This continuing medical education activity is jointly provided by the North Carolina Dermatology Association and Southern Regional Area Health Education Center.

SUNDAY PRESENTATIONS

JULY 7-9, 2017 | OMNI HOMESTEAD RESORT | HOT SPRINGS, VIRGINIA
ARTIFICIAL INTELLIGENCE AND MELANOMA DIAGNOSIS: AM I OUT OF A JOB?

http://mdacc.participoll.com

Kelly Nelson, MD FAAD
Associate Professor
Department of Dermatology
MD Anderson Cancer Center
• No conflicts
Melanoma Secondary Prevention

- Access
- Seeing it
- Diagnostic accuracy
Melanoma Secondary Prevention

Access

Seeing it

Diagnostic accuracy
Dermoscopy

Figure 2. SROC curves for the performance of the clinical diagnosis without dermoscopy (red line), dermoscopy by experts (black line), and dermoscopy by non-experts (blue line).
Automated dermoscopic analysis

MelaFind
- Automated multispectral dermoscopy analysis
- FDA approved
- Expensive
- Sn 98.4, Sp 9.9

Arch Dermatol 2011;147:188. PMID 20956633
Other diagnostic technologies

- Reflectance confocal microscopy
- Optical coherence tomography
- High frequency ultrasound
- Tape stripping
- Spectroscopy

- Expensive
- Bulky machines
- Challenging image acquisition
- True predictive capacity
Dermatologist-level classification of skin cancer with deep neural networks

Andre Esteva*, Brett Kuprel*, Roberto A. Novoa*, Justin Ko*, Susan M. Swetter†, Helen M. Blau‡ & Sebastian Thrun

Have your patients asked you about this?

A: yes

B: no
Artificial Intelligence and Image Recognition

- Feature extraction + Classification
- Deep Convolutional Neural Network
  - Overlapping data intake fields
  - Convolutional processing
  - Deep learning
- GoogleNet Inception v3 CNN architecture
Take Home Points

• Secondary Prevention: Patient Access, Seeing it, Diagnostic Accuracy
• Ideal Diagnostic Technology: Portable, Cheap, Accurate
• Validation is essential
Clinical and Pathologic Features of Indeterminate Cell Histiocytosis

Resident: Nathaniel Slater, MD
Attending: Natalie Sun, MD
UNC Department of Dermatology

NC Dermatology Summer Meeting
June 9, 2017
Our Case

• 55 yo man with a history of HTN and NAFLD presented with an asymptomatic, widespread papular eruption
• Complete ROS pan-negative
• Outside biopsy in June 2016 consistent with Langerhans Cell Histiocytosis (LCH)
• UCSF pathology consultation also favored LCH
Exam
Exam
Exam
Medical history

- **Past medical hx**
  - HTN, NAFLD, prior BCC

- **Family hx**
  - No autoimmune disorders
  - Mother: breast ca, 70s
  - Brother: Hodgkin’s, 40s
  - Pt is 1 of 10 children, no other FH of cancer

- **Social hx**
  - Environmental engineer, married with 12yo child.

- **Meds**
  - Irbesartan 150mg daily
  - Vascepa (rx fish oil) daily
  - Omeprazole 40mg daily
  - Sildenafil 100mg prn

- **NKDA**
Workup unrevealing for systemic disease

Labs

Alk Phos 123 (H); CMP, CBC, ESR, LDH, IgG/A/M, Ferritin, Uric acid, U/A unremarkable

Bone marrow biopsy

Normocellular marrow with no evidence of LCH, langerin negative.

No immuno-phenotypic abnormalities on flow cytometry

PET CT

No extra-cutaneous disease
Single-system Cutaneous LCH?

- Isolated skin disease is rare in adults
- **Clinical manifestations:** highly variable spectrum reported
  - Severe intertriginous or seborrheic dermatitis-like, papulopustular, xanthomatous, purpuric, hemorrhagic, pigmented variants reported (Querings et al., Cardoso et al.)
- **Course:** highly variable, unpredictable
  - Numerous indolent cases reported
  - Potential for persistence or progressive disease
- **Gamut of treatments reported** (mostly as case reports):
H&E c/w LCH

Top Right: low power
Left, 20X
Bottom Right, 40X
Immunophenotype

CD1a

S100

CD68

Negative for:
- Cytokeratin
- Tryptase
- Melan-A
- Langerin (CD207)
Immunohistochemistry of Histiocytoses

**Langerhans cell histiocytosis**
- S100
- CD1a
- Langerin
- Letterer-Siwe disease
- Hand-Schüller-Christian disease
- Eosinophilic granuloma
- Hashimoto-Pritzker disease

**Non-Langerhans cell histiocytosis**
- Indeterminate cell histiocytosis
- Rosai-Dorfman disease
- Various macrophage/monocyte and dermal dendrocyte markers

Benign cephalic histiocytosis
- Generalized eruptive histiocytoma
- Juvenile xanthogranuloma
- Necrobiotic xanthogranuloma
- Giant cell reticulohistiocytoma/multicentric reticulohistiocytosis
- Xanthoma disseminatum
Dx: Indeterminate Cell Histiocytosis (ICH)

- Consistent with LCH
  » H&E c/w with LCH; strong and diffuse CD1a positivity
  » CD68+ and focal S100 not specific either way

- Favoring ICH
  » Langerin-
  » Lack of epidermotropism, lack of eosinophils
  » Clinical picture most consistent with reported cases of ICH

<table>
<thead>
<tr>
<th></th>
<th>CD1a</th>
<th>S100</th>
<th>CD68</th>
<th>Birbeck granule</th>
<th>Langerin (CD207)</th>
<th>Factor XIIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCH</td>
<td>+</td>
<td>+</td>
<td>- / +</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>ICH</td>
<td>+</td>
<td>+ (or focal)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
What Is ICH?

• Enigmatic entity, displays LCH markers (CD1a; S100 which can be more focal), but also displays dermal histiocytic markers (CD68)

• Does not display Birbeck granules
  » Or Langerin (CD207)

• Somewhat controversial entity (< 50 cases reported, some have questioned whether this represents immature or de-differentiated LCH vs variant of non-LCH)
  » Multiple authors have suggested a spectrum between Langerhans and non-Langerhans histiocytoses
  » First described in 1985, incorporated into WHO classification in 2006
Clonality

- **LCH**
  - BRAFV600E in approximately ½ of cases
- **ICH**
  - No BRAF mutation
  - Clonal translocation in 3 of 4 ICH cases by next-gen sequencing and FISH
  - Evidence for ICH as its own clonal entity
Clinical Features of ICH

• Firm, red, yellow, or red-brown papules
• Isolated and (more commonly) generalized variants
• Predominantly affects adults; favors trunk and extremities
• Most without epidermal change (minimal epidermotropism)
• Clinical ddx: generalized eruptive histiocytoma, juvenile xanthogranuloma, congenital self-healing reticulohistiocytosis, PLC
• Behaves more like non-LCH / reactive macrocytic process
  » Most cases self-limited or non-progressive
  » Largest series (18 pts): most with stable disease, 2 with slow cutaneous progression, 2 developed systemic dz
  » Several reports associated with leukemia or low-grade B cell lymphoma
Additional Images of ICH

Logemann et al.

Zerbini et al.

Tardio et al.
Management of ICH

- Case reports of response to: observation, UVB (3 cases with good response), PUVA, low-dose MTX, isotretinoin, thalidomide, systemic anti-neoplasics

12 months of NB-UVB; Logemann et al.
Summary

• Indeterminate cell histiocytosis is an indolent neoplastic vs clonal reactive entity
• H&E similar to LCH; CD1a+, S100+ (focal), CD68+, Langerin (CD207) -
• Typically spares skin folds, without epidermal change
• Most cases self-limited or non-progressive, supporting conservative management
  » Our patient’s case cleared after UVB phototherapy
• Clinical follow-up indicated as there are a few reports of progressive disease or associated lymphoproliferative malignancy
References


References


A Case of Gemcitabine-associated “Pseudocellulitis”

Sean McGregor, DO, PharmD
Dermatology Resident, PGY-2
Wake Forest University School of Medicine
Department of Dermatology
History

• HPI: Patient is a 62 year-old female
  – Stage IIB (T1N1M0) mixed neuroendocrine and adenocarcinoma of the pancreas
  – Status post pylorus-sparing Whipple procedure
  – Currently on single agent gemcitabine chemotherapy
  – Developed fever, chills, and bilateral lower extremity swelling and redness 5 days after first dose of chemotherapy (1,000 mg/m²)

• Dermatology was consulted regarding bilateral lower extremity cellulitis
History

• Past Medical History
  – HTN, DM, HLD, and CVA
• Past Surgical History
  – Pylorus-sparing Whipple procedure
• Social History
  – Former smoker (45 pack-year history)
• Allergies
  – NKDA
History

• Current medications
  – Amlodipine 10 mg PO daily
  – Gabapentin 300 mg PO TID
  – Insulin detemir 10 units SQ daily
  – Metoprolol tartrate 12.5 mg PO BID
  – Pancrealipase 24,000 units PO TID
  – Simvastatin 40 mg PO daily
  – Pantoprazole 40 mg PO daily
  – Piperacillin/Tazobactam 3.375 g IV Q8H
Physical Examination

- Vital Signs: Temp: 99.7 (Tmax 101.3); BP: 145/72 mmHg; HR: 80 BPM; RR: 20/min; O2: 95% RA

Figure 1. Well demarcated erythema over distal lower extremities with 2+ lower extremity edema
Labs and Imaging

- WBC: 6.7 x 10^3/mm^3
- HgB: 7.9 g/dL
- Hct: 24.6%
- PLT: 272,000/mm^3
- Na: 134 mEq/L
- K: 4.2 mEq/L
- SCr: 0.48 mg/dL
- Glu: 232 mg/dL

- CT C/A/P
  - No evidence of pneumonia, intra-abdominal abscess, or other infectious foci

- Venous Duplex US BLE
  - Negative for DVT

- Blood cultures
  - Negative x2
Assessment and Plan

• Differential Diagnosis
  – Stasis dermatitis
  – Sclerosing panniculitis
  – Non-purulent cellulitis
  – Opportunistic (i.e. fungal/AFB) infection
  – Cutaneous reaction to gemcitabine?

• Plan
  – Punch biopsy (4 mm) sent for H&E and tissue culture
Results

Figure 2. H&E, 10X; sparse inflammatory infiltrate

Figure 3. H&E, 200X; Mixed cellular infiltrate with neutrophils

Figure 4. H&E, 400X; Mixed cellular infiltrate with neutrophils
Discussion

• Gemcitabine is a pyrimidine antimetabolite
  – MOA: Inhibition of DNA synthesis
    ▪ Inhibits DNA polymerase and ribonucleotide reductase
    ▪ Cell cycle-specific for the S-phase and blocks cellular progression at G1/S phase
• Active against solid-organ malignancies
• Adverse reactions typically include nausea, vomiting, anemia, and neutropenia
• Cutaneous reactions are less common, but have been reported (up to 30%)
Discussion

• “Pseudocellulitis” is a broad term used to classify a subset of cutaneous reactions
  – Radiation recall dermatitis
  – Erysipeloid eruptions
  – Scleroderma-like eruptions
  – Lipodermatosclerosis-like eruptions

• Pubmed search of “gemcitabine” and “pseudocellulitis” reveals 11 case reports

• Recent case series in JAAD proposed re-classification of the terminology
  – Acute Lipodermatosclerosis (ALDS)-like eruption
Discussion

  - A 76 year-old male with pancreatic cancer on adjuvant gemcitabine
  - New-onset erythema, edema and pain in bilateral lower extremities after 5th dose
  - Afebrile and no leukocytosis
  - Improved after topical clobetasol and compression therapy
Discussion

  - A 62 year-old female with metastatic pancreatic cancer on gemcitabine
  - New-onset erythema, edema and pain in bilateral lower extremities after 2nd dose
  - Had history of chronic edema in lower extremities
  - Afebrile but leukocytosis present
  - Biopsy showed neutrophilic infiltration
Discussion

  − A 77 year-old male with stage IV NSCLC status post radiation and carboplatin/pemetrexed chemotherapy on gemcitabine
  − Acute onset bilateral lower extremity erythema after 3rd dose (similar reactions after prior doses)
  − Afebrile and no leukocytosis
  − Biopsy showed edema and sparse mixed inflammation with lymphocytes, neutrophils, and rare eosinophils
• Similar cases of radiation-recall dermatitis and “pseudocellulitis” over areas of ascities reported
Discussion

• Mechanism of reaction is unclear
  – Increased vascular permeability
  – Direct endothelial damage
  – Release of vasoactive cytokines

• Widely distributed in tissues
  – Vd ranges from 50-370 L/m² (depending on infusion time)
  – Lipophilic and readily diffuses into extracellular compartment

• Decreased clearance and accumulation in cutaneous and subcutaneous tissues with resultant local toxicity?
Discussion

• Typically occurs on the lower extremities
• Patients often have bilateral involvement
• Develops within 2-5 days of gemcitabine infusion
• Leukocytosis and fever are usually absent
  – However, both have been reported
• May be associated with peripheral edema
  – Patients with underlying venous stasis may have higher risk of ALDS-like reaction
Discussion

- Problem — clinical confusion regarding diagnosis
  - Overlapping clinical features with cellulitis
  - Gemcitabine independently associated with fever (40%) and peripheral edema (15-20%)
  - Patients are often treated with antibiotics for presumed cellulitis
Discussion

• Treatment
  − Topical corticosteroids
  − Compression therapy
  − Leg elevation
  − NSAIDs
  − Discontinuation of gemcitabine?
    ▪ Most patients continue treatment despite reaction
    ▪ Reaction usually self-limited
    ▪ Patients typically improve after 1-2 weeks
    ▪ Recurrence usually occurs in similar distribution
Discussion

• Condition is underrecognized and underreported

• Recognition is important
  − Avoids interruption in treatment
  − Avoids unnecessary use of antibiotics
  − Avoids unnecessary hospitalization
  − Avoids unnecessary costs and complications

• Our recommendations:
  − Triamcinolone 0.1% ointment BID
  − Leg elevation
  − Compression therapy
References


Thank you!
Questions?
A rare cause of breast ulceration: diffuse dermal angiomatosis

Diana Norton, MD
Angelica Selim, MD, & Claude Burton, MD

July 9, 2017
Clinical Presentation

70 yo lady with four months of painful non-healing ulcerations on the breast
Past medical history

- **Severe obesity**, BMI 47 with **macromastia**
- **Venous insufficiency**—leg ulcers x1 year and varicose veins s/p radio frequency ablation
- **Former** smoker
- **No breast cancer**
Differential diagnoses

**MALIGNANCY**

Trauma
- Bras, seatbelts
- Radiation

Vascular
- Pyoderma gangrenosum
- Diffuse dermal angiomatosis

Infection
- Cellulitis, mastitis
- Zoster
Diffuse dermal angiomatosis

- Benign vascular disorder
- Cutaneous reactive angiomatosis
- Causes:
  - Local ischemia $\rightarrow$ hypoxic stimulus $\rightarrow$ increased vascular endothelial growth factor
  - Vascular occlusion $\rightarrow$ emboli $\rightarrow$ neoangiogenesis
Locations

• Lower extremities in severe atherosclerotic disease (majority of cases)
• Forearm adjacent to fistula in dialysis patient
• Pendulous breasts of women
Reports in the literature
Biopsy results

- Diffuse proliferation of endothelial cells lining capillary sized vessels in the reticular dermis

- Our patient:
  - Acanthosis, dermal edema, chronic inflammation
<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Comorbidities</th>
<th>Smoking habit</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Violaceous, non-healing, bilateral ulcerating macules on breast</td>
<td>No relevant medical history; large pendulous breasts</td>
<td>Yes</td>
<td>Isotretinoin</td>
<td>Completely resolved after 2 months</td>
</tr>
<tr>
<td>Bilateral painful ulcers on breast</td>
<td>No relevant medical history; large pendulous breasts; positive for anticardiolipin and antinuclear antibodies</td>
<td>NA</td>
<td>Daily low dose aspirin and pentoxifyline</td>
<td>Improved</td>
</tr>
<tr>
<td>Tenderness and focal ulceration of the left breast demonstrating reticulated erythematous induration and focal ulceration</td>
<td>Coronary cardiovascular disease with coronary artery bypass grafting; familial type ii hyperlipidemia; angina; fibromyalgia; osteoporosis</td>
<td>Yes</td>
<td>Isotretinoin and stent placement in occluded left subclavian artery</td>
<td>Improved with isotretinoin therapy, complete resolution 1 month after stent placement</td>
</tr>
<tr>
<td>Bilateral superficial ulcerations of the breast, perilesional skin showing telangiectasias dispersed in a livedoid plaque</td>
<td>Hypertension; dyslipemia; obesity; sub-occlusion of the right humeral artery</td>
<td>Yes</td>
<td>Oral corticotherapy</td>
<td>Improved</td>
</tr>
<tr>
<td>Ulcerating lesions demonstrating endothelial proliferation within the dermal stroma, pain from lesions</td>
<td>No relevant medical or surgical history; large pendulous breasts</td>
<td>Yes</td>
<td>Topical and systemic antibiotics, bilateral wise pattern reduction mammoplasty with excision of DDA involved areas</td>
<td>No relief through medical therapy, complete resolution with no recurrence 4 months post-operation</td>
</tr>
<tr>
<td>Bilateral ulcerations</td>
<td>Large pendulous breasts; calciphylaxis</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Multiple tender, painful reticulated erythematous macules, with focal ulceration and scarring areas, bilateral</td>
<td>Basal ganglia hematoma; hypertension; overweight; hepatic cirrhosis</td>
<td>Yes</td>
<td>Strict control of smoking habit</td>
<td>Complete healing after 6 months; no lesions after 18 months of follow-up</td>
</tr>
<tr>
<td>Multiple painful reticulated erythematous macules, with periareolar ulceration and scarring areas</td>
<td>Large pendulous breasts; breast cancer ductal invasive type treated with radical mastectomy plus lymphadenectomy; chronic cirrhosis due to hepatitis B virus infection treated with liver transplant</td>
<td>Yes</td>
<td>Strict control of smoking habit</td>
<td>Improved after 6 months, no lesions after 12 months of follow-up</td>
</tr>
<tr>
<td>Various asymptomatic reticulated erythematous-violaceous patches without ulceration, bilateral</td>
<td>Large pendulous breasts; lgG lambda monoclonal gammopathy with normal complementary studies and no past history of thrombosis</td>
<td>Yes</td>
<td>Strict control of smoking habit</td>
<td>Improved after 4 months, no lesions after 12 months of follow-up</td>
</tr>
</tbody>
</table>
Largest case series

Diffuse dermal angiomatosis of the breast: a series of 22 cases from a single institution

Ryan Reusche¹, Sebastian Winocour¹, Amy Degnim², Valerie Lemaîne¹

¹Division of Plastic Surgery, ²Division of General and Gastroenterologic Surgery, Department of Surgery, Mayo Clinic, Rochester, Minnesota 55905, USA
## Risk factors

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Sample size</th>
<th>Percent prevalence</th>
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<tbody>
<tr>
<td>Overweight</td>
<td>22</td>
<td>100.0</td>
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<tr>
<td><strong>Obese</strong></td>
<td>22</td>
<td>68.2</td>
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<tr>
<td>Current smokers</td>
<td>22</td>
<td>27.3</td>
</tr>
<tr>
<td><strong>Current/former smokers</strong></td>
<td>22</td>
<td>50.0</td>
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<tr>
<td>Current/former smokers</td>
<td>12</td>
<td>58.3</td>
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<tr>
<td>with confirmed biopsy</td>
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<td></td>
</tr>
<tr>
<td>Patient number</td>
<td>Biopsy confirmed</td>
<td>Descriptive breast size</td>
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<td>----------------</td>
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<td>-------------------------</td>
</tr>
<tr>
<td>1</td>
<td>Yes</td>
<td>42 DDD*</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Large, pendulous</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>44 DDD*</td>
</tr>
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<td>4</td>
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<td>6</td>
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<tr>
<td>7</td>
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<td>9</td>
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<td>12</td>
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<td>42 DD*</td>
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<tr>
<td>13</td>
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<td>46 DD*</td>
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<tr>
<td>22</td>
<td>No</td>
<td>Large, pendulous</td>
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</table>
Treatment options

Isotretinoin 50mg daily
Taper over several months

Our patient
Diligent wound care with ulcer resolution in 2 months without recurrence on 5 month follow up
Summary

• Diffuse dermal angiomatosis is a rare and poorly studied disease
• Consider in women with pendulous breasts and smoking history
• Biopsy may be helpful if it reveals proliferating vessels in the dermis
• No consensus on therapy—wound care, isotretinoin, surgery, revascularization
References


The Clinical Relevance of “Atypia” in a Dermatopathology Report

Paul B Googe, MD
Professor and Laboratory Director
UNC Dermatopathology Laboratory
Department of Dermatology
Atypia

• Abnormalities in pattern of growth, anatomic location
• Cytological abnormalities
  – Cell size
  – Nuclear configuration
  – Nuclear to cytoplasmic ratio
  – Cytoplasmic changes
  – Nucleoli
Atypia

• Mitotic activity
• Necrosis
• Size of tumor
• Staining characteristics
  – Unusual or aberrant immunohistochemical staining results
    • Cytokeratin positivity in melanoma or sarcoma
    • Cytokeratin 20 negative Merkel cell carcinoma
Atypia

• Difficulty in classification or ability to recognize a neoplasm
  – lack of familiarity
  – uncertainty

• Pathologic findings inconsistent with clinical, imaging, past medical history or laboratory findings
Definitions:

• Benign – may persist and enlarge, may clinically reappear if incompletely removed, but not expected to be locally destructive or metastasize or be fatal

• Atypia
  – same as benign
  – In some tumor constructs may relate to propensity for local recurrence or persistence and/or limited metastatic phenomenon

• Malignant – May be locally destructive, metastasize or be fatal
Important observations:

– Benign tumors can recur
– Well described phenomenon of some types of benign tumors that show regional lymph node presence
  • Cellular blue nevi
  • Congenital nevi
  • Hidradenoma
– Malignant tumors do not necessarily metastasize and are not uniformly fatal
– Heterogeneity of neoplasia with regard to lethal potential
– Genotype of a neoplasm may or may not be predictive of lethal potential
– Pathologic findings may provide information that is of prognostic use based on statistics, but prognosis of an individual may simply not be accurately predicted in some forms of neoplasia
Recurrent/Persistent Clear Cell Hidradenoma
“Atypia” in benign neoplasms

- Dermatofibroma
- Seborrheic keratosis
- Melanocytic nevi
- Hidradenoma
- Pilar tumor
“Atypical” neoplasms that have benign behavior

- Dysplastic nevi
- Atypical spitz nevus
- Atypical proliferating pilar tumor
- Atypical pilomatrixicoma
- Atypical hidradenomas
- Atypical cellular blue nevus
- Atypical intradermal smooth muscle neoplasm
What are dysplastic nevi?

• Dysplastic nevi are benign melanocytic neoplasms which have clinical and histological attributes that resemble what may be seen in early or evolving melanoma.
• Dysplastic nevi occur sporadically and in kindreds with familial melanoma.
• Dysplastic nevi have a histological pattern with certain, consistent features.
Dysplastic Nevus

Major Criteria

1. Basilar proliferation of melanocytes, often with nesting, usually extending beyond a dermal nevic component, if present

2. Melanocytic atypism
Melanocytic atypism in dysplastic nevi

- Increase in cell size
- Increase in size of nucleus
- Nuclear hyperchromasias
- Shape of nucleus
- Cytoplasmic alterations – pigment granules
Minor Criteria

1. Inflammatory infiltrate
2. Increased vascularity with evidence of endothelial-cell hypertrophy
3. Concentric eosinophilic fibrosis and/or lamellar fibroplasia
4. Bridging of rete by nests of melanocytes
Inflammatory Infiltrate
Increased vascularity
Concentric eosinophilic fibrosis
Lamellar fibroplasia
Bridging of rete by nests of melanocytes
DYSPLASTIC NEVUS, DIAGNOSTIC TERMINOLOGY, HISTOPATHOLOGIC

after Clark et al, WHO

• nevus with features of a dysplastic nevus
• dysplastic nevus with mild atypia
• dysplastic nevus with moderate atypia
• dysplastic nevus with severe atypia

N.I.H. Consensus Statement

• nevus with architectural disorder
• nevus with architectural disorder and mild melanocytic atypia
• nevus with architectural disorder and moderate melanocytic atypia
• nevus with architectural disorder and severe melanocytic atypia

Ackerman
“Clark’s nevus”
Clinical attributes of dysplastic nevi

- Larger than 5 mm
- Variability in contour
- Variability in color
Treatment of Dysplastic Nevus

Features of, Mild atypia or Moderate atypia
- No re-excision unless
  – Partial sampling
  – Concern for malignancy remains

Severe Atypia
  – Complete removal
Atypical Spitz Nevus
Atypical cellular blue nevus
Atypical intradermal Smooth Muscle Neoplasm
“Atypical” neoplasms that have malignant potential or are early patterns of malignancy

- Atypical fibroxanthoma
- Atypical lentiginous melanocytic hyperplasia
- Atypical vascular proliferation after radiation therapy
ATYPICAL FIBROXANTHOMA OF THE SKIN
A Clinicopathologic Study of 140 Cases
David F. Fretzin, MD, and Elson B. Helwig, MD

In an attempt to further understand the nature of atypical fibroxanthoma of the skin, 140 lesions were subjected to clinical, histologic, and histochemical studies. Atypical fibroxanthoma most commonly presented as a solitary, non-specific nodule or ulceronodule on exposed skin of the face in the elderly. A clinical variant occurred in much younger persons on the covered areas of the trunk and limbs. Histologically, atypical fibroxanthoma develops as a circumscribed, cellular proliferation within the dermis, with occasional infiltration into the subcutis. Morphological patterns vary from lesions showing plump spindle cells in interfacing fascicles to those with haphazardly arranged large polyhedral cells. Bizarre multinucleated giant cells with foamy cytoplasm and numerous mitotic figures enhance its disturbing sarcomalike appearance. Among 101 patients followed for periods up to 15 years, no metastatic lesions were found and only nine lesions recurred. Correlation of the clinical and follow-up data support the concept that in spite of its alarming histologic appearance, atypical fibroxanthoma of skin appears to behave in a benign manner.

Cancer June 1978
Atypical Fibroxanthoma

- Dermal based neoplasm
- Sun damaged skin older people
- Head and neck
- Microscopically highly malignant, sarcoma-like
- Infrequently recur locally
- Rarely metastasize
- Small diameter (typically 1 cm or so)
- Nonpigmented, sometimes ulcerated
- No horn
- Differential diagnosis: poorly differentiated SCC, desmoplastic melanoma
CK AE1/AE3

Vimentin
Clear cell Atypical fibroxanthoma
Case: Clinical History

- 73 year old white male presents to dermatology clinic for two new lesions developing on vertex of head (4/6/2011)
- 2 lesions measuring 1.5 cm each
  - red, nodular, with smooth borders
- Hx significant for multiple SCCs
- Hx of Radiation Treatment to the Right side of head x 30
  - Unknown amounts of occupational radiation exposure
- Biopsy of both lesions performed and submitted for pathology
Consistent with Aypical Fibroxanthoma (AFX)

- Spindle cell lesion in the dermis
- No perivascular or perineural invasion
- No necrosis
- No invasion into subcutis
- High mitotic activity with pleomorphic nuclei
Clinical History

• Patient returns to dermatology clinic 20 months later (11/17/2011)
  – 4 recurrent nodules on vertex of head
• Clinical exam is similar to the previous presentation
• Pathology diagnosis is AFX
  – Similar histology to previous biopsy
• Patient is referred for wide local excision
Satellite Metastasis
Immunohistochemistry

• Negative staining
  – AE1/3, S100, Melan-A, Tyrosinase, SMA, Desmin, CD34, CD31, CK5/6, 34be12, p63, Sox 10

• Positive staining
  – Vimentin, Procollagen, CD10
Recurrent atypical fibroxanthoma with satellite metastasis

Atypical fibroxanthoma (AFX) is a cutaneous neoplasm of uncertain etiology that develops on sun-exposed regions of elderly males. It is widely considered to act indolently, despite its highly malignant cytologic features. Reports of metastatic AFX are very rare, and recurrence is uncommon. We report a case of recurrent AFX exhibiting a pattern of satellite metastasis followed by evidence of regional lymph node metastasis. A 76-year-old male, with prior occupational and therapeutic radiation exposure and numerous squamous cell carcinomas had AFX of the left vertex scalp limited to the dermis completely removed by micrographic surgery. Twenty months later, multiple lesions appeared at the site of previous surgery. Imaging revealed no metastases or calvarial involvement. Wide local excision showed multiple well-defined nodules involving dermis and subcutis. The primary and recurrent neoplasms were similar and composed of pleomorphic epithelioid and spindled cells with marked nuclear atypia, hyperchromasia and mitotic activity. Immunohistochemistry was positive for CD10, procollagen I and vinculin and negative for cytokeratins AE1/AE3, cytokeratins 5/6, 34BE12, MNF116, p63, CD31, Myr1, smooth muscle actin, desmin, S100 and CD34. Forty-eight months after removal of the primary, left intraparotid and posterior triangle lymph nodes are suspected to be involved by metastasis using clinical and positron emission tomography/computed tomography examinations.

Keywords: AFX, metastasis, recurrence, satelliteosis

AFX with subcutaneous involvement, present in deep margin = pleomorphic dermal sarcoma
Pleomorphic Dermal Sarcoma

- Term proposed by C.D. Fletcher

Pleomorphic Dermal Sarcoma

• Differentiated histologically from AFX by
  – Necrosis
  – Ulceration
  – Deep subcutaneous invasion
  – Lymphovascular invasion
  – Perineural invasion

• Significant overlap of clinical picture, histology, and prognosis with AFX
• May be considered a part of a spectrum
Atypical Fibroxanthoma (small) vs Pleomorphic dermal sarcoma (big)

- Atypical fibroxanthoma
- Dermal
- Typically less than 2 cm
- Undifferentiated stromal neoplasm
- Tert mutation
- Sometimes recur
- Rarely metastasize

- Pleomorphic dermal sarcoma
- Subcutaneous
- 2 cm or greater
- Vascular/perineural invasion
- Undifferentiated stromal neoplasm
- Tert mutation
- Sometimes metastasize
Recurrent AFX
No Residual Tumor
Margins Free
Patient/Tumor Features Associated With Bad Outcome With Skin Cancers

• Advancing age
• Immunosuppression (organ transplant)
• Chronic lymphocytic leukemia
• Large tumor diameter, deep/thick invasion, perineural invasion
• Head and neck location
• Local recurrence
Questions to consider in “atypical” cases

- Is the neoplasm properly classified?
- Is the atypia a recognized phenomenon to occur in the class of neoplasm specified?
- Was the lesion well sampled and evaluable?
- How many special stains or studies were used to arrive at the conclusion?
- Is there a pertinent reference in the literature that substantiates the classification used?
- What are the consequences to patient management?
- Is there potential for bad or unexpected outcome?
Grading and Staging of Neoplasia

- **Histologic grade**
  - How malignant does it look under microscope?
    - High grade – bad – high risk for metastasis and death
    - Low grade – good – may recur locally, show limited metastatic potential and are unlikely to cause death
    - Intermediate grade - ? – depends on type of tumor

- **Staging**
  - How big? Volume of tumor
  - Anatomic compartment
  - Regional metastasis
  - Distant metastasis
Management of “Atypical” Neoplasms

Trust, but Verify
Management of “Atypical” Neoplasms

• Complete removal with a margin of normal tissue
• Thorough pathologic analysis
• Follow up
  » Clinical evaluation of regional lymph nodes
  » Consider imaging
  » Specialty clinic or specialist to assist in follow up care

• Repeat tissue sampling of potential recurrences or metastases
• Reassure patient and educate
  » Enlist patient/family to help watch for reappearance or new lesions
  » Don’t make promises