Cutaneous Signs of Systemic Disease

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Goals and Objectives

- To be able to identify prototypical images and patient presentations that signify underlying systemic disease.
- To recognize the association between the skin and underlying malignant disorders.
- To be able to relate these images and scenarios to patient care, workup and management.
Case 1

A 36 year old man presents with the following skin lesions. He describes them as intensely pruritic, and that they “turn white” when he scratches them. On exam, you note the oral findings, of which the patient was not aware.
Case 1

- **What is this called?**
  Lichen Planus

- **What blood test must you order?**
  Hepatitis Panel and LFTS (including ALKP)

- **Why?**
  Seen in Hepatitis Infections and Primary Biliary Cirrhosis
  Also seen in patients with Ulcerative Colitis, Diabetes Mellitus, Vitiligo and Myasthenia Gravis
Case 1

What is the treatment?

Steroid Creams +
Oral Antihistamine

Oral Steroids

PUVA/Retinoids/Cyclosporine
Case 2

A 20 year old female college student sees you in clinic for 3 weeks of a worrisome rash on her left shin and right pretibial region. Over this time it has been getting more painful. She also notes intermittent arthralgias in her knees.

What is This Called?

Erythema Nodosum

- Erythema nodosum is the most common type of panniculitis.
- Characterized by painful, erythematous nodules on the shins and occasionally elsewhere.
- Most commonly in young women, with a peak incidence between 20 and 40 years.
- In addition to the cutaneous findings, patients can have fever, malaise, arthralgias, or arthritis. Typically the eruption is self limited, lasting an average of 3 to 6 weeks.
Case 2

- A 20 year old female college student sees you in clinic for 3 weeks of a worrisome rash on her left shin and right pre-tibial region. Over this time it has been getting more painful. She also notes intermittent arthralgias in her knees.

What Medications can Cause this?
NSAIDS and Oral Contraceptives

What would you consider in a patient with this skin finding (EN), arthralgias and the following CXR:

Löfgren syndrome - Acute Sarcoidosis. Treat with NSAIDs or steroids if severe. Rarely get CNS or Liver involvement. >95% Cured
Case 2

- A 20 year old female college student sees you in clinic for 3 weeks of a worrisome rash on her left shin and right pretibial region. Over this time it has been getting more painful. She also notes intermittent arthralgias in her knees.

What would you consider in a patient with EN, cough and the following CXR?

TB, Cocci
A 20 year old female college student sees you in clinic for 3 weeks of a worrisome rash on her left shin and right pretibial region. Over this time it has been getting more painful. She also notes intermittent arthralgias in her knees.

What would you consider in an AIDS patient with EN, cough, hepatomegaly, pancytopenia and the following CXR?

Histoplasmosis
Case 2

A 20 year old female college student sees you in clinic for 3 weeks of a worrisome rash on her left shin and right pretibial region. Over this time it has been getting more painful. She also notes intermittent arthralgias in her knees.

What would you consider if this patient also complained of fevers/malaise, crampy abdominal pain, and diarrhea with intermittent blood per rectum?

Inflammatory Bowel Disease (especially Ulcerative Colitis)
A 20 year old female college student sees you in clinic for 3 weeks of a worrisome rash on her left shin and right pretibial region. Over this time it has been getting more painful. She also notes intermittent arthralgias in her knees.

What would you consider if this patient had a sore throat and fever?

Viral URI
Streptococcal Infections
Case 2

A 20 year old female college student sees you in clinic for 3 weeks of a worrisome rash on her left shin and right pre-tibial region. Over this time it has been getting more painful. She also notes intermittent arthralgias in her knees.

What if the patient had complained of very painful oral ulcers, genital ulcers, and a painful red eye?

Behcet’s Syndrome

Diagnostic Criteria?
Oral ulcers > 3x in 12 months + 2 of:
- Recurring genital sores/ulcers
- Eye inflammation with loss of vision
- Characteristic skin lesions
- Positive pathergy (skin prick test)

Tx: Corticosteroids are considered palliative; they are useful in controlling acute manifestations, but progression of CNS and ocular disease may occur. Cytotoxic medications are usually indicated in patients with ocular, CNS, and vascular disease.
A 20 year old female college student sees you in clinic for 3 weeks of a worrisome rash on her left shin and right pre-tibial region. Over this time it has been getting more painful. She also notes intermittent arthralgias in her knees.

In Case Review of >100 pts with Bx Proven Erythema Nodosum:

- IBD: 34%
- Sarcoid/Lofgrens: 22%
- Precedent URI: 20%
- Group A Strept: 7%
- TB and Fungal Dz: 5%
- Drugs: 3%
- Other: 9%

(Behcets, Underlying Cancer etc)
TABLE 46-1  Sign or Symptom at Time of Presentation of Sarcoidosis*

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema nodosum</td>
<td>14.1</td>
</tr>
<tr>
<td>Nonproductive cough</td>
<td>8.5</td>
</tr>
<tr>
<td>Joint pains</td>
<td>8.3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6.3</td>
</tr>
<tr>
<td>Fever</td>
<td>5.9</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>2.6</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>2.4</td>
</tr>
<tr>
<td>Eye involvement</td>
<td>1.6</td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Total number of pulmonary sarcoidosis patients was 505 of which 32% were detected by presentation of signs and symptoms, 57% of patients detected by routine health screening radiography, and 10% discovered by chance on a radiograph obtained for other reasons.
Sarcoid - Skin Findings

Review Time!
With Sarcoid - What other organ systems Involved?... How????

1) Pulmonary/UR Tract
2) Cardiac - Myocardial Disease and Arrhythmias / Heart Block / Cor Pulmonale
3) GI - Hepatic and Splenic
4) Ocular - uveitis, retinal vasculitis and keratoconjunctivitis
5) Neurologic - Aseptic Meningitis, Vasculitis, Stroke, Cranial Nerve Dz, Peripheral Neuropathy.
6) Endocrine - pituitary – DI
7) Others:
   Hypercalcemia
   Renal Failure
   Interstitial Nephritis
   Arthralgias
   Myositis
   BM Suppression
Sarcoid - Skin Findings

How do you Make the Diagnosis?
- Bronchoscopy with Transbronchial biopsies and Lymph Node Biopsies. Skin Bx.
- BAL with CD4/CD8 >4:1
- Gallium-67 Scan
- ACE?

What is the Treatment? When is it Indicated?
- Topical Steroids for Skin Disease -> HCQ if more severe skin disease
- Use Steroids and sparing agents for Systemic Complications (i.e. Cardiac, CNS, Severe Hypercalcemia) or symptomatic pulmonary disease
Case 3

- A 52 year old Caucasian Female sees you in clinic for a chief complaint of generalized pruritus for the past few months. She has no other complaints, and physical examination is normal with the exception of excoriations and post-inflammatory scarring on her forearms.

- What are the most common conditions you would be concerned about? (And these are DERM Dx!)
  - Xerosis (Patients do well with Emollients after bathing)
  - Scabies (may not be evident on exam)
  - Nodular Urticaria (associated with insect bites)
  - Neuropathic etiologies
Case 3

A scraping of her skin is negative for scabies and there is no help despite the use of insect repellants/antihistamines and emollients.

What systemic diseases would you consider as a cause of generalized pruritis?

**Workup:**
- CBC with PBS
- CXR
- BMP, LFTS
- TFTS, ESR
- Hepatitis and HIV
- SPEP/UPEP
- Bx and DIF of Skin
- Negative = Imaging

**TABLE 1–1 Systemic Diseases Associated with Pruritus**

<table>
<thead>
<tr>
<th>Category</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uremia</td>
<td>Myeloproliferative disorders</td>
</tr>
<tr>
<td>Obstructive biliary disease</td>
<td>Polycythemia vera</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Myelodysplasia</td>
</tr>
<tr>
<td>Biliary duct carcinoma</td>
<td>Lymphomas</td>
</tr>
<tr>
<td>Drugs</td>
<td>Hodgkin’s disease</td>
</tr>
<tr>
<td>Contraceptive drugs</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>chlorpromazine, testosterone</td>
<td>Solid tumors (anecdotal reports only)</td>
</tr>
<tr>
<td>Extrahepatic biliary obstruction</td>
<td>Breast carcinoma</td>
</tr>
<tr>
<td>Carcinoma of the head of the pancreas</td>
<td>Gastric carcinoma</td>
</tr>
<tr>
<td>Carcinoma of ampulla of Vater</td>
<td>Lung carcinoma</td>
</tr>
<tr>
<td>Intrahepatic cholestasis of pregnancy</td>
<td>Neurologic disorders</td>
</tr>
<tr>
<td>Infections hepatitis B and C</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Endocrine disease</td>
<td>Brain abscess</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>Central nervous system infarct</td>
</tr>
<tr>
<td>Myxedema</td>
<td>Mastocytosis</td>
</tr>
</tbody>
</table>
You are seeing a new patient in clinic - a 62 year old HM visiting in order to establish a PCP. Vital Signs are Normal, Physical Exam Reveals the Following:

What is this skin finding called?  
Acanthosis Nigricans
Case 4

- **What is your initial Approach/Thoughts**
  Insulin Resistance is first concern

- **You send a HgA1c and it returns at 5.8, labs also reveal normal renal function and a microcytic anemia. Other concerns? What Else is on your list of causes? What are the Types/Subclassification of Acanthosis Nigricans?**

**Type I: Hereditary benign AN** – *No associated endocrine disorder*

**Type II: Benign AN** – Associated with *various endocrine disorders:*
  - DM, Hypothyroidism, Addison’s, Acromegaly, Cushing’s, Androgenic states, etc

**Type III: Pseudo-AN** – Associated with *obesity and insulin resistance*

**Type IV: Drug induced AN** – *Nicotinic acid*, GH supplementation Rarely

**Type V: Malignant AN** – *Paraneoplastic syndrome* usually associated with adenocarcinoma of the GI (most commonly gastric) or GU tract. There have been reports of associations w/ Breast Ca. & Lymphoma
Case 4

Type V:
Case 5

- A 32 year old female is “found down” by her roommate. EMS is called because she is nonresponsive. She is brought into the emergency department and found to be hypotensive with a blood pressure of 82/45 with a pulse of 72. Her temperature is 96 degrees and she is saturating 100% on Non-Rebreather. The ER is planning to intubate her for airway protection.

On skin exam you see the following:
Case 5

- What is this skin finding?
  Vitiligo

- What diseases quickly run through your mind
  Pernicious Anemia, Celiac Disease, Myasthenia Gravis
  Autoimmune Thyroid Disease (Hashimoto/Graves)
  Diabetes Mellitus, Addison’s Disease

- What is your concern? How would you work her up?
A 42 year old male comes to the clinic complaining of one month duration of a LE “rash” and flaky dry skin. Skin exam reveals:

What is this called?
Ichthyosis (specifically “Acquired”)

Commonly See Hyperkeratosis as well:
Case 6

- What systemic disorders are associated with this finding?

**Cancer:** Lymphoma (HL>NHL). Also, Lung, Breast, Ovarian and Upper GI.

**Also:** Thyroid Disease, Leprosy, Sarcoidosis, Renal Failure, SLE

If Symmetric and adult-onset = **Underlying Disease!!**
Case 7

- A 47 year old WM with a history of DM (on Metformin) presents to you with fatigue and muscle weakness.
- Physical Examination Reveals: Decreased Strength In the proximal muscle regions, more pronounced in the upper extremities

Skin Exam Reveals:
Case 7

Description of the following and Dx?

- Heliotrope Rash
- Shawl Sign
- Dermatomyositis
- Gottron Papules
- Heliotrope Rash
How do you diagnose the patient with this initial thought of dermatomysositis? What is the workup for the disease and this patient?

**Diagnositic Criteria?**
1. Compatible cutaneous disease
2. Progressive proximal symmetrical weakness
3. Elevated muscle enzymes levels (AST/ALT/CK/Aldolase) – IN MOST CASES
4. Abnormal findings on electromyogram
5. Abnormal findings from muscle biopsy

So:
- Full skin examination
- Systemic examination
- Skin biopsy may be needed
- CBC with differential, ESR, LFTs, Liver Function
- Muscle enzyme Levels (CK and aldolase)
- MRI of muscles
- EMG and Muscle biopsy
- Several serologic abnormalities like: ANA, Anti-mi2, Anti-Jo
What are some systemic complications seen in patients with Dermatomyositis?

• Pulmonary Fibrosis
  [Anti-Jo1 Antibody is associated with pulmonary involvement (interstitial lung disease), Raynaud phenomenon, arthritis, and mechanic's hands]

• Restrictive Chest Wall Disease

• Dysphagia/Aspiration

• Increased Incidence of Peptic Ulcer Disease

• Myocarditis with CHF/Arrhythmias

• Cor Pulmonale
Case 7

What underlying “systemic” disease are You Concerned About with Dermatomyositis?

Underlying Malignancy

Various studies have shown that this is between 3-60%
Highest in Females and in patients over 40 (Especially Ovarian!)
Other cancers seen include cervical, lung, breast, pancreas and stomach

There have been some reports of polymyositis with underlying malignancy, but this is about 5%, and the association is unproven.
Case 7

What underlying “systemic” disease are You Concerned About with Dermatomyositis?

**General Workup:**

- Age-appropriate malignancy screening
- Pelvic/Transvaginal U/S in female
- CBC and CXR

**Directed Workup:**

- Consider Ua,
- Consider Serum PSA
- Consider FOBT regardless of Age
- Consider CT C/A/P or PET in those that are “high risk”
What is the Treatment of Dermatomyositis?

• Patients need high-dose Steroids - Acutely, especially with profound muscle weakness, a total dose of 60-80 mg daily is given. This is given for about a week total. Then patients can be slowly titrated to 20mg daily, which is eventually tapered.

• AZA and MTX commonly used as steroid-sparing agents.

• High dose IVIG if patient does not respond to the above

• Hydroxychloroquine for Skin Lesions may benefit some patients

• If patient does not respond to steroids, has multiple flares/refractory disease - **CANCER!!! = CT C/A/P**
Patient is a 43 year old White Female with a Past Medical History of DM, HTN and CKD Stage II who sees you in clinic for intermittent flushing.

There are multiple systemic disorders that can cause intermittent episodes of flushing - each with their own clinical scenario...
What if she presented with hematuria and Hgb of 17.3?

Renal Cell Carcinoma

Workup?

Imaging (CT A/P) or MRI

What is your approach based on imaging findings/size?

<1.5 cm: Observe with serial imaging
1.5-3cm: Biopsy
>3cm: Resect

Treatment?

Radical vs Partial Nephrectomy

Metastatic disease treated with targeted agents such as sunitinib, sorafenib, bevacizumab, temsirolimus, and everolimus
What if she presented with a thyroid mass, wt loss and hypocalcemia?

Medullary Thyroid Carcinoma

How do you make Diagnosis?

TFTS, Thyroid U/S and Biopsy

Treatment?

Thyroidectomy and central neck dissection. Autograft an inferior parathyroid gland + Tyrosine Kinase inhibitors (motesanib, sorafenib)
Case 8

What if she presented with a thyroid mass, wt loss and hypocalcemia?

Medullary Thyroid Carcinoma

What must you be concerned about/workup before surgery?

Primary hyperparathyroidism and/or pheochromocytoma — comorbid conditions that alter the surgical approach and surgical priorities.

Tumor Marker to Follow treatment?
Calcitonin
Case 8

What if she presented with intermittent flushing, diarrhea and tachycardia?
Carcinoid Syndrome

Location of Tumor that causes this?
Appendix, Small Intestine that met to Liver
or
Bronchial, Biliary, pancreas, stomach or ovarian carcinoids

Diagnosis?
24 Urine 5-HIAA, Serum Chromogranin A
UGI Series and CT Abdomen/Pelvis
Indium 111 or $^{131}$I-MIBG Scan

Treatment?
Surgery and Somatostatin Analogues

Other Symptoms/Problems?
Pellagra, Right Sided Valve Disease, Bronchospasm, Hypotension
# Case 8

## TABLE 1  Systemic causes of flushing

<table>
<thead>
<tr>
<th>Condition</th>
<th>Screening investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>scombroid fish poisoning (histamine fish poisoning)</td>
<td>• urine histamine levels</td>
</tr>
<tr>
<td>renal cell carcinoma</td>
<td>• renal ultrasound (US)</td>
</tr>
<tr>
<td></td>
<td>• CT of the abdomen/pelvis</td>
</tr>
<tr>
<td>pancreatic tumours</td>
<td>• elevated plasma vasoactive intestinal polypeptide (VIP) levels (need stool volume &gt; 1L/day)</td>
</tr>
<tr>
<td></td>
<td>• abdominal/pancreatic US</td>
</tr>
<tr>
<td></td>
<td>• CT of the abdomen/pelvis</td>
</tr>
<tr>
<td>medullary thyroid carcinoma</td>
<td>• thyroid function tests</td>
</tr>
<tr>
<td></td>
<td>• calcitonin levels</td>
</tr>
<tr>
<td></td>
<td>• thyroid US</td>
</tr>
<tr>
<td></td>
<td>• fine needle aspiration biopsy</td>
</tr>
<tr>
<td>carcinoid syndrome</td>
<td>• 24-hour urine for 5-hydroxyindoleacetic acid (5-HIAA)</td>
</tr>
<tr>
<td></td>
<td>• blood or platelet serotonin levels (if suspecting carcinoid but urine 5-HIAA is negative)</td>
</tr>
<tr>
<td></td>
<td>• CT of the abdomen/pelvis</td>
</tr>
<tr>
<td>mastocytosis or mast cell leukemia</td>
<td>• skin biopsy</td>
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<tr>
<td></td>
<td>• serum tryptase</td>
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<tr>
<td></td>
<td>• complete blood count with differential</td>
</tr>
<tr>
<td></td>
<td>• bone marrow biopsy</td>
</tr>
<tr>
<td>pheochromocytoma</td>
<td>• 24-hour urine for norepinephrine, epinephrine, dopamine</td>
</tr>
<tr>
<td></td>
<td>• CT of the abdomen/pelvis</td>
</tr>
</tbody>
</table>
Case 9

A 62 year old WF with newly diagnosed DM, on Metformin, presents with complaints of diarrhea and the following rash. She also has abdominal pain and weight loss. CT A/P shows a pancreatic head mass.

Findings: Glossitis, Stomatitis, NME, Hyperglycemia, Diarrhea, Anemia, weight loss, psychosis, increased risk of thrombosis, alopecia.

Diagnosis: Glucagon Level, Octreotide Scan/Somatostatin receptor scintigraphy (95%)

Treatment: Somatostatin/Zinc for Rash. Treat with Surgery and Chemo.
Case 10

A 45 year old Female Nurse presents to you in clinic for complaint of painful bumps on her legs and hands. She also complains of fevers, fatigue, myalgias and arthralgias.

You consult Derm and the biopsy says:

“Superficial papillary dermal edema with diffuse dense neutrophilic infiltrate and no evidence of a leukocytoclastic vaculitis:”
Given the biopsy reading, what is this called?
Sweet Syndrome (aka febrile neutrophilic dermatosis)

• One or more tender red papules or plaques. These enlarge and persist for several weeks. They may have blisters, pustules or ulcers. Sometimes they appear to clear in the center.

• High or moderate fever with fatigue and malaise

• Arthralgias and headache are common

• Eyes and mucous membrane involvement can occur

• Sometimes other organs are affected including bones, nervous system, kidneys, intestines, liver, heart, lungs, muscles and spleen.

• Labs usually reveal Leukocytosis and Poly Shift.
Case 10

What are some disease that cause Sweet’s Syndrome?

**Classic (87%)** – Inflammatory diseases: URI, Strep, RA, Crohn’s, Sarcoid, Behcet’s etc

**Neoplastic (10%)** – hematologic malignancies, usually AML, Myelodysplasias, Lymphoma, Solid tumors (GU)

**Others (3%)** Pregnancy, Medications, Vaccinations

**Treatment?**

Prednisone (30-40) usually causes resolution of symptoms and skin lesions improve in a few days. These are tapered over weeks. If this doesn’t work, colchicine or dapsone are used, in addition to anti-TNF
Case 11

A 62 year old White Male who states he has no past medical history presents to you with the following.

In General, What would you call this?

Palpable Purpura / Leukocytoclastic Vasculitis
What would be the cause of Palpable Purpura in a Patient with:

A 22 year old with acute renal failure, arthralgias and abdominal pain
Henoch-Schonlein Purpura

A 49 year old with bilateral wrist, knee and elbow pain, and 2 hours of morning stiffness
Rheumatoid Arthritis

A 58 year old with Hepatitis C and a Low C’ Glomulonephritis
Cryoglobulinemia

A pt w/ tender anterior cervical lymphadeopathy, tonsilar exudates and fever
Streptococcal Pharyngitis

A 52 year old with foot drop, refractory HTN and abdominal pain out of proportion to exam (with normal basic labs and normal CT Abdomen/Pelvis)
Polyarteritis Nodosum
Case 11

What would be the cause of Palpable Purpura in a Patient with:
A 42 year old woman with Trouble Chewing Crackers, Parotid Gland Swelling and an RTA
Sjogren’s Syndrome

A 25 year old with difficult to control allergic rhinitis, arthralgias and peripheral eosinophil count of 1700
Churg-Strauss Syndrome

A 48 year old Female with Aplastic Anemia on Anti-thymocyte Globulin
Serum Sickness

A 68 yo with DM, HTN and CAD one week s/p Cardiac Cath for Unstable Angina
Cholesterol Emboli Syndrome

A 58 year old man with history of IVDU, Jaundice and other signs of ESLD?
Hepatitis C
Case 11.5

A 42 year old WF presents with the following rash on her arms and legs

What would you call this rash?
Livedo Reticularis

What would be the cause of this in a patient with DVT in Right Lower Extremity and history of miscarriages?
Antiphospholipid Antibody Syndrome

Medications that cause this?
Amantadine and Hydroxyurea

Note: Think causes of most of the causes of palpable purpura: including Cholesterol Emboli Syndrome, PAN, SLE, RA, Cryoglobulinemia.
References


Odell WD. *Paraneoplastic Syndromes, Principles of Enocrine Therapy*. 2001


Questions?