Dermatologic Diseases Presenting in the Emergency Room Setting

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Paraneoplastic Pemphigus (PNP)
Clinical features - PNP

- Disseminated polymorphous erythematous papules and plaques - cutaneous lesions usually come after mucosal ones
- Cutaneous lesions also may resemble LP with violaceous papules
- Mucosal ulcers with tendency to involve lateral portions of tongue
- Circulating antibodies to desmoplakin I, an intercellular adhesion molecule
- Intercellular and basement membrane staining with IgG and C3 on direct immunofluorescence

Paraneoplastic pemphigus

- Clinical features
  - Usually associated with internal malignancies particularly non-Hodgkins lymphoma, Castleman’s tumor, follicular dendritic cell sarcoma, CLL and thymoma
  - Also has been seen in SCC of the skin and head and neck, adenocarcinoma of colon, breast, prostate, pancreas and some sarcomas
  - Patients often develop bronchiolitis obliterans and subsequent respiratory failure
  - Mortality rate may approach 90%
Histologic features - PNP

- Ragged appearing epidermis with band-like inflammatory infiltrate along the dermal-epidermal junction
- Dense infiltrate of lymphocytes with basal layer dyskeratosis and vacuolar alteration
- Other variable features including pemphigus-like acantholysis with intraepidermal blister formation or bullous pemphigoid-like subepidermal blister formation
Paraneoplastic pemphigus

- Immunofluorescence:
  - Autoantibodies (IgG) recognize following proteins:
    - Desmoplakin I
    - Bullous pemphigoid antigen I (230kD)
    - Periplakin
    - Desmoplakin II
    - Envolplakin
  - DIF demonstrates intercellular staining (frequently negative, though), but requires rat bladder epithelial substrate
  - Tumor cells actually produce these antigens, provoking B cell antibody production
  - Antibodies decrease with treatment of primary tumor
## Differential Diagnosis - PNP

- Lichen planus
- Erythema multiforme – more to follow
- Pemphigus vulgaris
- Bullous pemphigoid

## Lichen Planus

- 5 P’s of Pruritic, Purple, Polygonal, Papules and Plaques
- No association with visceral malignancy, although weak association with diabetes mellitus
- Histologic features include epidermal hypergranulosis with a dense band-like infiltrate with basal layer dyskeratosis and vacuolar change
- Subepidermal vesiculation, and acantholysis exceptional
- Direct immunofluorescence shows non-specific positivity with IgM and C3 within dyskeratotic cells
Lichen Planus

Pemphigus Vulgaris

- Uncommon disseminated vesiculobullous disorder with widespread fragile blisters, crusts and oral ulceration
- 15% mortality in association with secondary cutaneous infection
- Rare association with visceral malignancy (lung, breast)
- Prominent intraepidermal acantholysis with intraepidermal blister formation
- Circulating antibodies to desmoglein 3 and DIF with intraepidermal intercellular IgG and C3 staining
Pemphigus Vulgaris
Bullous Pemphigoid

- Systemic subepidermal vesiculobullous disorder characterized by widespread tense blisters without oral ulceration
- Association with medications particularly penicillins, sulfas, NSAIDS and diuretics, also with autoimmune disorders (SLE, RA, PBC, DM, and UC)
- Circulating antibodies to bullous pemphigoid antigens 1 and 2 - hemidesmosome components
- DIF positive for IgG and C3 along the dermoeidermal junction
Bullous Pemphigoid
Bullous Pemphigoid

Paraneoplastic Pemphigus

- Acute care:
  - Requires underlying neoplasm to be surgically excised
  - This results in complete resolution or marked improvement in vast majority of patients
  - Chemotherapy may help
  - Mucosal lesions are remarkably resistant to treatment
Calciphlaxis
(Calcific Uremic Arteriolopathy)
Calciphylaxis

- Described (Selye) in 1962
- Involves small to medium sized vessels
- Usually associated with chronic renal disease and secondary hyperparathyroidism
- Occurs in about 4% of hemodialysis patients
- Incidence: 1/100 hemodialysis pts/yr
- May occur without renal or parathyroid disease
- 60-80% mortality rate - sepsis, organ failure
- Manifests as cutaneous necrosis

Calciphylaxis

- Clinical features:
  - Acute onset of geographic areas of intensely painful ulceration following livido reticularis pattern that is very pruritic
  - Bilaterally symmetrical, usually on extremities, occasionally trunk, not usually head
  - Non-healing ulcers resulting in eschar formation
  - Resembles thrombophlebitis clinically
  - Internal organ calcification
Calciphylaxis - trigger factors

- High calcium x phosphate product
- Hypercalcemia
- * Hyperphosphatemia
- Hyperparathyroidism
- * Females
- Caucasians
- Long-term obesity
- Corticosteroids
- Subcutaneous insulin injections
- Hypercoagulable states
- Low serum albumin
- Albumin infusions
- Iron-dextran injections
- Warfarin
- Vitamin D therapy
- Immunosuppression
- Trauma
- * Diabetes mellitus
- Dialysis dependency

*Strongest risk factors on multivariate analysis

Calciphylaxis

- Histologic features
  - Intravascular calcium deposition in absence of inflammation
  - No evidence of atherosclerotic plaques
  - Secondary changes of vascular ischemia
  - Occasional extravascular calcium deposition
  - Fat necrosis in areas of affected vasculature
Proposed Pathogenesis of Calciphylaxis

A. 3 pro-thrombotic processes:
1. Reduced blood flow (tethered dermal vessels)
2. Vascular endothelial injury (subintimal fibrosis)
3. Hypercoagulable state secondary to endothelial cell dysfunction - release TNF-α

B. Vascular calcification
1. TNF-α also responsible (in part) for inducing osteogenic phenotype in smooth muscle perhaps through NFκB

Weenig RH. JAAD 2008; 58: 458-471
Calciphylaxis

• Differential diagnosis:
  – Dystrophic calcification - localized destructive process healed with calcium deposits (panniculitis, ruptured cysts)
  – Calcinosis secondary to systemic hypercalcemia - very rare in skin
  – Calcinosis universalis secondary to dermatomyositis - much more diffuse and not within vessels
  – Calcification secondary to atherosclerosis

Calciphylaxis

• Treatment:
  – Transcutaneous oxygen tension - treat skin prophylactically for ischemia
  – Phosphate binders
  – Increased hemodialysis
  – Parathyroidectomy - assoc. with longer survivals
Erythema Multiforme: toxic epidermal necrolysis variant (also known as TEN)

Toxic Epidermal Necrolysis

- Clinical:
  - Major variant of erythema multiforme
  - Extensive desquamation, most commonly following exposure to therapeutic drug (> 95% of cases)
  - Idiopathic response – can even occur with no prior history of hypersensitivity to agent
  - Mortality rate 25%-50%
  - Highest risk is during initial week of drug exposure and with drugs that have longer half lives
Toxic epidermal necrolysis

- Treatment:
  - Discontinuation of causative drug(s)
  - Treatment of hypovolemia, electrolyte imbalance, renal insufficiency and sepsis (identical to burn patients)
  - Daily wound care
  - Tried but not standardized:
    - Cyclosporine
    - Cyclophosphamide
    - Plasmapheresis
    - Corticosteroids
    - IVIg

Erythema Multiforme

- Disseminated annular and targetoid erythematous papules especially involving the palmar surfaces
- Hypersensitivity reaction to occult or concurrent infections including HSV, mycoplasma, streptococci, and histoplasmosis as well as an association with autoimmune disorders (RA, SLE) and inflammatory bowel disease
- Histology yields interface lymphocytic dermatitis with basilar vacuolar change
- DIF shows non-specific binding with IgM within dyskeratotic cells
Erythema multiforme (minor)

Stevens Johnson

- Clinical:
  - Other major variant of erythema multiforme
  - Involves mucosal surfaces (including eyes) and can result in serious complications including death (5% mortality rate)
  - Mortality directly related to speed with which offending agent is recognized and removed
  - 50% clearly related to drug exposure
  - Rarely related to immunizations, vaccines and infections
Stevens Johnson Syndrome

Stevens Johnson Syndrome
Erythema Multiforme

Erythema multiforme
Erythema multiforme
Differential diagnosis

- Pemphigus (vulgaris and paraneoplastic)
- Bullous pemphigoid
- Staphylococcal scalded skin syndrome

Staph Scalded Skin Syndrome

- Clinical:
  - Most common in infants or children < 6 y.o.
  - Adults with renal insufficiency or immunosuppression can also be affected
  - Much more common in males than females
  - Malaise, fever, irritability, tenderness of skin
  - Erythema generalizes and then flaccid bullae appear
Staph Scalded Skin Syndrome

• Caused by phage group II strains of *S. aureus*
• *S. aureus* secretes exotoxins that cause exfoliation at the level of the stratum corneum
• No organisms present within the skin: NOT a direct cutaneous infection
• If extensive, requires hospitalization, IV antibiotics
Staph Scalded Skin Syndrome

Staph Scalded Skin Syndrome
Staph Scalded Skin Syndrome
Pustular psoriasis

• Clinical:
  – Generalized eruption begins abruptly (often) with erythema and pustulation
  – Painful skin, fevers and malaise
  – Usually occurs as an acute exacerbation in patients with history of psoriasis
  – Triggering events may include: pregnancy, abrupt withdrawal of systemic steroids, hypocalcemia and infections
Pustular psoriasis

• Differential diagnosis:
  – Acute generalized exanthematous pustulosis

Acute generalized exanthematous pustulosis

• Clinical:
  – Acute febrile drug eruption
  – High fever on day rash begins
  – Numerous small, non-follicular pustules within large areas of erythema
  – Often lesions begin on face or intertriginous
  – >90% drug-induced:
    • Antibiotics (most commonly penicillins, cephalosporins)
    • Calcium channel blockers
    • Anti-malarials
How to maximize biopsy information

• Best choice of biopsy:
  – Punch biopsy (4 mm)
  – Small elliptical incisional biopsy

• Not useful:
  – Shave biopsy

• Simple removal of exfoliated skin:
  – Suboptimal but can work for frozen sections if biopsy impossible or too difficult

• Ideal location for biopsy(ies)
• NOT Ideal location for biopsy(ies)

Other information

• Direct immunofluorescence:
  – Cannot be done on tissue that has been in formalin (even for 5 seconds)
  – Useful for diagnosis of autoimmune blistering diseases:
    • Pemphigus (vulgaris and paraneoplastic)
    • Bullous pemphigoid
    • Linear IgA bullous dermatosis
  – Not useful for other blistering diseases:
    • Erythema multiforme
    • Staph scalded skin
Ideal biopsy site for immunofluorescence

Frozen section

- Appropriate use:
  - Will the information gleaned from a final (or preliminary) diagnosis affect your immediate treatment of the patient?
  - Can it wait until the next day?
    - Rush processing allows for superior microscopic sections and greater diagnostic accuracy
Frozen sections

• When is this appropriate/helpful?
  – Easy to differentiate staph scalded skin syndrome from toxic epidermal necrolysis
  – Impossible to distinguish pemphigus vulgaris from paraneoplastic pemphigus
  – Impossible to diagnosis calciphylaxis
    • Focal changes
    • Will not cut adequately on frozen section

Thank you!

• Its delightful to be back in Arkansas!
• Thanks for your attention!