Skin Signs of Internal Disease: Case-based Challenges

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Case 1 - 61-year-old man

- “Intractable” pruritus for over 2 years
- Previous biopsies: H&E c/w folliculitis; DIF negative
- Previous workup by his internist was completed which was normal or not clinically significant including allergy testing and extensive blood work (CBC, CMP, ceruloplasmin, hormone panel, and vitamin levels).
- Abnormal:
  - Allergy testing: elevated IgG to casein and whey
  - low testosterone
  - slightly elevated PSA
  - slightly elevated ANA
Case 1 - continued

• Previous treatments
  – Triamcinolone 0.1% cream, betamethasone spray
  – Hydroxyzine
  – Intramuscular triamcinolone, prednisone
  – Loratadine, montelukast

• Physical examination: non-specific lesions on the abdominal wall with superficial crusts, prurigo nodules on the arms
What evaluation should be performed?

1. Biopsy of lesions on the abdominal wall
2. Biopsy of the prurigo nodules on the arms
3. Direct immunofluorescence microscopy
4. Chest X-ray
5. Immunofixation electrophoresis
6. All of the above
7. No additional testing is needed
Further work-up

- Biopsy for H&E showed acantholysis consistent with transient acantholytic dermatosis.
- Biopsy for direct immunofluorescence was negative.
- Indirect immunofluorescence showed a 1:160 titer of IgG on monkey esophagus, DSG1 and DSG3 were normal
- Negative hepatitis panel, quantiferon TB and normal serum immunofixation
- Chest x-ray showed left hilar and upper lobe mass-like lesions concerning for lung neoplasm
- Further evaluation with CT of the chest with contrast was performed
Patient course

• CT scan showed multifocal lymphadenopathy, and biopsy of mass and lymph node was performed which showed Hodgkin lymphoma. Bone marrow biopsy was negative.
• He was diagnosed with Stage IIb Classical Hodgkin lymphoma, nodular sclerosing type and was treated with chemotherapy with brentuximab, doxorubicin, vinblastine and dacarbazine
• His pruritus responded rapidly to chemotherapy treatment, and at follow-up had completely resolved
Pruritus and Hodgkin Lymphoma

• Itching may be the only symptom of Hodgkin lymphoma
• Can occur in up to 30% of patients
• May precede the clinical diagnosis by up to 5 years
• Often more severe in elderly patients
Generalized Pruritus

Work up (after failing initial therapy)

• Without primary skin lesions
  – CBC
  – CMP
  – TSH
  – HIV
  – CXR
Pruritus in HD

- This case highlights the importance of a systemic work-up for underlying disease in cases of pruritus without primary rash, and in some acantholytic dermatoses.

- Severe pruritus is the most common and well-recognized cutaneous finding in Hodgkin lymphoma (HD)
  - Usually present prior to diagnosis and can be the presenting complaint as in our case

- Previous study showed hazard ratio of 2 for hematologic malignancies in chronic pruritus, however incidence is very low

- Mechanism felt to be related to T-cell dysregulation with increase in Th2 cytokines as well as release of histamine, leukopeptidases, bradykinin and IL-31 from malignant cells
Algorithm for the evaluation of pruritus

Pruritus

Generalized
- With primary skin rash
  - Skin diseases
    - Systemic diseases
    - Psychogenic itch
    - Advanced aging
    - Drugs
  - Skin biopsy (if needed)
- Without primary skin rash
  - CBC and differential
  - Liver function tests
  - Renal function tests
  - Thyroid stimulating hormone
  - Chest radiograph

Localized
- With rash
  - Site-specific: Seborrheic dermatitis, LSC, vaginal, etc
- Without rash
  - Site-specific: Neuropathic
  - Psychogenic pruritus

LSC: lichen simplex chronicus; CBC: complete blood count.
Discussion

• Remember to order a chest X-ray in patients with unexplained chronic pruritus
Case 2 - 65-year-old woman

- **HPI:** Two-year history of painful, non-healing ulcers on bilateral pretibial leg.
- **Previous biopsies by outside dermatologists:**
  - 2018: c/w pretibial myxedema
  - 2017: morphea profunda vs. necrobiosis lipoidica (NL)
  - 1994: NL
- **ROS:** revealed joint ache, but negative for abdominal pain, bleeding problems, cough, fevers/chills, muscle weakness, SOB, wheezing, unintentional weight loss
- **Medications:** pentoxifylline, mycophenolate mofetil, home UVA twice weekly x 1 year, timolol drops x 1 month
Medical History

- PMH: chronic kidney disease, insulin dependent diabetes, neuropathy, osteoarthritis vs rheumatoid arthritis, hypertension, hypercholesterolemia, hypothyroidism, seizures, MRSA+ wound infection
- ANA 1:160, SSA/Ro+, RF+
- PSH: right knee repair 2/2 MVA
- Extensive diagnostic work-ups for benign breast neoplasm and colon adenoma w/ Gadolinium exposure
What is your diagnosis?

1. Nephrogenic systemic fibrosis
2. Necrobiosis lipoidica
3. Pyoderma gangrenosum
4. Vasculopathy
5. Morphea
What is the next step in your evaluation?

1. Obtain old biopsies for review
2. Rebiopsy the patient
3. Order an Anti-neutrophil cytoplasmic antibody
4. Culture the ulcers
Course

• We chose to obtain the outside biopsies
March 2018

Biopsy from 2018

This was a superficial shave and our interpretation was that it was non-specific
Biopsy from 2017

February 2017
Now what is your diagnosis?

1. Necrobiosis lipidica
2. Morphea
3. Nephrogenic fibrosing dermopathy
4. Lipodermatosclerosis
5. Medium sized vasculitis
Our Working Diagnosis

• Necrobiosis lipoidica
Diagnostic Work-Up

- Glucose 112
- ANA, SSA/Ro, dsDNA equivocal
- Rheumatoid factor, 13.7
- Hypogammaglobulinemia (IgA, IgM) without monoclonal protein
- MTHFR, heterozygous carrier
- Mixed flora, Gram+ cocci and bacilli, Gram- bacilli
- Coagulation panel and factors, ANCA, cryoglobulins, Hepatitis panel, and TB quant WNL
Necrobiosis lipoidica

- Female to male, 3:1
- Idiopathic chronic granulomatous disease
- Microangiopathy
- Association with systemic disease, trauma, metabolic changes, collagen
- Koebnerization
- Inconsistent response to therapy
Necrobiosis Lipoidica and Diabetes

- Incidence in diabetics, 0.3-1.2%
- Prevalence of diabetes in pts w/ NL, 11-60%
- Ulceration, 35%
  - Following trauma
  - Diabetics vs nondiabetics, 35% vs 33%; no difference in healing
  - Possible risk of malignancy
- Clinical course is independent of glucose control
Local Therapies of Ulcerated NL

- Data on therapies to heal necrobiosis lipoidica ulcers are limited.
- Local therapies
  - topical tacrolimus
  - bovine collagen
  - PUVA photochemotherapy
  - mesh graft transplants
  - UVA1 phototherapy
  - PDT
  - hyperbaric oxygen
  - intralesional infliximab
  - surgical excision
Systemic therapies for Necrobiosis Lipodica

- Hydroxychloroquine
- Colchicine
- Doxycycline
- Fumaric acid esters
- Pentoxifylline
- Clofazimine
- Thalidomide
- Intravenous immunoglobulin
- Cyclosporine
- Mycophenolate mofetil
- TNF-alpha inhibitors
- Ustekinumab
- Ruxolitinib
- Aspirin
- Dipyridamole
Clinical Course

• Discontinued mycophenolate mofetil
• Continued pentoxifylline
• Started 3-month trial with hydroxychloroquine 200 mg BID
• Suggested a JAK-inhibitor as alternative treatment option
Treatment with Ruxolitinib

Case 3 – 28 year-old woman

- **HPI:** 4 months h/o a rash on her abdomen which spread to involve her upper thighs. The patient reported that blisters developed occasionally. She complains of pain of the skin. She used a heating pad on the area 3-4 times a week “over clothing” and only on the upper abdomen. She denies use of a laptop.

- **PMH:** Systemic lupus erythematosus, rheumatoid arthritis, seizures, thrombophlebitis, endometriosis, asthma

- **Medications:** prednisone 20mg daily, rituximab (q16weeks), IVIG weekly, hydroxychloroquine 200mg BID, ketorolac, ondansetron, aspirin, hydrocodone-acetaminophen, lorazepam, tizanidine, vitamin D & calcium and dextroamphetamine/amphetamine
What is the best diagnosis?

1. Livedo racemosa
2. Medium-sized vessel vasculitis
3. Erythema ab igne
4. Anti-phospholipid antibody syndrome
5. Sneddon’s syndrome
Laboratory Testing

- CBC wnl other than Hb 11.1
- Lupus anticoagulant not detected
- IFE wnl
- Factor V Leiden negative
- Cardiolipin antibodies negative
- ANCA negative
- Cryoglobulin negative
- RF negative

- C3 wnl, C4= 9 (ref range 15-57)
- MTHFR + for one copy of A`190C variant
- DsDNA: 6 (0-4)
- Mitochondrial ab: negative
- Aldolase wnl
Now what is the best diagnosis?

1. Livedo racemosa
2. Medium-sized vessel vasculitis
3. Erythema ab igne
4. Anti-phospholipid antibody syndrome
5. Sneddon’s syndrome
Erythema Ab Igne

• Cutaneous disorder characterized by erythematous reticulated hyperpigmentation caused by long-term exposure to heat below the threshold for thermal burn.
  – Heating pads, laptops, space heaters, fireplaces, heated car seats, occupational hazards (ex bakers and chefs)

• Histopathologic findings are nonspecific, but helpful to exclude other differential diagnoses.
  – May see epidermal keratinocyte atypia, elastosis in the dermis, melanin incontinence and hemosiderin deposition in the dermis

• Exposure time varies from two weeks to a few months
What treatment should be prescribed?

1. Aspirin
2. Higher doses of prednisone
3. Switch from hydroxychloroquine to chloroquine
4. No therapy is effective
Erythema Ag Igne

- Secondary development of cutaneous malignancies such as SCCs and Merkel Cell Carcinomas within the affected area have been reported.
- Treatment: removal of the responsible heat source or discussing safe practice guidelines for using heating pads (15-20 minute intervals)
  - 5-fluorouracil cream has been recommended for patients whose skin lesions demonstrate pre-cancerous changes.
Conclusion

• Erythema ab igne is an erythematous, reticular hyperpigmentation that results from prolonged thermal radiation exposure insufficient to cause a burn

• Livedo reticularis can mimic erythema ab igne; suspicion of the later condition should prompt questions about potential heat exposure in order to establish the diagnosis of erythema ab igne

• If non-healing wound or ulceration is noted within an erythema ab igne lesion, a skin biopsy is warranted to rule out malignancy