment: The histologic findings are suggestive of adult type staphylococcal scalded skin syndrome (SSSS). Clinical images were reviewed. Correlation with clinical findings is recommended.
Outline

• Leading Differential Diagnosis
  – Staphylococcal Scalded Skin Syndrome
  – Necrotizing Fasciitis
  – Purpura Fulminans
  – Levamisole-induced Vasculitis

• Patient Outcome
Differential Diagnosis

• Staphylococcal Scalded Skin Syndrome
• Purpura Fulminans
• Necrotizing Fasciitis
• Levamisole-Induced Vasculitis
Staphylococcal Scalded Skin Syndrome

Background

• Superficial blistering disorder caused by *Staph aureus*.
  – Mostly in children and neonates; rarer in adults

• Exfoliative toxins (ETA and ETB) by *Staph aureus*
  – Protease that target desmoglein-1
  – Separation of epidermis beneath granular cell layer
  – Spreads hematogenously
Staphylococcal Scalded Skin Syndrome

Presentation

• Diffuse erythematous rash
  – Begins centrally
  – Sandpaper-like → wrinkled appearance
  – Eventual exfoliation (patchy or sheet-like)
What is the pattern of desquamation in Staphylococcal Scalded Skin Syndrome?

A. Starts on the palms and soles
B. Starts cephalad and goes caudal
C. Accentuated in the skin folds
D. Starts caudal and goes cephalad
Staphylococcal Scalded Skin Syndrome

Workup

• **WBC** – sometimes elevated, often normal
• **ESR**
• Bullae tissue culture - negative

• **Blood culture**
  – Children: usually negative
  – Adults: usually positive

• PCR for toxin
Staphylococcal Scalded Skin Syndrome
Histology

- Subcorneal splitting
- Sparse neutrophils
- Immunofluorescence is negative
# Staphylococcal Scalded Skin Syndrome

<table>
<thead>
<tr>
<th>SUPPORTING</th>
<th>CONTRADICTING</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;E with intraepidermal acantholysis</td>
<td>Erythema did not progress to exfoliative dermatosis</td>
</tr>
<tr>
<td>↑ESR</td>
<td>Purpuric dermatosis</td>
</tr>
<tr>
<td></td>
<td>Blood culture negative for staph aureus (+ strep)</td>
</tr>
</tbody>
</table>
Staphylococcal Scalded Skin Syndrome

Treatment

• **Supportive Care**
  – Fluid rehydration
  – Topical wound care

• **Antibiotics to cover *Staph Aureus***
Differential Diagnosis

- Staphylococcal Scalded Skin Syndrome
- **Necrotizing Fasciitis**
- Purpura Fulminans
- Levamisole-Induced Vasculitis
Necrotizing Fasciitis

Background

Rapidly progressive inflammatory infection of the fascia with secondary necrosis of the subcutaneous tissues

Most frequently develops after trauma

Frequency is increased in immunocompromised patients

Mortality rate: 20-40%

Higher rate with:

- Female sex
- Older age
- Greater extent of infection
- Delay to first debridement
- Elevated Creatinine
- Elevated Lactic Acid
- 2/2 Group A streptococci
- Organ Dysfunction
Necrotizing Fasciitis
Pathophysiology

• Causative bacteria - aerobic, anaerobic, or mixed flora.
  – polymicrobial > monomicrobial

• Three most common:
  – Type I – polymicrobial (most common in adults)
  – Type II – group A streptococcal (most common in children)
  – Type III – gas gangrene or clostridial myonecrosis
Necrotizing Fasciitis
Presentation

Intense pain and tenderness → Erythematous patch that spreads over course of hours to days → Skin develops dusky or purplish discoloration → Patches expand and produce large gangrenous skin
Necrotizing Fasciitis

Workup

• CBC
  – WBC >14,000

• CMP
  – Na <135
  – BUN >15

• Imaging
  • X-ray
  • Ultrasound
  • CT with contrast
  • MRI

• Finger Test
  • Fascial tissue biopsy

• Blood - Group A Beta-hemolytic Streptococcus

• Tissue cultures - Group A Beta-hemolytic Streptococcus
## Necrotizing Fasciitis

<table>
<thead>
<tr>
<th>SUPPORTING</th>
<th>CONTRADICTING</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of trauma (assault + fall)</td>
<td>Finger test negative</td>
</tr>
<tr>
<td>Intense pain</td>
<td>CXR/CT/US – no gaseous process</td>
</tr>
<tr>
<td>Presentation of erythema progressing to purpura and necrosis</td>
<td>MRI – not done</td>
</tr>
<tr>
<td>Tissue culture + group A streptococcus</td>
<td>Fascia tissue biopsy – not done</td>
</tr>
</tbody>
</table>
Necrotizing Fasciitis

Treatment

• **Surgical Emergency**
  – SICU, burn center, or trauma center
  – Surgical debridement

• **Empiric Broad Spectrum Antibiotic**

• **Supportive Care**
  – Fluids
  – Nutritional support
  – IVIG

• **Hyperbaric Oxygen**
Differential Diagnosis

- Staphylococcal Scalded Skin Syndrome
- Necrotizing Fasciitis
- **Purpura Fulminans**
- Levamisole-Induced Vasculitis
Purpura Fulminans

Background

• Rare syndrome of rapidly progressive intravascular thrombosis or hemorrhagic infarction of skin
• Majority arise in infancy and early childhood
  – rare in adults
• Three forms:
  1. Neonatal - Hereditary deficiency of protein C or S
  2. Idiopathic (post-infectious) - Febrile illness (bacterial or viral)
    → acquired protein S deficiency
  3. Acute Infectious - Associated with infection and DIC
    – Most common causes: *Neisseria, Group B Streptococcus, VZV*
## Purpura Fulminans
### Presentation

<table>
<thead>
<tr>
<th>Neonatal</th>
<th>Acute Infectious</th>
<th>Idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 72 hours after birth</td>
<td>90% of cases Occurs at any age</td>
<td>7-10 days after infection</td>
</tr>
<tr>
<td>Purpuric lesions over many sites</td>
<td>Large purpuric skin lesions</td>
<td>Sudden and progressive erythema → purpura</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Fever</td>
<td>Abnormal coagulation factors</td>
</tr>
<tr>
<td>Possible signs of UTI</td>
<td>Hypotension</td>
<td>Major organ dysfunction</td>
</tr>
<tr>
<td></td>
<td>DIC</td>
<td></td>
</tr>
</tbody>
</table>
Fig 1. Patient 12 with purpura fulminans (Table I). A. Note purpuric patches and hemorrhagic bullae involving acral areas and evolving gangrene of feet. B. Two days later, purpuric patches have progressed to hemorrhagic bullae to both forearms.
Purpura Fulminans
Workup

• Blood cx — group A beta hemolytic streptococcus

• Diagnosis of DIC
  • **Thrombocytopenia (171k → 71k)**
  • ⇧ PTT and ⇧PT
  • ⇩ Protein C
  • ⇩ Protein S
  • Antithrombin
  • ⇩ fibrinogen
  • D-Dimer
Purpura Fulminans
Histology

Hemorrhage
Subcorneal splitting
Thrombi in small vessels and mild perivascular infiltrate

Three days later: subepidermal bullae and epidermal necrosis
Purpura Fulminans

<table>
<thead>
<tr>
<th>SUPPORTING</th>
<th>CONTRADICTING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden and progressive erythema (\rightarrow) purpura</td>
<td>Sepsis with Group A Streptococcus</td>
</tr>
<tr>
<td>Abnormal coagulation factors</td>
<td>H&amp;E without thrombi or vasculitis</td>
</tr>
<tr>
<td>Major organ dysfunction</td>
<td></td>
</tr>
<tr>
<td>(thromboembolic events to liver and kidneys)</td>
<td></td>
</tr>
</tbody>
</table>
Purpura Fulminans

Treatment

**Neonatal Purpura Fulminans**
- Platelet concentrate
- Fresh frozen plasma $\rightarrow$ low-molecular weight heparin (LMWH) $\rightarrow$ warfarin
- Debridement of necrotic tissue

**Idiopathic Purpura Fulminans**
- Antibiotic therapy
- Excision of gangrenous areas
- APC

**Acute Infectious Purpura Fulminans**
- Antibiotic therapy
- Early administration of APC
- IVIG
- Consider tPA
43 year old male with 10 year cocaine use with dissemination violaceous plaques with some flaccid bullae

Abnormal coagulation factors

Tissue culture: streptococcus pneumoniae

Diagnosed as purpura fulminans and vasculopathy associated with levamisole-associated cocaine
Differential Diagnosis

• Staphylococcal Scalded Skin Syndrome
• Purpura Fulminans
• Necrotizing Fasciitis
• Levamisole-Induced Vasculitis
Levamisole

- Synthetic antihelminthic agent used in veterinary medicine
- Limited use in humans
  - Previous treatment of autoimmune diseases, pediatric kidney diseases, infections, and cancers
  - Currently FDA approved as adjuvant chemotherapy for colon cancer
• Used as an **additive or filler in 2/3 of cocaine** entering USA

• The US Department of Justice estimates that approximately **70% of cocaine in the US** may be contaminated with levamisole
Levamisole Toxicity

**Cutaneous reactions:**
- Lichenoid drug eruptions
- Fixed drug eruptions
- Lichen planus
- Vasculitis
- Vascular occlusive disease
- Ulcerations
- Nodules
- Erythema Nodosum

**Most severe reactions:**
- Agranulocytosis
- Vascular Occlusive Disease
- Thrombotic Vasculopathy (with or without vasculitis)

Leprosum
Levamisole-Induced Vasculopathy Overview

• 1978 - First reported case of levamisole-induced vasculitis in a breast cancer patient who developed a severe cutaneous necrotizing vasculitis.
• Over 30 cases of levamisole-induced vasculopathy with cocaine use
Levamisole-Induced Vasculopathy

Presentation

• Tender purpuric plaques → bullae, necrosis, eschar, ulcers
  – Ears, cheeks, nose, and digits

• Trunk or extremities with retiform or stellate purpura

• asymptomatic ↔ fever with systemic infection
Levamisole-Induced Vasculopathy

Histology

Medium power: showing focally **confluent** epidermal necrosis with underlying abundant **extravasated erythrocytes**

High power: **occlusive thrombi** and **leukocytoclasia**.
Levamisole-Induced Vasculopathy

Workup

Neutropenia (initial WBC 1.8k)

↑ ANA
↑ Anticardiolipin antibody
↑ Lupus anticoagulant
↑ p-ANCA

↑ c-ANCA
↑ HNE ANCA
↑ antiphospholipid antibody
↑ Anti-ds DNA
When should Levamisole levels be ordered?

A. < 24 hours
B. < 48 hours
C. < 72 hours
D. < 1 week
Levamisole Level

- Levamisole urine or blood
- Must be perform within 48 hours of cocaine use
- Levamisole half life is 5-6 hours
# Levamisole-Induced Vasculopathy

## SUPPORTING
- History of chronic polysubstance abuse (including cocaine and crack)
- Tox screen + cocaine + opiates
- Initial neutropenia
- Purpura → necrosis
- Generation of autoantibodies (↑ lupus anticoagulant)

## CONTRADICTING
- Urine levamisole (neg)
- ANA, Anticardiolipin - wnl
- ANCA studies – not done
- H&E without vasculitis
Levamisole-Induced Vasculopathy
Treatment and Prognosis

• **Discontinue levamisole**
  – Complete clinical resolution after 2-3 weeks
  – Serologies normalize within 2 to 14 months.

• **Antibiotics to treat concomitant infection**
Back to our patient

- **CBC**
  - WBC 1.3 → 22.8 → 33.4 → 19.0
  - Plt 171 → 72

- **CMP**
  - ↓Na (123)
  - ↑Creatinine
  - ↑BUN

- **Tox Screen**
  - +cocaïne
  - +THC
  - +opiate

- **Coagulation Studies**
  - ↑PT
  - ↑PTT
  - ↑Fibrinogen (552)

  - ↓Protein C
  - ↓Protein S
  - Anti-cardiolipin Ab – negative
  - Beta-2 glycoprotein Ab – negative
  - ANCA – not done

  - Levamisole – none detected
Back to our patient...

- XR wnl
- CT w/o contrast wnl
- CTA with multi-infarcts to liver and kidney
- ECHO and TEE wnl

- Blood cx – Group A beta hemolytic Streptococcus
- Tissue cx – strep pyogenes
- Urine cx/Fungal Cx - negative

- Frozen section
- H&E – acantholytic process
Back to our patient...

• IVIG x 3 days
• Broad spectrum antibiotic/antifungal
  – Vanc and zosyn → meropenem, vancomycin, micafungin, clindamycin, gentamicin (x 1 day)
• Consultants
  – General Surgery
  – Infectious Disease
  – Dermatology
  – Heme/Onc
  – Nephrology
  – Wound Care
Day 6 of Admission
Back to our patient....

- Patient continued to have progression of skin involvement with full-thickness skin necrosis
  - Transferred to burn unit

- Per next of kin:
  - 3 surgical operations
  - Hyperbaric oxygen
  - Told it was secondary to “gator” (levamisole)
  - Extubated and eating PO
History of Present Illness

• **CC:** 79 year old female presented with a persistent inguinal rash. Son was present and provided history. Onset was in the spring. Patient denied any pruritus, burning, or pain. She has previously treated the site with clotrimazole cream with no improvement.

• **ROS:** --fevers --weight loss --headache --cough --sore throat --shortness of breath --diarrhea --palpitations --numbness --weakness --dizziness --urinary complaints --eye/ear
HPI

- **Past Medical History:** dementia, HTN, osteopenia, stress incontinence, hyperparathyroidism, BCC on nose
- **Past Surgical History:** Mohs surgery
- **Allergies:** NKDA
- **Medications:** amlodipine, calcium, vitamin D, clotrimazole
- **Social History:** Lives at home with son and has caretaker. No cigarette smoking, alcohol consumption, or illicit drugs.
Differential Diagnosis

• Intertrigo
• Contact Dermatitis
• Inverse Psoriasis
• Lichen Sclerosis et Atrophicans
• Extra-mammary Paget’s Disease
• Hailey-Hailey
Patient MQ

- A. Skin, Left Inguinal Fold, Punch Biopsy
S17-04790
H&E, 4x

S17-04790
CK7, 4x

S17-04790
CEA, 4x

S17-04790
EMA, 4x
St. Barnabas Pathology Report

• Diagnosis:
  – Atypical intraepithelial proliferation, most compatible with extra-mammary Paget’s disease.
  – Diagnosis supported by positive straining with PAS special stains, CK7, EMA, and CEA. Negative for CK20
Extra-mammary Paget’s Disease

- Background
- Clinical Presentation
- Histopathology
- Pathophysiology
- Treatment
- Back to our patient
Extra-mammary Paget’s Disease (EMPD)

Background

- In 1874, Sir James Paget reported mammary Paget's disease (PD)
- In 1889, Crocker recognized and reported EMPD as a distinct clinical entity
- Rare form of intraepithelial adenocarcinoma
- Morphologically and histologically identical to PD of nipple with the primary difference being the anatomic location.
Extra-mammary Paget’s Disease

Clinical Presentation

• Typically occurs in 50-60 year olds
• Most often in Caucasians; rare in African Americans
• 4.5 Females : 1 Male
• Most cases involve apocrine-rich areas:
  – Most common site is the vulva
  – Others: perineal, scrotal, perianal, and penile skin
• Average time from symptom onset to accurate diagnosis is ~4 years
“Strawberry and Cream”
Extra-mammary Paget’s Disease (EMPD)

**Histopathology**

- + Mucicarmine, alcian blue, colloidal iron, PAS
- + Epithelial membrane antigen (EMA)
- + Carcinoembrionic antigen (CEA)
- + CAM 5.2
- + CK7
  - Primary EMPD = CK7+/CK20-
  - Secondary EMPD = CK+7/CK20+
<table>
<thead>
<tr>
<th>EMPD</th>
<th>SCC</th>
<th>Melanoma</th>
<th>MF</th>
<th>Seb CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMA</td>
<td>EMA</td>
<td>EMA</td>
<td>EMA</td>
<td>EMA</td>
</tr>
<tr>
<td>CEA</td>
<td>CEA</td>
<td>CEA</td>
<td>CEA</td>
<td>CEA</td>
</tr>
<tr>
<td>CK7</td>
<td>CK7</td>
<td>CK7</td>
<td>CK7</td>
<td>CK7</td>
</tr>
<tr>
<td>CAM 5.2</td>
<td>CAM 5.2</td>
<td>CAM 5.2</td>
<td>CAM 5.2</td>
<td>CAM 5.2</td>
</tr>
<tr>
<td>S100</td>
<td>S100</td>
<td>S100</td>
<td>S100</td>
<td>S100</td>
</tr>
<tr>
<td>HMB45</td>
<td>HMB45</td>
<td>HMB45</td>
<td>HMB45</td>
<td>HMB45</td>
</tr>
<tr>
<td>CD3</td>
<td>CD3</td>
<td>CD3</td>
<td>CD3</td>
<td>CD3</td>
</tr>
</tbody>
</table>
Extra-mammary Paget’s Disease (EMPD)

Pathophysiology

• Most cases of EMPD arises as a primary cutaneous adenocarcinoma
  – Derived from pluripotential cells in the epidermis
  – Underlying in-situ adnexal carcinoma which sampling had not discovered

• **25%** of EMPD are associated with an underlying in situ or invasive neoplasm (most likely adnexal apocrine carcinoma)
  – Others: carcinomas of the Bartholin’s glands, urethra, bladder, vagina, cervix, endometrium, and prostate
  – **10-15%** have an internal carcinoma involving rectum, prostate, bladder, cervix, or urethra
What is the significance of EMPD anatomic location?

A. Associated carcinoma
B. Survival rate
C. Depth of invasion
D. Staging
Extra-mammary Paget’s Disease (EMPD)

Prognosis

• Anatomic location of EMPD plays a role in predicting risk of associated carcinoma
  – **Genital disease** is associated with carcinoma in 4-7% of cases
  – **Perianal disease** is associated with underlying colorectal carcinoma in 25-35% of cases

• **Dermal invasion** occurs in about 20% of cases
  – Associated with decreased overall survival rate
  – One of the most **important prognostic factors**
Subset of EMPD cases show overexpression of **HER2 (protein)** and amplification of **ERBB2 (gene)**

**Indicator of biological aggressiveness of EMPD**
- depth of invasion
- lymph-node metastases
Chemokine Receptors CXCR4 and CXCR7 are Associated with Tumor Aggressiveness and Prognosis in Extramammary Paget Disease

Kun Chang¹, Gao-Xiang Li¹*, Yun-Yi Kong²*, Xu-Xia Shen², Yuan-Yuan Qu¹, Zhong-Wei Jia¹, Yue Wang⁴, Bo Dai¹✉, Ding-Wei Ye¹✉

• Expression of CXCR4 and CXCR7 were evaluated by 92 EMPD specimen

• High expression of CXCR7 correlated with:
  • Depth of invasion

• High expression of CXCR4 and CXCR7 correlated with:
  • Regional lymph node metastasis
  • Presence of lymphovascular invasion
Extra-mammary Paget’s Disease

Treatment

- **Multi-disciplinary approach:**
  - Dermatology, gynecology, urology, gastroenterology, surgery

- **Surgery**
  - Wide local excision
  - Mohs micrographic surgery

- **Topical Imiquimod**

- **Radiation therapy**

- **Chemotherapy**
A matter of margins: Surgical and pathologic risk factors for recurrence in extramammary Paget's disease.

Long B¹, Schmitt AR², Weaver AL³, McGree M³, Bakkum-Gamez JN⁴, Brewer J², Cliby WA⁴.

- Medical records of 154 patients (75 F, 65 M)
- Evaluated 5-year follow-up after primary surgery
- Evaluated for risk factors associating recurrence and margins

Compared to MMS, WLE had
- Significantly higher risk of positive margins
- Greater risk of recurrence among patients with negative margins

Conclusion
- MMS should be considered to improve outcomes for EMPD patients
• EMPD frequently extends beyond clinically visible borders

• No standardized resection margin
  • Typically 1-3 cm but recurrence is common (15-43%)
  • Some advise 5 cm margins

• Mohs micrographic surgery is the best option
  • Time-consuming
  • Labor intensive
  • Limited access

• AIM of study: Correlate conventional fluorescence diagnosis (FD) determinations with histopathologic findings
Clinical Benefits of Preoperative Conventional Fluorescence Diagnosis in Surgical Treatment of Extramammary Paget Disease

Miaojian Wan, MD, PhD,* Han Ma, MD,* Yue Zhao, MD,* Lin Xie, MD,† and Zhirui Chen, MS*

• Border of FD = 72.6% samples were +Paget cells

• MSB (2 mm past the edge) = 10.3% were +Paget

• Average number of stages = 1.78 (max = 3)
• Maximum distance beyond FD was 12 mm

• Fairly strong correlation borders of FD and histopathology
  • FD combined with MSB was more accurate than FD alone
  • May reduce recurrence rates
  • May reduce number of stages and operation time
Paget’s Disease of the Vulva Treated with Imiquimod: Case Report and Systematic Review of the Literature

• Imiquimod
  • Targets TLR 7 as a receptor agonist
  • direct antitumor activity

• Systemic review of Imiquimod as adjuvant to surgical excision
  • 71% of cases achieved complete remission
  • 16% achieved partial remission
  • generally well tolerated with mild-to-moderate local

• Propose that topical imiquimod may be used to avoid repeated and mutilating surgeries.
Radiotherapy can be used as an alternative therapeutic approach for patients with extensive inoperable disease or medical contraindications. Adjuvant radiotherapy may be considered in the presence of risk factors associated with local recurrence.
Back to our patient...

• Considerations:
  – Prognostic factors: inguinal fold, CK7+/20-
  – Son (POA) prefers non-surgical options

• Referral to:
  – Gyn/Oncology
  – Gastroenterology
  – Mohs surgeon
• CC: Rash on extremities

• HPI: Patient is a 17 year old female presenting with over 5 years of asymptomatic rash on arms and legs. Rash worsened by cold.

• ROS: Denies fever, chills, weight loss, hematuria, hematochezia

• PMH: N/A

• Meds: None

• Allergy: NKDA
Differential Diagnosis

- Livedo Reticularis
- Erythema Ab Igne
- Retiform Purpura
- Reticulated Erythematous Mucinosis
- Viral Exanthem (parvovirus B19)
- Dermatomyositis
- Mycosis Fungoides
• Diagnosis:
  – THROMBOTIC VASCULOPATHY, SEE NOTE

  Note: The vessels are telangiectatic and contain prominent fibrin deposition. No vasculitis is identified. The differential diagnosis includes coagulation disorders, platelet disorders and cryoglobulinemia. Clinical-pathologic correlation is necessary. This case was studied and reviewed at consensus conference.

  PAS stain is negative for fungi and significant basement membrane thickening, and Alcian blue stain demonstrates no significant increase in dermal mucin.
Livedo Reticularis
Outline

• Clinical Characteristics

• Disease Associations

• Pathogenesis

• Treatments
Livedo Reticularis (LR)

- Violaceous, red or blue, reticular or mottled pattern of the skin consisting of regular unbroken circles. Appearing “netlike”
- Livedo Racemosa- irregular broken circles. Appearing “branchlike”

[Pattern of Livedo Reticularis versus Livedo Racemosa]
### Recognize

<table>
<thead>
<tr>
<th>Livedo reticularis</th>
<th>Livedo racemosa</th>
<th>Retiform purpura</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Synonyms</strong></td>
<td>Cutis marmorata</td>
<td>Broken pattern livedo</td>
</tr>
<tr>
<td><strong>Morphology</strong></td>
<td>Net-like rings</td>
<td>Branched</td>
</tr>
<tr>
<td><strong>Colour</strong></td>
<td>Livid</td>
<td>Livid</td>
</tr>
<tr>
<td><strong>Blanchability</strong></td>
<td>Blanchable</td>
<td>Partially blanchable or non-blanchable</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Generalized</td>
<td>Localized, segmental or widespread</td>
</tr>
<tr>
<td><strong>Symmetry</strong></td>
<td>Symmetrical</td>
<td>Non-symmetrical</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>Physiological or Pathological</td>
<td>Always pathological</td>
</tr>
<tr>
<td><strong>Examples of underlying conditions</strong></td>
<td>• Primary: Physiological</td>
<td>Medium-sized vasculitis, antiphospholipid syndrome</td>
</tr>
<tr>
<td></td>
<td>• Secondary: Hyperviscosity syndromes, connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td><strong>Subtypes</strong></td>
<td>• Vasospastic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Venocongestive</td>
<td></td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>Rare</td>
<td>• Retiform pigmentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Retiform ulceration</td>
</tr>
</tbody>
</table>
Retiform Purpura

Livedo Racemosa
Pathogenesis

• Results from alterations in blood flow though the cutaneous microvasculature

• Decreased blood flow to perpendicularly oriented arterioles and stasis of blood in venous plexus leads to the clinical findings of LR
Each arteriole supplies a hexagonal distribution of skin

Atrophy Blanche
Causes

Congenital
- Cutis Marmorata Congenita

Acquired w/o Systemic Disease
- Physiologic- temperature dependent
- Primary/idiopathic – some fluctuation w temp
Causes Continued

Secondary to Systemic Disease
- Vasospasm- often have connective tissue d/o (CTD)
- Vessel Wall pathology- medium sized arterioles affected
- Intraluminal pathology- hypercoaguable states

Other
Drugs (amantadine, interferon, norepinephrine), infection (Hep C), malignancy, and neurologic (reflex sympathetic dystrophy)
## Causes

### Causes of Livedo Reticularis

<table>
<thead>
<tr>
<th>Congenital Livedo Reticularis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutis marmorata telangiectatica congenita</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acquired Livedo Reticularis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasospasm</td>
</tr>
<tr>
<td>Cutis marmorata/physiologic livedo reticularis</td>
</tr>
<tr>
<td>Primary (idiopathic) livedo reticularis</td>
</tr>
<tr>
<td>Autoimmune connective tissue diseases (e.g. SLE)</td>
</tr>
<tr>
<td>Raynaud's phenomenon/disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vessel wall pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasculitis</td>
</tr>
<tr>
<td>Cutaneous polyarteritis nodosa</td>
</tr>
<tr>
<td>Systemic polyarteritis nodosa</td>
</tr>
<tr>
<td>Cryoglobulinemic vasculitis</td>
</tr>
<tr>
<td>Autoimmune connective tissue disease-associated vasculitis (e.g. rheumatoid arthritis, SLE, Sjögren's syndrome)</td>
</tr>
<tr>
<td>Calciphylaxis</td>
</tr>
<tr>
<td>Sneddon syndrome</td>
</tr>
<tr>
<td>Livedoid vasculopathy (also intraluminal obstruction)</td>
</tr>
</tbody>
</table>

### Intraluminal pathology

- Increased normal blood components
  - Thrombocytethmia
  - Polycythemia vera
- Abnormal proteins
  - Cryoglobulinemia
  - Cryofibrinogenemia
  - Cold agglutinins
  - Paraproteinemis
- Hypercoagulability (see Table 105.9)
  - Antiphospholipid syndrome
  - Protein S and C deficiencies
  - Antithrombin III deficiency
  - Factor V Leiden mutation
  - Homocystinuria, hyperhomocysteinemia
  - Disseminated intravascular coagulation
- Thrombotic thrombocytopenic purpura
- Embolic
  - Cholesterol emboli
  - Septic emboli
  - Atrial myxoma
  - Nitrogen (decompression sickness)
  - Carbon dioxide arteriography
- Hyperoxaluria

### Other

- Medications (e.g. amantadine, norepinephrine, interferon)
- Infections (e.g. hepatitis C [vasculitis], Mycoplasma spp. [cold agglutinins], syphilis)
- Neoplasms (e.g. pheochromocytoma)
- Neurologic disorders (e.g. reflex sympathetic dystrophy, paralysis)
- Moyamoya disease
Livedo Racemosa

Classically associated with:

- Antiphospholipid syndrome- abortions, raynaud’s, vasculitic lesions, livedo
- Sneddon’s Syndrome- neurologic, labile HTN, livedo

- Rash may precede the systemic findings by years

Less common:

- PAN
- Livedoid vasculopathy
- SLE
- Polycythemia Vera
- Essential thrombocythemia
Evaluation

Serious systemic causes must be ruled out
Comprehensive history and physical needed

Ask About
- Location of lesions
- Exacerbating or remitting factors
- Duration of attacks
- Symptoms
- Symptoms of CTD
- Hx of hypercoaguability
- Infections
- Medications
Evaluation

**Fig 2.** Algorithm for evaluation of patient presenting with livedo reticularis (LR). aPLs, Antiphospholipid antibodies; N, no; Y, yes.
Workup

• Biopsy- ideally a wedge or large punch in a central area of blanching
• Lab work according to history and physical
• No consensus on the best labs to order
• Lupus anticoagulant is the exception

Labs to consider include:
- CBC, CMP, PT/PTT/INR, ANA, ANCA, antiphospholipid, Factor V leiden, cryoglobulins, protein C & S, hepatitis panel, antithrombin III, serum electrophoresis
Treatment

- Treat the underlying systemic condition
- Smoking Cessation
- May try cold avoidance, leg elevation and compression stockings
- Medications have unclear efficacy in treating livedo
- Reserved for symptomatic patient with underlying systemic disease

-Anti-platelet or anti-coagulants like aspirin, clopidogrel, coumadin
-Vasodilators Ca+ channel blockers or ACE inhibitors

http://www.xdiagnosis.net/causes
• Case Report of 50y/o F with ulcerations 2/2 Sneddon’s Syndrome
• Treatment with intravenous alprostadil (prostaglandinE1 [PGE-1])
• Doses of 60 μg every 24 hours for 5 days and then a dose of 60 μg every 24 hours monthly as maintenance.
• Rapid amelioration of cutaneous pain
• Within 3 months total resolution of skin lesions
• 98 individuals with history of asymptomatic +antiphospholipid antibody were randomized to receive aspirin or placebo
• 48 received aspirin and 50 received placebo
• After ~1 year no significant difference in acute thrombosis incidence
• Suggests no benefit for prophylactic aspirin use in individuals with asymptomatic antiphospholipid antibody positivity
Livedoid vasculopathy and high levels of lipoprotein (a): response to danazol

Paulo Ricardo Criado*, Danielle Priscilia de Souza Espineli†, Neusa Yuriko Sakai Valente‡, Afsaneh Alavi‡ & Robert S. Kirsner§

• A retrospective analysis of medical records of 4 patients with a clinical and histopathologic diagnosis of LV, with high levels of lipoprotein a [LP(a)] received danazol

• LP(a) has a triple effect: pro-atherogenic, prothrombotic and antifibrinolytic

• Study showing improvement of skin lesions as well as decrease in LP(a) levels by a mean of 70% with low dose therapy, 200mg/day
Strokes in Sneddon Syndrome without Antiphospholipid Antibodies

Laure Bottin, MD,1 Camille Francès, MD,2,3 Dominique de Zuttere, MD,4 Pierre-Yves Boëlle, MD,5 Ioan-Paul Muresan, MD,1 and Sonia Alamowitch, MD1,3

- 53 patients with diagnosed Sneddon’s Syndrome, negative for antiphospholipid antibody
- All had prior history of CVA or TIA
- Treated with either anti-platelet or anticoagulant for ~6yrs.
- **No significant difference in stroke recurrence between the two**
- Recommend using anti-platelet therapy over anticoagulation
• Case reports on 2 patients with Livedoid Vasculopathy treated with rivaroxaban having failed prior treatment with warfarin and non-fractionated heparin
• Both patients received 20mg PO daily and within weeks had resolution of pain and LE ulcerations
• Authors suggest rivaroxaban may be an alternative to standard anticoagulant treatments as it does not require laboratory monitoring and is easy to administer
Hydrophilic Polymer Embolization: An Emerging Cause of Livedo Reticularis

Kelli M. Danowski DO, Megan Morrison DO, Jessica Ghaferi MD and Jenny Cotton MD PhD

Department of Dermatopathology, St. Joseph Mercy Health System, Ann Arbor, MI

- Case Report of patient with LR and TIA following transcatheter aortic valve implantation
- Embolization of hydrophilic polymer coating on intravascular catheter
- Polymer used commonly, helps decrease friction between sheath and vessel wall
- Biopsy showed amorphous, non-refractile, non-polarizable basophilic material within vessels
- **Always consider recent surgical procedures in acute onset LR**
• Relatively new entity called DADA2 first published on in 2014
• ~50 individuals now reported who developed early-onset stroke, intermittent fevers, and systemic vasculopathy
• Identified recessively inherited mutations in the CECR1 gene which encodes adenosine deaminase 2 (ADA2) which is implicated in endothelial cell and leukocyte development
• Most common manifestation is livedo racemosa
• May also have CVA, immunosuppression, portal HTN, PAN
• Treatment with TNF-a drugs may reduce CVA
• Significant overlap with Sneddon’s syndrome
Our Patient

- Asymptomatic livedoid rash for 5 years
- Completely negative lab workup

- Biopsy showing thrombotic vasculopathy
- Normal blood pressure and ROS negative except for occasional fatigue and cold hands
- Family history negative for CTD
- Has been evaluated by both rheum and heme-onc
- Meds- Recently started an OCP
- Previously failed aspirin and plaquenil
- Considering starting her on immunosuppressant or Ca+ channel blocker
Question

• What is the ideal biopsy technique of suspected livedo reticularis?

  • A. Punch of peripheral red margins
  • B. Normal appearing skin outside net pattern
  • C. Punch biopsy of normal appearing skin in center of net pattern
  • D. Excisional biopsy of normal appearing skin in center of net pattern
- Indurated, sclerotic plaque in R axilla
- Generalized edema of R upper extremity
HPI

• Patient is a 87yo F with pmh of CHF, HTN, DM, afib, asthma, and dementia presenting to dermatology consult service with new onset (~2 months) of painful lesion on her R clavicle. Admitted to hospital for acute respiratory failure with sepsis and pneumonia.

• ROS- Denies fever, chills, nausea, vomiting. +weight loss, decreased appetite, fatigue
• Medications- meropenem, eloquis, lantus
• Allergy- None
• Soc hx- Denies ETOH or smoking
• Fam hx- No hx of malignancy
Differential?

- Breast cancer
- Angiosarcoma
- SCC
- BCC
- Lymphoma
- Melanoma
- Other visceral metastasis
- Deep fungal
- Atypical mycobacterial
HER2 (3+)
FINAL DIAGNOSIS

• Metastatic Invasive Ductal Carcinoma, Gr II (tubule formation 3/3, nuclear pleomorphism 3/3, mitotic activity 1/3, combined score 7/9)
  – CK7 and E-Cadherin positive

• ER, PR, CK20 negative

• HER2 positive (3+ on IHC)

Dr. Richard Hwang Reviewed and approved the report
Saint Barnabas Hospital Pathology Dept.
Cutaneous Metastases

- Occur in 0.6%–10.4% of all patients with cancer
- Represent 2% of all skin tumors
- Can be challenging due to variable clinical presentation
- Leads to delayed diagnosis and poorer outcomes
- Discovery may follow or precede diagnosis of underlying visceral malignancy
Internal Malignancies (frequency)

Men
- Lung
- Large intestine
- Oral cavity
- Kidney
- Breast
- Esophagus, pancreas

Women
- Breast
- Ovary
- Oral cavity
- Lung
- Large intestine
<table>
<thead>
<tr>
<th>Primary malignancy</th>
<th>Percentage of all patients with metastatic disease who developed cutaneous metastases*</th>
<th>Percentage of all patients with cutaneous metastases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>45</td>
<td>18</td>
</tr>
<tr>
<td>Breast</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>SCC (head and neck)¹</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Endocrine glands</td>
<td>12.5</td>
<td>1</td>
</tr>
<tr>
<td>Esophagus</td>
<td>8.5</td>
<td>1</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>8</td>
<td>1.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>7.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Gallbladder/bile ducts</td>
<td>5.5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Liver</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Kidney</td>
<td>4.5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>4.5</td>
<td>4</td>
</tr>
<tr>
<td>Ovary</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>Lung</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Stomach</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Prostate</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Testes</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*The percentages are for men and women combined.

¹Larynx, oropharynx, nasal sinuses.
Cutaneous Metastasis

• Cutaneous metastases herald a poor prognosis
• Average survival time is a few months
• May be the first sign of clinically silent visceral cancer (37% in men and 6% in women)
• Can indicate recurrence of known disease
Clinical Variation
Pathogenesis

- Hematogenous, lymphatic spread, direct contiguous tissue invasion, and iatrogenic implantation

Necessary steps include:
- Vessel formation (angiogenesis)
- Cell attachment
- Invasion (matrix degradation and cell motility)
- Cell proliferation
Regional Distribution of Skin Metastases

<table>
<thead>
<tr>
<th>Anatomic location</th>
<th>Primary malignancy (men)</th>
<th>Primary malignancy (women)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp</td>
<td>Lung, renal</td>
<td>Breast</td>
<td>Can lead to alopecia</td>
</tr>
<tr>
<td>Face &amp; neck</td>
<td>SCC of the head &amp; neck*, lung</td>
<td>Breast</td>
<td>Eyelid metastases from breast carcinoma have been reported; breast &amp; lung metastases can lead to a &quot;clown nose&quot;</td>
</tr>
<tr>
<td>Upper extremities</td>
<td>Lung, kidney, colon</td>
<td>Breast</td>
<td>Uncommon site in men and usually occurs late during disease</td>
</tr>
<tr>
<td>Lower extremities</td>
<td>Melanoma &gt; lung, kidney</td>
<td>Melanoma &gt; lung, kidney</td>
<td>Uncommon site: 36% of BSA but site of only 4% of metastases</td>
</tr>
<tr>
<td>Chest</td>
<td>Lung</td>
<td>Breast</td>
<td>Sister Mary Joseph nodule: most commonly gastric, colon, ovarian or pancreatic cancers</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Colon, lung, stomach</td>
<td>Colon, ovary, breast</td>
<td>20% of BSA, but site of 8% of metastases</td>
</tr>
<tr>
<td>Back</td>
<td>Lung</td>
<td>Breast</td>
<td>Site of 8% of cutaneous metastases</td>
</tr>
<tr>
<td>Pelvis</td>
<td>Colon</td>
<td>Colon, ovary</td>
<td></td>
</tr>
</tbody>
</table>

*e.g. larynx, oropharynx, nasal sinuses.
Histopathologic Patterns and Features

- Nodular, Infiltrative, Diffuse, or Intravascular
- Characteristic of the underlying causative primary tumor
- Dermal deposit of pleomorphic cells
- Mitotic figures
- If poorly differentiated may require IHC staining
<table>
<thead>
<tr>
<th>Antibody tumor site</th>
<th>CK 7</th>
<th>CK 20</th>
<th>Cam 5.2</th>
<th>CK 5/6</th>
<th>CK 17</th>
<th>CK 19</th>
<th>CEA</th>
<th>Cdx2</th>
<th>Vimentin</th>
<th>TTF-1</th>
<th>CA 19.9</th>
<th>CA 125</th>
<th>ER</th>
<th>BER-EP4</th>
<th>CD 10</th>
<th>S 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bladder</td>
<td>+</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Breast</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>(o)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Colorectal</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>(o)</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Endocervical cancer</td>
<td>+</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>(o)</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>+</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gastric</td>
<td>+</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Germ cell</td>
<td>+</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>-</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lung adenoacarcinoma</td>
<td>(o)</td>
<td>-</td>
<td>(o)</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Merkel cell</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mesoethelioma</td>
<td>(o)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ovarian mucinous</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>(o)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ovarian serous</td>
<td>(o)</td>
<td>-</td>
<td>(o)</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pancreas</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>(o)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prostate</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Renal</td>
<td>-</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>-</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>carcinoma</td>
<td>(o)</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thyroid</td>
<td>+</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>+</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>+</td>
<td>(o)</td>
<td>(o)</td>
<td>-</td>
<td>(o)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* +: Always positive, +*: Usually positive, -: Usually negative, (o): Occasional rare positive cells, -: Always negative, TTF: Thyroid transcription factor
Cutaneous Breast Metastasis

- Most common metastasis to skin in women
- 3.5% presenting sign
- 80% non tender, flesh colored, rubbery, firm, nodules, ant chest wall
- Other presentation: telangiectatic carcinoma, carcinoma erysipeloid, carcinoma-encuirasse, and alopecia neoplastica
Lichenified papules: An unusual cutaneous presentation of metastatic breast cancer.

Jeffery T¹, Kumarasinghe P¹, Lam M².

Cutaneous metastasis of inflammatory breast carcinoma mimicking an erythema annulare centrifugum: a sign of locally recurrent cancer

V. Sabater,¹,² F. Ferrando,³ A. Morera² and L. Palomar⁴

Breast Cancer Metastasis Misdiagnosed as an Angiokeratomatous Eruption. An Infrequent Presentation. Case Report
<table>
<thead>
<tr>
<th>Origin</th>
<th>Histopathology</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lobular carcinoma</td>
<td>CK7, estrogen-R, progesteron-R, GCDFP-15, CEA, EMA, mammaglobin</td>
<td>S100, E-cadherin, podoplanin, P63</td>
</tr>
<tr>
<td></td>
<td>Inflammatory carcinoma</td>
<td>CD31, podoplanin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Telangiectatic carcinoma</td>
<td>CD31</td>
<td>Podoplanin</td>
</tr>
<tr>
<td></td>
<td>Mammary Paget disease</td>
<td>MUC1, CK7</td>
<td>MUC2, MUC5AC, CK20</td>
</tr>
</tbody>
</table>
Management

• Excision $\rightarrow$ decrease in total tumor burden, improve quality of life or increased functionality (No evidence based studies on margins)

• Treatment of primary lesion may improve cut mets
• Electrochemotherapy
• PDT
• Radiotherapy
• Intrallesional
• Topical
Entailed 47 studies of 4,313 cutaneous metastases

Response to SDT is high
Well tolerated with low recurrence, 9.2%
Improved QOL
Complete response rate 35.5%
Objective response rate 60.2%
**Analysis of the Factors Influencing the Quality of Life of Patients with Advanced or Recurrent Breast Cancer**

Kojiro Shimozuma, Hiroshi Sonoo, and Kiyoshi Ichihara

---

**Table 3.** Multiple regression analysis of the factors associated with the overall QOL score of patients with advanced or recurrent breast cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin metastasis</td>
<td>-33.880</td>
<td>5.62304</td>
<td>6.025</td>
<td>0.0000***</td>
</tr>
<tr>
<td>Body weight</td>
<td>-0.3177</td>
<td>0.06163</td>
<td>5.155</td>
<td>0.0000***</td>
</tr>
<tr>
<td>Endocrine therapy</td>
<td>11.850</td>
<td>2.89460</td>
<td>4.094</td>
<td>0.0001***</td>
</tr>
<tr>
<td>Primary lesion</td>
<td>12.666</td>
<td>12.6656</td>
<td>3.755</td>
<td>0.0003***</td>
</tr>
<tr>
<td>Types of surgery</td>
<td>9.7957</td>
<td>2.85473</td>
<td>3.431</td>
<td>0.0009***</td>
</tr>
<tr>
<td>Bone metastasis</td>
<td>-12.102</td>
<td>3.58546</td>
<td>3.375</td>
<td>0.0010***</td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td>-7.6546</td>
<td>2.42104</td>
<td>3.162</td>
<td>0.0021**</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>-9.4996</td>
<td>3.11061</td>
<td>3.054</td>
<td>0.0029**</td>
</tr>
<tr>
<td>PS</td>
<td>6.1856</td>
<td>2.20592</td>
<td>2.804</td>
<td>0.0060*</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>3.6017</td>
<td>2.22431</td>
<td>1.619</td>
<td>0.1084</td>
</tr>
</tbody>
</table>
Effective treatment of intractable cutaneous metastases of breast cancer with electrochemotherapy: Ten-year audit of single centre experience

Mike G. Bourke¹ · Slav P. Salwa¹ · Mira Sadadcharam¹ · Maria C. Whelan¹ ·

- Retrospective study of 24 patients
- Failed numerous other modalities
- Best results with smaller lesions <4cm²
Topical Imiquimod Plus Nab-paclitaxel for Breast Cancer Cutaneous Metastases: A Phase 2 Clinical Trial
• Marked improvement in **symptoms** of cutaneous metastases: ulceration, pain, bleeding, infiltration, smell

• Improvements in skin often (70%) paralleled systemic

• Symptoms of disease important QOL
Our Patient

Metastatic invasive mammary duct carcinoma HER2+

Heme-onc

• Percocet for pain, Gabapentin for itch
• Mammogram
• US breast/CT abd, chest, pelvis
• PET scan
• Currently on herceptin as palliative, family refuses taxol
Question

• Which malignancy is most likely to be found as a metastasis on the scalp that can potentially lead to alopecia?

• A. Colon CA
• B. Pancreatic CA
• C. Renal CA
• D. Melanoma
• E. Ovarian CA
Summary

• Cutaneous metastases are an infrequent, but significant finding in metastatic visceral malignancies
• Denote a poor prognosis and significant morbidity
• Various clinical presentations
• Need improved guidelines for cutaneous metastases
• Treatment can lead to improved quality of life and possibly extend survival
History of Present Illness

• A 17yo M with no significant pmh presents with itchy rash all over trunk and extremities for over a year. Rash relapses and remits. Previous treatment with topical steroids, UV and doxycycline.

• ROS: Denies any fever, chills, nausea, vomiting, blood in stools, diarrhea, arthralgia or shortness of breath
• Medications: None
• Allergy- NKDA
• Soc hx- Denies smoking or ETOH
• Fam hx- non-contributory
Differential

- Lymphomatoid papulosis
- Pityriasis lichenoides
- Anaplastic large cell lymphoma (ALCL)
- Arthropod Bites
- Dermatitis herpetiformis
- Folliculitis
- Mycosis fungoides
Diagnosis:

A. LEFT INFERIOR MEDIAL MID BACK; BIOPSY:
   - Lymphomatoid papulosis, favor type A.

B. RIGHT RADIAL DORSAL HAND; BIOPSY
   - Lymphomatoid papulosis, favor type A.
Lymphomatoid papulosis (LyP)

- Rare CD30+ lymphoproliferative disorder
- Chronic
- Waxes and wanes
- Self healing, possible PIH or scarring
- Appears as erythematous papules and nodules sometimes with necrotic, crusted or hemorrhagic centers, usually located on proximal legs>arms, trunk
Lymphomatoid papulosis

- Worldwide incidence is 1.2 to 1.9 cases per 1,000,000
- Peak incidence later in life (5\textsuperscript{th} decade), but may occur at any age
- Increased risk of secondary lymphomas \( \sim 20\% \text{ of patients} \)
- Good prognosis- Nearly 100\% survival at 10 years
Pediatric LyP

• Generally similar to adults, though more rare
• 10% of LyP patients are under the age of 20 (median 7.5yrs)
• Lower risk of secondary lymphoma 5.6-10%
• Pediatric Variants:
  1. Lesions gradually decrease in size and number per outbreak until d/o ceases completely
  2. Chronic localized lesion with slow progression to generalization
  3. Presentation with hundreds of lesions
Pathogenesis and Diagnosis

- Unknown pathogenesis
- T cell proliferation disorder
- Usually a CD4 predominant d/o, but CD8 types occur

- **Diagnosis** by biopsy of suspected lesions and immunohistochemical staining for CD30+ cells
Histologic Subtypes of LyP

- **Type A** - dermal infiltrate of large pleomorphic lymphocytes in a background of mixed inflammatory cells
- **Type B** - epidermotropic population of small lymphocytes mimicking mycosis fungoides
- **Type C** - sheets of large atypical lymphocytes in the dermis mimicking anaplastic large cell lymphoma
- **Type D** - epidermal hyperplasia with marked epidermotropism of atypical, variably sized CD8-positive lymphocytes and a wedge-shaped, predominantly perivascular dermal infiltrate of monomorphous cells
- **Type E** - dermal angiocentric, angiodestructive infiltrates of variably sized pleomorphic lymphocytes with positivity for CD4 or CD8, usually with necrosis of adjacent and overlying tissue

<table>
<thead>
<tr>
<th>LyP type</th>
<th>Morphology</th>
<th>Epidermotropism</th>
<th>Immunophenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Hodgkin-like)</td>
<td>Scattered large atypical cells admixed with numerous small lymphocytes, neutrophils, eosinophils</td>
<td>Variable</td>
<td>CD4+/CD30+</td>
</tr>
<tr>
<td>B (MF-like)</td>
<td>Small to medium atypical cells with scant inflammatory background</td>
<td>Marked</td>
<td>CD4+/CD30-</td>
</tr>
<tr>
<td>C (ALCL-like)</td>
<td>Sheets of large atypical cells with mild to moderate inflammatory background</td>
<td>Mild, by small cells, if present</td>
<td>CD4+/CD30+</td>
</tr>
<tr>
<td>D (Berti-like)</td>
<td>Sheets of medium and large sized atypical cells with scant or none inflammatory background</td>
<td>Moderate to marked, by small and large cells</td>
<td>CD8+/CD30+</td>
</tr>
</tbody>
</table>

ALCL, cutaneous anaplastic large cell lymphoma; LyP, lymphomatoid papulosis; MF, mycosis fungoides.
Treatment

- Some recommend no treatment due to eventual self resolution
- Treat if severe scarring develops or symptomatic
- **Secondary lymphomas cannot be prevented by pharmacologic intervention**
- Lifelong follow up every 6-12 months to monitor for malignancy

- **Medications:**
  - High potency topical steroids, ILK
  - Oral/topical antibiotics
  - Acyclovir/valacyclovir
  - UV therapy
  - Oral/topical bexarotene
  - Topical nitrogen mustard
  - Methotrexate
• 7/25 patients had concomitant atopic dermatitis
  Suggested AD as a **predisposing factor**
• A different 7/25 also had **preceding infection**
  → **Activation of CD30**
• H&E showed large numbers of eosinophils 40% of cases

**Lymphomatoid papulosis in children: a retrospective cohort study of 35 cases.**

Nielsen T¹, Curiel-Lewandrowski C, Kadin ME.

• These findings support LyP as reactional rather than neoplastic
Evaluated Various Treatment options in multiple articles:

- Topical steroids utilized most often
- Antibiotics second most common - generally poor efficacy
- UV light 3rd
  - 1 treatment- 53.7 %
  - 2 treatments- 26 %
  - 3 treatments- 16.7 %
  - 4 treatments- 1.9 %

### Table 3: Different treatment modalities reported in children with lymphomatoid papulosis

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical corticosteroids</td>
<td>75</td>
<td>(59.5)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>48</td>
<td>(38.1)</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>11</td>
<td>(8.7 )</td>
</tr>
<tr>
<td>UV light (all)</td>
<td>33</td>
<td>(26.2)</td>
</tr>
<tr>
<td>UVB</td>
<td>15</td>
<td>(11.9)</td>
</tr>
<tr>
<td>UV light</td>
<td>9</td>
<td>(7.1 )</td>
</tr>
<tr>
<td>PUVA</td>
<td>9</td>
<td>(7.1 )</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>6</td>
<td>(4.8 )</td>
</tr>
<tr>
<td>Excision</td>
<td>5</td>
<td>(4.0 )</td>
</tr>
<tr>
<td>Retinoids/bexarotene</td>
<td>4</td>
<td>(3.2 )</td>
</tr>
<tr>
<td>Intralrealional corticosteroids</td>
<td>4</td>
<td>(3.2 )</td>
</tr>
<tr>
<td>Pimecrolimus/tacrolimus</td>
<td>5</td>
<td>(4.0 )</td>
</tr>
<tr>
<td>Radiation</td>
<td>3</td>
<td>(2.4 )</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>3</td>
<td>(2.4 )</td>
</tr>
<tr>
<td>Caryolysine (mechlorethamine)</td>
<td>3</td>
<td>(2.4 )</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>2</td>
<td>(1.6 )</td>
</tr>
<tr>
<td>Antifungal</td>
<td>2</td>
<td>(1.6 )</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>2</td>
<td>(1.6 )</td>
</tr>
<tr>
<td>Disodium glycyrrhizinate</td>
<td>1</td>
<td>(0.8 )</td>
</tr>
<tr>
<td>Doxepin</td>
<td>1</td>
<td>(0.8 )</td>
</tr>
<tr>
<td>Mistletoe extract</td>
<td>1</td>
<td>(0.8 )</td>
</tr>
<tr>
<td>Antiseptic</td>
<td>1</td>
<td>(0.8 )</td>
</tr>
</tbody>
</table>
300-380nm UVB treatment twice weekly for 6 wks

Full resolution of lesions with recurrence 9 months later, successfully retreated with UVB and no relapse after 12 months
2/5 children given methotrexate at various doses 2.5-15mg/week

Both saw **drastic improvement/total resolution of lesions**

Significant relapse upon discontinuation

No complications
• 20 LyP patients included
• Administered intravenously at 1.8 mg/kg every 21 days for a maximum of eight doses
• **73% overall response rate and 35% complete response rate**
• **SE- Neuropathy** occurred in 67%—grade 1 in 30/31 cases
  If progression to grade 2, decreased dosage
  Fully resolved for 14/31 patients in median of 41.5 wks
Lymphomatoid papulosis: Treatment response and associated lymphomas in a study of 180 patients

Iris Wieser, MD,a,b Chee Won Oh, MD,a Rakhshanda Talpur, MD,a and Madeleine Duvic, MDa

Table V. Treatment and response

<table>
<thead>
<tr>
<th>Medication</th>
<th>n</th>
<th>(%)</th>
<th>CR (n)</th>
<th>PR (n)</th>
<th>NR (n)</th>
<th>CRrelapse (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical steroids</td>
<td>151</td>
<td>83.8</td>
<td>7.9 (12)</td>
<td>38.4 (58)</td>
<td>53.6 (81)</td>
<td>—</td>
</tr>
<tr>
<td>Acyclovir/valacyclovir</td>
<td>58</td>
<td>32.2</td>
<td>1.7 (1)</td>
<td>31.0 (18)</td>
<td>67.2 (39)</td>
<td>—</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>54</td>
<td>30.0</td>
<td>20.4 (11)</td>
<td>37.0 (20)</td>
<td>35.2 (19)</td>
<td>7.4 (4)</td>
</tr>
<tr>
<td>Oral antibiotics</td>
<td>50</td>
<td>27.8</td>
<td>4.0 (2)</td>
<td>20.0 (10)</td>
<td>76.0 (38)</td>
<td>—</td>
</tr>
<tr>
<td>Topical antibiotics</td>
<td>42</td>
<td>23.3</td>
<td>7.1 (3)</td>
<td>16.7 (7)</td>
<td>76.2 (32)</td>
<td>—</td>
</tr>
<tr>
<td>Bexarotene topical &amp; oral</td>
<td>39</td>
<td>21.6</td>
<td>2.6 (1)</td>
<td>33.3 (13)</td>
<td>64.1 (25)</td>
<td>—</td>
</tr>
<tr>
<td>Brentuximab vedotin</td>
<td>21</td>
<td>11.7</td>
<td>14.3 (3)</td>
<td>19.0 (4)</td>
<td>33.3 (7)</td>
<td>33.3 (7)</td>
</tr>
<tr>
<td>Psoralen ultraviolet A</td>
<td>25</td>
<td>13.9</td>
<td>—</td>
<td>56.0 (14)</td>
<td>44.0 (11)</td>
<td>—</td>
</tr>
<tr>
<td>Nitrogen mustard</td>
<td>22</td>
<td>12.2</td>
<td>18.2 (4)</td>
<td>40.9 (9)</td>
<td>40.9 (9)</td>
<td>—</td>
</tr>
<tr>
<td>Oral steroids</td>
<td>13</td>
<td>7.2</td>
<td>—</td>
<td>23.1 (3)</td>
<td>61.5 (8)</td>
<td>15.4 (2)</td>
</tr>
<tr>
<td>Topical imiquimod</td>
<td>12</td>
<td>6.7</td>
<td>8.3 (1)</td>
<td>—</td>
<td>91.7 (11)</td>
<td>—</td>
</tr>
<tr>
<td>Retinoid</td>
<td>11</td>
<td>6.1</td>
<td>—</td>
<td>36.4 (4)</td>
<td>63.6 (7)</td>
<td>—</td>
</tr>
<tr>
<td>No treatment</td>
<td>10</td>
<td>5.6</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

CR, Complete remission; NR, no response; PR, partial remission.
Methotrexate for topical application in an extemporaneous preparation

Johannes Wohlrab, Reinhard H.H. Neubert, Julia Michael, Sandy Naumann

Topical methotrexate for lymphomatoid papulosis

Jane S. Bergstrom, MD, and Christine Jaworsky, MD

Cleveland, Ohio
Our patient

- Failed PUVA, topicort spray, doxycycline
- Excimer laser showed most improvement
- Regular follow up with PCP
Question

• What is the most commonly associated malignancy in patients with LyP?

• A. B cell lymphoma
• B. Mycosis fungoides
• C. ALCL
• D. Hodgkin’s lymphoma
HPI

- 9y11m F with PMH asthma consulted for diffuse rash
- Onset: 2 weeks
- Mother reports bumps on face and legs after visiting Coney Island (7/3), believed to be mosquito bites
- Treated in the ED 7/10 with Benadryl and Calamine lotion
- Worsening rash with drainage and crusting; pruritic per patient
- No recent travel history
- No other family members with similar rash
- Admitted and treated for presumed Cellulitis with IV Clindamycin and Benadryl
• DIFFERENTIAL DIAGNOSIS?
• Which of the following are the most common cause of eosinophilic infiltrates on histopathology?
  – Arthropod reaction
  – Drug reaction
  – Allergic contact dermatitis
  – All of the above
Which of the following are the most common cause of eosinophilic infiltrates on histopathology?

– Arthropod reaction
– Drug reaction
– Allergic contact dermatitis
– All of the above
Vesicular Arthropod Reaction

• The most common causes of eosinophilic infiltrates include arthropod bites, drug eruptions, allergic contact dermatitis and atopic dermatitis.

• Insect bites produce a wide spectrum of clinical lesions

• Characteristic insect bite reactions are grouped or disseminated, erythematous urticarial papules that are markedly pruritic and often excoriated

• Typically resolve over 5–10 days but may persist for weeks, sometimes reactivating when new bites occur in different locations.

• In addition to lesions restricted to the sites of bites, papular urticaria may develop as a generalized phenomenon following insect bites.

• Most clinical manifestations relate to the individual’s immune response
Quick Review of Basic Science

• Atopy: Susceptibility to Type I Immediate Hypersensitivity is genetically determined
• Localized Type I HSR (allergies, asthma, eczema) – Atopic individuals have a high level of IgE and eosinophils
• Specific target tissue or organ involved, in this case, the skin
• Salivary gland surface proteins are major immunogenic components of mosquito bites
• Eosinophils are important in late-phase reaction, recruit cells that amplify and sustain the inflammatory response
• The delayed mosquito-bite papules seem to be cutaneous late-phase reactions mediated by eosinophils
Exaggerated Bite Reaction
Well’s Syndrome

- **Recurrent pruritic indurated plaques** resembling cellulitis, blistering may occur.
- Pathogenesis is unknown, but the possibility of local hypersensitivity has been proposed.
- So-called “triggers” have been described in some patients, including infections/infestations (dermatophytes, viruses), insect bites or stings, and drugs.
- The most common systemic complaint in patients is malaise, with fever occurring in <25% of patients.
- The extremities are most frequently affected, but truncal involvement also occurs.
- The classic histologic appearance is that of a diffuse dermal infiltrate of eosinophils and characteristic “flame figures”.
- Patients have often been previously misdiagnosed as having erysipelas or acute cellulitis. The histopathologic findings of both erysipelas and bacterial cellulitis can include significant edema similar to that seen in Wells’ syndrome, but usually neutrophils are the predominant inflammatory cell in those two entities, in contrast to the eosinophils of Wells’ syndrome.
- Peripheral blood eosinophilia is common. **Eos: 8.8% (ref range 0.7-5.8)**
- Initial therapy usually consists of oral corticosteroids, typically prednisone at a dose of 10–80 mg daily, and this typically results in dramatic improvement within a few days. Tapering of the corticosteroid dose over 1 month is well tolerated in most patients.
Cellulitis

• Lower dermis and subcutaneous fat infection characterized by poorly demarcated erythema, swelling, warmth and tenderness
• The tetrad of key physical findings *rubor*, *dolor*, *calor* and *tumor* that are taught in medical school are in actuality non-specific markers of inflammation. As a result, there are many diseases that clinically mimic cellulitis, known as pseudocellulitides.
• In children, cellulitis most often affects the head and neck and is usually caused by S. aureus > GAS
• Cellulitis is often preceded by systemic symptoms such as fever, chills and malaise.
• The borders are usually ill-defined and non-palpable.
• Clinical diagnosis
• In the absence of trauma to both legs, bilateral cellulitis is exceedingly rare.
<table>
<thead>
<tr>
<th>CAUSES OF “PSEUDOCELLULITIS”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and bites</strong></td>
</tr>
<tr>
<td>• Arthropod bite reactions (e.g. insect, spider)</td>
</tr>
<tr>
<td>• Erythema migrans</td>
</tr>
<tr>
<td>• Herpes zoster</td>
</tr>
<tr>
<td>• Toxin-mediated erythema (e.g. recurrent toxin-mediated perineal erythema)</td>
</tr>
<tr>
<td><strong>Neutrophilic dermatoses</strong></td>
</tr>
<tr>
<td>• Sweet’s syndrome, neutrophilic panniculitis</td>
</tr>
<tr>
<td>• Familial Mediterranean fever, other periodic fever syndromes</td>
</tr>
<tr>
<td><strong>Drug reactions</strong></td>
</tr>
<tr>
<td>• Fixed drug eruptions (especially non-pigmenting)</td>
</tr>
<tr>
<td>• Vaccine/injection site reactions</td>
</tr>
<tr>
<td>• Toxic erythema of chemotherapy (e.g. due to gemcitabine)</td>
</tr>
<tr>
<td><strong>Other inflammatory disorders</strong></td>
</tr>
<tr>
<td>• Allergic contact dermatitis (including airborne and dermal)</td>
</tr>
<tr>
<td>• Phytophotodermatitis</td>
</tr>
<tr>
<td>• Well’s syndrome</td>
</tr>
<tr>
<td>• Panniculitis, e.g. lipodermatosclerosis, erythema nodosum</td>
</tr>
<tr>
<td>• Thrombophlebitis</td>
</tr>
<tr>
<td>• Angioedema</td>
</tr>
<tr>
<td>• Interstitial granulomatous dermatitis, inflammatory granuloma annulare</td>
</tr>
<tr>
<td><strong>Metabolic disorders</strong></td>
</tr>
<tr>
<td>• Gout</td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
</tr>
<tr>
<td>• Erysipeloid skin metastases (especially breast carcinoma)</td>
</tr>
</tbody>
</table>
Impetigo

• Most common bacterial skin infection in children
• S. aureus
• Peak incidence in summer
• Extremely contagious
• Occurs at sites of disrupted skin barrier
• Bullous impetigo is more likely to develop on clinically intact skin
• Histology: intense neutrophilic and lymphocytic infiltrate with presence of Gram + cocci
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-bullous impetigo</th>
<th>Bullous impetigo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>~70% of all cases of impetigo, children most often affected</td>
<td>Less common, often occurs in the neonatal period (see Ch. 34), but children also affected</td>
</tr>
<tr>
<td><strong>Clinical lesions</strong></td>
<td>Early: single 2–4 mm erythematous macule that rapidly evolves into a short-lived vesicle or pustule. Late: superficial erosion with a typical “honey-colored” yellow crust and rapid direct extension of infection to surrounding skin.</td>
<td>Early: small vesicles enlarge into 1–2 cm superficial bullae. Late: flaccid, transparent bullae measuring up to 5 cm in diameter; after rupture there is a collarette of scale, but no thick crust; usually little surrounding erythema.</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Face (around the nose and mouth) and extremities</td>
<td>Face, trunk, buttocks, perineum, axillae and extremities</td>
</tr>
<tr>
<td><strong>Associated findings</strong></td>
<td>Mild lymphadenopathy may be present</td>
<td>Usually no systemic symptoms but can be associated with weakness, fever and diarrhea</td>
</tr>
<tr>
<td><strong>Clinical course</strong></td>
<td>Usually a benign, self-limited process. Usually resolves within 2 weeks without scarring if untreated.</td>
<td>Usually resolves in 3–6 weeks without scarring if not treated</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>In 5% of cases, non-bullous impetigo caused by S. pyogenes (serotypes 1, 4, 12, 25 and 49) results in acute post-streptococcal glomerulonephritis (APSG)*. Risk of APSG is not altered by treatment with antibiotics. Impetigo has not been linked to a risk of rheumatic fever.</td>
<td>In infants/young children and adults with immunodeficiency or renal failure, exfoliative toxin may disseminate and cause staphylococcal scalded skin syndrome.</td>
</tr>
<tr>
<td></td>
<td>Most common</td>
<td>Less common</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------------------------------</td>
<td>--------------------------------------------------------------</td>
</tr>
<tr>
<td>Non-bullous impetigo</td>
<td><strong>Insect bites</strong></td>
<td>Inflammatory tinea corporis/faciei</td>
</tr>
<tr>
<td></td>
<td>Eczematous dermatoses</td>
<td>Varicella</td>
</tr>
<tr>
<td></td>
<td>Herpes simplex viral infection</td>
<td>Scabies</td>
</tr>
<tr>
<td></td>
<td>Candidiasis</td>
<td>Pediculosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pemphigus foliaceus</td>
</tr>
<tr>
<td>Bullous impetigo</td>
<td>Bullous insect bite reactions</td>
<td>Autoimmune bullous dermatoses (e.g. linear IgA bullous dermatosis, bullous pemphigoid)</td>
</tr>
<tr>
<td></td>
<td>Thermal burns</td>
<td>Bullous erythema multiforme</td>
</tr>
<tr>
<td></td>
<td>Herpes simplex viral infection</td>
<td>Stevens–Johnson syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bullous mastocytosis</td>
</tr>
</tbody>
</table>
A patient presents with recurrent itchy erythematous indurated plaques on the extremities resembling cellulitis. Which of the following statements are true?

– Peripheral eosinophilia is common
– Flame figures may be present on histology
– Systemic steroids are the treatment of choice
– All of the above
A patient presents with recurrent itchy erythematous indurated plaques on the extremities resembling cellulitis. Which of the following statements are true?

– Peripheral eosinophilia is common
– Flame figures may be present on histology
– Systemic steroids are the treatment of choice
– All of the above
Take Home Points

• History!
• Patients with atopy may often present with more robust response to insect bites
• Bilateral cellulitis is almost always impossible and very unusual
• Impetigo is a superficial self-limited infection with crusting
• Cellulitis presenting with atypical features, consider eosinophilic cellulitis
History of Present Illness

54 year old female from Peru presented with thick, tight skin.

• Onset at **16-17 years old**

• Skin on her back became **red then purple tight “scar-like” lesions.** It progressed to **involve her more of her trunk, head, left arm, and left leg.**

• Moved from Peru to US with her family 4 years ago.

• **ROS:** difficulty ambulating, restriction of movement of knee joint, purplish discoloration of bilateral fingers in cold
A Case of Dark Spots
History of Present Illness

• CC: “dark spots”

• HPI: 66 year old Latin American male referred by his primary care physician for evaluation of asymptomatic dark spots on his trunk and extremities present for about 12 months.
  • Non-pruritic
  • No prior treatments

• ROS: negative
History of Present Illness

• **PMH**: HTN, IDDM

• **Meds**: Lisinopril

• **Allergies**: NKDA

• **Surgery**: none

• **FH**: non-contributory

• **SH**: no alcohol, tobacco, or illicit drug use. Retired.
Differential Diagnosis?
Differential Diagnosis

• Hypertrophic Lichen Planus
• Granuloma Annulare
• Lichen amyloidosis
• Confluent and reticulated papillomatosis
• Sarcoidosis
• Deep fungal
• LSC
• Acanthosis Nigricans
• Epidermal Nevi
Histology:

Biopsy date 10/23/2017
H&E, 4x
A. R UPPER MEDIAL BACK
B. R UPPER LATERAL BACK

DIAGNOSIS:

- A. Skin with increased mucin in papillary dermis and mildly increased spindle cells and macrophages. See comment.

  Comment: PAS stain is negative for organisms. Differential diagnosis includes granuloma annulare or lichen myxedematosis. Clinicopathologic correlation is advised. The case was reviewed in the dermatopathology daily intradepartmental conference with Dr. Phelps and the members present concur with above diagnosis.

- B. Skin with increased mucin in papillary dermis and mildly increased spindle cells and macrophages. See comment.

  Comment: PAS stain is negative for organisms. Differential diagnosis includes granuloma annulare or lichen myxedematosis. Clinicopathologic correlation is advised. The case was reviewed in the dermatopathology daily intradepartmental conference with Dr. Phelps and the members present concur with above diagnosis.
Which plasma cell dyscrasia is most commonly associated with Scleromyxedema?

- IgG Lambda
- IgG Kappa
- IgM Lambda
- IgM Kappa
• Which plasma cell dyscrasia is most commonly associated with Scleromyxedema?
  • IgG Lambda
  • IgG Kappa
  • IgM Lambda
  • IgM Kappa
Lichen Myxedematosus (Papular Mucinosis)

- Localized variant of Scleromyxedema
- Patients develop small, firm, waxy papules (or nodules and plaques produced by the confluence of papules) that are limited to only a few sites – usually the upper and lower limbs and/or trunk.
- The skin is the only site of involvement and these variants, in contrast to scleromyxedema, are not associated with sclerosis, paraproteinemia or systemic involvement, nor are they associated with thyroid disease.
Localized Variants of Lichen Myxedematosus

- **4 Subtypes:**
  - discrete papular form
  - acral persistent papular mucinosis
  - cutaneous mucinosis of infancy
  - a pure nodular form
    - Nodular lichen myxedematosus is characterized by multiple nodules on the limbs and trunk, with a mild or absent papular component.
- May be observed in association with HIV or Hepatitis C
- Incidence and prevalence unknown
Atypical Lichen Myxedematosus

• Occasional patients with lichen myxedematosus have atypical features or features intermediate between scleromyxedema and localized lichen myxedematosus.

• Atypical classification:
  • Patients with scleromyxedema who lack a monoclonal gammopathy
  • Individuals with localized forms of lichen myxedematosus who also have a monoclonal gammopathy and/or systemic symptoms
  • Localized forms with mixed features of the subtypes
  • Other not well-specified cases
Discrete Papular Type
Acral Persistent Papular Mucinosis
Cutaneous Mucinosi of Infancy
**Scleromyxedema**

- Generalized
- Multiple firm papules, often linear
- Face/neck
- Sclerodermoid changes
- Evidence of plasma cell dyscrasia

**Lichen myxedematosus**

- Localized
- Multiple papules
- Symmetric
- Trunk and Extremities
- Facial sparing
- No laboratory abnormalities
Scleromyxedema
Treatment Options

• Localized lichen myxedematosus does not require therapy and there is no definitive treatment.

• Topical application of corticosteroids, pimecrolimus or tacrolimus may be of some benefit.

• Spontaneous resolution may occur, even in the setting of HIV infection.
SHORT REPORT

Atypical discrete papular lichen myxedematosus associated with monoclonal gammopathy: report of four cases and review of the literature

C. Hermans,¹,* I. Goldscheider,¹ T. Ruzicka,¹ F. Rongoletti²

¹Department of Dermatology and Allergy, Ludwig- Maximilian University Munich, Munich, Germany
²Department of Medical Science, Unit of Dermatology, University of Cagliari, Cagliari, Italy
*Correspondence: C. Hermans. E-mail: Cecilia.Hermans@med.uni-muenchen.de

Abstract

Background Discrete papular lichen myxedematosus (DPLM) is a rare form of localized lichen myxedematosus that presents with skin involvement only and without systemic involvement.

Objective To describe our experience with atypical cases of DPLM associated with monoclonal gammopathy.

Methods Data were collected from patients with clinicopathological evidence of DPLM associated with monoclonal gammopathy who presented to the Department of Dermatology of two tertiary university-affiliated medical centres from 2000 to 2015 and were followed prospectively.

Results The sample included four patients (three males) with a mean age of 58 years. No clinicopathological differences from typical cases of DPLM were observed, except for the presence of monoclonal gammopathy. The patients were followed up for a mean of 34 months (6–72 months) and no progression to scleromyxedema, multiple myeloma or systemic involvement was observed. No therapy was applied, except for topical tacrolimus or steroids, and the eruptions remained stable.

Conclusion Our experience indicates an excellent prognosis of DPLM even for atypical cases in spite of the presence of monoclonal gammopathy.

Received: 23 February 2016; Accepted: 24 May 2016
Discrete Papular Lichen Myxedematosus with an Unusual Segmental Presentation

Discrete papular lichen myxedematosus, a subtype of localized papular lichen myxedematosus, is an idiopathic cutaneous mucinosis. It typically presents symmetrically, involving the trunk and extremities. We report on an unusual case of discrete papular lichen myxedematosus with a segmental presentation.

An otherwise healthy 23-year-old man presented with a gradual accumulation of asymptomatic papules on the lower abdomen over the previous year. Physical examination revealed multiple, well-defined, discrete and coalescing, 1-5mm, smooth, indurated, dark brown, slightly erythematous papules, with variable surrounding hyperpigmentation, involving the skin of the right lower abdomen in a segmental distribution (Figure 1). A punch biopsy specimen was obtained. Histopathological examination revealed mucin deposition in the superficial to mid-reticular dermis, moderate proliferation of fibroblasts, and an inflammatory infiltrate composed of plasma cells and lymphocytes (Figures 2A, B). The clinical and pathologic features were consistent with discrete papular lichen myxedematosus.

The laboratory work-up, including a complete blood count with differential and liver function tests,
Discrete papular lichen myxedematosus: a rare entity or an under-diagnosed disease?

Iman Hadj,1,* Salim Gallouj,1 Mariame Meziane,1 and Fatima Zahra Mernissi1

Letter

Treatment of localized lichen myxedematosus of discrete type with tacrolimus ointment

Franco Rongioletti MD, Elisa Zaccaria MD, Emanuele Cozzani MD, Aurora Parodi MD
Clinical Review

Updated classification of papular mucinosis, lichen myxedematosus, and scleromyxedema

Franco Rongioletti, MD, and Alfredo Rebora, MD Genoa, Italy

Lichen myxedematosus (LM) is an idiopathic cutaneous mucinosis; its classification dates back to 1953, when Montgomery and Underwood distinguished 4 types of LM: a generalized lichenoid eruption, later called scleromyxedema, a discrete papular form, a localized or generalized lichenoid plaque form, and an urticarial plaque form. In the literature, the terms LM, papular mucinosis, and scleromyxedema have been often used indiscriminately as synonyms, but most reported cases of LM or papular mucinosis without indication of the subtype appear in fact to be cases of scleromyxedema. On the basis of personal experience, the anatomoclinical manifestations of published cases of LM, papular mucinosis, and scleromyxedema are reviewed to distinguish clearly between a generalized form with systemic, even lethal, manifestations and a localized form, which does not run a disabling course. LM includes two clinicopathologic subsets: a generalized papular and sclerodermoid form (also called scleromyxedema) and a localized papular form. Diagnosis of scleromyxedema should fulfill the following criteria: (1) generalized papular and sclerodermoid eruption; (2) mucin deposition, fibroblast proliferation, and fibrosis; (3) monoclonal gammopathy; and (4) the absence of thyroid disease. The criteria for localized LM are as follows: (1) papular or nodular/plaque eruption; (2) mucin deposition with variable fibroblast proliferation; and (3) the absence of both monoclonal gammopathy and thyroid disease. The localized form is subdivided into 5 subtypes: (1) a discrete papular form involving any site; (2) acral persistent papular mucinosis
Clinical Course

• 09/12/2017 – INITIAL VISIT
  • Dermatitis, unspecified
  • DDx included LSC and Prurigo nodularis
  • Treated with Triamcinolone acetonide 0.1% ointment BID

• 10/23/2017 – Follow-up
  • No improvement with TAC
  • Punch biopsy performed of both nodular and papular/plaque component
Clinical Course

• 11/23/2017 – Follow-up
  • Punch Biopsy: Lichen myxedematosus
  • SPEP/UPEP ordered
  • Rx Halobetasol propionate 0.05% ointment BID

• 12/18/2017 – Follow-up
  • Improved texture and decreased pigmentation with Halobetasol per patient
  • Rx for Tacrolimus ointment
Differential

- Scleroderma
- Morphea
- Nephrogenic Systemic Fibrosis
- Scleredema
- Scleromyxedema
Morphea (Localized Scleroderma)

- **Fibrosing inflammatory** condition limited to the skin, subcutaneous tissue, bone, and (rarely) the underlying central nervous system

- Incidence of US is 0.4-2.7 per 100,000 people\(^1\)

- 3 Female: 1 Male

- Prevalence is equal in adults and children\(^3\)
  - In adults, peak incidence is in 3\(^{rd}\) and 4\(^{th}\) decade\(^1,3\)

- Prognosis and morbidity varies according to variant
Morphea – Clinical Presentation

**Early lesions:** erythematous to dusky violaceous patches and plaques

**Later lesion:** sclerotic, hairless, anhidrotic plaques with varying amounts of post-inflammatory hyperpigmentation

*Fig 1.* Morphea en plaque with characteristic violaceous border.

*Fig 3.* Generalized morphea. Widespread hyperpigmented sclerotic plaques covering the patient’s chest and upper back.

*Fig 4.* Linear morphea. Linear band of hyperpigmentation and sclerosis, with evidence of previous skin break down and underlying tissue atrophy.
### Table II. Morphea classification according to Laxer and Zulian

<table>
<thead>
<tr>
<th>Classification</th>
<th>Included subtypes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumscribed morphea</td>
<td>Superficial variant, Deep variant</td>
<td>Oval areas of induration limited to epidermis and dermis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oval areas of deep induration including the subcutaneous tissue (may</td>
</tr>
<tr>
<td></td>
<td></td>
<td>include fascia and muscle); overlying skin may not be involved</td>
</tr>
<tr>
<td>Linear morphea</td>
<td>Trunk/limb variant, Head variant,</td>
<td>Linear induration involving the dermis and subcutaneous tissue (may</td>
</tr>
<tr>
<td></td>
<td>En coup de sabre</td>
<td>include muscle and bone)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linear induration involving the dermis of the face and scalp (may involve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>underlying muscle, bone, and central nervous system)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of dermis, subcutaneous tissue, muscle and bone of the unilateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>face</td>
</tr>
<tr>
<td>Generalized morphea</td>
<td></td>
<td>Four or more individual indurated plaques &gt; 3 cm each, involving ≥ 2 of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>seven anatomic sites (head-neck, each extremity, anterior trunk, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>posterior trunk)</td>
</tr>
<tr>
<td>Pansclerotic morphea</td>
<td></td>
<td>Circumferential involvement of limbs involving epidermis, dermis, sub</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cutaneous tissue, muscle, and bone; may affect other areas of the body</td>
</tr>
<tr>
<td>Mixed variant morphea</td>
<td></td>
<td>Combination of 2 or more previous subtypes</td>
</tr>
</tbody>
</table>
Parry-Romberg Syndrome

- **Hemifacial atrophy** with progressive loss of subcutaneous fat; *little or no sclerosis*
  - Distribution of trigeminal nerve (may have neuropathy)

- 20% of patients will have *intracranial manifestations*\(^5\)
  - ex. cerebral atrophy, seizures, ophthalmic changes

- Onset usually 1\(^{st}\) and 2\(^{nd}\) decade of life → Progressive for 2-20 years → quiescent\(^5\)

- Diagnosis usually done via clinical and exclusion of other diseases with histopathology and imaging studies\(^5\)
Treatment Algorithm

ACTIVE
New lesions ≤6 month's duration, disease extension, inflammation (erythema, edema), sclerotic or indurated periiphery

SUPERFICIAL

LOCALIZED
- Topical (bid, occluded)
  - Calcipotriene
  - Tacrolimus
- Phototherapy
  - Localized or whole body
  - NB UVB, BB UVA, UVA-1

GENERALIZED
- Phototherapy (whole body)
  - NB UVB, BB UVA, UVA-1

DEEP

LOCALIZED
- Functional/cosmetic threat
- Systemic
  - MTX
  - PCMT

GENERALIZED

*INACTIVE/DAMAGE
Pigmentary changes, static size, atrophy, central sclerosis

FUNCTIONAL IMPAIRMENT:
- PT/OT
- Otolaryngology
- Orthopedics
- Podiatry
- Rheumatology
- Oral maxillofacial surgery
- Plastic surgery

COSMETIC IMPAIRMENT

Confirmed long-term disease inactivity

Work-up negative for deep muscle, fascia, bone involvement

Local excision
Inject fillers (face)
THANK YOU!

Charles Gropper, MD
Chair of Dermatology
Saint Barnabas Hospital
Bronx, NY