Highlighted cases from:

*The 59th Annual Zola Cooper Seminar*

A Clinical and Dermatopathologic Seminar

November 10, 2012

**Case 1**

- 6 week old infant with birthmark on left neck and axilla, persisting into childhood
- Observed shortly after preterm birth at 36 WGA complicated by transient abdominal ascites, bilateral inguinal hernias mild electrolyte abnormalities, mild normocytic anemia
- Echocardiogram demonstrated newborn transitional heart with a patent foramen ovale, patent ductus arteriosus, and normal valve function
What is your diagnosis?
Case 1

Diagnosis

Patch-like Congenital Segmental Glomangiomas (Glomulovenous malformations)

Congenital Segmental Glomangiomas

- Mutations in glomulin gene (GLMN); protein product is key to vascular development.
- GVMs present at an early age, arise in groups of nodules or plaques
- Majority are inherited (autosomal dominant w/ incomplete penetrance)
- Segmental GVMs reflect somatic mosaicism in individuals whose germ line is heterozygous mutant GLMN with localized novel loss-of-heterozygosity GLMN mutations in affected areas

Regarding congenital segmental glomangiomas:

- Most lesions are painful
- Inherited in autosomal dominant fashion with incomplete penetrance
- Are indistinguishable histologically from subungual glomus tumors
- Mutation is in glomulin gene
- B and D

Case 2

- 7 year old Caucasian girl with 4 year history of papules on neck, upper back and chest
- History of macrocephaly, bifid ribs, fused vertebrae, jaw cysts
- Hearing loss due to a spindle cell carcinoma of the ear ossicles treated by an otolaryngologist in 2009
- Possible absence seizures which started when she was 3 years old (EEG evaluation negative)
- No significant family history and no person in family with similar symptoms
What is your diagnosis?
What will a skin biopsy show?

Case 2
Diagnosis
Neviod Basal Cell Carcinoma Syndrome (NBCCS)
Nevoid BCC Syndrome

- First described by Robert Gorlin, oral pathologist, and Robert Goltz, a dermatologist, in 1960
- Autosomal dominant multisystem disorder with complete penetrance and variable expressivity; mutation in the PTCH1 tumor suppressor gene which encodes patched protein localized to chromosome 9q22.3
- Major clinical manifestations: two BCCs or one BCC under the age of 20, 3 or more palmar or plantar pits, odontogenic keratocysts of jaw, ectopic calcification with a lamellar pattern, early falx cerebri calcification, bifid or fused ribs, or a first degree relative with NBCCS
- Minor criteria: macrocephaly, ovarian fibromas or childhood medulloblastoma, oral-facial deformities including cleft lip, cleft palate, frontal bossing or course facies, eye anomalies including cataracts, microphthalmia or nystagmus, skeletal deformities including Sprengel’s deformity, pectus deformities, digital syndactyly, polydactyly or hypertelorism, and radiographic abnormalities including bridging of the sella turcica or vertebral anomalies.

Which of the following is not characteristic of Nevoid BCC Syndrome?

a. Autosomal dominant inheritance
b. Basal cell carcinomas simulating skin tags clinically
c. Response to Vismodegib
d. Microcephaly
e. Medulloblastoma

Case 3

- 41-year-old Asian man presented with fast-growing lesion on posterior left leg in
- Present for 4 months and began as small spot becoming progressively larger
- History of burn injury 25 years previously
- Diagnosis of keratoacanthoma on three punch and incisional biopsies
- Wide local excision in
- Lesion recurred and invaded into underlying bone six months later
- Above knee amputation performed
What is your diagnosis?
What is next step in work-up?

Case 3
Diagnosis
Keratoacanthoma Centrifugum Marginatum
Evolved into Invasive Squamous Cell Carcinoma

Keratoacanthoma Centrifugum Marginatum

- KCM: rare form of KA; only few cases resulting from previous trauma
- Usually solitary lesion measuring up to 30 cm in size with progressive peripheral expansion and concomitant central healing
- The course 2-3 times longer than simple KA without spontaneous resolution
- Transformation of KA to SCC rare
- In contrast to squamous cell carcinoma, there is no tendency to develop distant metastasis even in advanced cases
- This case shows distinctive features of KCM clinically and histopathologically; first reported case to have arisen from a burn injury

KA and SCC

- Not all KA’s are SCC
  - Many small, develop rapidly, regress
  - Eruptive forms, those caused by BRAF inhibitors NOT SCC
  - Can be treated more conservatively, ie, IL 5-FU, MTX
  - May Koebnerize following surgery
- Divided into 3 groups:
  - KA: classic histology with architecture
  - Crateriform SCC: more endophytic, more atypia
  - SCC, KA-type: architecture of KA with greater atypia

Regarding keratoacanthoma:

- May be locally aggressive and extend deeply
- All are squamous cell carcinomas
- Acantholysis is common histologic feature
- May recur rapidly following excision and “Koebnerize”
- A and D

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Case 4

- Series of 46 cases from MD Anderson of patients with scaly dermatitis around the waist
- All cases itchy; mostly in men wearing elastic containing underwear
What is your diagnosis?
What do you predict patch testing would reveal?

Case 4
Diagnosis
"Waistband" Mycosis Fungoides, Stage Ib
“Waistband” Mycosis Fungoides

- Involves sun-protected areas of body
- Mimics the distribution of other waistband dermatitides including contact dermatitis and intertrigo
- May represent the cusp between inflammation and malignancy with clothing as a possible initial irritant
- Underscores that diagnosis of MF requires careful and repeated clinicopathological correlation

Which of the following is true regarding dermatitis of the waist band area?

a. Patients may be patch test negative to rubber components and new elastic yet still allergic to components in the waistband
b. Sodium hypochlorite may produce N,N-dibenzylcarbamyl chloride from the rubber accelerator, zinc dibenzyldithiocarbamate which may be the allergen
c. Allergic contact dermatitis may simulate mycosis fungoides clinically and histologically
d. Some experts propose that mycosis fungoides may be induced by longstanding contact dermatitis
e. All of the above

Case 5

- 56 year old African American man from Mississippi with plaque on right leg for 10 years
- Initially started as a small scaly patch that progressively enlarged
- Did not seek evaluation until the lesion developed a fungating component
What is your presumptive diagnosis? What would a skin biopsy show?
**Woringer-Kolopp Disease (Pagetoid Reticulosis)**

- Rare variant of mycosis fungoides
- Most commonly affects middle aged men
- Typically present with solitary plaque on extremity that behaves with an indolent clinical course
- Histologically, atypical lymphocytes primarily localized to epidermis with a CD4+, CD8+, or CD4-/CD8- phenotype
- CD30 expression variable
- 2 main forms of pagetoid reticulosis: localized (Woringer-Kolopp) and widespread (Kettron-Goodman)

**Regarding mycosis fungoides:**

a. Pagetoid reticulosis may simulate melanoma histologically
b. Other forms include xanthoerythroderma perstans and Kettron-Goodman disease
c. Pagetoid reticulosis forms generally have a poorer prognosis than other forms
d. A and B
e. A and C

**Case 5**

**Diagnosis**

Woringer-Kolopp Disease (Pagetoid Reticulosis)

**Case 6**

- 55 year old woman with longstanding eruption of trunk and extremities recently began developing "swellings" of skin of legs and back of neck
- Biopsy had been previously performed and interpreted as sarcoidosis
- Lesions had been continuing to increase in size and she noted that the skin overlying some of these areas had began to become wrinkled
Diagnosis: Granulomatous Slack Skin Syndrome and Mycosis Fungoides both conventional and granulomatous types

- T-cell and histiocyte infiltrates with loss of elastic fibers lead to atrophy often resulting in large pendulous folds especially in the flexures
- Patients may have pruritus and erythema
- May be preceded by patches or plaques and may coexist with classical MF
- May develop as a consequence of patient developing a granulomatous reaction in response to the MF
- May have indolent or aggressive course
- May coexist with Hodgkin's or non-Hodgkin's lymphoma
- Rarely seen in other settings including CD30+ lymphoma

Which of the following regarding granulomatous slack skin syndrome is false?

a. May be misdiagnosed as sarcoidosis
b. Often associated with large pendulous skin folds
c. Large histiocytes stain positively with S-100 protein
d. May be seen in patients with other forms of CTCL
e. May be associated with Hodgkin's lymphoma

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Case 7

56 year old woman with an 8 month history of erythroderma, headache, fever and chills.

Blurred vision
Dry eyes
Optic neuritis
What is your diagnosis?  
What additional work-up would you perform?

**Diagnosis:** Erythrodermic Sarcoidosis

**Erythrodermic Sarcoidosis**

- **Clinical:**
  - Cutaneous lesions seen in 20-35% of patients with systemic sarcoidosis, occasionally present as erythroderma
  - Anterior uveitis—presents as red eye, blurred vision, ocular pain, and photophobia; found in 80% of patients with ocular disease
  - Serum ACE level—elevated in 90% of patients with active disease
- **Histology:**
  - Non-caseating granulomatous infiltrate
  - Can involve subcutaneous fat
  - Differential includes mycobacterial and fungal infections, foreign body reactions, and other granulomatous disorders including granulomatous MF

**Erythrodermic Sarcoidosis**

- Sarcoidosis may simulate many different inflammatory disorders and is one cause of erythroderma
- Extremely rare variant, however
- May simulate granulomatous MF histologically
  - No atypical lymphocytes, epidermotropism
  - Usually minimal lymphocytic infiltrate at all
Sarcoidosis:

a. May present with uveitis
b. Papules of the nasal alae are characteristic
c. Lacrimal enlargement is associated with hilar adenopathy
d. Histology is pathognomonic
e. A, B and C are correct

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Case 8

- 64 year old woman with history of IgG monoclonal gammopathy and ulcerated plaques on temples, chest
- Primarily affect the periocular region, right and left temporal areas, neck, and anterior chest
- Ulcerated; painful
- Scarring secondary to ulceration of periocular plaques hinders vision
- Periodic fever
What is your diagnosis?
What work-up would you perform?

Case 8
Diagnosis

Necrobiotic Xanthogranuloma with Associated Monoclonal Gammopathy

- Rare, multisystem, progressive disorder with asymptomatic firm yellow papules, nodules, or plaques; periorbital region most common
- Average onset sixth decade; M:F
- Associated with paraproteinemia; 80% monoclonal IgG
- Paraproteinemia may be inciting event or cofactor in initiating granulomatous inflammation
- May extend into the orbit
- Lymphadenopathy, hepatosplenomegaly, mucosal, myocardial, and pulmonary lesions may be present
- Bone marrow exam reveals leukopenia, plasmacytosis, frank myeloma or myelodysplastic syndrome.
- Sheets of histiocytes and associated inflammatory cells with degenerated collagen and caseation necrosis with cholesterol clefts
- Treatment directed at treating paraproteinemia
Which of the following is true regarding NXG?

a. Paraproteins may precipitate and lead to secondary granulomatous dermatitis  
b. Periorbital involvement characteristic  
c. Most paraproteins are monoclonal IgG  
d. Lesions often ulcerate  
e. All of the above

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**Case 9**

- 45 year old African American man with plaque on back for six months
- History of bowel A-V malformation requiring multiple abdominal angiography; more than fifteen abdominal angiograms performed

*Image courtesy of Dr. Thomas Nicolai*
What is the diagnosis? What is unusual about the histology?

**Fluoroscopy-Induced Subacute Radiation Dermatitis**

- Histologic findings may be subtle
- May have relatively minimal sclerosis
- May simulate an interface dermatitis
  - Has been seen in patients with LE and on meds raising question as to whether it is analogous to a photosensitivity dermatitis induced by radiation rather than UV

**Case 9**

**Diagnosis**
Fluoroscopy-Induced Subacute Radiation Dermatitis

**Fluoroscopy associated dermatitis:**

- a. Demonstrates histologic features identical to other forms of radiation dermatitis
- b. Develops only after prolonged exposure to radiation
- c. Patients often are taking other photosensitizing drugs
- d. Clinical lesions may simulate factitial conditions
- e. C and D

**Case 10**

- 73 year old woman with a pink “rash” of left shoulder and upper arm
- 7 ½ years s/p radical mastectomy for infiltrating ductal carcinoma
- 12 of 24 lymph nodes showed evidence of metastases; Er, Pr receptor studies negative
- Two full courses of radiotherapy, alternating regimens of adjuvant chemotherapy over last 7 years
Case 10
Metastatic Breast Carcinoma Simulating Angiosarcoma

Subsequent Course
- Over the next two months, numerous firm papules appeared on her abdomen and trunk adjacent to the purpuric areas
- Additional biopsy confirmed additional metastases of breast carcinoma within vascular spaces
- Patient entered hospice care and expired shortly after
Proposed Pathogenesis

• Microscopic metastases likely in transit within lymphatic vessels at time of surgery and subsequent radiotherapy
• Post-radiation fibrosis and surgical destruction of normal lymphatic channels leads to lymphatic obstruction.
• Microscopic metastases “trapped” within lymphatics or localize there (“locus minoris resistentiae”)
• Over time lymphatic vessel dilatation occurs outside of surgical and radiotherapy fields
• Blood vessels become compromised as well allowing leakage of blood into the dilated lymphatic channels thereby resulting in the “angiosarcomatous” clinical appearance

Which of the following is true regarding cutaneous metastatic breast carcinoma?

a. Most common histologic finding is diffuse involvement with cords and strand of cells between collagen bundles
b. One variant may appear similar to BCC
c. Mammary Paget’s disease is one form
d. Cytokeratin 7 is a useful marker
e. All of the above

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Case 11

• 63 year old woman with history of breast cancer metastatic to liver treated with chemoembolization of doxorubicin beads
• Complained of painful pruritic eruption on abdomen.
Case 11
Diagnosis
Deposition of Doxorubicin Drug Eluting Beads in Cutaneous Vasculature Status Post Chemoembolization

What is your diagnosis?

Deposition of Doxorubicin Drug Eluting Beads in Cutaneous Vasculature Status Post Chemoembolization

- Minimally invasive therapeutic options explored for therapy of liver metastases including radiofrequency ablation, laser induced thermotherapy, transarterial chemoembolization and drug-eluting bead therapy
- Drug eluting beads can deliver higher doses of chemotherapy directly to tumor without systemic side effects
- Reports of interstitial pneumonitis complicating post-operative course
- First report of cutaneous deposition of doxorubicin drug-eluting beads

Which of the following is true regarding treatment of breast carcinoma?

- a. Radiation dermatitis may be improved by dilute bleach baths
- b. Dermatologists may play an important role in performing biopsies to confirm diagnosis and evaluate hormone receptor status
- c. Hand-Foot syndrome may be caused by capecitabine
- d. Nail abnormalities may develop with tamoxifen
- e. All of the above

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- e. All of the above
Case 12

- 42 year old man presented to ER after alcohol withdrawal seizure complicated by right humerus fracture
What is your diagnosis? What would you expect to see with direct IF testing?

Case 12
Diagnosis

“Fracture” blister

(Proposed diagnosis: pressure bulla)

“Fracture” Blister

- Develop in 2.7% of acute hospitalized fractures
- Thought to result from “skin strain” during fracture deformation
- Post-fracture edema and hypoxia from injured vessels and lymphatics contributes to vesicle formation
- This case may be purely related to pressure as patient was “found down” lying on injured area

Which disorders are in the differential diagnosis of “fracture” blister?

a. Pseudoporphyria
b. Epidermolysis bullosa acquisita
c. NSAID-associated cell poor blister
d. Epidermolysis bullosa
e. All of the above

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Case 13

- 78 year old man with multiple non-healing crusted plaques on the scalp which did not resolve with cryotherapy
- History of SCC treated with Mohs Surgery that did not heal for 18 months after surgery
- History of “crusted scalp AKs” treated with LN2 dating back to 1992.
- Repeat cultures positive for *Pseudomonas aeruginosa*; failed to respond to 16 courses of various antibiotics, antifungals or debridements
- Biopsy 18 months after initial surgery showing SCC-IS

Additional Case

- 72 yo WM
- Scalp with “persistant lesion” and areas of ulceration. Scalp previously treated with topical 5-fluorouracil
- R/o SCC
What is your diagnosis? Would you perform additional biopsies (and not trust your dermatopathologist’s diagnosis)?

Case 13
Diagnosis
Erosive Pustular Dermatosis of the Scalp
**Erosive Pustular Dermatosis of the Scalp**

- Inflammatory disease characterized by pustules, erosions and crusting in areas of atrophic alopecia
- Occurs after trauma on actinically damaged scalp thought to result from exuberant immune reaction to actinically damaged skin
- May arise following cryotherapy or topical treatment as treatment leads to exposure of additional antigens and triggers immune response refractory to normal regulation
- Underrecognized; may have diagnostic delay of up to 3-5 years
- Can be colonized or secondarily infected further delaying diagnosis
- Responds rapidly to topical steroids, tacrolimus, and Dapsone

Which of the following is true regarding erosive pustular dermatosis?

a. It may involve sites other than the scalp
b. It is thought to be caused by bacterial superinfection
c. Most cases have evidence of underlying solar keratosis
d. Diagnosis usually readily apparent
e. Histology pathognomonic

**Case 15**

- A 25 year old man presented with a history of pustular lesions of the skin, mouth and genital ulcers and non-descript complaints of arthritis and eye dryness and blurriness
- Previously healthy although had recently had what he described as the flu

Which of the following is true regarding levamisole mediated thrombotic vasculopathy?

a. Levamisole may exhibit effects that simulate effects of cocaine
b. Rarely present in US cocaine supply
c. Serologic studies positive for c-ANCA
d. Levamisole commonly used for treatment of helminth infestation
e. Most cases are fatal
What is your diagnosis? What is the relationship of the history of the viral illness to the diagnosis?
Diagnosis: Behcet’s Disease

Behcet’s Disease

• Systemic disorder of recurrent acute inflammation
  – oral aphthous ulcers
  – genital ulcers
  – uveitis
  – skin lesions
• Mucocutaneous lesions
  – Oral/genital aphthae
    • Painful, 1-3 cm, yellow fibrinous base
  – Others
    • Lesions resembling pustular vasculitis, erythema nodosum, Sweet’s syndrome, pyoderma gangrenosum, palpable purpura

Behcet’s Disease

Systemic lesions

• Posterior uveitis
  – Most diagnostically relevant lesion
  – Can lead to blindness
• Anterior uveitis, hypopyon (pus in ant chamber), cataracts, glaucoma, neovascular lesions
• Arthritis
  – Nonerosive, asymmetric oligoarthritis
• Vascular aneurysms, arterial/venous occlusions, varices
• Cardiac involvement
  – Myocarditis, coronary arteritis, endocarditis, valvular dz
• GI tract aphthae may lead to perforation

Behcet’s Disease

Systemic Lesions

• Renal manifestations
  – Proliferative or rapidly progressive crescentic glomerulonephritis
• Neurologic manifestations (in <25%)
  – Meningoencephalitis, central venous sinus thrombosis, benign intracranial hypertension, cranial nerve palsies, brainstem lesions, pyramidal/extrapyramidal lesions
  – Poor prognosis associated with progressive course, relapse after tx, repeated attacks, and cerebellar symptoms

Diagnosis

• Oral aphthae plus 2 of the following:
  – Genital aphthae, uveitis, cutaneous EN/papulopustular lesions or pathergy
• No evidence of IBD, SLE, Reiter’s, herpetic infections
• Other DDx
  – Bowel Associated Dermatitis-arthritis syndrome, complex aphthosis, pustular vasculitis

Associations

• HLA B51
• Heat shock proteins
• Herpes simplex virus
• Streptococcal infection
• Parvovirus B19 (New association)
Parvovirus and Behcet’s

- Quantity of Parvovirus B19 DNA in nonulcerative BD lesions was significantly different from ulcerative lesions in the study group and from the skin of healthy controls (p<0.01)
- First study that provides evidence of a possible causal link between BD and parvovirus B19

Source: Clinical and Experimental Dermatology 32:186-90, 2007

Which of the following is not required in order to make a definitive diagnosis of Behcet’s disease?

a. Genital aphthae
b. Pathergy
c. Anterior uveitis
d. Cerebellar disease
e. All of the above

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Case 16

- 8 month old Hispanic boy presented for delayed development
- Enlarged “belly”, patulous mouth, drooling
- Thickened doughy skin with multiple skin colored papules

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Hurler’s Syndrome

- Mucopolysaccharidosis type I (gargoyleism)
- Genetic disorder resulting in buildup of glycosaminoglycans due to deficiency of alpha-L-iduronidase, responsible for the degradation of mucopolysaccharides
- Buildup of heparan sulfate and dermatan sulfate
- Early death often due to cardiac or respiratory disease
- Histology identical to coincidental mucin deposition
- Treatment unsatisfactory

Which of the following disorders is not a mucopolysaccharidosis?

a. Hurler’s syndrome
b. Hunter’s syndrome
c. Morquio’s syndrome
d. Sanfilippo syndrome
e. Noonan syndrome
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