California Society of Allergy, Asthma and Immunology July 9, 2022

Rashes that Look Like Allergies but Aren't







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Disclosure

- Research Grant: (to NYU Langone Hospital-Long Island)
 - Genentech
 - Astra Zeneca
 - Pfizer
 - Regeneron
- Advisory Board:
 - Regeneron
 - Abbvie
 - Lilly
 - Pfizer



Objectives:

- 1. Discuss rashes seen in the allergy office but aren't allergic
- 2. Discuss some differentiating features of eczematous diseases
- 3. Discuss the causes of pruritus without a rash and the available therapies
- 4. Recognize differences in morphology of atopic dermatitis in skin of color



Inflammatory Skin Disorders

Dermatitis and Eczema

 Atopic D, Contact D, Seborrheic D, Pruritus, Nummular Eczema, Erythroderma, Lichen Simplex Chronicus/Prurigo Nodularis, Dyshidrosis, Pityriasis Alba

Papulosquamous disorders

- Psoriasis
- Parapsoriasis
 - Acute: Pityriasis lichenoides et varioliformis acuta
 - Chronic: Pityriasis Lichenoides Chronica
 - Lymphomatoid Papulosis
- Pityriasis
 - Pityriasis Rosea
 - Pityriasis Rubra Pilaris
- Lichenoid
 - Lichen Planus
 - Lichen Nitidus
- Drug Eruption: SJS, TEN, E Nodosum
- Other Erythemas: E. Annulare, E Centrifugum, E Marginatum, E Toxicum, Necrolytic Migratory Erythema



Nummular eczema

- Pruritic
- Plaques of closely set, thin walled vesicles on erythematous base
- Clearly demarcated edge
- Limbs more than trunk
- Variable intermittent course
- ? High incidence of atopy









61 y.o. female with 5 year duration of pruritic eczematous rash. No family history of atopy. She has since discontinued her only medication for HTN. Trial of topical corticosteroids did not help





Cutaneous T-Cell Lymphoma (Mycosis Fungoides)

Stages:

- Patch (atrophic or nonatrophic)
 - Often goes on for many years
 - Patches with thin, wrinkled quality, often with reticulated pigmentation
 - Pruritus varies
 - minimal or absent
 - common in premycotic phase
 - may precede MF by years
 - Often on lower trunk & buttocks
- Plaque
- Tumor









Papulosquamous Disorder

Papules +/- Plaques and scales (scaly papules and plaques)

- **Psoriasis** (red, scaly lesions)
- Parapsoriasis (resembles psoriasis)
 - Large Plaque Parapsoriasis
 - Small Plaque Parapsoriasis
 - Pityriasis Lichenoides
 - Pityriasis lichenoides et varioliformis acuta
 - Pityriasis lichenoides chronica
- Pityriasis (flaking or scaling)
 - *Pityriasis* Rosea
 - Pityriasis rubra pilaris
- **Lichenoid** (resembles lichen: organisms consisting of a symbiotic association of a fungus
 - Lichen Planus
 - Lichen Nitidus





Psoriasis

- Plaque psoriasis
- Guttate psoriasis
- Pustular psoriasis
- Nail psoriasis
- Erythrodermic psoriasis



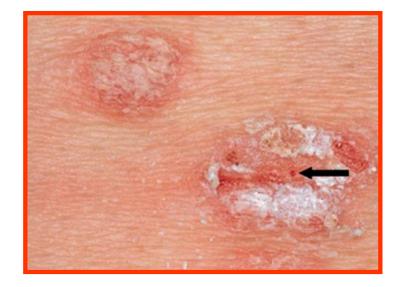




Psoriasis



Plaques typically have dry, thin, silvery-white or micaceous scale



Auspitz sign Removing scale reveals a smooth, red, glossy membrane with tiny punctate bleeding



Guttate psoriasis

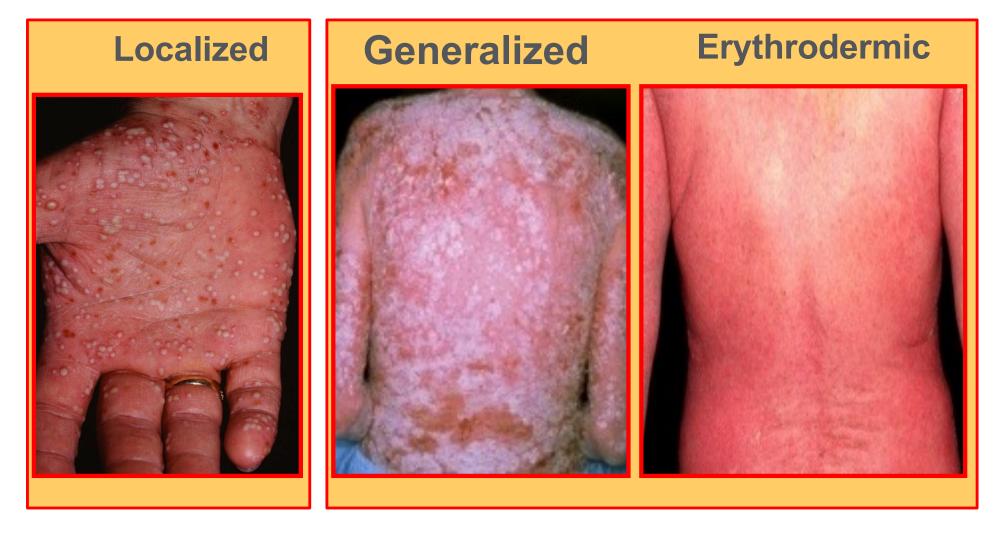
- Abrupt acute eruption of small (< 1 cm) psoriatic lesions
- Typically child or young adult with no history of psoriasis
- Primarily the trunk
- Strong association with recent strep infection with serologic evidence (26-58 %)



Telfer NR; Chalmers RJ; Whale K; Colman G The role of streptococcal infection in the initiation of guttate psoriasis. Arch Dermatol 1992 Jan;128(1):39-42



Pustular Psoriasis





55 y.o F with 5 year duration of increasing slightly pruritic, round, slightly scaly patches (> 6 cm) on limbs & trunk.

Lesions have faint red-to-salmon color, flaky thin scales, atrophic, cigarette paper or tissue paper, wrinkling quality





Parapsoriasis

Parapsoriasis: A Complex Issue

- Resembles Psoriasis (red, scaly)
- Unrelated to pathogenesis, histopathology or treatment
- Large Plaque Parapsoriasis
- Small Plaque Parapsoriasis
- Pityriasis Lichenoides
 - Pityriasis lichenoides et varioliformis acuta
 - Pityriasis lichenoides chronica



Parapsoriasis

T-cell–predominant skin infiltrates

- Large plaque parapsoriasis
 - indolent & progresses over years, sometimes decades
 - treatment may prevent progression to CTCL (~ 10%)
- Small plaque parapsoriasis
 - benign; rarely progresses
 - lasts several months to years
 - can spontaneously resolve







52 y.o female complained of headache, fever & malaise followed by burning, pruritic crops of pink papules with central vesiculation, then reddish brown crust







Mucha-Habermann disease

Pityriasis lichenoides et varioliformis acuta

- Abrupt onset of multiple papules on trunk, buttocks, proximal extremities
- Rapidly progress to vesicles & hemorrhagic crusts
- Minor constitutional symptoms fever, malaise & myalgias

Pityriasis lichenoides chronica

- May develop over days
- Same distribution





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Lichenoid skin eruptions

- Subcategory of papulosquamous skin disease
- Papules tend to remain small & discrete
- Scale often subtle
- Occasionally, confluent plaques may form



35 y.o female

- Pruritic papules spreading within 8 weeks
- Violaceous, shiny, polygonal with fine, white lines
- Painful mouth erosions
- Nail grooving & ridging









Lichen Planus

A disease characterized by "P-words":

- Plentiful
- Pruritic
- Polished
- Purple
- Polygonal
- Planar
- Papules



Lichen planus

- Groups of lines or circles
- Flexor surfaces of upper extremities
- Wickham striae: fine, white lines on papules
- Pruritus common but varies in severity
- > 50% resolve within 6 mo.
 85% subside within 18 mo.
- Other areas of involvement:
 - Mouth: white or gray streaks in linear or reticular pattern
 - Genital
 - Nail plate thinning, grooving, ridging, pterygium
 - Cicatricial alopecia











- 62 y.o male with ulcerative colitis referred for recurrent abscesses
- Initial lesion are painful small, red papule or pustule changing into a larger ulcerative lesions
- Similar lesions seen on left knee & left hand







Pyoderma Gangrenosum

- 50% have systemic illnesses
- Arthralgias & malaise often present
- Commonly associated diseases
 - inflammatory bowel disease (ulcerative colitis or Crohn's)
 - seronegative or seropositive polyarthritis
 - hematologic disorders (leukemia, preleukemia, monoclonal gammopathies (primarily Ig A)
 - less common: psoriatic arthritis, osteoarthritis, spondyloarthropathy; hepatitis; SLE







After 1 treatment of Infliximab







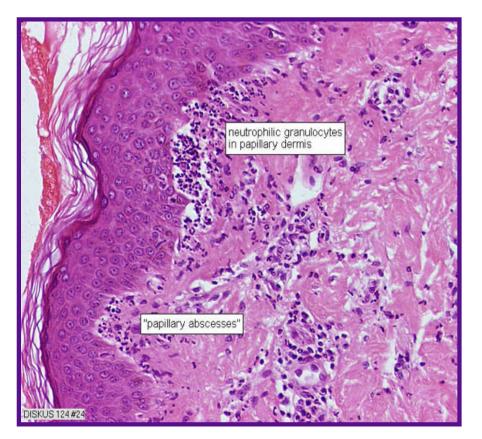
Dermatitis Herpetiformis

- Young to middle age
- Intensely pruritic
 - Symmetrically grouped papules & vesicles
 - Elbows, knees, buttocks, scapula, scalp

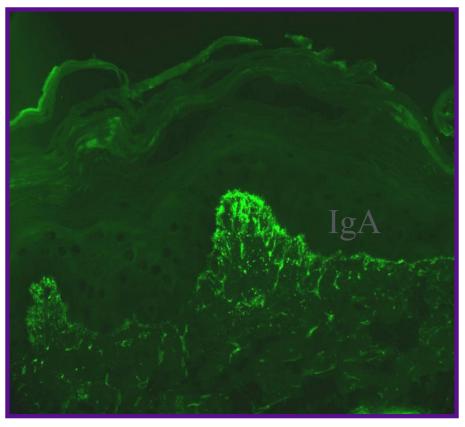




Dermatitis Herpetiformes



Neutrophils in tips of dermal papillae Microabscesses containing neutrophils & eosinophils



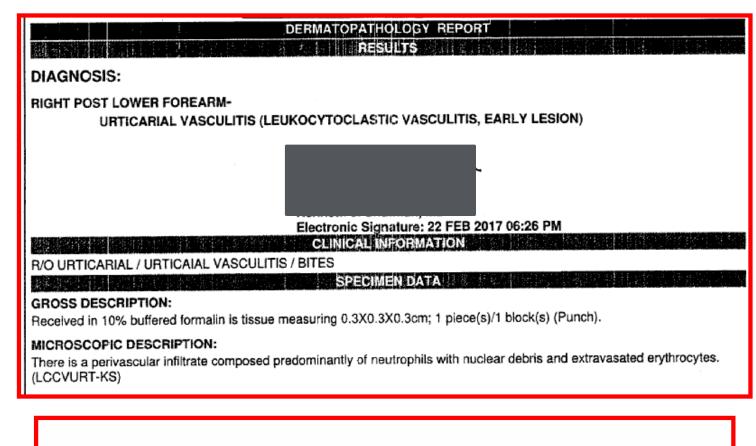
DIF: ~90% (+) granular deposition of IgA at dermal papillae & occ along DE border IIF: ~65% positive











CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE ©

Bullous Reactions to Bedbug Bites Reflect Cutaneous Vasculitis

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56 y.o. referred for insect bite sensitivity



- 6-12 months duration
- Starts with large local reaction to mosquito bite, blisters and progress to cellulitis
- Heals with necrotic center



Livedo reticularis

- Head ache
- Bilateral

pneumonia last year

 Joint pains & low back pain with episodes of falling

• EMG: radiculopathy



DERMATOPATHOLOGY REPORT

DIAGNOSIS:

RIGHT LOWER LEG - LEUKOCYTOCLASTIC (ALLERGIC) VASCULITIS Note: Please refer to the companion immunofluorescence report (HI09-832).

CLINICAL IMPRESSION: POSSIBLE VASCULITIS

GROSS DESCRIPTION : PUNCH, 0.4X0.4X0.6CM

MICROSCOPIC DESCRIPTION:

There is a superficial and mid-dermal perivascular and interstitial mixed inflammatory cell infiltrate that contains lymphocytes, histiocytes, eosinophils and many neutrophils. There are nuclear dust, fibrin within the vessel walls and numerous extravasated erythrocytes. (82A-MT)

DIAGNOSIS:

RIGHT LOWER LEG - POSITIVE DIRECT IMMUNOFLUORESCENCE STUDY FOR VASCULITIS Note: There are deposits of C3 and IgM about vessels. This could represent leukocytoclastic vasculitis. Please refer to the companion report of light microscopic findings (HD09-176034).

CLINICAL IMPRESSION: RASH/POSSIBLE VASCULITIS

GROSS DESCRIPTION : PUNCH, 0.3X0.3X0.4CM

MICROSCOPIC DESCRIPTION:

Specimen is treated with a panel of four immunoglobulins (IgG, IgA, IgM, and C3).

An H&E stained section shows perivascular dermatitis. There are deposits of C3 and IgM about vessels. IgG and IgA are not present in this area. All four antibodies tested are not present in the epidermis, basement membrane zone, or dermis.





- 56 M sudden spontaneous rash since 5 mo. ago, persisting and worsening
- Affected arms, trunk, neck, extremities
- Facial erythema



- Initial biopsy: lichenoid & interface dermatitis w/ perivascular lymphocytic infiltrate c/w photosensitivity reaction
- Labs: low CH50, nl C3, Elevated C4,
- (+) ANA 1:80 (+) RF, (+) SSA, (-) DNA

DIAGNOSIS:					
LEFT UPPER ARM- COLLAGEN VASCULAR DISEASE Note: These findings are compatible with a manifestation of lupus erythematosus.					
BJ					
Bonnie A. Lee, MD Electronic Signature: 16 JUL 2015 05:12 PM CLINICAL INFORMATION					
ERYTHEMATOUS PAPULAR RASH					
SPECIMEN DATA					
GROSS DESCRIPTION: Received in 10% buffered formalin is tissue measuring 0.4X0.4X0.7cm; 2 piece(s)/1 block(s) (Punch).					
MICROSCOPIC DESCRIPTION: There is a sparse superficial perivascular inflammatory cell infiltrate that obscures the <u>dermo-epidermal junction</u> where there is <u>vacuolar alteration</u> and smudging of the basement membrane zone. The inflammatory cell infiltrate consists of lymphocytes and histocytes as well as melanophages. <u>There is nuclear dust</u> . There is mild hyperkeratosis. (CVD-BL)					



Subacute Cutaneous Lupus Erythematosus

Annular Polycyclic Papulosquamous

- 60 % of SACL have (+) DIF on lesional skin
- Some (usually those with SLE features) have (+) Lupus Band Test





poorly localized, non-adaptive, usually unpleasant sensation, which elicits a desire to scratch







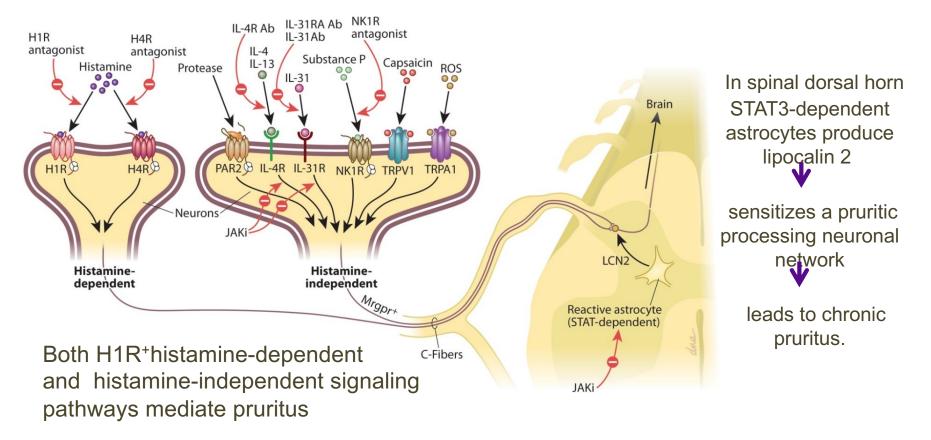








Mechanisms of pruritus in AD



Antipruritic drugs block each pruritic pathway IL-4, IL-13 & IL-31 elicit their functions through JAK-STAT signaling.



Paller AS, Kabashima K, Bieber, T. Therapeutic pipeline for atopic dermatitis: End of the drought? J ALLERGY CLIN IMMUNOL SEPTEMBER 2017



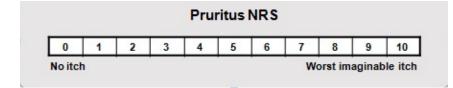
Chronic Pruritus

V	•	↓	V	
Dermatologic With Primary Rash	Neurologic	Systemic	Psychogenic	Idiopathic
 Xerosis Atopic Dermatitis Contact dermatitis Scabies Psoriasis Lichen Planus 	 Notalgia Paraesthetica Brachioradial Pruritus Multiple sclerosis Post Herpetic itch 	 Thyroid disease Primary biliary cirrhosis Chronic renal failure Hodgkin's disease Polycythem ia Vera HIV Metabolic states Drugs 	 OCD substance abuse delusional parasitosis 	NYULong Island



Severity of Pruritus 0-10:

6 distracts from activities 8 awakens from sleep 10 is the worst imaginable



SEVERE	MODERATE
Scabies, mite infestation	Psoriasis
Pediculosis, insect bites	Seborrheic dermatitis
Contact & atopic eczema	Pityriasis Rosea
Urticaria	Sunburn
Prickly Heat	Fungal disease
Lichen Planus	Asteatotic skin
Dermatitis Herpetiformis	Urticaria pigmentosa



NRS Fig from Phan NQ et al. Acta Derm Venereol

Asteatotic Eczema (Senile eczema, winter eczema, eczema craquele`)

- Failure of skin to retain moisture
- Extensive & generalized eczema craquele`in trunk, arms & legs
- Surface of skin marked in crisscross fashion
- Finger "parchment pulp' dry & cracked
- Contributory factors
 - Increasing age (experienced by at least 50% of people >70 y.o)
 - Environment: low humidity, dry cold wind, winter
 - Cleansers & solvents
 - Presenting sign of myxedema, Zinc deficiency
 - Medications: diuretics, cimetidine
 - Case reports associated with malignant lymphoma, angioimmunoblastic lymphedema, gastric adenocarcinoma







Dermatologic Causes of Itch with a Rash

Endogenous Eczema

- Atopic dermatitis
- Seborrheic dermatitis
- Asteatotic eczema
- Nummular eczema
- Eczema associated w/systemic disease
- Eczematous drug eruption





Exogenous Eczema

Clearly defined exogenous triggers

- Contact Dermatitis
 - Irritant
 - •Allergic
 - •Photo-allergic
- Infective dermatitis
- Dermatophytide
- Post-traumatic eczema







Itch without a primary rash may have Secondary Skin Lesions

Excoriations from rubbing & scratching Non specific Dermatitis Prurigo Nodularis Lichen Simplex Chronicus

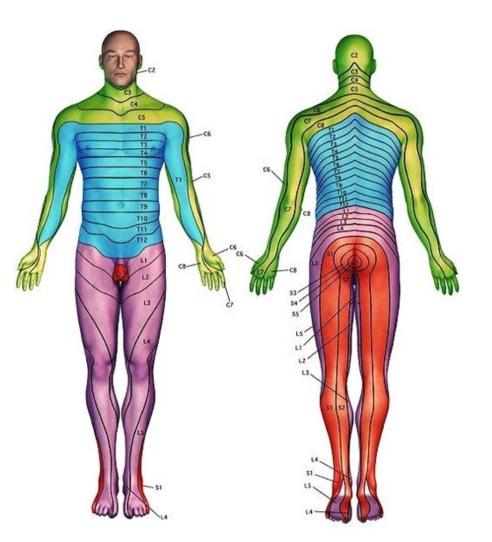


Look for Underlying Cause



Neurologic Causes of Intense Itching

- Association with other sensory symptoms
- Dermatomal distribution
- Presence of other neurologic sensory signs
- Presence of nerve
 damage
 - Motor deficits
 - Autonomic dysregulation





Neurologic Causes of Intense Itching

Brachioradial Pruritus

- Localized to outer aspect of elbow & adjacent lower & upper arms
- May have cervical pain (irritation of cutaneous branch of radial nerve or cervical spine)





Notalgia Paraesthetica

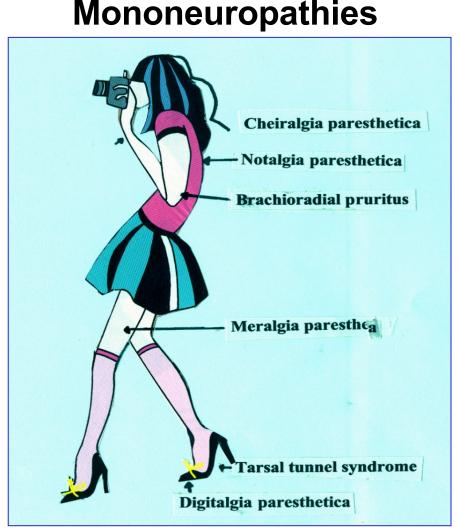
- Persistent burning pruritus localized in mid-scapular
- Mild lichenification & pigmentation
- May be localized sensory neuropathy (nerve entrapment of posterior rami at T2-T6)





Localized Neuropathic Itch Related to Spinal Nerve Compressions

- Scalp Itch
- Brachioradial
- Notalgia parasthetica
- Meralgia parasthetica
- Vulvar and Scrotal itch



Respond well to Gabapentin or Pregabalin



Systemic Causes of Pruritus without Primary Skin Lesions

- Infections:
 - HIV
 - Hep B, Hep C
- Malignancy
 - Leukemia
 - Lymphoma
 - Multiple myeloma
- Pregnancy
- Food/Drug

- Chronic renal disease
- Cholestasis
- Gluten enteropathy
- Hematologic disease
 - Iron deficiency
 - Polycythemia Vera
- Endocrine diseases
 - Hypothyroidism
 - Hyperthyroidism
 - Diabetes mellitus

*The incidence of generalized pruritus associated with significant internal disease is difficult to assess but is estimated to be ~10%



Drugs reported to cause pruritus

- Aspirin
- Allopurinol
- Chloroquine
- Sulfonamides
- Amiodarone,
- Quinidine
- Estrogens

- Opium Alkaloid
- Calcium channel blockers
- ACE-inhibitors
- Hydrochlorothiazide
- Simvastatin
- Niacinamide
- CNS stimulant/depressant
- Cimetidine



Topicals

- Bland Emollients: 1st line therapy
 - Repairs skin barrier function
- Topical (+/- occlusion) or intralesional corticosteroids
- TCIs: tacrolimus, pimecrolimus
- Distractions (cold packs)
- "Anti-Itch" Preparations
 - 3% Calamine
 - 0.47% Camphor
 - Menthol 1-5% (activate A-delta cold afferents)
 - Topical Strontium-containing hydrogel (Tricalm)
- Topical Antihistamines (may be sensitizing)
 - Benadryl cream
 - Doxepin 5% cream
- Anesthetics: Capsaicin, Lidocaine cream/patch
 - Higher concentration (up to 0.1%) may be more effective
 - Examples: Pramoxine HCI 1% or 2.5% Cream
 - Mixture of Lidocaine and Prilocaine 2.5% cream





Step 1 Oral Medications

- Antihistamines: limitations
 - Diphenhydramine
 - Hydroxyzine
- Anti-depressants
 - Doxepin 10 mg qhs, increase up to 100 mg qhs
 - binds to histamine receptor with 800x affinity of hydroxyzine
 - SSRIs: Sertraline100 mg/d: cholestatic itch
 - Mirtazapine 15 mg/day: cancer-related itch
 - Amitriptyline: neuropathic, psychogenic itch





Step 2 Oral Medications

- Anti-convulsants:
 - Gabapentin up to 2400 mg
 - Pregabalin
 - effective for several types of pruritus
 - Chronic renal disease (100-300 mg 3 x a week)
 - Post Herpetic Itch
 - Brachioradial pruritus
 - Prurigo Nodularis
- Mu-opiate antagonists: Naltrexone, Naloxone
 - effective in CIU, AD, cholestasis, chronic renal disease



Alternatives

- Phototherapy: PUVA, narrow-band UVB
 - Chronic Renal Disease
 - Psoriasis
 - -AD
 - Cutaneous T Cell lymphoma
- Immunosuppressants:
 - Mycophenolate Mofetil
 - as low as 500 mg q 2-3 days
 - Methotrexate
 - Azathioprine





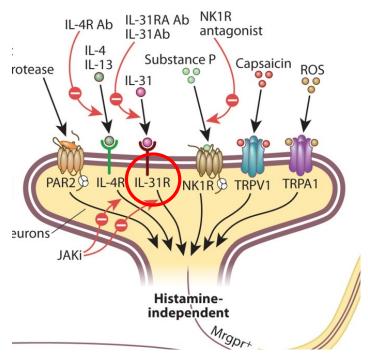
Specific targets for pruritus

Anti-IL31R: Nemolizumab (CIM331)

- IL31 expressed on C-fibers.
- Phase 2 trial:

•IGA:% of patients with SIGA ≤1: 20.9% vs 4.7%

- Reduced sleep onset latency
- Increased total sleep time
- Decreased use of topical hydrocortisone
 Common AEs: AD exacerbation and nasopharyngitis, as well as a few cases of edema







In Summary

- Chronic pruritus (itching > 6 weeks) may be caused by dermatologic, systemic, neurologic or psychogenic disorders.
- The presence of a rash does not necessarily indicate a primary skin disease, scratching can cause secondary lichenification, prurigo nodules, patches of dermatitis, and excoriations.
- Initial evaluation of pruritus of undetermined origin could include a CBC with differential, hepatic, renal, thyroid function and CXR.
- Initial treatment includes use of mild cleansers, emollients, topical anesthetics and coolants.
- Sedating antihistamines may be used, primarily to help sleep.
- Anticonvulsants, antidepressants, and mu-opioid antagonists appear to be helpful in some forms of chronic itch.
- Patients with itch of undetermined origin should be reevaluated regularly and periodically until itch resolves.

















Date 02/07/2022





Palmoplantar Keratoderma



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MICROSCOPIC DIAGNOSIS:

A: LEFT SUP BACK LICHENOID LYMPHOCYTIC INFILTRATE WITH EXOCYTOSIS

NOTE: In the context of the findings in specimen (B), the features are consistent with erythrodermic mycosis fungoides. Multiple serial sections have been examined.

B: RIGHT POST SHOULDER ATYPICAL T-CELL CD4(+) LYMPHOPROLIFERATIVE PROCESS WITH EPIDERMOTROPISM

NOTE: The findings are consistent with erythrodermic mycosis fungoides. Systemic work-up is recommended to evaluate for Sezary syndrome. Multiple serial sections have been examined.



Lessons Learned

Erythema in Skin of Color



Palmoplantar Keratoderma in Mycosis fungoides





Clinical Features in Darker Skin Types Erythema





- Erythema in darker skin is more violaceous and may be missed
- Scoring systems that rely on erythema underestimates severity of AD in darker skin
- After adjusting for erythema score, "black" children have a 6 times higher risk of severe AD than their "white" counterparts.



Clinical Features in Different Skin Colors

Hypopigmentation



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Darker Skin Types

Follicular accentuation





Grayish-white skin ("ashy skin")

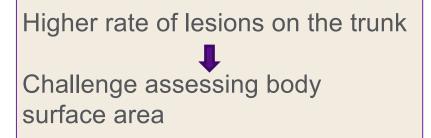


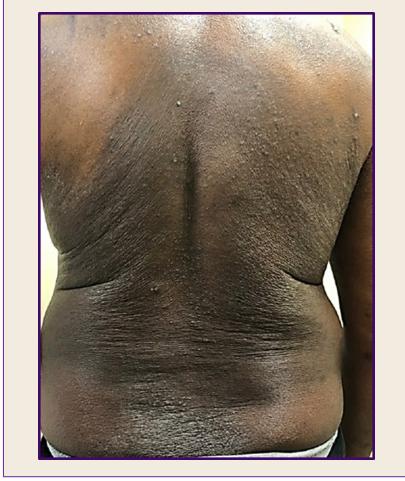




Profound Xerosis & lichenification









Prurigo Nodularis

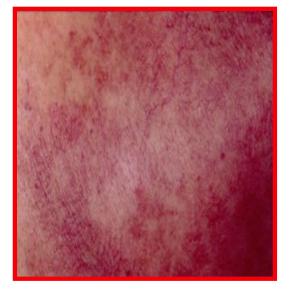






Difficult to monitor Topical Corticosteroid side effects





Striae



Atrophy





Other Social and Ethnic Differences

- Black compared to Caucasian/white children in the US
 - higher prevalence of AD
 - increased persistence of childhood AD
 - more severe AD
 - more sleep impairment
- Black & Hispanic with AD compared to Caucasian children
 - lower household income
 - more likely to be uninsured or underinsured
 - reported insufficient time during the patient-physician encounter
- Black children and adults with AD
 - less likely to have an ambulatory visit for AD &/or more likely to have an ED or urgent care visit & be hospitalized for AD

Lower income and lack of private insurance do not account for all of the racial/ethnic disparities observed in AD

School of Medicine













