Cutaneous Manifestations of Systemic Disease: Nutritional Deficiencies

Jessica Hoy, D.O.
OhioHealth O’Bleness Hospital Dermatology Residency
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Contributors

- Dr. Rich Winkelmann, PGY-3
- Dr. Kylee Sacksteder, PGY-3
- Dr. Gabriela Maloney, PGY-2
- Dr. Alyson Ridpath, PGY-2
• No disclosures
Objectives

• Case presentation
• Review select nutritional deficiencies and the differential diagnosis
  • Clinical presentation
  • Work up
  • Treatment
  • Pathology
Patient BB

- Past medical history
  - HTN
  - Seizures
  - Anxiety
  - Depression
  - DVT

- Past surgical history
  - Gastric bypass in 2001 (Roux-en-Y)
  - Cholecystectomy

- Medications
  - Pantoprazole
  - Paroxetine
  - Furosemide
  - Methylphenidate
  - Warfarin
  - Docusate sodium
  - Ferrous sulfate
Differential diagnosis

• Nutritional deficiencies
  • Acrodermatitis enteropathica
  • Pellagra
  • Riboflavin
  • Pyridoxine
  • Essential fatty acid
  • Biotin

• Necrolytic acral erythema
• Necrolytic migratory erythema
• Acrokeratosis paraneoplastica
Work up

- CBC with diff
  - Hb 9.0 g/dL
  - MCV 103.0

- CMP
  - K+ 5.2 mmol/L
  - BUN 22 mg/dL
  - Cr 0.8 mg/dL
  - Ca2+ 7.5 mg/dL
  - Albumin 1.9 g/dL
  - Total protein 4.0 g/dL

- B12
  - 501 pg/mL

- Folate
  - >24.8 ng/mL

- Vit D 25-OH
  - 20 ng/mL

- Niacin
  - 2.16 ug/mL

- Zinc
  - 0.40 mcg/mL (ref 0.66-1.10)

- ANA
  - <40
Acquired acrodermatitis enteropathica

- Supplemented with Zinc 50mg PO daily (0.5-1mg/kg/day)
- Supplemented with Niacin 500mg daily
- Refer to GI for work up of chronic diarrhea and likely malabsorption in setting of prior gastric bypass surgery
Follow up at 4 weeks
Zinc deficiency

Acquired acrodermatitis enteropathica

• Clinical features
  • Symmetrical eczematous or vesiculobullous lesions located perioral, acral, intertriginous
  • Glossitis, angular cheilitis, alopecia, diarrhea

• Risk factors
  • IBD, **gastric surgery**, malabsorption, anorexia, HIV, **alcoholics**
Zinc deficiency

Acrodermatitis enteropathica

• Triad: periorificial dermatitis, alopecia and diarrhea present in 20% of patients
• Occurs in 4 clinical scenarios
  1. Premature infants (poor absorption and ↑ requirement of zinc) when weaned off breast milk
  2. Inherited form (AR) manifests when weaned off breast milk
    • Mutation in zinc transporter gene SLC394
  3. Healthy infants if low zinc level in maternal milk
  4. Acquired form if malabsorption or inadequate nutrition
Zinc Deficiency
Acrodermatitis enteropathica
Differential diagnosis

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B vitamin deficiencies

- B-complex vitamins serve as coenzymes in many metabolic pathways that are functionally closely related
- A lack of one of the vitamins has the potential to interrupt a chain of chemical processes, including reactions that are dependent on other vitamins
- Many vitamin deficiency dermatoses share similar clinical features
Vitamin B2 (Riboflavin) Deficiency
Vitamin B2 (Riboflavin) deficiency

• AKA Oral-ocular-genital syndrome
• Riboflavin is a water soluble vitamin that is absorbed in the small intestine by the human riboflavin transporters RFVT1 and RFVT3
• It functions in intracellular oxidation-reduction reactions related to:
  • Energy production
  • Enzyme functions
  • Normal fatty acid and amino acid synthesis
  • Reproduction of glutathione
Vitamin B2 (Riboflavin) deficiency

• Clinical features
  • Angular cheilitis
  • Atrophic, sore, magenta-colored tongue
  • Seborrheic dermatitis-like changes (nose, mouth, eyes)
  • Genital dermatitis
  • Photophobia
  • Conjunctivitis
  • Anemia due to bone marrow hyperplasia
  • Mental retardation in infants
Vitamin B2 (Riboflavin) deficiency

• Risk factors
  • Achlorhydria and GI malabsorption
  • Alcoholism
  • Hypothyroidism
  • Neonatal phototherapy for hyperbilirubinemia
  • Chlorpromazine, probenecid, TCAs
Vitamin B2 (Riboflavin) Deficiency = Oral-ocular-genital syndrome
Vitamin B₃ (Niacin) Deficiency
Vitamin B3 (Niacin) Deficiency

• AKA Pellagra

• Involved in reduction-oxidation reactions; tryptophan precursor amino acid

• Clinical features
  – 4 D’s
    • Photosensitive dermatitis
      – Primary finding- 33%
    • Dementia
    • Diarrhea
    • Death
  – Angular cheilitis
  – Perianal dermatitis
Vitamin B₃ (Niacin) Deficiency

• Risk factors
  • Corn only diet
  • Malabsorption
  • EtOH abuse
  • Isoniazid
  • Post Gastrectomy
  • Carcinoid syndrome

• Hartnup disease can present with a pellagra-like dermatosis
  • SLC6A19
  • Aminoaciduria and tryptophan deficiency
Symmetrical, burning, and hyperkeratotic photodermatitis, “Casal’s Necklace”
Vitamin B6 (Pyridoxine) Deficiency

• Ubiquitous in all foods
• Role in amino acid and fatty acid metabolism

• Clinical Hallmarks:
  – **Seb Derm-like**
  – **Periorificial Dermatitis**
  – **Peripheral neuropathy**
  – **Sideroblastic anemia**

• Relevant Associations
  – Cirrhosis
  – Uremia
  – **Isoniazid** - requires B6 supplementation
  – **OCPs**
  – Malnutrition
Essential Fatty Acid Deficiency
Essential Fatty Acid Deficiency

• Unsaturated fatty acids:
  • **Linoleic**
  • **Linolenic**
  • **Arachidonic acids** (can be metabolized from linoleic acid)

• Must be obtained from an exogenous source

• Constitutes up to one quarter of the fatty acids of the stratum corneum
Essential Fatty Acid Deficiency

• Clinical features
  • Erythema, widespread eczematous dermatitis and an intertriginous weeping eruption
  • Hair becomes lighter in color with diffuse alopecia
  • Poor wound healing, growth failure, and increased risk of infection may occur

• Risk factors
  • Parenteral nutrition without EFA, aggressive low fat diet, GI abnormalities, low-birth-weight infants, cystic fibrosis
Essential Fatty Acid Deficiency
Vitamin B7 (Biotin) Deficiency
Vitamin B7 (Biotin) Deficiency

- Universally available and produced by intestinal bacteria
- **Multiple carboxylase deficiency, AR**
  - Holocarboxylase deficiency - neonatal form
  - Biotinidase deficiency - juvenile form
- Permanent neurologic sequelae if delay in treatment
Biotin Deficiency

- Clinical features
  - Periorificial dermatitis
  - Alopecia
  - Seborrheic dermatitis
  - Fissures may be prominent on the feet, face and the perianal area
  - Neonatal- erythroderma
  - Juvenile- resembles acrodermatitis enteropathica
  - Neurologic: Depression, seizures, paresthesias

- Risk factors
  - Short gut, malabsorption, ingestion large amount of raw egg whites, anticonvulsants
Biotin Deficiency
<table>
<thead>
<tr>
<th>Vitamin or trace mineral</th>
<th>Recommended lab test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riboflavin (B2)</td>
<td></td>
</tr>
<tr>
<td>Niacin (B3)</td>
<td></td>
</tr>
<tr>
<td>Pyridoxine (B6)</td>
<td></td>
</tr>
<tr>
<td>Biotin (B7)</td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td></td>
</tr>
<tr>
<td>Essential Fatty Acids</td>
<td></td>
</tr>
</tbody>
</table>
## Treatment

<table>
<thead>
<tr>
<th>Vitamin or trace mineral</th>
<th>Treatment of deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riboflavin</td>
<td>3-10mg/day</td>
</tr>
<tr>
<td>Niacin</td>
<td>5—300mg/day</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>50-100 mg/day</td>
</tr>
<tr>
<td>Biotin</td>
<td>1-10mg/day</td>
</tr>
<tr>
<td>Zinc</td>
<td>1-3mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>50mg zinc per 220mg zinc sulfate tablet</td>
</tr>
<tr>
<td>Essential fatty acids</td>
<td>PO or IV fat emulsion</td>
</tr>
</tbody>
</table>
Differential diagnosis

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• Necrolytic acral erythema
• Necrolytic migratory erythema
• Acrokeratosis paraneoplastica
Necrolytic Acral Erythema
Necrolytic Acral Erythema

• Fewer than 100 cases worldwide since it was first described in 1996
• Clinical features
  • Hyperkeratotic pink to violet-brown plaques involving acral sites, particularly lower extremities
  • Blisters and erosions are common
  • May be painful or pruritic
• Associations
  • **Hepatitis C virus**
    • Prevalence of NAE in HCV is 1.7%
  • Zinc deficiency has rarely been reported
Necrolytic Acral Erythema
Necrolytic Acral Erythema

• Treatment options
  • Therapy for underlying HCV
    • Interferon alone or in combination with ribavirin
  • Supplementation with zinc may improve NAE even in the absence of zinc deficiency
    • Variable success
Necrolytic Migratory Erythema
Necrolytic Migratory Erythema

• AKA Glucagonoma Syndrome = NME + weight loss + adult-onset DM + glossitis

• Clinical features
  • Eroded, erythematous patches and plaques involving intertriginous areas, face (particularly perioral) and distal extremities
  • May be painful or pruritic
  • Recurs over weeks to months

• Associations
  • Glucagon-secreting tumor of the pancreas (α-cell tumor)
  • Severe liver disease
Necrolytic Migratory Erythema

- Treatment involves addressing the underlying cause
  - Surgical resection of pancreatic tumor
  - Replacement therapy for deficiency states
Acrokeratosis Paraneoplastica
Acrokeratosis Paraneoplastica

• AKA Bazex syndrome
• Primarily affects Caucasian males over 40 years of age
• Associations
  • Squamous cell carcinomas of the higher aerodigestive tract and lung neoplasms
  • Liposarcoma, bladder, prostate and breast cancer has also been reported
• In 67% of cases reported, cutaneous manifestations preceded the diagnosis of cancer by approximately one year
• In 18% of patients, cutaneous lesions and cancer are diagnosed concomitantly and in 15% of the cases the diagnosis of cancer occurs first
Acrokeratosis Paraneoplastica

• Clinical features
  • Psoriasiform eruption with desquamative erythematous lesions with a bluish or violet discoloration
  • Lesions are typically located symmetrically on acral surfaces
  • Palmoplantar keratosis
  • Nose and ears are affected in 63% and 79% of patients respectively
  • Blisters of hands and feet is common in African-American patients
Acrokeratosis Paraneoplastica

• Bazex syndrome can progress in three stages:
  • (1) cutaneous lesions in ears, fingers and nails
  • (2) palmoplantar keratosis
  • (3) involvement of knees, elbows and torso

• The primary tumor tends to become symptomatic during the stage of palmoplantar keratosis
Acrokeratosis Paraneoplastica (Bazex Syndrome)
Pathology

Acute lesions

- Pallor of upper 2/3 of epidermis
- Ballooning or vacuolar degeneration
- Subcorneal vesiculation
- Confluent keratinocyte necrosis

- Seen in Acrodermatitis enteropathica, Necrolytic acral erythema, Necrolytic migratory erythema

Pathology

Chronic or resolving lesions
- Psoriasiform hyperplasia
- Confluent parakeratosis
- Hypogranulosis
- Minimal to absent epidermal pallor


In summary

• Cutaneous findings often the first signs of nutritional deficiency, therefore the dermatologist can play a key role in diagnosis

• Common dermatoses not responding to conventional therapy should alert the clinician to search for nutritional deficiencies

• Initiating treatment can often provide diagnostic information as lab work-up can be unreliable
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  • Dr. Alyson Ridpath
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