This continuing medical education activity is jointly provided by the North Carolina Dermatology Association and Southern Regional Area Health Education Center.
Outpatient Consultations in Complex Medical Dermatology
Selected Aspects: 2019

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Conflict of Interest

Advisory Boards/Honoraria
Amgen

Quote from an anonymous patient:
“What I am told on the first visit is patient education – on the second an excuse.”
Possibilities for a patient who presents with a complex medical dermatosis and systemic signs and symptoms:

1. Clinicopathologic diagnosis of dermatosis integrates all findings eg. Sarcoidosis – skin, eye, lungs, etc
2. Clinicopathologic diagnosis reveals a reactive dermatosis – communication with internist or pediatrician will outline underlying medical conditions eg. Vasculitis
3. No direct relationship – eg. Scabies/Fibromyalgia

Patients wishes to know from the internet whether they need x or y therapy for their presumptive diagnosis. Instead it is important to not let the patient “drive” for their own benefit.

Step 1. – Clinicopathologic diagnosis- Caution influence of therapy on biopsy and clinical appearance
Step 2. – Assess the extent (internal manifestations of disease)
Step 3. – Assess for etiology
Step 4. - Therapeutic ladder
Urticaria

An inflammatory dermatosis resulting from vasodilatation, increased vascular permeability, and extravasation of protein and fluids. Individual lesions, by definition, last less than 24 hours.

Definitions

- Urticaria (hives) - reaction in the superficial dermis; lesions last less than 24 hours
- Urticarial reaction - similar, but lesions last more than 24 hours
- Angioedema - reaction in the submucosa, deep dermis, and subcutaneous tissue
- Acute urticaria - less than 6 weeks
- Chronic urticaria - more than 6 weeks

A Personal Classification of Urticarial Reactions

- IgE-dependent urticaria and angioedema
  - Specific antigen identified
  - Physical urticarias
- Non-IgE dependent urticaria angioedema
  - Direct mast cell effects
  - Arachidonic acid pathway effects
- Angioedema related to complement
  - Hereditary
  - Acquired
- Urticarial reactions probably related to immune complexes
  - Urticarial vasculitis
  - Serum sickness-like reactions
- Idiopathic
IgE-Dependent Urticaria: Some examples of implicated causes

- Infections: Bacterial (e.g., Dental abscess, sinusitis)
  - Fungal (e.g., Candida, dermatophyte)
  - Viral (e.g., Hepatitis B)
  - Other
- Infestations: Helminths, protozoa, other
- Drugs and Chemicals: Penicillin, sulfonamides, other
- Foods: Eggs, nuts, chocolate, shellfish, other
- Inhalants: Pollens, animal dander, other
- Systemic Disease: Lymphomas, collagen vascular diseases, other

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**Fig. 19.7 Causes of acute urticaria.**
(Data from Zuberbier. 1996.)

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**Fig. 19.8 Causes of chronic urticaria.**
Autimmune represents those patients with functional autoantibodies against FcεRI or the Fc portion of IgE.

From Bolognia, Jorizio & Rapini: Dermatology 2e. © 2008 Elsevier, Ltd.
IgE-Dependent Urticaria

- Rarely proven by RAST, Scratch testing, or other methods
- Suggestive evidence for reagins (IgE or IgG4) in urticaria

Urticaria

Clinical Lesions: Urticarial Wheal

Clinical Lesions: Generalized Wheals
Urticaria
Clinical Lesions: Angioedema

Symptomatic Dermatographism: Diagnosis

- Stroke skin of back with fingernail or even use dermographometer
- Observe for wheal formation
  - Onset - Minutes
  - Duration - 2 to 3 hours
- Delayed form exists
Urticaria
Clinical Lesions: Symptomatic dermatographism

Cholinergic Urticaria
Diagnosis
- Exercise testing (Does not exclude exercise-induced anaphylaxis-Caution!)
- Hot bath testing - Immerse 1/2 of patient at 43°C (Raise oral temperature 1° to 1.5°C)
  Best Test
- Intradermal injections (methacholine, etc.)
  Unreliable
- Observe for wheal formation
  Onset - 2-20 minutes
  Duration - 30 minutes to 1 hour

Cold Contact Urticaria - Diagnosis
- Exclude secondary cold urticaria
- Ice filled copper beaker with thermometer
  Vary exposure
- Ice cube test (use plastic gloves)
- Cold immersion - One arm in water 8° - 10°C for 5 minutes
- Cold air - Expose 1/2 the patient to a cold room for 20-30 minutes
  Extreme caution
- Observe for wheal formation
  Onset - 2-5 minutes
  Duration - 1-2 hours
Urticaria
Clinical Lesions: Cold Contact Urticaria

Other Physical Urticarias

- Pressure Urticaria - 8kg/4cm weight to thigh
  Onset - 3-12 hours
  Duration - 8-24 hours
- Heat Urticaria - Cooper beaker with 50-55°C water
  Onset - 2-5 minutes
  Duration - 1 hour

Other Physical Urticarias - Continued

- Aquagenic Urticaria - Water compress with thermometer to maintain temperature at 35-36°C for 30 minutes
  Onset - Several minutes to 30 minutes
  Duration - 30 minutes
- Vibratory Angioedema - Vibrating mixer against skin
  Onset - 2-5 minutes
  Duration - 1 hour
Non-IgE-Dependent Urticaria:
Some agents which effect mast cells directly

- Radiocontrast material
- Opiates (eg. Morphine)
- Polymyxin B
- Curare and d-tubocurarine

Non-IgE-Dependent Urticaria:
Arachidonic acid pathway modification

- Non-steroidal anti-inflammatory drugs
  (not sodium salicylate)
- Up to 10% of asthma patients and 50% of urticaria patients are intolerant to aspirin
- Possible associated intolerance to azodyes
  (eg. Tartrazine and benzoate preservatives)
- Mechanism related to increased lipoxygenase products after cycloxygenase blockade

Angioedema Related to Complement

- Hereditary: Dominant inheritance with functional or absolute deficiency of the inhibitor of the first component of complement
  (C1-normal, family members may be abnormal)
- Acquired: Lymphoma patients
  (C1-reduced, family members normal)
Urticarial Reactions Probably Related To Circulating Immune Complexes

- Urticarial vasculitis
- Serum sickness-like reactions

Patients often have fever, urticarial lesions lasting more than 24 hours, lymphadenopathy, myalgias, arthralgias or arthritis, and possibly proteinuria, elevated liver function tests, leukocytosis, and high sedimentation rate.

Urticaria

Clinical Lesions: Urticarial vasculitis

Clinical Lesions: Urticarial serum sickness-like reaction
Chronic Idiopathic Urticaria: Update 2019

Anti-FcεRI Autoantibodies Mediate Release and Account for About One-Quarter of Cases of Chronic Urticaria

- Circulating histamine - releasing factors
- Autoantibodies against the IgE high-affinity receptor, FcεRI in sera
- 163 patients with CIU versus healthy controls
- Histamine release from mast cells and basophils
- 1/4 of patients had antibodies which could do this


Chronic Idiopathic Urticaria: Newer Data on Autoimmunity

- Autologous serum skin test
- Subgroup with autoimmune thyroid disease
- Basophil activating IgG autoantibodies
### My Evaluation of Patients with Chronic Idiopathic Urticaria

- Complete history and physical examination by Primary Care Physician (PCP)
- Screening laboratory tests and follow up of positives by PCP (e.g., if eosinophilia then stool for ova and parasites and other complete evaluation)
- Review medications and avoid all non-steroidal anti-inflammatory drugs (due to increased lipoxygenase products)
- Discuss anaphylactoid symptoms and signs and give appropriate prophylaxis (e.g., Epipen® or Anakit® if needed)

### My Evaluation of Patients with Chronic Idiopathic Urticaria (continued)

- Circle lesions - biopsy if circled lesion lasts more than 24 hours (not urticaria by definition therefore, exclude urticarial vasculitis, etc.)
- Consider (3) day rice and water elimination diet
- Review prognosis and limited chance for total cure
- Consider activated charcoal therapy

### My Treatment Approach for Patients with Chronic Idiopathic Urticaria

- Avoid (and/or taper to zero if already receiving) systemic corticosteroids
- Recognize impact of disease on quality of life
- Review that antihistamine will only flatten lesions and reduce pruritus not "eliminate the red" as corticosteroids do
- Combine several antihistamines from different classes with different sedating potential and H₁ and H₂ blocking effects taking half life into effect
For example combining one or two from first category:

Non-sedating or low sedating antihistamine
Levocetirizine 5mg 1x/day
or Loratidine or 10mg 1x/day
or 180mg 1x/day

With Doxepin 10 – 75 mg at bedtime

Consider adding other classes or montelukast, stonozolol 2mg bid medication (eg. Terbutaline sulfate, nifedipine, colchicine, dapsone, zafirlukast-leukotriene inhibitor)

Consider (realizing risks and frequent lack of success) immunosuppressive approach for patients with very refractory disease as follows:
- Psoralen ultraviolet A (PUVA)
- Methotrexate (weekly low dose)
- Azathioprine daily
- Cyclosporine (short course 3-4 months only)
- Pulse cyclophosphamide
- Oral Tacrolimus
- IVIG
- Omalizumab (Xolair – anti IgE) 150 or 300 mg SQ q weeks (150mg/site max)
Bullous Pemphigoid

Key Features

- Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease; it predominantly affects the elderly.
- It is usually a chronic disease, with spontaneous exacerbations and remissions, which maybe accompanied by significant morbidity.
- BP is associated with tissue-bound and circulating autoantibodies directed against BP antigen 180 (BP180, BPAG2 or type XVII collagen) and BP antigen 230 (BP230 or BPAG1e), components of junctional adhesion complexes called hemidesmosomes that promote dermal-epidermal cohesion.
Bullous Pemphigoid

Key Features (Cont.)

- The spectrum of clinical presentations is extremely broad. Characteristically, BP is an intensely pruritic eruption with widespread blister formation. In early stages, or in atypical variants of the disease, only excoriated, eczematous or urticarial lesions (either localized or generalized) are present.

- Diagnosis relies on immunopathologic examinations, particularly direct and indirect immunofluorescence microscopy as well as anti-BP180/BP230 ELISAs.

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**Fig. 30.2 Bullous pemphigoid – bullous presentation.** Classic presentation with multiple tense bullae arising on normal and erythematous skin. Several of the bullae have ruptured, leaving circular erosions.
Fig. 30.3 Bullous pemphigoid – urticarial (and bullous) presentation. (A) Pink urticarial papules and plaques as well as tense bullae containing serous fluid. (B) Firm annular urticarial plaques.

Fig. 30.4 Bullous pemphigoid – eczematous presentation. (A), (B) Large pink eczematous plaques on the trunk and upper extremities.

Fig. 30.5 Bullous pemphigoid – unusual clinical variants. Grouped vesicles and bullae on the palms (A) and toes (B) that can resemble pompholyx (dyshidrotic form pemphigoid). (C) Vegetating plaque in the inguinal crease (pemphigoid vegetans). (D) Toxic epidermal necrolysis-like lesions with large erosions.
Fig. 30.6 Childhood bullous pemphigoid. (A) Generalized tense bullae and crusted erosions. (B) Localized vulvar involvement (vulvar childhood pemphigoid).

Fig. 30.7 Bullous pemphigoid localized to a psoriatic plaque. No obvious trigger was detected, as the patient was not receiving phototherapy. Courtesy, Jean L. Bolognia, MD.
Abnormal Erythrocyte Morphology in Patients with DRESS

Kathryn L. Anderson, MD (PGY-4)

BACKGROUND

• Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a severe cutaneous adverse drug reaction
• Variable presentations often makes diagnosis difficult

BACKGROUND

• Reliant on diagnostic criteria to establish diagnosis, most often RegiSCAR criteria, which includes:
  - Fever
  - Lymphadenopathy
  - Eosinophilia
  - Atypical lymphocytes
  - Duration
  - Exclusion of other causes
• Abnormal erythrocytes are not currently a criteria for DRESS

METHODS

- Retrospective chart review from January 2012 thru July 2018
- Two cohorts, DRESS versus Other Drug Reaction
- Demographics, RegiSCAR criteria, and presence or absence of abnormal erythrocytes was collected

RESULTS

- 38 cases of DRESS were identified (based on RegiSCAR criteria of 2 or above)
- 215 cases of other drug eruptions
- In the DRESS cohort, 55% of patients had abnormal erythrocyte morphology (AEM), significantly more than the 24% in the Other Drug Reaction cohort (p = 0.0003)
RESULTS

• RegiSCAR findings in patients in the DRESS cohort:
  • Fever – 71%
  • Lymphadenopathy – 16%
  • Eosinophilia – 76%
  • Hepatic abnormalities – 60%
  • Renal abnormalities – 37%
  • Abnormal erythrocyte morphology – 55%

<table>
<thead>
<tr>
<th>Erythrocyte abnormality</th>
<th>(% of patients with DRESS with AEM [N=21; all DRESS patients that had an AEM])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poikilocytosis</td>
<td>10 (48)</td>
</tr>
<tr>
<td>Polychromasia</td>
<td>10 (48)</td>
</tr>
<tr>
<td>Burr Cells</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Ovalocytes</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Schistocytes</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Target Cells</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Anisocytosis</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Nucleated erythrocytes</td>
<td>2 (10)</td>
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</tbody>
</table>

DISCUSSION

• AEM occurred significantly more frequently in patients with DRESS than other drug eruptions
• AEM occurred at a frequency similar to other clinical findings incorporated into the DRESS validation score
• Reason for AEM is unclear
  • Possibly due to toxic eosinophilic granule proteins released
  • Possibly due to liver disease/inflammation

LIMITATIONS

• Single medical center
• Included patients with possible, probable, and definite cases of DRESS

CONCLUSION

• Diagnosis of DRESS is often difficult
• Additional diagnostic markers may improve diagnostic accuracy
• Abnormal erythrocyte morphology can be considered as additional data when evaluating patients with suspected DRESS

REFERENCES

THANK YOU

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PALLIATIVE DERMATOLOGY
Alexandra Zeitany, MD

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III Summary

THE WAY WE PRACTICE MEDICINE IS BEING CALLED INTO QUESTION

The New York Times

Skin Cancers Rise, Along With Questionable Treatments

By JENNY GONYER and SANDY FOREMAN. JUN 20, 2017
THOUGH WE MAY NOT AGREE WITH ALL OF IT, THE ARTICLE MAKES SOME VALID POINTS

THE MAJORITY OF THESE CANCERS OCCUR IN THE ELDERLY

80%
Occur in patients older than 65

1 in 5
Americans will develop NMSC by age 70

THE MAJORITY OF THESE CANCERS ARE NOT LETHAL

1/1000
AKs become SCC

20-60%
Individual AKs spontaneously regress

<5%
SCC metastasize

<1%
BCC metastasize
TREATING NMSC IS A COSTLY PROBLEM

$8.1 billion
Annual treatment costs in the U.S.

126% vs 25%
Increase in annual treatment cost vs. all other cancers combined from 2007 - 2011

OUR TREATMENTS HAVE ASSOCIATED MORBIDITY

20% vs 3.8%
65 and older population vs. non-age restricted population with post-operative complications

BRIEF CASE OVERVIEW: A CUTE OLD LADY WITH A NOT SO CUTE TUMOR

96 year-old female
PMH:
• Hx of DVT on rivaroxaban
• Hx of CVA on statin and ASA
• HTN on amlodipine and furosemide
• No hx of skin cancer but has never seen a dermatologist

5mm erythematous papule on the left medial canthus
• Unclear how long this has been present
• Asymptomatic
• “My primary care doctor told me I should get this checked out”
IN ORDER TO IMPROVE, WE NEED TO ADDRESS THREE MAJOR BARRIERS

1. Increased time with patients
2. Fear of not giving our patients the gold standard
3. Lagging reimbursement

INCREASED TIME WITH PATIENTS

NEED FOR SPEED

Given that we are a fast-paced specialty normally seeing 30-60 patients per day, we need a systematic, efficient approach.

<table>
<thead>
<tr>
<th>Practice Step</th>
<th>Change Impact</th>
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<tbody>
<tr>
<td>Practice Step 1</td>
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<tr>
<td>Practice Step 2</td>
<td></td>
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<tr>
<td>Practice Step 3</td>
<td>LOW</td>
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</table>

ASSESS LIFE EXPECTANCY: LOW IMPACT TO PRACTICE

There are two ways to determine morbidity scores:

• Self-assessment survey
• Provider discussion with patients

The results? The patient self-assessment survey actually outperformed the provider discussion in determining accurate morbidity scores.

Bottom line: Adding a patient survey won’t add time to physicians’ or nurses’ schedules as patients can complete this in the waiting room.

NEED FOR SPEED

Given that we are a fast-paced specialty normally seeing 30-60 patients per day, we need a systematic, efficient approach.

ASSESS RISK: NO IMPACT TO PRACTICE

Performing the risk assessment is something we all already do, but for a quick reminder:
**NEED FOR SPEED**

Given that we are a fast-paced specialty normally seeing 30-60 patients per day, we need a systematic, efficient approach.

<table>
<thead>
<tr>
<th>Patient Visit Step</th>
<th>Change Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LOW</td>
</tr>
<tr>
<td></td>
<td>NONE</td>
</tr>
<tr>
<td></td>
<td>MED</td>
</tr>
<tr>
<td></td>
<td>LOW</td>
</tr>
</tbody>
</table>

- **LOW**
- **NONE**
- **MED**
- **LOW**

**WEIGHING THE RISKS AND BENEFITS WITH PATIENTS**

This can potentially impact provider time, so how best can we do it?

**QUESTION**

- Understand the natural history of the lesion
  - Symptomatic
  - Cosmetically bothersome
- Understand the patient’s social situation
  - Support system
  - Transportation issues
  - Financial concerns/insurance coverage

**EDUCATE**

- **Natural history of NMSC**
  - Slow-growing tumors with low metastatic potential
- Treatment options and associated burden/post-operative concerns
  - Morbidity
  - Recurrence rate
  - Number of visits required
  - Wound care

**PATIENT DISCUSSION**

- More than 1 year
- Less than 1 year
- No, high risk
- Yes, low risk

**Treatment**

- Active Surveillance
  - Photograph, measure and follow up with patient in 3 months
- Discuss likely diagnosis, prognosis, advise biopsy and treatment
- Discuss likely diagnosis, prognosis, advise biopsy and treatment
- Discuss likely diagnosis, prognosis, advise biopsy and treatment

**TIME FEAR REIMBURSEMENT**
REMEMBER:
MOST OF THIS IS A ONE TIME DISCUSSION!

- Understanding patient’s life expectancy
- Understanding patient’s GOtreatment preferences
- Discussing history of NMSc

FEAR OF NOT GIVING OUR PATIENTS THE GOLD STANDARD

EXAMINING THE GOLD STANDARD

Gold Standard = Surgical Intervention

NCCN Guidelines:
- “…most commonly treated with surgery”
- “…best results were obtained with surgery”
- “The goal of primary treatment is the cure of the tumor”

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<tr>
<th>Treatment</th>
<th>BCC</th>
<th>SCC</th>
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<tbody>
<tr>
<td>Topical</td>
<td>85%</td>
<td>84%</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>87%</td>
<td>90%</td>
</tr>
<tr>
<td>PDT</td>
<td>70-90%</td>
<td>70-90%</td>
</tr>
<tr>
<td>ED&amp;C</td>
<td>91-97%</td>
<td>92-96%</td>
</tr>
</tbody>
</table>

However...

We shouldn’t be afraid to pass on surgery considering other interventions also have good cure rates.
BUT WHAT IF WE TAKE THIS A STEP FURTHER…

“Palliative care is an approach that improves the quality of life of patients through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.”

Palliation does not mean we are not treating the patient.
Palliation means shifting treatment goals to provide better individualized care.

WHAT IS THIS FEAR ROOTED IN?

- Fear of bad patient outcomes
- Fear of judgement from colleagues
- Fear of litigation

LAGGING REIMBURSEMENT
LAGGING REIMBURSEMENT

CPT Telephone Consultation Codes
• Time based
• Medicare and most commercial carriers don’t reimburse for this but do have associated RVUs

CPT Chronic Care Management Codes
• Time based (per month)

E&M Level of Service based on time

GOING BACK TO OUR PATIENT... WHAT SHOULD WE DO?

TREATMENT?
• Neoplasm in high value real estate

ACTIVE SURVEILLANCE?
• Asymptomatic
• Unnoticed by patient
• >90 yo with multiple comorbidities

SUMMARIZING KEY POINTS

• The silver tsunami is coming at the same time we are moving towards personalized medicine and we must respond to these changes
• You can devise a personalized treatment plan in a timely manner while still giving the patient THEIR “gold standard”
• Reimbursement may be lagging behind, but we’ll get there!
• Bottom Line: Have open, honest communication with your patients (and document everything)

“We’ve been wrong about what our job is in medicine. We think our job is to ensure health and survival. But really it is larger than that. It is to enable wellbeing.”
-Atul Gawande
## REFERENCES


PLASMACYTOSIS

CASE

A 67-year-old man presented to our outpatient dermatology office for evaluation of a rash. He was previously diagnosed with biopsy proven granuloma annular and despite treatment with topical corticosteroids, intralesional corticosteroids, and dapsone the lesions had progressively worsened. The past medical history was positive for untreated hypercholesterolemia, prostate biopsy with benign results, and ehrlichiosis septic shock requiring prolonged and intensive hospitalization. The social history was negative for high risk behaviors. The physical exam revealed the following:

PHYSICAL EXAMINATION

Distributed over both proximal distal legs were hyperpigmented coalescing papules and plaques with no significant epidermal change
• The patient began rifampin and doxycycline for suspected disseminated granuloma annulare.
• The patient repeatedly reported improvement. However, objectively the lesions progressively expanded.
HISTOLOGY

CD 20
CD 79a

Kappa
Lambda

CASE

- CBC, CMP, and lipids were within normal limits (WNL)
- Re-biopsy of the lesion revealed a dense dermal infiltrate of lymphocytes, histiocytes, and plasma cells with:
  - Small aggregates of CD20+ B cells
  - CD3+ T-cells
  - Low Ki-67 activity
  - Negative CD-30
  - Kappa and lambda light chain in-situ hybridization showed polyclonal plasma cells
  - Findings consistent with cutaneous lymphoid hyperplasia

CASE

- Discussion of extensive clinical picture with pathologist.
- With concerns for a plasma cell dyscrasia further labs included:
  - Serum protein electrophoresis
  - M protein Urine
  - VT 832
  - Ferritin
  - UA
  - PSA
  - Iron
  - VDRL
  - CXR
  - Ehrlichiosis IgG and IgM
  - Anaplasma IgG and IgM
  - Prostate specific antigen (Hx of prior prostate biopsy)
The patient declined further workup and treatment despite extensive counseling on the risk of an underlying systemic disease.

With continued intermittent phone calls to the patient he agreed to follow up over a year later with the following physical examination findings.

The patient felt like he was getting better but did agree to get the labs performed.

Repeat labs 2yr after presentation:

- Hb: 12.3g/dL (<13.2g/dL)
- ferritin: 85nm/mL (WNL)
- reticulocyte count: 1.4%
- total iron: 53mcg/dL (WNL)
- TIBC: 325mcg/dL (WNL)
- iron % saturation: 16% (low normal)
- ferritin: 85nm/mL (WNL)
- Vit. B12: WNL
- MCH: 26pg (<27pg)
- CMP:
  - Glucose: 114
  - Creatinine: 1.61mg/dL
  - BUN: 21mg/dL
  - eGFR: 51ml/min/1.73m2
  - Serum total protein: 8.9g/dL (WNL)
  - Alpha 1 globulin: 0.4g/dL (WNL)
  - Alpha 2 globulin: 1.0g/dL (WNL)
  - Beta1 and 2 globulin: WNL
  - Gamma Globulin: 2.4g/dL (WNL)
  - Abnormal protein band: 1
- PSA: 11.8ng/mL (>4.0ng/mL)
- E. Chaffeensis ab: IgG Positive at 1:256 dilution
- Anaplasma negative
**Pending Work Up**

- Renal ultrasound
- Bone marrow biopsy
- Light chain assay
- Kappa/Lambda

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**Cutaneous and Systemic Plasmacytosis**

**Epidemiology and Pathogenesis**

- Most common in Asians*
- Uncertain pathophysiology
  - Thought to be secondary to persistent auto or microbial antigenic stimulation
  - Cases have been reported to be associated with latent or chronic infections [1]
  - Potentially IL-6 mediated** [2]

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**Clinical Manifestations**

- Cutaneous plasmacytosis
  - Triad of cutaneous lesions, lymphadenopathy, polyclonal hypergammaglobulinemia
  - Classic multiple, persistent, asymptomatic to mildly pruritic plaques or nodules with a violaceous to brown color
  - Minimal to no epidermal change
  - Distribution on trunk (MC), face, and proximal extremities
- Systemic involvement
  - Constitutional symptoms in up to ~25%
  - Lungs [1,3]
  - Intestinal or nodular involvement
  - Lymph nodes, Kidney, Liver, Spleen, [1]
DIAGNOSIS

- Often diagnosis is delayed months to decades due to indolent growth\[1,4]\.
- Laboratory evaluation:
  - Polyclonal Hypergammaglobulinemia (MC)
  - Often kappa overexpression
  - Anemia (often mild)
  - Elevated erythrocyte sedimentation rate
  - Total serum protein elevation
  - Hypoalbuminemia (often mild)
  - Immunoglobulins
    - IgG elevation (MC)
    - IgG > 5.0 g/dL may be associated with constitutional symptoms or extracutaneous involvement \[5\]
    - IgA elevation
    - IgM elevation (uncommon)\[6\]
    - IgE elevation
    - Bence-Jones protein negative

DIAGNOSIS

- Skin biopsy
  - Dermal infiltrate of mature plasma cells with minimal to no atypia
  - Variable admixed lymphocytes and histiocytes
  - Perivascular or perifollicular superficial dermal prominence more commonly than a deep diffuse pattern
  - Lymphoid follicle formation may occur

DIAGNOSIS

- Systemic disease
  - Treat underlying cause identified*
  - However, treatment of coexisting diseases of does NOT result in improvement of plasmacytosis**
- Clinical signs and symptoms guide additional studies
  - Screening chest x-ray
  - CT scan
    - May have nodular or reticular patterns
  - Bone marrow biopsy
  - Lymph node biopsy
  - Renal biopsy***
### DDX
- Multicentric plasma cell variant of Castleman disease (MPCD)
  - More aggressive clinical course
  - Generalized lymphadenopathy
  - Polyclonal hypergammaglobulinemia
  - Often lambda overexpression
  - Anemia
  - Constitutional symptoms
  - HHV-8 positive
    - Even present in up to 50% of HIV-negative patients
- Idiopathic plasmacytic lymphadenopathy
  - More indolent course
  - Low risk of associated secondary disease
  - May be a HIV-negative variant of MPCD
- IgG4-related disease
  - Multigland lymphoplasmacytic disease
  - Serum and lesional IgG4 elevated

### TREATMENT
- **Cutaneous manifestations**
  - Topical or systemic corticosteroids are minimally helpful
  - Intralosomal corticosteroids: Some benefit
  - Topical calcineurin inhibitors
  - Phototherapy
  - Radiotherapy
  - Intralosomal interferon-gamma
- **Lymphadenopathy**
  - Systemic corticosteroids
  - Systemic treatment
    - Alkylating chemotherapies
      - May provide partial response
    - Thalidomide
    - Other minimally effective [6-9]

### PROGNOSIS
- Rare with uncertain spectrum of disease
- If aggressive similar appearing diseases negative than tends to have slowly progressive course
- HHV-8 negative and not lambda restricted (i.e., multicentric plasma cell variant of Castleman disease)
- IgG4 disease
- Systemic manifestations may occur years to decades after initial cutaneous lesions
- Rarely death associated with pulmonary or renal involvement

---
SUMMARY

- Cutaneous plasmacytosis is a poorly defined entity and may be representative of an indolent systemic process.
- Diagnosis is suspected by the presence of multiple red-brown plaques with little epidermal change and established by histopathology. This demonstrates dermal perivascular and periadnexal plasma cells. Polyclonal hypergammaglobulinemia is often present.
- No consistent therapy.

REFERENCES

Infections and Infestations
What's eating you?

Tammie Ferringer, MD
Geisinger Medical Center,
Danville, PA
tferringer@geisinger.edu

I do not have any relevant relationships with industry

Case 1
A husband and wife returned from Costa Rica with nodules on the scalp
Diagnosis?

Myiasis
- Infestation of tissue by larvae of Diptera
- Wound and furuncular myiasis
**Furuncular Myiasis**

- Botfly: Dermatobia hominis
- 2 to 6 rows of dark hook-like setae prevent dislodgment
- Warm humid, low land forests of Central and S America
- Usually exposed sites
- Subcutaneous mass with pore
9 year old with lump on right posterior scalp

Furuncular Myiasis

Undulating chitinous wall

Pigmented setae

Stable fly macro
DDx-Tungiasis

- Acral skin
- Spines
- Chitinous wall
- Perforated muscle

Take Home

- Furuncular Myiasis
  - Botfly- Dermatobia hominis
  - Pigmented setae
- Tungiasis
  - Sand flea- Tunga penetrans

Case 2

This was removed from an African natural stationed at Lackland
Diagnosis?

Onchocercoma

- Nematode *Onchocerca volvulus*
- Vector: Black fly (*Simulium*)
- Clinical
  - Subcutaneous nodule (onchocercoma)
  - Hanging groin
  - Sowda's reaction: hyperpigmented, lichenified plaques due to microfilaria in skin
  - African River Blindness
Onchocercoma

- Fibrous nodule containing multiple coiled adult worms
- Weak band of muscle
- Microfilaria in paired uteri
DDx Sparganosis
- Cestode (tape worm)
- *Spirometra*
- Drinking impure water contaminated by the first intermediate host (copepods)
- Eating raw or undercooked second intermediate hosts (frogs or snakes)
- Use of frog or snake poultice

DDx Sparganosis

Take Home
- Oncocerciasis
  - Nematode: *Onchocerca volvulus*
  - Vector: Black fly
- Sparganosis
  - Cestode: *Spirometra*
  - Intermed host: Frogs
29 year old female with pruritic firm papules and plaques in a zosteriform pattern for approximately 3 months

Case 3

Courtesy Rute Lellis
Diagnosis?

Schistosomiasis
- Blood fluke (Trematode)
- Anogenital lesions typical
Swimmer’s Itch
- Cercarial dermatitis
- Non-human schistosomal larvae
  - Can’t complete life cycle
- Freshwater lakes and ponds
- Exposed areas

Schistosomiasis
Take Home: Helminths

Platyhelminths
- Flat Worms
- Cestodes
- Tapeworms

Trematodes
- Flukes

Nematodes
- Round Worms

- Sparganosis
- Schistosomiasis
- Pinworm
- Cutaneous larva migrans
- Strongyloides
- Loa loa
- Filariasis
- Onchocerciasis

Case 4

Multiple erythematous papules coalescing into scaling plaques on back and upper arms. Favor contact vs eczematous drug, rule out CTD (SCLE) vs less likely PRP vs eczematous BP vs other.
Scabies

[Images of skin lesions and microscopic view of mites]


Clues to Scabies: Pigtails

Chitin pigtails

Part of the egg case
Other Clues to Scabies-DHR

Table 1. Number of scabies cases demonstrating specific diagnostic features (n=250)

<table>
<thead>
<tr>
<th>Histopathologic feature</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicles/papillae associated with mite</td>
<td>19 (76%)</td>
</tr>
<tr>
<td>Hair follicles (empty egg cysts)</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Mite burrows</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Mite tracks</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Superficial fibroblasts</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Granular inclusions</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Spongiosis</td>
<td>15 (60%)</td>
</tr>
<tr>
<td>Neutrophilic microabscesses</td>
<td>17 (68%)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Superficial perivascular infiltrates</td>
<td>15 (60%)</td>
</tr>
<tr>
<td>Superficial perivascular infiltrates</td>
<td>15 (60%)</td>
</tr>
<tr>
<td>Eosinophilic infiltrates</td>
<td>15 (60%)</td>
</tr>
<tr>
<td>VESicles</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

Elwood H, JCP 2015.

Beware CD30
Beware CD30

CD30 antigen expression in cutaneous inflammatory infiltrates of scabies: a dynamic immunophenotypic pattern that should be distinguished from lymphomatoid papulosis.

Beware CD1a

Langerhans cell hyperplasia in scabies: a mimic of Langerhans cell histiocytosis.
Non-Human Scabies

- “Mange” is an infestation by mites
- Sarcoptic mange (burrowing)
  - Intense pruritus, hair loss, ears and limbs most
- Cheyletiella (non-burrowing)
  - Asymptomatic to dry scale and pruritus on the back and shoulders
Scabies and Cheyletiella
- Bite and run
  - Do not burrow
- Pruritic, papular eruption in areas of contact
- 1/3 of human contacts are susceptible

Treatment consists of eradication of the source
- Involve the vet

Take Home- Scabies
- Human scabies
  - Histologic clue: Pig tails
- Mange
  - Sarcoptic and cheyletiellosis
  - Bite and run
- Beware CD30 and CD1a
Festoons

- Ixodes scapularis
- Deer or black legged tick
- Orange-red body surrounds black scutum
- No festoons
- Transmits Lyme, anaplasmosis, and babesiosis
Dermacentor variabilis
- Dog or wood tick
- Ornate scutum against a dark brown body
- Festoons
- Transmits RMSF and tularemia

Ixodes: smooth bottom, boring scutum, anterior anal groove

Tick Borne Disease
Lyme disease

- 300,000 new cases in USA and 100,000 new cases in Europe annually

Erythema Migrans: Clinical Appearance

55 yo with history of myeloma and 4 days of fever, nausea, and fatigue
Superficial and deep perivascular and interstitial
Lymphs, plasma cells, neutrophils
Eosinophils at bite
**Borrelia burgdorferi**
- Spirochete 10-25μm long

**Spirochete Identification**
- Silver stains positive in up to 40%
- Bite: cluster in center of inflammatory process
- EM: most organisms at periphery between collagen bundles

**Borrelia IHC**
Contaminate

Case 6  75 year old female

- 1 year history of undiagnosed joint pain
- 6 month history of redness, swelling and pain of the dorsal feet and hand
- Favor erythromelalgia, may also consider pernio
Diagnosis?
Differential

- Inflammatory morphea
- Necrobiosis lipoidica
- IgG4 related sclerosing disease
- Plasma cell dyscrasia
- Acrodermatitis chronica atrophicans
Decreased expression of the human progenitor cell antigens (CD34) in morphea.

- CD34
- IgG and IgG4
- Kappa and lambda
- Silver stain
- No increase of IgG4
- CD34 interstitial loss
- Kappa:lambda normal
- Silver stain negative

**Additional History**

- Traveled to France in 1998
- Lyme titers positive in 9/10 IgG bands and 2/3 IgM bands
3 mos s/p 4 week course of doxycycline her cutaneous and rheumatologic symptoms resolved, discoloration improved and she can wear her wedding band.
Acrodermatitis Chronica Atrophicans

- Red to violet distal extremities with swelling
- Can be sclerodermatous or lichen sclerosus-like
- Late atrophic lesions resemble crumpled tissue paper
- Older women
- 20% have history of EM 6 months to 8 years prior


Identification of Three Species of *Borrelia burgdorferi* Sensu Lato (B. burgdorferi Sensu Stricto, B. garinii, and B. afzelii) Among Isolates from Acrodermatitis Chronica Atrophicans Lesions

**Table II. Frequency of isolation of *Borrelia* spp. from acrodermatitis chronica atrophicans lesions**

<table>
<thead>
<tr>
<th>Species</th>
<th>LRFP</th>
<th>No. of isolates obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>B. burgdorferi sensu stricto</em></td>
<td>M102</td>
<td>1</td>
</tr>
<tr>
<td><em>B. garinii</em></td>
<td>M102</td>
<td>9</td>
</tr>
<tr>
<td><em>B. afzelii</em></td>
<td>M101</td>
<td>17</td>
</tr>
</tbody>
</table>

Take Home

- Swelling of the distal extremity with bluish red plaques and diffuse infiltrate of histiocytes and plasma cells, consider ACA
- Can mimic interstitial GA and morphea
Case 7

Diagnosis?
**DDx Parasitized Histiocytes**

- Penicillium marneffii (fungal)
- Histoplasmosis (fungal with halo)
- Granuloma Inguinale (bacterial, Donovan bodies)
- Rhinoscleroma (bacterial, Mikulicz cells)
- Leishmaniasis (protozoa)
- Leprosy (mycobacterial)

**PCR was positive for L. panamensis**

**Leishmaniasis**

- Protozoa
- Phlebotomus and Lutzomyia sand fly
- Cutaneous, destructive mucocutaneous and visceral
Leishmaniasis

- Histoplasma capsulatum
- Mississippi and Ohio river valleys
- Bird and bat feces, caves, chicken coops
- Look at the border of the necrotic and viable tissue

Histoplasmosis

- Histoplasma capsulatum
- Mississippi and Ohio river valleys
- Bird and bat feces, caves, chicken coops
- Look at the border of the necrotic and viable tissue

Take Home

- Leishmania
  - Protozoa
  - Sandfly
- Histoplasmosis
  - Fungal
  - Inhaled
Case 8

Oozing nodules on the face of a horse farmer
Diagnosis?

Orf

- Also known as ecthyma contagiosum
- Parapoxvirus
- Sheep and goats
- Humans usually develop a single lesion on the hand 2-6 days after inoculation

Six stages each lasting one week
1. Erythematous maculopapular
2. Targetoid
3. Acute weeping nodule
4. Dry crusted nodule
5. Papillomatous
6. Regressive
Orf DDx Milker’s Nodule

- Poxvirus-Paravaccinia
- Cows have crusted erosions and papules around the nose and teats
- Same six stages as orf
- Lesions typically smaller than orf

Reticular Degeneration DDx: HFMD

HFMD
Reticular Degeneration DDx: Smallpox

Resurrected DP
- Jar found by the janitor in the basement at IU

Case 9
7 yo foster child with scalp nodules draining large grains
Mycetoma
- Tumefaction, draining sinuses, and grains of filamentous structures
- 2 types: Fungal and Bacterial

Eumycetoma
- Fungal
- Hands and feet in tropical areas
Eumycetoma

- Dark grains:
  - Madurella mycetomatis
  - Madurella grisea
  - Exophiala jeanselmei (My greasy jeans are back)
- Non-pigmented grains:
  - Pseudoallescheria boydii
  - Fusarium
  - Acremonium
**Case 9: Microsporum canis**

**DDx Actinomycetoma**
- Filamentous bacteria
- Light grains
- *Nocardia Actinomyces*
- *Streptomyces*
- Thin filaments less than 1 micron

**DDx Botryomycosis**
Case 10: 92 yo with history of trauma while working on farm
Phaeohyphomycosis
- Infection by pigmented (dematiaceous) hyphae
- Variety of pigmented fungi, including
  - Alternaria, Bipolaris, Curvularia, Exophiala, Phialophora
- Cystic granuloma (pseudocyst) often due to a splinter, in immunocompetent patients
DDx: Chromomycosis
45yo Honduran man with eruption on the dorsal hand
DDx: Hypertrophic LP vs SCC

PEH with Pus

Bug Hunt

- Check
  - Pus
  - Border of necrotic zone
  - Multinucleate giant cells
  - Crust
  - Vacuoles
  - Foreign body (especially splinter)

“Here come big green leafy veggies”
- Halogenoderma
- Chromomycosis
- Blastomycosis
- Granuloma inguinale
- Leishmaniasis
- Pemphigus vegetans
Chromoblastomycosis

- Congenital
- Dermatophytes
- Malassezia
- Keratinophilic fungi

Case 11

35 yo neutropenic AML patient with fever and cough
**Aspergillosis**

- Opportunistic fungi of soil and decomposing vegetation
- Cutaneous
  - Primary-IV catheters, adhesive tape
  - Secondary-hematogenous or contiguous spread, usually from sinuses or lungs
  - Red-purple necrotic patches or plaques

- Slender, thin walled, septate hyphae
- Dichotomously branching
- Bubbly blue cytoplasm
- Vasculotropic with thrombosis, infarction, and hemorrhage

**DDx Fusarium**

<table>
<thead>
<tr>
<th>Fusarium</th>
<th>Aspergillus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septate</td>
<td>Septate</td>
</tr>
<tr>
<td>Vesicular swellings</td>
<td></td>
</tr>
<tr>
<td>Thick refractile wall</td>
<td></td>
</tr>
</tbody>
</table>
DDx Zygomycosis

- Red, thick walled hollow hyphae that are broad and irregular
- Mucor, Absidia, Rhizopus, Cunninghamella

Questions?
Fig. 30.8 Urticarial phase of bullous pemphigoid – histologic features. Eosinophils are present within the dermis as well as the epidermis (eosinophilic spongiosis). Some of the eosinophils have lined up at the dermal-epidermal junction, a typical finding in the urticarial stage of BP. Courtesy, Lorenzo Cerroni, MD

Fig. 30.9 Bullous pemphigoid – histologic features. Subepidermal blister which contains fibrin, eosinophils and mononuclear cells (see inset). Courtesy, Lorenzo Cerroni, MD
**Tips for Bullous Pemphigoid**

1. Antibacterial body washes/Bleach baths
2. Topical triamcinolone 0.1% cream 3:1 in Silvadene cream
3. Weekly methotrexate corrected for age/creatinine
4. Lower dose prednisone
5. 2 year program
6. Keep perfect
7. Rituximab is an option for resistant disease


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**Lichen Planus**

**Key Features**

- Idiopathic, inflammatory disease of the skin, hair, nails and mucous membranes, seen most commonly in middle-aged adults
- Flat-topped violaceous papules and plaques favoring the wrists, forearms, genitalia, distal lower extremities and presacral area
- Clinical variants include annular, bullous, hypertrophic, inverse, linear, ulcerative, vulvovaginal-gingival, drug-induced and lichen planopilaris
- Some lichenoid drug eruptions have a photodistribution, while others are clinically and histologically indistinguishable from idiopathic lichen planus

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**Lichen Planus**

**Key Features (Cont.)**

- The most commonly incriminated drugs include angiotensin-converting enzyme (ACE) inhibitors, thiazide diuretics, antimalarials, quinidine and gold
- Histologically there is a dense, band-like lymphocytic infiltrate and keratinocyte apoptosis with destruction of the epidermal basal cell layer
- In this T-cell-mediated autoimmune disorder, basal keratinocytes express altered self-antigens on their surface
Fig. 11.5 Lichen planus on the dorsal surface of the hand. Wickham's striae can be easily identified in the upper lesion. Note the flat-topped nature of the lesions and the post-inflammatory hyperpigmentation. Courtesy, Frank Samarin, MD.
Fig. 11.6 Lichen planus. Violaceous papules and plaques with white scale and Wickham's striae.

Fig. 11.7 Koebnerization of lichen planus into the site of the excision of the saphenous vein. Lesions also appeared where Steri-Strips™ had been applied.

Fig. 11.8 Annular lichen planus of the glans penis (A) and the trunk (B). On the penis, the lesions have led to a figurate outline with central hyperpigmentation.

A, Courtesy, Frank Samarin, MD
Fig. 11.9 Exanthematous lichen planus. Papulosquamous lesions on the back.

Fig. 11.10 Unusual variants of lichen planus. (A) Atrophic lichen planus of the lower extremities. (B) Bullous lichen planus on the shin. (C) Lichen planus pemphigoides in a patient with anti-basement membrane zone antibodies.

Fig. 11.11 Hypertrophic lichen planus. (A) On the shin, very thick discrete plaques with dyspigmentation are admixed with smaller linear plaques and areas of postinflammatory hyperpigmentation. (B) On the dorsal digits, thin violaceous plaques in addition to thick keratotic plaques that favor the knuckles.

B. Courtesy Joyce Rico, MD
Fig. 11.12 Inverse lichen planus. Oval thin violaceous plaques in the axilla. Postinflammatory hyperpigmentation is also present. Courtesy, Jeffrey P. Callen, MD

Fig. 11.13 Lichen planopilaris. (A) Keratotic spines surrounded by a violaceous rim in a linear variant and (B) scattered on the trunk. (C) Cicatricial alopecia with “end-stage” changes centrally, but perifollicular inflammation at the margins.

Fig. 11.14 Linear lichen planus. Coalescence of violaceous lesions with Wickham’s striae along the lines of Blaschko on an extremity. Note the postinflammatory hyperpigmentation proximally. Courtesy, Joyce Rico, MD
Fig. 11.15 Nail lichen planus. (A) Thinning of the nail plate with lateral loss. (B) Longitudinal fissuring of shortened nail plates. (C) Violaceous discoloration of the periungual area with pterygium formation.

Fig. 11.16 Oral lichen planus. (A) White lacy pattern and an erosion on the buccal mucosa, the most common location for the reticular form. Note the ring configuration with short radiating spines. (B) Erosions on the lateral aspect of the tongue in addition to lacy white plaques and scarring. B. Courtesy, Louis A. Fragola, Jr, MD

Fig. 11.17 Lichenoid drug eruption. Photodistributed lichenoid eruption due to hydrochlorothiazide (note sparing under watchband).
Fig. 11.18 Histopathologic features of lichen planus. Hyperkeratosis, focal increase in the granular layer, sawtoothing of the epidermis with keratinization of the basal layer, and a lichenoid infiltrate. Apoptosis of keratinocytes and melanophages are also present (H&E). Courtesy, Lorenzo Cerroni, MD

TIPs for Oral Lichen Planus

- Water pick
- Manage Candida acutely with fluconazole and chronically with daily clotrimazole troche
- CREST whitening (dilute peroxide)
- 1mg tacrolimus capsule – open & dissolve in ½ liter water swish and spit for 2 minutes (Ortonne)
- Topical and/or intralesional corticosteroids
- Oral methotrexate or mycophenolate if needed
- Biopsy as indicated for exclusion of SCC

Torti DC, Jorizzo JL. Arch Dermatol 2007;143:511-515
Pemphigus Vulgaris

Key features
- Pemphigus is a group of autoimmune blistering diseases of the skin and mucous membranes that is characterized by:
  - Histologically, intraepidermal blisters due to the loss of cell-cell adhesion of keratinocytes
  - Immunopathologically, the finding of in vivo bound and circulating IgG autoantibodies directed against the cell surface of keratinocytes
  - Pemphigus is divided into three major forms: pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus

Key features (cont.)
- The functional inhibition of desmogleins, which play an important role in cell-cell adhesion of keratinocytes, by IgG autoantibodies results in blister formation
- Patients with pemphigus vulgaris and pemphigus foliaceus have IgG autoantibodies against desmoglein 3 and desmoglein 1, respectively, while patients with paraneoplastic pemphigus have IgG autoantibodies against plakin molecules in addition to autoantibodies against desmogleins
- IgA autoantibodies directed against the keratinocyte cell surface define IgA pemphigus, the pathophysiology of which is yet to be clarified

Classification of Pemphigus
- Pemphigus vulgaris
- Pemphigus vegetans
- Pemphigus foliaceus
- Pemphigus erythematosus localized
- ligo salvagens endemic
- Herpetiform pemphigus
- Drug-induced pemphigus
- Neoplastic pemphigus
- IgG pemphigus

Table 20.1 Classification of pemphigus.
Fig. 29.1 Indirect immunofluorescence of pemphigus sera with normal human epidermis as a substrate. The hallmark of pemphigus is the finding of IgG autoantibodies directed against the cell surface of keratinocytes.

A. Pemphigus vulgaris sera containing anti-desmoglein 3 (anti-Dsg3) IgG alone stain the cell surfaces in the lower epidermis.

B. Pemphigus vulgaris sera containing both anti-Dsg3 IgG and anti-Dsg1 IgG stain the cell surfaces throughout the epidermis.

C. Pemphigus foliaceus sera, which contain only anti-Dsg1 IgG, stain the cell surfaces throughout the epidermis, but more intensely in the superficial layers.

### Table 29.1 Target antigens in pemphigus

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Nature of Antibody</th>
<th>Target Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemphigus vulgaris</td>
<td>IgG</td>
<td>Desmoglein 3</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>IgG</td>
<td>Desmoglein 1</td>
</tr>
<tr>
<td>Pemphigus foliaceus</td>
<td>IgG</td>
<td>Desmoglein 1</td>
</tr>
<tr>
<td>IgG pemphigus*</td>
<td>IgG</td>
<td>Desmoglein 1</td>
</tr>
</tbody>
</table>

*Denotes only a minor contribution to disease pathology.

**Table 29.2 Treatment for pemphigus vulgaris**

<table>
<thead>
<tr>
<th>Standard Treatment</th>
<th>Topical Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral prednisone 1.0 mg/kg/day</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Oral azathioprine 2-3 mg/kg/day</td>
<td>Topical corticosteroids</td>
</tr>
<tr>
<td>Oral mycophenolate sodium 3 g/day</td>
<td>Topical corticosteroids</td>
</tr>
<tr>
<td>Oral ciclosporine 150 mg/day</td>
<td>Topical corticosteroids</td>
</tr>
<tr>
<td>Oral mercaptopurine 1 mg/kg/day</td>
<td>Topical corticosteroids</td>
</tr>
<tr>
<td>Oral dapsone 10 mg/kg/day</td>
<td>Topical corticosteroids</td>
</tr>
<tr>
<td>Oral retinoids 100 mg/day</td>
<td>Topical corticosteroids</td>
</tr>
<tr>
<td>Oral methotrexate 5 mg/day</td>
<td>Topical corticosteroids</td>
</tr>
<tr>
<td>Oral tetracycline 300 mg/day</td>
<td>Topical corticosteroids</td>
</tr>
<tr>
<td>Oral acitretin 10 mg/day</td>
<td>Topical corticosteroids</td>
</tr>
<tr>
<td>Oral etretinate 50 mg/day</td>
<td>Topical corticosteroids</td>
</tr>
<tr>
<td>Oral thalidomide 50 mg/day</td>
<td>Topical corticosteroids</td>
</tr>
</tbody>
</table>

*Denotes either a minor contribution to disease pathology or a high risk of toxicity.
Tips for Pemphigus Vulgaris

- Waterpick
- Manage Candida acutely with fluconazole and chronically with daily clotrimazole troches
- CREST whitening (dilute hydrogen peroxide)
- 1mg tacrolimus capsule (open & dissolve in ½ liter of water – swish and spit for 2 minutes (Ortonne))
- Topical and/or intralesional corticosteroids
- Choose: Rituximab versus Prednisone and Mycophenolate


Sarcoidosis

Key Features

- A systemic granulomatous disorder of unknown origin that most commonly involves the lungs
- Cutaneous manifestations of sarcoidosis are seen in up to one-third of patients, and they may be the first clinical sign of the disease
- Red-brown to violaceous papules and plaques appear most often on the face, lips, neck, upper back and extremities
- Variants of sarcoidosis include subcutaneous, lupus pernio and ulcerative
- Erythema nodosum is a non-specific inflammatory skin finding associated with acute, transient sarcoidosis
- Histologically, sarcoidosis is characterized by non-caseating epitheloid granulomas, usually without surrounding lymphocytic inflammation (i.e. ‘naked’ granulomas)
Sarcoidosis: Systemic Features

- SURT
- Intrathoracic
- Ocular
- Lymph Nodes
- Musculoskeletal
- Neurosarcoidosis
- Hepatic sarcoidosis
- Cardiac
- Endocrine metabolic
Sarcoidosis: Pathogenesis

- Unknown
- Genetically susceptible host
- Environmental trigger
- Toll-like receptors (innate immune system) and Th17 as well
- Key cytokines: Th1 (Il-2, 12, 18); IFNgamma, granulocyte-monocyte stimulating factor, and TNF alpha
- Secretion of angiotensin converting enzyme (not reliable for diagnosis)

Sarcoidosis: Evaluation

- Clinicopathologic correlation
- Exclude infections and foreign body granulomas
- Organs effected:
  - Eyes – Ophthalmology
  - Lungs – Pulmonary Medicine
  - Calcium and Phosphate
  - EKG
  - PFTs with diffusion studies
  - CXR +/− imaging
  - Chemi/CBC/u/A
  - Quantiferon gold
Granuloma Annulare

Key Features

- Small grouped papules assuming an annular configuration often in a symmetrical and acral distribution
- Seen primarily in children and young adults
- Clinical variants include localized, generalized, micropapular, nodular, perforating, patch and subcutaneous forms
- Reports of an association with diabetes mellitus are controversial
- Histopathologic specimens show infiltrative or palisading granulomatous dermatitis with focal degeneration of collagen and elastin and deposition of mucin
Treatment of Granuloma Annulare

- Topical Corticosteroids (3)
- Intralesional corticosteroids (2)
- Cryosurgery (2)
- Topical calcineurin inhibitors (3)
- Topical imiquimod (3)
- Hydroxychloroquine (6mg/kg/day) or chloroquine (3mg/kg/day)\(^\diamond\) (2)
- Niacinamide (nicotinamide: 500 mg TID) (3)
- PUVA (psoralen plus UVA) or UVA1 (2)
- Pentoxifylline (3)
- Intralesional interferon-\(\gamma\) (3)
- 5-lipoxygenase inhibitor (zileuton) plus vitamin E\(^t\)
- Dapsone (100mg/day) (3)
- Isotretinoin (0.5-0.75 mg/kg/day), acitretin (3)
- Minocycline + ofloxacin + rifampin\(^*\) (3)
- Methotrexate (3)
### Treatment of Granuloma Annulare (Cont)

- Prednisone (3)
- Cyclosporine (3-4mg/kg/day x 3 months) (3)
- TNF-α inhibitors (adalimumab, infliximab) (3)
- Fumaric acid esters (3)
- Chlorambucil (3)
- Photodynamic therapy with topical 5-aminolevulinic acid (3)
- Lasers: CO₂, pulsed dye (585nm), excimer (308nm) (3)
- Electodesiccation (3)
- Surgical excision (3)

*Currently recommended doses to minimize retinopathy (see Ch. 130): hydroxychloroquine 5mg/kg (real weight)/day and chloroquine 2.3 mg/kg (real weight)/day

* Administered monthly: minocycline (100mg), ofloxacin (400mg) and rifampin (600mg) 3 months; improvement not observed in subsequent studies.

†Doses of 2400 mg po daily (zileuton) and 400 IU daily (vitamin E).

### Necrobiosis lipoidica

**Key Features**

- Plaques with violaceous to red-brown, palpable peripheral rims and yellow-brown atrophic centers with telangiectasias
- The most common site is the shins
- Ulceration can occur following trauma
- The proportion of patients with diabetes mellitus varies from 14% to 65%
- Pathogenesis is unknown but correlates with retinopathy and nephropathy
- Pathology shows palisading granulomatous dermatitis with a 'layered' appearance, often with perivascular plasma cells
Necrobiosis lipoidica Treatment

- Topical corticosteroids – pulse superpotent
- Keratolytic topicals plus – topical tacrolimus
- Aspirin/Dipyridomol
- Pentoxifylline
- Nicrotinamide
- Clofazimine
- Misc: topical retinoids, heparin, antimalarials, thalidomide, cyclosporine, biologics, surgery, photodynamic therapy, etc