Skin Signs of Internal Disease: Case-based Challenges

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Disclosure (previous 12 months)

• Consultant – Biogen/IDEC, Lilly, Amgen
• Editorial Boards – UpToDate (editor-in-chief, Dermatology), JAMA Dermatology (Associate Editor), Cutis, emedicine.com, Journal of Drugs in Dermatology, Medicine, Journal of Psoriasis and Psoriatic Arthritis
• Equity holdings (trust accounts) - Celgene; Pfizer; 3M; Johnson and Johnson; Merck; Abbott Laboratories; AbbVie; Procter and Gamble; CVS; Walgreens; Allergen; Amgen
• I will discuss “off-label” uses of some of the currently available agents and will identify which are labeled v. off-labeled uses.

February 2018
Case 1
44-year-old man

- HPI: Presented in March 2017 with a 1-yr h/o “skin ripping” and genital edema affecting the penis and scrotum
- PMH: 3-year h/o Crohn’s Disease with anorectal fistulas previously treated with adalimumab which was stopped due to MRSA abscesses. Vedolizumab was begun in January 2015.
- ROS: revealed h/o purulent drainage from the penis and inguinal lymphadenopathy, but was negative for abdominal pain, bleeding problems, cough, fevers/chills, joint aches, weight loss or gain
- Medications: Vedolizumab 300 mg IV q monthly, testosterone 0.75 mg q weekly, doxycycline, ibuprofen
What is your diagnosis?

1. Metastatic Crohn’s disease
2. Hidradenitis suppurativa
3. Lymphedema
4. Sarcoidosis
5. Balanoposthitis
Course

- At the time of his visit, he informed us that he had seen urology and they had performed a biopsy of the penis and scrotum
- He was told that the findings were “non-specific”
What is the next step in evaluation of this patient?

1. Biopsy of the penis
2. Biopsy the perianal skin
3. Obtain the prior slide for review
4. Order Sacchaeryomyces Cerevisiae antibody
5. Order Antineutrophil cytoplasmic antibodies
Biopsy findings

• The slides from prior biopsies were obtained and revealed non-specific changes from the penis, but demonstrated focally granulomatous zones (non-caseating) as well as lymphocytic and plasmacytic inflammation which is compatible with Cutaneous Crohn’s Disease (aka Metastatic Crohn’s Disease)
What therapy should be recommended?

1. Oral metronidazole
2. SQ ustekinumab
3. Oral azathioprine
4. SQ methotrexate
5. SQ adalimumab
6. Oral mesalamine
Course

- His bowel disease was deemed to be reasonably well controlled, but his perianal fistula disease was active
- GI switched from vedolizumab to ustekinumab (GI dosing)
- We suggested the addition of metronidazole which he took for 3 months and reported little change
Ano-genital Granulomatosis and Crohn’s Disease: A Case Series of Males Presenting with Genital Lymphoedema

Table 2. Proportion and distribution of anatomy affected in male patients diagnosed with ano-genital granulomatosis (AGG) both with and without Crohn’s disease (CD).

<table>
<thead>
<tr>
<th>Anatomy affected by lymphoedema</th>
<th>AGG no CD</th>
<th>AGG + CD</th>
<th>All AGG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penis</td>
<td>87%</td>
<td>100%</td>
<td>92%</td>
</tr>
<tr>
<td>Scrotum</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Mons pubis</td>
<td>27%</td>
<td>30%</td>
<td>28%</td>
</tr>
<tr>
<td>Buttock</td>
<td>27%</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Perineum</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Perianal</td>
<td>13%</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>Natal cleft</td>
<td>13%</td>
<td>10%</td>
<td>12%</td>
</tr>
</tbody>
</table>
Which of the following statements is accurate?

1. “Metastatic Crohn’s disease” is synonymous with “cutaneous Crohn's disease”
2. Presence or severity of metastatic Crohn’s disease does not correlate with severity or activity of the GI disease
3. Treatment of underlying GI disease leads to resolution of skin lesions
4. Patients with metastatic Crohn’s disease have less frequent involvement of the colon
Metastatic Crohn’s Disease

- First described in 1965 by Parks, et al.
- A rare granulomatous inflammation of skin noncontiguous with the GIT
- May occur prior to, simultaneously with GI disease or following GI surgery
- The severity of skin involvement does not always parallel severity of GIT disease
- 56% genital involvement; 44% non-genital involvement (extremities, trunk, intertriginous/flexural skin, face/lips)
- Children tend to have more genital involvement than adults
Fig 1. Crohn’s disease. Granulomatous erosion of peri-
Fig 2. Crohn’s disease. Labial swelling.
Fig 3. Crohn’s disease. Typical cobblestoning of the hard

From Thrash et al. JAAD. 2013. 68(2) e1-e33.
Crohn's disease of the vulva.

Treatment options

- Topical, intralesional, systemic corticosteroids
- Antibiotics
  - Dapsone
  - Sulfasalazine
  - Metronidazole
  - Tetracycline
- Immunosuppressive agents:
  - Azathioprine or 6-Mercaptopurine
  - Mycophenolate mofetil
- Biologics:
  - TNF-alpha inhibitors (infliximab, adalimumab, certolizumab, etc.)
  - Ustekinumab
- Thalidomide
- Surgical debridement, hyperbaric oxygen, and fecal diversion useful in resistant cases
Conclusions

• Consider MCD in the clinical differential diagnosis of hidradentitis supprativa, dermatitis, intertrigo, chronic cellulitis, sarcoidosis, mycobacterial or fungal infections, erysipelas, etc.

• High degree of clinical suspicion is necessary

• Consider MCD particularly in children with genital and/or perianal fissures, ulcers, “skin tags” or unusual swelling
Case 2
63-year-old man

- 1-yr h/o waxing and waning eruption on the inner thighs and left inner arm.
- He denies any associated fever, chills, fatigue, night sweats, weight loss, abdominal pain, nausea, diarrhea. He said that the areas seems to flare after golfing or working outdoors.
- Outside biopsy in October 2016 interpreted as Sweet syndrome, in August 2017 as interstitial granulomatous dermatitis
- PMH: allergies, hypertension, GERD, prior hepatitis C
- Medications: baby aspirin, fexofenadine, atenolol, omeprazole, sertraline, tamsulosin
What is your diagnosis?

1. Granuloma annulare
2. Interstitial granulomatous dermatitis
3. Sweet syndrome
4. Palisaded neutrophilic and granulomatous dermatitis
5. Sarcoidosis
What is the most appropriate next step?

1. Obtain outside biopsies for review
2. Biopsy current eruption
3. Order a chest X-ray
4. Order an immunofixation electrophoresis
5. Order serologic testing for lupus and rheumatoid arthritis
6. All of the above
Evaluation

• The outside biopsies were reviewed and several new biopsies were performed which revealed changes c/w PNGD
• Laboratory testing revealed normal CBC, CMP, ANCA, IFE, RF, Hepatitis C viral load, ACE level, antiphospholipid antibodies, G-6PD, TMPT
• ANA 1:80, anti-nDNA 58 IU/mL (nl <5), Ro/SS-A 48 AU/mL (nl < 40), Hepatitis C antibody, MTHFR polymorphism
What is the most appropriate diagnosis now?

1. Palisaded neutrophilic and granulomatosus dermatitis
2. Sarcoidosis
3. Interstitial granulomatous dermatitis drug reaction
4. Interstitial granulomatous dermatitis
5. Reactive granulomatous dermatitis
What is the most appropriate therapy at this time?

1. Treat with prednisone
2. Treat with methotrexate
3. Treat with plaquenil
4. Treat with dapsone
Course

• He was started on hydroxychloroquine 200 mg twice daily
• 2 weeks later an ophthalmologist called and reported that his eyes were crossing and he had double vision and advised that the hydroxychloroquine be stopped
• At that time, he reported that his rash had resolved and he was asymptomatic
What should be done at this time?

1. Observation
2. Start dapsone
3. Start methotrexate
4. Start azathioprine
5. Refer to rheumatology
Course

• He was not given any new therapy
• His eye symptoms resolved quickly
• He was seen 2 months later and remained asymptomatic and there was minimal erythema of the previously affected areas
• 1-month later he called to get treatment or further evaluation to “get to the bottom of this”
The Histopathologic Spectrum of Palisaded Neutrophilic and Granulomatous Dermatitis in Patients With Collagen Vascular Disease

Paul Chu, MD; M. Kari Connolly, MD; Philip E. LeBoit, MD

Palisaded neutrophilic granulomatous dermatitis with leukocytoclastic vasculitis in a patient without any underlying systemic disease detected to date
<table>
<thead>
<tr>
<th>Disease</th>
<th>Strength of Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connective tissue disease</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus$^{3,20,76,81}$</td>
<td></td>
</tr>
<tr>
<td>Limited systemic sclerosis$^8$</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated connective tissue disease$^{23}$</td>
<td></td>
</tr>
<tr>
<td>ANCA-associated vasculitis$^{3,9}$</td>
<td></td>
</tr>
<tr>
<td>Erythema elevatum diutinum$^{14}$</td>
<td></td>
</tr>
<tr>
<td>Sjögren’s syndrome$^6$</td>
<td></td>
</tr>
<tr>
<td>Mixed cryoglobulinemia$^8$</td>
<td></td>
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<tr>
<td>Takayasu’s aortitis$^{82}$</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis$^{3,11,14,17,22,23}$</td>
<td></td>
</tr>
<tr>
<td>Ankylosing spondylitis$^{83}$</td>
<td></td>
</tr>
<tr>
<td>Lymphoproliferative disease</td>
<td></td>
</tr>
<tr>
<td>Acute myelogenous leukemia, multiple myeloma, lymphoma$^{3,84}$</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis$^{18,19,25}$</td>
<td></td>
</tr>
<tr>
<td>Ulcerative colitis$^{3,12}$</td>
<td></td>
</tr>
<tr>
<td>Celiac disease and type I diabetes$^{85}$</td>
<td></td>
</tr>
<tr>
<td>Behçet’s$^6$</td>
<td></td>
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<tr>
<td>Multiple sclerosis$^8$</td>
<td></td>
</tr>
<tr>
<td>Cellulitis (in patient with SLE), subacute bacterial endocarditis, hepatitis, streptococcal infection$^{3,86}$, AIDS$^{87}$</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>TNF inhibitors, allopurinol$^{15}$</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>Strength of Association</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>++</td>
</tr>
<tr>
<td>SLE&lt;sup&gt;36,39,40,88,89&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated connective tissue disease&lt;sup&gt;37&lt;/sup&gt;</td>
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<tr>
<td>Inflammatory arthritides</td>
<td>+++</td>
</tr>
<tr>
<td>Rheumatoid arthritis&lt;sup&gt;38,40,43,47,50,73,90&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Seronegative arthritis&lt;sup&gt;38,49,55,70,91,92&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Hematologic disorders</td>
<td>++</td>
</tr>
<tr>
<td>IgA gammopathy&lt;sup&gt;38&lt;/sup&gt;, anemia and thrombocytopenia&lt;sup&gt;38,40&lt;/sup&gt;, lymphoma&lt;sup&gt;38,93,94&lt;/sup&gt;, myelodysplastic syndrome&lt;sup&gt;95&lt;/sup&gt;, myelodysplasia with leukemic progression&lt;sup&gt;96&lt;/sup&gt;, leukemia&lt;sup&gt;97&lt;/sup&gt;</td>
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<tr>
<td>Solid organ malignancies</td>
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<td>Breast&lt;sup&gt;38,46&lt;/sup&gt;, endometrial&lt;sup&gt;38&lt;/sup&gt;, lung&lt;sup&gt;98&lt;/sup&gt;, esophageal&lt;sup&gt;99&lt;/sup&gt;</td>
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<tr>
<td>Other</td>
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<td>Autoimmune hepatitis&lt;sup&gt;52&lt;/sup&gt;, uveitis&lt;sup&gt;42&lt;/sup&gt;, chronic inflammatory demyelinating polyneuropathy&lt;sup&gt;48&lt;/sup&gt;, autoimmune thyroiditis&lt;sup&gt;40,100,101&lt;/sup&gt;, antiphospholipid antibody syndrome&lt;sup&gt;102&lt;/sup&gt;, diabetes&lt;sup&gt;40&lt;/sup&gt;, vitiligo&lt;sup&gt;40&lt;/sup&gt;, pulmonary coccidiomycosis&lt;sup&gt;103&lt;/sup&gt;, Borrelia burgdorferi infection&lt;sup&gt;105&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Medications&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>TNF inhibitors&lt;sup&gt;60&lt;/sup&gt;, soy&lt;sup&gt;56&lt;/sup&gt;, angiotensin converting enzyme inhibitors&lt;sup&gt;59&lt;/sup&gt;, furosemide&lt;sup&gt;59&lt;/sup&gt;</td>
<td></td>
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<tr>
<td></td>
<td>PNGD</td>
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<tr>
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</tr>
<tr>
<td>Clinical morphology</td>
<td>Symmetric umbilicated papules on the elbows</td>
</tr>
<tr>
<td>Histology</td>
<td>Intense neutrophilic inflammation, ± leukocytoclastic vasculitis, degenerated collagen, palisading granulomas, minimal mucin</td>
</tr>
<tr>
<td>Associations</td>
<td>Connective tissue diseases, inflammatory arthritis, hematologic disorders</td>
</tr>
<tr>
<td>Evaluate for drug-induced disease</td>
<td>Review of medications</td>
</tr>
<tr>
<td>----------------------------------</td>
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</tr>
<tr>
<td>Evaluate for systemic disease</td>
<td>Connective tissue disease</td>
</tr>
<tr>
<td>Arthritis</td>
<td>RF/CCP, Rheumatology evaluation, Consider imaging</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Age appropriate malignancy screen, CBC with differential, SPEP/UPEP with IFE</td>
</tr>
<tr>
<td>Other</td>
<td>Chest radiography, Occult infections (endocarditis, hepatitis, pulmonary fungal infection)</td>
</tr>
<tr>
<td>Management</td>
<td>General</td>
</tr>
<tr>
<td>RGD specific</td>
<td>Watchful waiting, Topical or intralesional corticosteroids, NSAIDs, Dapsone, Hydroxychloroquine, Systemic corticosteroids, Consider additional agents in extensive/recalcitrant cases</td>
</tr>
</tbody>
</table>
Case 3
35-year-old woman

- Developed purpuric lesions on the legs and arms in January 2015
- Worsened in October 2015 at which time her internist sent her to a general surgeon for a skin biopsy which was interpreted as “urticarial vasculitis”
- Treated with intermittent prednisone tapers
- Noted to have elevated CRP, ESR and rheumatoid factor
- Referred to a rheumatologist in late 2015 whose evaluation excluded rheumatoid arthritis and treated with patient with colchicine 0.6 mg twice daily with little effect
- Rheumatologist referred the patient for management
HPI, PE and Labs: April 2016

- Denied abdominal pain, blood in urine, headaches, muscle, joint, bone pain, shortness of air, alcohol consumption
- Labs sent from rheumatology
  - ESR 39, Rheumatoid factor 950, ANA negative, ANCA negative, Anti-glomerular basement membrane ab negative, elevated transaminases, negative hepatitis profile, and urinalysis which revealed hematuria but not proteinuria or casts.
- PMH: hypertension
- Medications: lisinopril
- PE: massively obese (BMI = 42 kg/m²), purpuric lesions on legs, arms and buttocks
What should be done now?

1. Obtain slides from prior biopsy
2. Re-biopsy for routine processing
3. Biopsy for direct immunofluorescence microscopy
4. No additional biopsies are needed, go ahead and treat
5. 1, 2 and 3
What laboratory testing should be performed?

1. ANA
2. Anti-Ro/SS-A
3. Repeat hepatitis profile
4. Cryoglobulin
5. ANCA
DIF result

RESULTS
IgG: 1+ few superficial dermal blood vessels with grains in vessel walls, weak particulate intercellular, and few weak scattered and clumped cytoids

IgG4: Few weak scattered and clumped cytoids

IgM: 1-2+ few superficial dermal blood vessels with grains in vessel walls, weak focal granular basement membrane zone, and 3+ several scattered and clumped cytoids

IgA: 1-2+ few superficial dermal blood vessels with grains in vessel walls, weak focal granular basement membrane zone, and weak scattered and clumped cytoids

C3: 1-2+ few superficial dermal blood vessels with grains in vessel walls, weak focal granular basement membrane zone, and 1-2+ few scattered and clumped cytoids

Fibrinogen: 3+ patchy deposition on connective tissue fibers including perivascular
DIF interpretation

COMMENTS
These direct immunofluorescence findings are consistent with vasculitis based on vascular staining for IgG, IgM, IgA, and C3. The pattern of staining showing granules in blood vessel walls is typical of that observed in IgA vasculitis (Henoch Schönlein purpura). There is a slight prominence of IgA vascular staining. However, with the granular immune deposits along the basement membrane zone, the type of vasculitis associated with connective tissue disease including lupus erythematosus or hypocomplementemic urticarial vasculitis is suggested.

The IgG staining, in particular, also shows intercellular particulate (dust-like staining) which is weak and likely nonspecific but suggestive of the subacute cutaneous lupus erythematosus variant along with the vasculitis. Correlation with histopathological examination of formalin-fixed tissue, connective tissue disease serologies, and complement levels is needed.
Laboratory evaluation

- Abnormalities: AST 216 (nl < 46), ALT 439 (nl <69), Rheumatoid factor 426 IU (nl < 20), ANA 1:80 speckled, IFE – polyclonal pattern, IgG 1910 (nl <1618), IgA 529 (nl <378), cryoglobulin IgM 2.0 mg/dL (nl = 0)
- Normal or negative CBC, urinalysis, total hemolytic complement, C2, ANCA, Ro/SS-A, La/SS-B, IgM level on IFE
What is this patient’s diagnosis?

1. Henoch-Schönlein purpura
2. Hypersensitivity vasculitis
3. Vasculitis due to collagen vascular disease
4. Cryoglobulinemic purpura
5. Hyperglobulinemic purpura of Waldenstrom
What therapy should be administered now?

1. Dapsone
2. Leflunomide
3. Methotrexate
4. Azathioprine
5. Rituximab
6. Intravenous immune globulin
7. No therapy is needed
Course

• The patient was begun on dapsone and the dose escalated to 150 mg/day
• She was instructed to lose weight and a request was made for a liver biopsy to be performed and for her primary care physician to arrange for a dietitian to become involved
• The liver biopsy was performed, but the patient has not had meaningful weight reduction
• She continued over the next six months to have joint pain and showers of purpuric lesions, primarily on the legs
Subsequent Laboratory Evaluation

• 6-months
  – AST 111 (nl < 46), ALT 146 (nl <56), urinalysis – unremarkable, CBC normal
  – Liver biopsy – steatohepatitis with bridging fibrosis present

• 12-months
  – AST 136, ALT 219, urinalysis nl, CBC normal, Rheumatoid factor 451.2

• 15-months
  – IFE – IgG 1936 (nl < 1618), IgA 611 (nl< 378), Rheumatoid factor 241
What therapy should be administered now?

1. Add colchicine to the dapsone
2. Rituximab
3. Intravenous immune globulin
4. Azathioprine
5. Leflunomide
Course

• Colchicine was restarted and dapsone was continued
• No effect was noted
• Rituximab was initiated 18 months following initial presentation
  – 1 gram initially, repeated at 2 weeks
• Follow-up at 21-months
  – Clinically fewer lesions, but some continue
  – Weight loss of only 10 pounds
  – AST 37, ALT 43, IgG normal, IgA 386, Rheumatoid factor 183
• Labs at 23 months
  – AST and ALT normal, Rheumatoid factor 114
Cryoglobulinemic vasculitis v. Henoch-Schönlein purpura (aka IgA vasculitis)

<table>
<thead>
<tr>
<th>Cryoglobulinemic vasculitis</th>
<th>Vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with serum cryoglobulins.</th>
<th>Leukocytoclastic vasculitis of small vessels (postcapillary venules, small veins or arterioles) associated with serum cryoglobulins (usually type II and III)</th>
<th>Skin-limited cryoglobulinemic vasculitis</th>
<th>Cryoglobulinemic vasculitis of the skin without systemic vasculitis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA vasculitis (Henoch-Schönlein)</td>
<td>Vasculitis, with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles).</td>
<td>Leukocytoclastic IgA1-dominant vasculitis of postcapillary venules and arterioles in the skin, with vascular IgA deposits</td>
<td>Skin-limited IgA-vasculitis</td>
<td>Cutaneous IgA-dominant vasculitis without systemic vasculitis.</td>
</tr>
</tbody>
</table>
Inclusion criteria: purpura, histology of SVV, IgA predominant disease and at least one of the following: GI, renal or joint involvement

Treatments compared corticosteroids alone, to corticosteroids plus cyclophosphamide or colchicine

Findings: CS alone was most effective
- Responses CS alone (64/80), CTX (23/30), colchicine (10/17)
Comment

• Large cohort of patients
• Selected to include patients with evidence of systemic disease, particularly nephritis
• Limitations:
  – Retrospective analysis
  – Selection bias (referral bias)
  – Underpowered to detect differences between CS and CS+CYT
  – Small number of patients treated with colchicine
  – No patients were treated with dapsone
Study of 22 patients with IgA vasculitis
- At onset 21 had purpura (necrotic or bullous lesions 8), 18 had GI involvement (pain 18, hemorrhage 7), 20 had kidney involvement (15 had kidney biopsies), 17 had joint disease

Indication for RTX – refractory disease (8), relapse (8), contraindication to CS and/or immunosuppressive therapy (6)

Rituximab either 375 mg/mm² x 4 wks or 1 gm infusions x 2
Rituximab for the Treatment of Adult-Onset IgA Vasculitis (Henoch-Schönlein)
• Remission was common, but relapse occurred in 35%, but retreatment was effective
• Adverse reactions:
  – 2 patients had infusion reactions – 1 with urticaria and one with dyspnea
  – One patient with cirrhosis died due to pneumonia 60 months after infusions
• Limitations:
  – Small sample size
  – Use of concomitant therapies including immunosuppressives and ARBs or ACE inhibitors
  – Inclusion of severe patients with nephritis
  – Retrospective analysis
Diagnosis – cryoglobulinemnic vasculitis v. HSP in a patient with steatohepatitis

• Dilemmas:
  – Should patients with skin-only symptoms/signs be treated aggressively?
  – What is the meaning of IgA deposition in the DIF result?
  – What is the “best” therapy for this patient?
  – When should the rituximab be re-administered?
Case 4
69-year-old woman

• 5-week h/o pruritic, blistering eruption on the neck, arms, legs and trunk
• PMH – RA, COPD, former smoker
• Medications – amlodipine, leflunomide, gabapentin, propranolol, adalimumab (previously treated with Golimumab and etanercept), three inhalers and OTC guaifenesin
What is your diagnosis?

1. Linear IgA bullous dermatosis
2. Dermatitis herpetiformis
3. Bullous pemphigoid
4. Epidermolysis bullosa acquisita
5. Bullous lupus erythematosus
6. Lichen planus pemphigoides
Results

A. Right Proximal Dorsal Forearm, Biopsy by Punch Method

Subepidermal blistering dermatosis, inflammatory, see comment below
L98.9

B. Right Elbow, Biopsy by Punch Method

Subepidermal blistering dermatosis, inflammatory, see comment below

COMMENT: A and B) Both biopsy specimens exhibit features compatible with a subepidermal inflammatory blistering process. Neutrophils predominate over eosinophils (especially in the B biopsy specimen) and there is also focal neutrophilic papillitis. These features, along with the clinical impression, would favor one of the neutrophil-rich blistering processes such as linear IgA bullous dermatosis or dermatitis herpetiformis. Lupus erythematosus may also demonstrate a neutrophil-rich inflammatory infiltrate. With the presence of scattered dermal eosinophils, I would also consider disease in the category of pemphigoid, including anti-p200 pemphigoid and cicatricial pemphigoid. Correlation with clinical findings, immunofluorescence analysis and other laboratory evaluation should prove helpful in further diagnostic classification. (L98.9)
What is the best diagnosis now?

1. Linear IgA bullous dermatosis
2. Dermatitis herpetiformis
3. Bullous pemphigoid
4. Epidermolysis bullosa acquisita
5. Bullous lupus erythematosus
6. Lichen planus pemphigoides
Where should a biopsy be performed for immunoflourescence?

1. A fresh blister
2. An eroded area
3. Perilesional skin
4. Uninvolved skin on the buttocks
5. Previously involved skin that is clinically normal
IgA x 400
Which of the following diseases are associated with LABD?

1. Ulcerative colitis
2. Gluten sensitive enteropathy
3. Crohn’s disease
4. Diabetes mellitus
5. Rheumatoid arthritis
Which of the following findings is more likely with Drug-induced LABD?

1. Mucosal involvement
2. Targetoid lesions
3. String of pearls distribution
4. Erosions
Linear IgA bullous dermatosis: comparison between the drug-induced and spontaneous forms

What does this study add?

- Drug-induced LABD, often with Nikolsky sign and large erosions, is more severe than the spontaneous form.
# Drug-induced linear IgA bullous dermatosis

<table>
<thead>
<tr>
<th>Common</th>
<th>Less common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>Penicillins</td>
<td>Phenytoin</td>
<td>Amiodarone</td>
</tr>
<tr>
<td></td>
<td>Cephalosporins</td>
<td>Sulfonamide antibiotics: sulfamethoxazole, sulfisoxazole</td>
<td>Angiotensin receptor blockers: candesartan, eprosartan</td>
</tr>
<tr>
<td></td>
<td>Captopril &gt;other ACE inhibitors</td>
<td></td>
<td>Atorvastatin</td>
</tr>
<tr>
<td></td>
<td>NSAIDs: diclofenac, naproxen, oxaprozin, piroxicam</td>
<td></td>
<td>Carbazepine</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Cylosporine</td>
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<td>Furosemide</td>
</tr>
</tbody>
</table>

## References

ACE: angiotensin converting enzyme; NSAIDs: nonsteroidal antiinflammatory drugs. Reproduced from: Zone JJ. Dermatitis herpetiformis and linear IgA bullous dermatosis. In: Dermatology, 2nd ed, Bologna JL, Jorizzo JL, Rapini RP (Eds), Elsevier, 2008. Table used with the permission of Elsevier Inc. All rights reserved.
What is the best therapy for this patient?

1. Dapsone
2. Colchicine
3. Gluten free diet
4. Mycophenolate mofetil
5. Cyclosporin
6. Rituximab
Course

- Low-dose dapsone (75 mg three days per week, 50 mg on alternate days) resulted in control of her skin disease
- Mild anemia (hemoglobin 11 gm/dL) developed
- After 6-months of therapy she developed respiratory symptoms requiring oxygen
What testing should be performed now?

1. Methemoglobin levels
2. Reticulocyte count
3. High resolution CT scan
4. No additional testing is needed
How should dapsone be handled?

1. Stop it
2. Lower the daily dose
3. Administer vitamin E concomitantly
4. Add cimetidine therapy
Strategies for managing dapsone toxicity

• Co-administration of cimetidine might improve patient tolerance to dapsone by diminishing the formation of the methemoglobin-forming N-hydroxylated metabolites

• Co-administration of vitamin E 800 U/d reduces hemolysis
  – Arch Dermatol 1992; 128: 210-3
If you choose to stop the dapsone, what alternative therapy will you prescribe?

1. Colchicine
2. Prednisone
3. Nicotinamide and doxycycline
4. Mycophenolate
5. Rituximab
Idiopathic linear IgA bullous dermatosis: prognostic factors based on a case series of 72 adults

J. Gottlieb,1,2 S. Ingen-Housz-Oro,1,2,3 M. Alexandre,2,4 S. Grootenboer-Mignot,2,5 F. Aucouturier,2,6 E. Sbidian,1,3,7 E. Tancrede,2,8 P. Schneider,2,8,9 E. Regnier,2,10 C. Picard-Dahan,2,11 E. Begon,12 C. Pauwels,13 K. Cury,2,14 S. Hüe,2,3,15 C. Bernardeschi,2,9 N. Ortonne,2,3,16 F. Caux,2,4,17 P. Wolkenstein,1,2,3 O. Chosidow1,2,3,7 and C. Prost-Squarcioni2,4,17,18

Methods

• Retrospective case series; 1995-2012 Autoimmune Inflammatory Bullous Disease referral centers
• Inclusion criteria:
  – Adults (>15 yo) with idiopathic LABD; positive DIF – linear pure IgA or predominant IgA+G/M deposits at the DEJ
• Exclusion criteria:
  – <15 yo, drug-induced LABD, bullous lupus erythematosus
  – Drug-induced LABD – any new drug within in 4 weeks before disease onset
Heterogeneous clinical presentation
Clinical presentation - II
Clinical Manifestations

• Skin lesions involved the head or neck of 29 patients (40%) and scalp of 16 patients (22%).

• String of pearls or herpetiform arrangement tended to be more frequent in patients with pure IgA deposits (P = .011)

• There were 43 patients (60%) who had mucosal involvement at diagnosis; 39 oral (91%), 18 nose and throat (42%), 15 eyes (35%), 10 genital (23%) and six anal (14%)

• Four of those with mucosal disease developed laryngeal stenoses or conjunctival synechiae
Co-morbidities

• IBD
  – Crohn disease with sclerosing cholangitis (IgA anti-GP2 negative)
  – Ulcerative colitis

• Malignancies
  – Following diagnosis - Breast cancer, Hodgkin lymphoma (1 case each)
  – Pre-diagnosis without recurrence – one case each of liver, colon and prostate, colon and pancreas, or breast

• Paraproteinemia
  – 1 with IgG monoclonal gammopathy of undetermined significance
  – 1 with IgG myeloma
Treatments

- First-line therapy was potent (or highly potent) topical steroids alone for 29 patients (40%), combined with dapsone and/or sulfasalazine for 45 patients (63%).
- Overall, 16 patients (22%), all with mucosal involvement, required one or more adjunctive immunosuppressant
  - Cyclophosphamide - 15
  - Rituximab - 9
  - Mycophenolate mofetil - 4
  - Methotrexate - 2
  - Intravenous immunoglobulin (IVIg) - 3
  - TNF antagonists were used in combination with cyclophosphamide - 2
Comment

- Course
  - 36% sustained CR
  - 29% CR w/ subsequent relapse
  - 35% chronic lesions w/o CR

- Age >70 and lack of MM associated w/ CR

- Strengths/Weaknesses of this observational study
  - (+) sample size, available data
  - (-) Variability of therapies selected
  - Analysis limited to complete responders
  - Selection bias for severe cases