I am honored!

- Dr. Stembridge:
  - Revered member of UTSW for > 40 years!
  - Department Chair for 23 years
  - Gifted teacher – motivated countless medical students to become pathologists
  - President of the ASCP, APC and American Registry of Pathology

  - (Aude esse verus) DARE TO TELL THE TRUTH!

The Importance of Clinico-pathologic correlation

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Professor, Department of Dermatology
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Our Diagnosis:

• Necrolytic acral erythema

Necrolytic Acral Erythema

• Clinical features
  – Affects primarily dorsa of feet
  – Most patients between 35 and 55 y.o.
  – All patients with active hepatitis C
  – Well circumscribed dusky erythematosus areas with flaccid blisters in early stages
  – Hyperkeratotic scales later in course

• Clinical (continued)
  – Effective treatment with interferon alfa-2b and oral (zinc) - (despite normal serum levels of zinc)
Necrolytic Acral Erythema

• Histologic features
  – Histologic changes similar to those in necrolytic migratory erythema, acrodermatitis enteropathica
  – Early with spongiosis, neutrophilic infiltrate, subcorneal pustules - not specific
  – Well-developed lesions with epidermal pallor and confluent parakeratosis

Necrolytic Acral Erythema

• Histologic features (continued)
  – Late lesions - resemble “papillomatous” lichen simplex chronicus
  – Hyperkeratosis, hypergranulosis, dermal fibrosis, focal dying keratinocytes, slight lymphoid infiltrate in papillary dermis
Necrolytic Acral Erythema

Differential diagnosis
- Acute: spongiotic dermatitis
- Well developed:
  - necrolytic migratory erythema
  - acrodermatitis enteropathica
  - Other nutritional deficiencies
- Chronic: Lichen simplex chronicus
Case #2
Histologic features of this case:

• Atrophic epidermis
• Aggregation of large histiocytes with abundant eosinophilic (oncocytic) cytoplasm
• Occasional multinucleated giant cells
• Minimal cytologic atypia, scattered mitoses

Our diagnosis:

• Multicentric reticulohistiocytosis
Clinical features - multicentric reticulohistiocytosis

- Multiple nodules, often ulcerated on dorsum of hands, overlying joints
- Mutilating arthritis frequently present
- Onset in middle age, rare in childhood
- More common in women
- Resolves spontaneously in 5-10 years

Clinical features - multicentric reticulohistiocytosis (continued)

- Associated with internal malignancy, especially hematopoietic in up to 30% of cases
- Normolipemic
- Frequent xanthelasmas
- Rarely involves lungs, bone marrow, lymph nodes
- May involve mucosa of oral cavity, nose, pharynx

Multicentric Reticulohistiocytosis
Multicentric Reticulohistiocytosis

Histologic features - multicentric reticulohistiocytosis
- Flattened epidermis
- Grenz zone
- Dermal aggregation of mononuclear and multinucleated histiocytes with “ground glass” or oncocytic cytoplasm
- Rare foamy cells
- Lymphocytic infiltrate common
- Mitoses unusual
- Cells express CD68, but not CD1a or MAC387

Multicentric reticulohistiocytosis
Multicentric reticulohistiocytosis

Differential diagnosis - multicentric reticulohistiocytosis

- Solitary reticulohistiocytoma
- Xanthogranuloma
- Xanthoma disseminatum
Solitary reticulohistiocytoma

- Histologically indistinguishable
- Only one lesion clinically
- Essential differential diagnosis as solitary form not associated with systemic illness

Xanthogranuloma

Xanthogranuloma (juvenile)

- Most common in children
- No predilection for extremities
- No underlying joint changes
- Similar histology but without oncocytic changes in cytoplasm (subtle), and more Touton giant cells (in well-developed lesions)
- Normolipemic
Juvenile xanthogranuloma

Xanthoma disseminatum
- Diffuse orange-yellow papules
- Diabetes insipidus in many cases
- Histology indistinguishable from xanthogranuloma but markedly different clinical presentation
- Normolipemic
Our diagnosis:

• Paraneoplastic pemphigus

Clinical features - paraneoplastic pemphigus

• Disseminated polymorphous erythematous papules and plaques with mucosal ulcers
• Usually associated with internal malignancies particularly non-Hodgkins lymphoma

Paraneoplastic pemphigus - pathogenesis

• Circulating antibodies to desmoplakin I, an intercellular adhesion molecule
Histologic features - paraneoplastic pemphigus

- Ragged appearing epidermis/mucosa 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

Direct immunofluorescence

- Intercellular and basement membrane staining with IgG and C3 on direct immunofluorescence
- Indistinguishable from pemphigus vulgaris – but often requires RAT BLADDER as substrate for indirect immunofluorescence

Paraneoplastic Pemphigus - esophagus
Paraneoplastic Pemphigus

Differential Diagnosis of Paraneoplastic Pemphigus

- Lichen planus
- Pemphigus vulgaris
- Erythema multiforme
- Bullous pemphigoid

Lichen planus

- Clinical features:
  - Reticulated, lacy white streaks along buccal mucosa
  - “leukoplakia” (simply means white plaque)
  - Ulcers common in some patients - very refractory to treatment
  - Much more common on trunk and especially extremities as flat-topped, purple, pruritic, polygonal papules
Lichen planus

Histologic features:
- Similar to changes in cutaneous lesions
- Hyperkeratosis (despite site) and focal parakeratosis
- Obscuration of mucosal/submucosal junction by dense infiltrate of lymphocytes and plasma cells
- Scattered plasma cells (site specific)
- Dying keratinocytes - if confluent, result in small subepidermal blisters (Max-Joseph spaces)
Oral lichen planus

Associations:
- Hepatitis C
- Porphyria cutanea tarda
- HLA-DR6 - especially cases of oral LP
- Rare development of squamous cell carcinoma in long-standing cases of oral LP (estimated at 1% of cases)
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 (pattern indistinguishable from paraneoplastic pemphigus)
Pemphigus vulgaris - DIF

Case #4
Histologic features of this case:

- Subepidermal blister
- Predominantly neutrophilic infiltrate
- No epidermal necrosis
- Inflammation largely confined to papillary dermis
- Eosinophils scant
Our diagnosis:

• Dermatitis herpetiformis

Clinical features - DH

• Intensely pruritic, erythematous papules
• Symmetrical distribution
• Often on extensor surfaces of extremities - elbows and knees
• Sacrum
• Rare to find intact blisters - too pruritic
• Excoriations common
• Most common in young to middle-aged adults

Clinical features (continued) - DH

• Gastrointestinal anomalies seen in all patients - villous atrophy in small intestine
• Usually sub-clinical
• Rare patients with symptoms of celiac sprue
• Autoimmune thyroid disease
• Lupus, rheumatoid arthritis, other autoimmune processes
• Associated with GI lymphomas:
  – Enteropathy-type T-cell lymphoma, MALTomas
Dermatitis herpetiformis

Histologic features - DH

- Rare to find intact blisters
- Microabscesses within papillary dermal tips
- Subepidermal blisters often involve only 1-2 rete ridges
- Superficial perivascular lymphocytic infiltrate
- Scattered eosinophils
Histologic features - DH (continued)

- Dying keratinocytes not a common feature
- Involvement of deep dermis not expected finding

Dermatitis herpetiformis

Dermatitis herpetiformis
Dermatitis herpetiformis

Immunologic features - DH

- Granular deposits of IgA within papillary dermal tips
- Must distinguish from linear staining along DEJ seen in linear IgA bullous dermatosis
- Best to biopsy peri-lesional skin
- (Neutrophils may enzymatically degrade immune deposits)

Dermatitis herpetiformis - DIF
Dermatitis herpetiformis - DIF

Treatment - DH

- Treat with dapsone and gluten-free diet
- Dapsone alone will cause resolution of the lesions and histologic changes, but IgA deposits will persist
- Long-term gluten-free diet will result in negative direct immuofluorescence
- Also prevents lymphoma risk

Lymphoma associated with DH

- "Enteropathy-type" T-cell lymphoma (ETL)
- Progression from gluten-sensitive enteropathy to refractory sprue to ETL
- Antigen-driven proliferation of intraepithelial cytotoxic T-cells results in neoplastic, dominant clone
- In rare cases, reversal has been reported
- Aggressive disease with high morbidity and mortality
Celiac sprue in patient with DH

ETL in patient with DH

ETL in patient with DH
ETL immunostains

- ETL slides generously loaned by Dr. Dennis O’Malley, hematopathology, University of Indiana

Differential diagnosis - DH

- Linear IgA bullous dermatosis
- Bullous dermatosis of childhood
- Epidermolysis bullosa acquisita
- Bullous lupus erythematosus
- (Cicatricial pemphigoid)

Linear IgA bullous dermatosis

- Larger blisters, may be intact - often associated with drug ingestion in adults (especially vancomycin)
- Larger subepidermal blisters with linear array of neutrophils in papillary dermis
- Linear IgA staining along dermal-epidermal junction
Epidermolysis bullosa acquisita

- Blisters and milia formation often on extremities - at sites of repeated minor trauma
- Most cases non-inflammatory, but can be neutrophil-rich
- Scarring seen in older lesions
- DIF - linear IgG along the floor of the blister (antibody directed against type VII collagen)
Bullous lupus erythematosus

- Patients usually with other cutaneous manifestations of LE and focal blisters
- Often superficial and deep perivascular and peri-appendageal lymphocytic infiltrate along with the subepidermal blister and neutrophils
- DIF - granular IgG/IgM/C3 along DEJ (typical of LE)
Histologic features of this case:

- Well-circumscribed, lobular proliferation of sebocytes
- Sebocytes not fully mature, but minimal cytologic atypia
- Occasional mitoses (none atypical)
Our diagnosis:

• Sebaceous adenoma

Clinical features - sebaceous adenoma

• Non-descript cutaneous tumor with slightly yellowish hue in some cases
• NOT the same as adenoma sebaceum (angiofibroma) associated with tuberous sclerosis
Histologic features - sebaceous adenoma

- Well-circumscribed islands of keratinocytes within the dermis
- Peripheral cells are basaloid with progressive orderly maturation to sebocytes towards center of aggregates
- Basaloid cells usually comprise less than 50% of cells in tumor
- Mitoses seen on occasion, but no atypical forms
- Necrosis not a feature
- Tumors associated with Muir-Torre often with unusual histologic features, especially cystic spaces
Sebaceous adenoma

Muir Torre syndrome
- Autosomal dominant
- Subset of Lynch syndrome
- Cutaneous manifestations
  - Multiple sebaceous neoplasms (not sebaceous hyperplasia)
  - Keratoacanthomas
  - Epidermal cysts
- May precede or follow GI tumors
Muir Torre syndrome

- Extracutaneous manifestations
  - Gastrointestinal carcinomas
    - Tend to be indolent with low metastasis rate
  - Colonic polyps
  - Laryngeal carcinomas
  - GU tumors in men
  - Ovarian and uterine neoplasms
  - Rarely lymphoma

Muir Torre syndrome

- Genetic anomaly:
  - Mutations in either hMLH1 or hMSH2 reported in some patients
  - These are DNA mismatch repair genes
Differential diagnosis - sebaceous adenoma

- Sebaceous hyperplasia
- Sebaceous epithelioma
- Sebaceous carcinoma
- Nodular (clear cell) hidradenoma
- Balloon cell nevus
- Metastatic renal cell carcinoma

Sebaceous hyperplasia

- Often multiple yellow papules on sun-exposed skin
- Frequently confused with BCC clinically
- Full maturation with only a peripheral layer of basaloid cells
- Crucial distinction - not associated with Muir-Torre syndrome
Sebaceous epithelioma

- No distinguishing clinical characteristics
- More than 50% basaloid cells - may be BCC with sebaceous differentiation
- No capacity for metastasis
- Not an important distinction - also associated with Muir-Torre syndrome

Sebaceous carcinoma

- Majority around eye lids, but can be at other body sites
- In general, high rate of metastasis, but not so in patients with Muir-Torre syndrome
- Nuclear atypia, pleomorphism, mitotic activity, necrosis, lack of circumscription, Pagetoid spread all favor carcinoma over adenoma
Sebaceous carcinoma

Nodular (clear cell) hidradenoma
- No scalloped nuclei
- Cytoplasmic vacuole larger, no microvesiculation
- No palisade of basalog cells around periphery of tumor lobules
- Ductular formation
- Reduplication of type IV collagen (hyalinized)
Nodular hidradenoma

• Nesting pattern
• Usually areas with more typical melanocytes or pigment
• Intraepidermal melanocytes in many cases
• Maturation present
• S100 positive

Balloon cell nevus
Metastatic renal cell carcinoma

- Cytologic atypia and mitoses
- Increased vascularity
- No peripheral palisade of basaloid cells
- Nuclei without scalloping
- S100 positive (unlike sebaceous tumor)
Metastatic renal cell carcinoma

Thank you for your attention and for the invitation to present!