Acral Lesions in Dermatopathology

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Overview

• Non-inflammatory
  – Circumscribed palmar hypokeratosis
  – Bullous acral erythema

• Dermatitis
  – Necrolytic acral erythema
  – TNF-alpha inhibitor reactions

• Lymphoid infiltrates
  – APACHE
  – Primary cutaneous acral CD8+ lymphoproliferative disorder

• Spindle cell lesions
• Adnexal lesions
• Other
Circumscribed hypokeratosis
Circumscribed palmar/plantar hypokeratosis

- Round lesion with very well-defined borders and erythematous central area (Clinical DDx: Bowen’s disease or porokeratosis)
- Tendency for thenar/hypothenar areas, medial side of sole
- Middle-aged women
- Indolent
Histologic Features

- Well-demarcated decrease in thickness of stratum corneum
- Diminished granular layer
- No inflammation
- No coronoid lamella
Background
-- First described in 2002 (Perez, et al JAAD), ~60 cases have been reported in the literature
-- Proposed etiology: chronic localized defect in keratinization (vs. trauma?)

Treatment:
-- Topical corticosteroids or topical retinoids are ineffective
-- Possible benefit form photodynamic therapy or calcipotriol treatment
Circumscribed Palmar or Plantar Hypokeratosis: First Report on a Nonacral Site With Unique Histologic Features

Tatyana Groysman, DO, Jeremy Rothfleisch, MD, and Marisa F. Baldassano, MD

Lesion on chest of 63 y/o man

Granular parakeratosis

Features suggestive of trauma

June 2013. Am J Dermopath
Brief Report

Hyper- and Circumscribed Palmar or Plantar Hypokeratosis: First Report on a Nonacral Site With Unique Histologic Features

Tatyana Groysman, DO,* Jeremy Rothfleisch, MD,† and Marisa F. Baldassano, MD‡

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June 2013. Am J Dermpath
Bullous acral erythema
Bullous acral erythema

- Variant of chemotherapy-induced acral erythema

- 3 weeks s/p treatment initiation: Acral dysthesia followed by erythema, blisters, and desquamation

- May be related to number of sweat glands at this site, which excrete the chemotherapy

- Cytarabine and methotrexate most common drugs

Pojjasek and Camilleri, J Cutan Pathol, 2012
Histologic features

- Pauci-inflammatory, subepidermal bullae, DIF-negative
- Can see considerable basilar vaculopathy and areas of epidermal necrosis
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Necrolytic Acral Erythema
Necrolytic Acrall Erythema

- Sharply-demarcated scaly plaques on dorsum of hands and feet
- Approx 50 patients reported since 1996
- Strong association with HCV
Histologic features

- Early lesions may show only psoriasiform hyperplasia with scattered and grouped dyskeratotic cells
- Well-developed lesions include parakeratosis, neutrophils, hypogranulosis (but more papillomatous than classic psoriasis)
Necrolytic acral erythema without hepatitis C infection

Necrolytic acral erythema is a newly described entity characterized by sharply demarcated scaly plaques on the dorsum of the hands and feet. More than 30 patients have been reported since 1996, all of whom had

Potential association with dysregulated zinc metabolism and other nutritional deficiencies
TNF-alpha antagonist reaction
Pustular folliculitis, psoriasis, interface dermatitis, neutrophilic eccrine hidradenitis, Sweet’s syndrome, lupus, vasculitis, and palmoplantar pustulosis

40% of patients develop palmoplantar pustulosis
Palmoplantar pustulosis

Hawryluk et al. *J Cutan Pathol*, 2012
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Acral pseudolymphomatomatous angiokeratoma of children (APACHE)
Acral pseudolymphomatomous angiokeratoma of children (APACHE)

- APACHE likely represents a spectrum of benign lesions in adults in children
- Multiple, hyperkeratotic erythematous/violaceous papules and nodules that are usually asymptomatic
- Predilection for acral sites
- Etiology unknown

Acral pseudolymphomatous angiokeratoma of children (APACHE)

Subepidermal, dense lymphoid infiltrate. Often proliferation of thick-walled blood vessels.

Predominantly T-cells (mixed CD4 and CD8) with scattered B-cells.

APACHE Proposed alternate name:
T-cell-rich angiomatoid polypoid pseudolymphoma of the skin

J Cutan Pathol, 2011; 38, 6: 475-82
Primary cutaneous acral CD8+ T-cell lymphoproliferative disorder
Primary cutaneous acral CD8+ T-cell lymphoproliferative disorder

• Provisional entity in 2016 WHO classification where it is termed a “lymphoma”.
  – Monoclonal and loss of T-cell antigens
• Solitary slow, growing nodule with indolent clinical behavior
• Similar to the CD8+ T-cell lymphoproliferative disorder of the ear
• Adults >50 y/o
Most cases demonstrate a Grenz zone with sparing of the epidermis. Angiocentricity, necrosis, and ulceration are absent.
Extrafacial indolent CD8-positive cutaneous lymphoid proliferation with unusual symmetrical presentation involving both feet

Indolent CD8+ cutaneous lymphoid proliferation represents a recently described entity among cutaneous T-cell lymphomas that typically presents with solitary skin lesions on the face or at acral sites and usually follows an indolent clinical course. Histopathologically, this entity is characterized by a dense dermal infiltrate of non-epidermotropic, small- to medium-sized pleomorphic CD8+ T-cells of the non-activated cytotoxic phenotype showing a clear-cut grenz zone and a

Marion Wobser¹, Tony Petrella², Hermann Kneitz¹, Andreas Kerstan¹, Matthias Goebeler¹, Andreas Rosenwald³ and Eva Geissinger³
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Spindle cell lesions

- Superficial acral fibromyxoma (aka digital fibromyxoma)
- Cellular digital fibroma
- Sclerosing perineurioma
- Fibromatosis
- Lipofibromatosis
- DFSP
- Calcifying Aponeurotic Fibroma
- Myxoinflammatory fibroblastic sarcoma (aka inflammatory myxohyaline tumor of distal extremities)
- EWSR1-SMAD3-rearranged fibroblastic tumor
Superficial acral fibromyxoma (aka digital fibromyxoma) and cellular digital fibroma
• ages 14-72
• nail region often affected
• 1-5 cm, usually well-delimited, painful
• Dermal-based
• Occasional recurrences
Histologic features

- Moderate cellularity, possible focal cytologic atypia, but low mitotic activity
- Stellate to spindled fibroblasts in myxoid to collagenous stroma
- Minimal inflammation, except mast cells
Cellular digital fibromas: distinctive CD34-positive lesions that may mimic dermatofibrosarcoma protuberans

**Background:** Digital fibromas are common benign acral tumors typically reported as angiofibromas (AFs) or acquired digital fibrokeratomas (ADF). Cellular variants are not well recognized.

**Methods:** We collected 14 acral fibrocytic lesions showing a spindle cell morphology from our files, and evaluated CD34, Factor XIIIa, epithelial membrane antigen (EMA), and S100 protein staining of these lesions. We compared the histologic and immunohistochemical patterns of these lesions with a study by Weidman and Balch.

Jennifer M. McNiff, Antonio Subtil, Shawn E. Cowper, Rossitza Lazova and Earl J. Glusac
Departments of Dermatology and Pathology, Yale University School of Medicine, New Haven, CT, USA

“intersecting fascicles of relatively bland CD34-positive spindle cells in fibrous or fibromyxoid stroma”
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“intersecting fascicles of relatively bland CD34-positive spindle cells in fibrous or fibromyxoid stroma”
Sclerosing perineurioma
Clinical presentation

• Children and young adults
• Well-circumscribed dermal or subcutaneous nodules on hands (including palms)
• Profile of acquired digital fibrokeratoma
• Dense lamellar stroma, reminiscent of sclerotic fibroma
Dense collagenous stroma
Epithelioid and spindle cells with wavy nuclei, elongated cytoplasmic processes
EMA (and GLUT-1) stains the long cytoplasmic processes of perineural cells.

EMA (100%) CD34 (65%), Glut 1
Palmar-plantar fibromatosis
Palmar / plantar fibromatosis

- Young adults
- Solitary or multiple nodules attached to aponeurosis

Palmar / plantar fibromatosis

• Monomorphic bland spindle cells with long fascicles, embedded in collagenous stroma that blends with fascia
• Can be cellular with plump cells
• Some mitotic activity
• B-catenin IHC + in 85% of cases
Palmar / plantar fibromatosis

Images courtesy of Mark Wick
Calcifying Aponeurotic Fibroma
Calcifying Aponeurotic Fibroma

• Affects children and adults
• Solitary, firm mass
• *FN1-EGF* gene fusion (8/9 cases), not reported in association with other neoplasms
Calcifying Aponeurotic Fibroma

- Fascicles of spindle cells, akin to fibromatosis
- Areas of calcification with fibrocartilaginous proliferation surrounded by epithelioid cells

Images courtesy of Mark Wick
Lipofibromatosis
Lipofibromatosis

- Pediatric population (11d-12y)
- Predilection for acral sites
- Painless, slow-growing
Lipofibromatosis

• 1-7 cm, poorly marginated, infiltrative
• Abundant fat (>50% of lesion) with accompanying fibroblastic proliferation
• Spindled areas with CD34, CD99, SMA variably bcl-2, S100, MSA
• Recurrences common

Unlike classic fibromatosis, the fibroblastic proliferation remains confined to septal areas
Small collections of univacuolated cells where fat and fibroblastic component merge (but no extensive displacement or destruction of fat)
Molecular studies

- 2018 USCAP meeting in Vancouver, case report of lipofibromatosis recurred and showed classic features of calcifying aponeurotic fibroma

- Subset of lipofibromatosis had characteristic gene fusion of CAF. Others had alternate gene fusions, while some lacked gene fusions

- Morphologically distinct, but genetically heterogeneous

Aberrant receptor tyrosine kinase signaling in lipofibromatosis: a clinicopathological and molecular genetic study of 20 cases.
Al-Ibraheemi A¹, Folpe AL², Perez-Atayde AR¹, Perry K³, Hofvander J⁴, Arbajian E⁴, Magnusson L⁴, Nilsson J⁴, Mertens F⁵,⁶.
Author information
Dermatofibroma sarcoma protuberans
**Dermatofibrosarcoma Protuberans**

- Usually young adults
- Recent case series (n=27) on distal extremities and acral sites
- CD34+ by IHC
- t(17;22), COL1A1-PDGFB gene fusion

Myxoinflammatory fibroblastic scarcoma

Acral myxoinflammatory fibroblastic sarcoma. A low grade tumor of the hands and feet
Meis-Kindblom JM, Kindblom L-G.

2002 WHO name: Myxoinflammatory fibroblastic scarcoma
Clinical Features

• All ages: range 4-91 yrs (median 45 years)
• No sex predilection
• Non-tender mass on an extremity (70% upper and 30% lower)
• Recurrence rates vary from 6-67%
• Generally considered a “low grade” sarcoma, though lymph node metastases have been reported
**Myxoinflammatory fibroblastic sarcoma**

Tumor Depth

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendon</td>
<td>35%</td>
</tr>
<tr>
<td>Synovium</td>
<td>20%</td>
</tr>
<tr>
<td>Subcutis</td>
<td>45%</td>
</tr>
</tbody>
</table>
Histologic features

- Dense chronic inflammatory infiltrate
- Myxomatous adjacent to hyalinized stroma *characteristic*
- Collections of short spindled and rounded epithelioid cells
• Epithelioid cells may have large, bizarre cells with macronucleoli
• Low mitotic index
• Lesional cells express CD34, EGFR, and CD163
Table 1. Immunohistochemical staining of Acral myxoinflammatory fibroblastic sarcoma (AMFS)

<table>
<thead>
<tr>
<th>No. positive (%)</th>
<th>Average strength of staining when staining present (scale of 1 to 3+, with 3+ strongest)</th>
<th>Average per cent (%) of lesional cells staining when staining present (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD163 16/16 (100)</td>
<td>2.9</td>
<td>50 (5-90)</td>
</tr>
<tr>
<td>CD34 17/18 (94)</td>
<td>2.4</td>
<td>38 (&lt;10-95)</td>
</tr>
<tr>
<td>EGFR 14/16 (86)</td>
<td>2.3</td>
<td>46 (10-90)</td>
</tr>
<tr>
<td>EMA 13/18 (72)</td>
<td>2.0</td>
<td>15 (&lt;10-70)</td>
</tr>
<tr>
<td>CD117 7/18 (39)</td>
<td>1.0</td>
<td>25 (&lt;10-50)</td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor; EMA, epithelial membrane antigen.


Consistent t(1;10) with Rearrangements of TGFB3 and MGEA5 in Both Myxoinflammatory Fibroblastic Sarcoma and Hemosiderotic Fibrolipomatous Tumor

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1Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY
2Department of Pathology, Massachusetts General Hospital, Boston, MA
3Department of Pathology, Brigham and Women's Hospital, Boston, MA

83% of cases
[Superficial, acral]
EWSR1-SMAD-1-rearranged fibroblastic tumor
EWSR1-SMAD3–rearranged Fibroblastic Tumor
An Emerging Entity in an Increasingly More Complex Group of Fibroblastic/Myofibroblastic Neoplasms

Michael Michal, MD,*†‡ Ryan S. Berry, MD,§ Brian P. Rubin, MD,§ Scott E. Kilpatrick, MD,§ Abbas Agaimy, MD,|| Dmitry V. Kazakov, MD,*‡ Petr Steiner, MD,*‡ Nikola Ptakova, MSc,*‡ Petr Martinek, PhD,*‡ Ladislav Hadravsky, PhD,*‡ Kvetoslava Michalova, PhD,*‡ Zoltan Szep, PhD,# and Michal Michal, MD,*‡

- Rare, women mid-30s
- Subcutaneous location
- ~1 cm in size

Hyalinized areas
• Hypercellular and hyalinized areas both contain bland spindle cells, with focally wavy nuclei
• Pleomorphism, atypia, and mitoses are absent

### Table showing DDx of spindle cell tumors on acral sites

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical Presentation</th>
<th>Histopathologic findings</th>
<th>Immunohistochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plantar/Palmar fibromatosis</td>
<td>Young adults, solitary or multiple nodules affecting aponeurosis.</td>
<td>Monomorphous bland spindle cells of long fascicles, embedded in a collagenous stroma that blends with the fascia.</td>
<td>Can be positive for Beta Catenin (~85% of cases) and SMA.</td>
</tr>
<tr>
<td>Perineurioma</td>
<td>Young adults, solitary cutaneous or subcutaneous nodule.</td>
<td>Well-circumscribed, composed of bland elongated spindle to ovoid cells.</td>
<td>Positive for EMA, CD34, Claudin-1 and GLUT-1.</td>
</tr>
<tr>
<td>Superficial acral fibromyxoma</td>
<td>Usually adults, solitary tumor occurring on subungual/periangual areas of fingers or toes.</td>
<td>Dome shaped, fibroblastic proliferation in the dermis that is unencapsulated. Usually show alternating fibrous and myxoid stroma.</td>
<td>Positive for CD34.</td>
</tr>
<tr>
<td>Cellular digital fibroma</td>
<td>Wide age range, solitary, papule on fingers and toes.</td>
<td>Proliferation of uniform slender fibroblasts in short intersecting fascicles in parallel orientation. Associated with variably dense dermal collagen.</td>
<td>Positive for CD34.</td>
</tr>
<tr>
<td>Inclusion body fibromatosis</td>
<td>Presents on infancy as firm nodule on dorsal or lateral surface of distal phalanges of fingers or toes.</td>
<td>Bland dermal spindle cells with intracytoplasmic, eosinophilic spherical inclusions in varying amounts of extracellular collagen. Masson’s Trichrome highlight inclusions.</td>
<td>Positive for SMA, Desmin, and CD99.</td>
</tr>
</tbody>
</table>
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• Spindle cell lesions

• **Adnexal lesions**

• Other
Digital Papillar Adenoma/Adenocarcinoma

Digital papillary adenocarcinoma: a tumour that should be considered in the differential diagnosis of neoplasms involving the digits

Richard A. Scolyer*, Roosdiya Z. Karim*, John F. Thompson†, Jonathan R. Stretch†, Stanley W. McCarthy* and Rajmohan Murali*
• Strong male predominance
• Mean age 43 yrs
• All involved a finger or toe, with most involving the distal part of the digit
• Subcutaneous extension in 50% of cases
• Histologic features (including presence of myoepithelial cells) not predictive of outcome
Digital Papillary Adenoma/Adenocarcinoma

- Beware of partial biopsies—some regions may appear more like nodular hidradneomas
- Gene expression profiling studies show FGFR2 overexpression in these tumors

Surowy, Br. J Dermatol 2018
Myepithelioma and myoepithelial carcinoma
Myoepithelioma

- Recently described in the skin
- Painless cutaneous nodule
- Involving extremity
- Younger patients (22 yrs median age)
Histologic features

- Epithelioid cells with scant eosinophilic cytoplasm
- Solid, spindled, plasmacytoid, and combinations
- Stroma may vary
- CK+, S100+, and SMA+
Myoepithelial Carcinoma

- No criteria for malignancy in cutaneous lesions

- Presence of cytologic atypia and increased mitotic index are most important factors
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Clear Cell Sarcoma
Clear Cell Sarcoma

- Young adults, 3rd to 4th decade
- 40% involve foot/ankle
- Slow-growing lesion
- $t[12;22]$ with EWS ATF1 fusion
- 37% - 59% mortality
- Nodal mets in 50%
CASE REPORT

Two cases of clear cell sarcoma with different clinical and genetic features: cutaneous type with \textit{BRAF} mutation and subcutaneous type with \textit{KIT} mutation


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Primitive non-neural granular cell tumor (PNGCT)
Primitive non-neural granular cell tumor (PNGCT)

- 1991 Leboit et al “primitive polypoid granular cell tumor (GCT)”
- Two larger series as “PNGCT” and “dermal non-neural GCT”
- Not neural or Schwannian in origin, but line of differentiation remains unknown
- Solitary painless nodule most typically on extremity of adult
- Typically benign, but one report of a lymph node metastasis has been documented
Histologic features

- Relatively circumscribed
- No well-developed PEH
- Mitotic index from 1-3 per mm² with occasional atypical forms
- S100-, CD68+, NKI-C3+
- EM confirmed lysosomes

Congenital epulis of the newborn

- S100-negative epithelioid granular cells
- Usually involves the alveolar ridge of females