Going Viral
Selected Challenging Cases in Dermatopathology Diagnostic Practice

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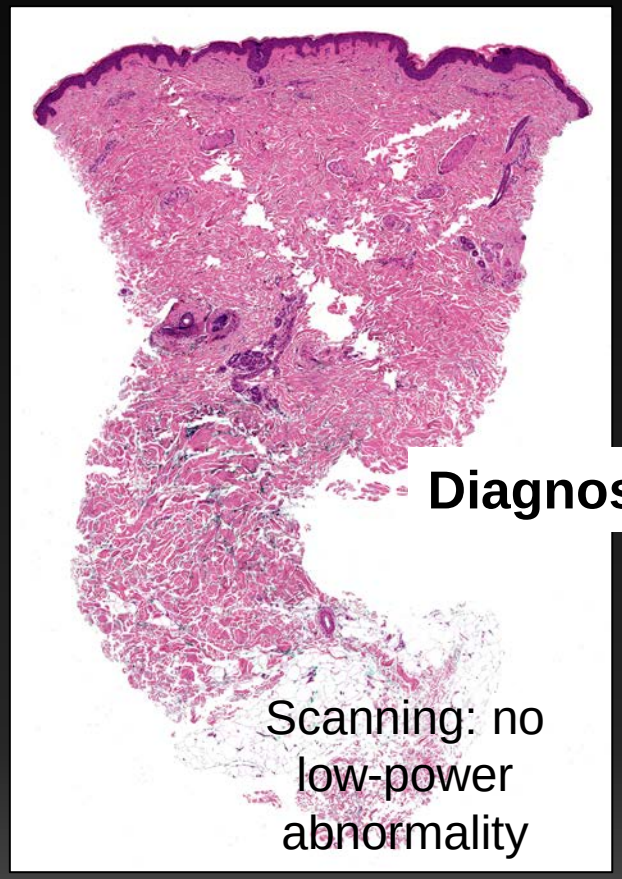
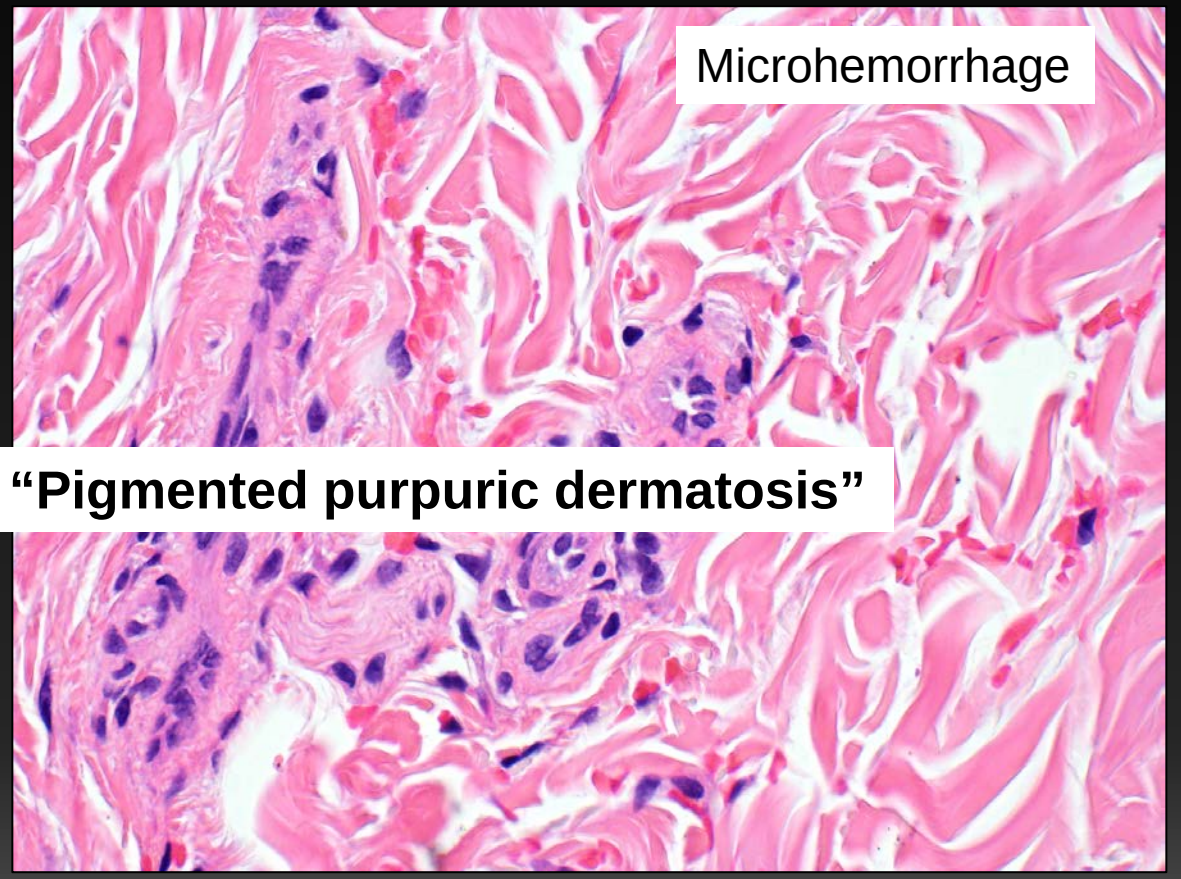
Case #1

Case #1: History

- 29F with history of lesions on ear, shoulder, and abdomen
- Previously diagnosed as ecchymoses
- Clinical ddx: lupus, sarcoid, purpura, hobnail hemangioma
- Punch biopsy was taken of an area on the shoulder

Case #1: H&E



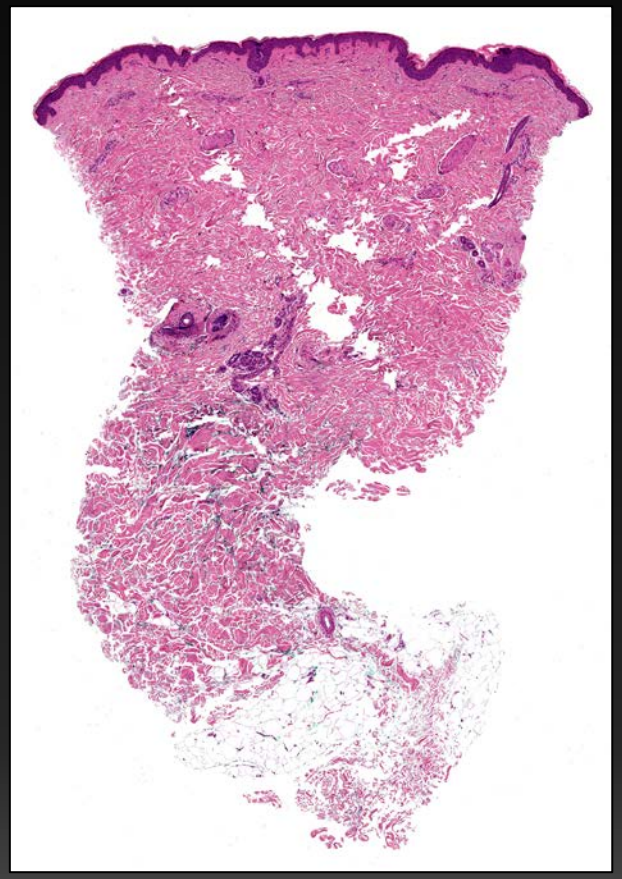


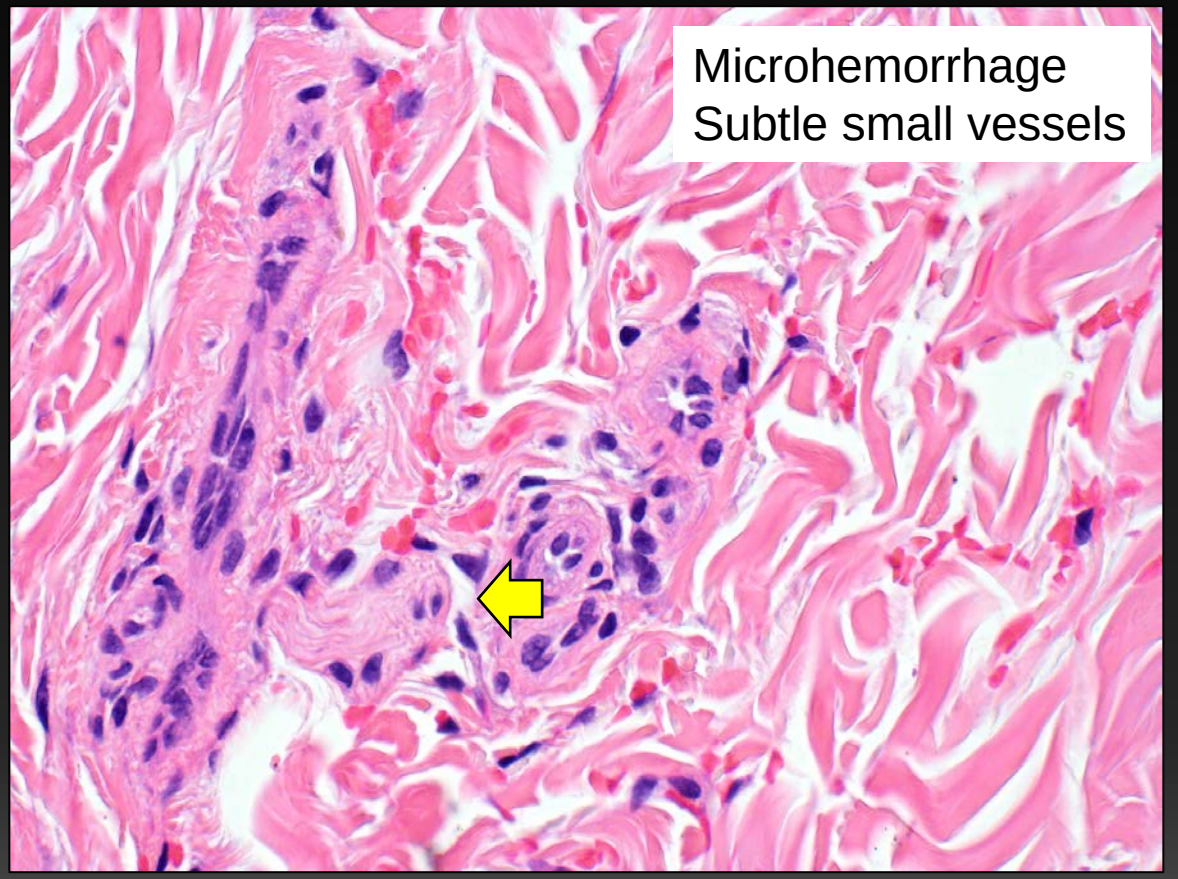
Diagnosis: “Pigmented purpuric dermatosis”

Case #1
Additional History

- Patient presents to Michigan Medicine for re-evaluation
- Now admits to history of untreated HIV
- Prior punch biopsy is requested for review

Case #1: H&E





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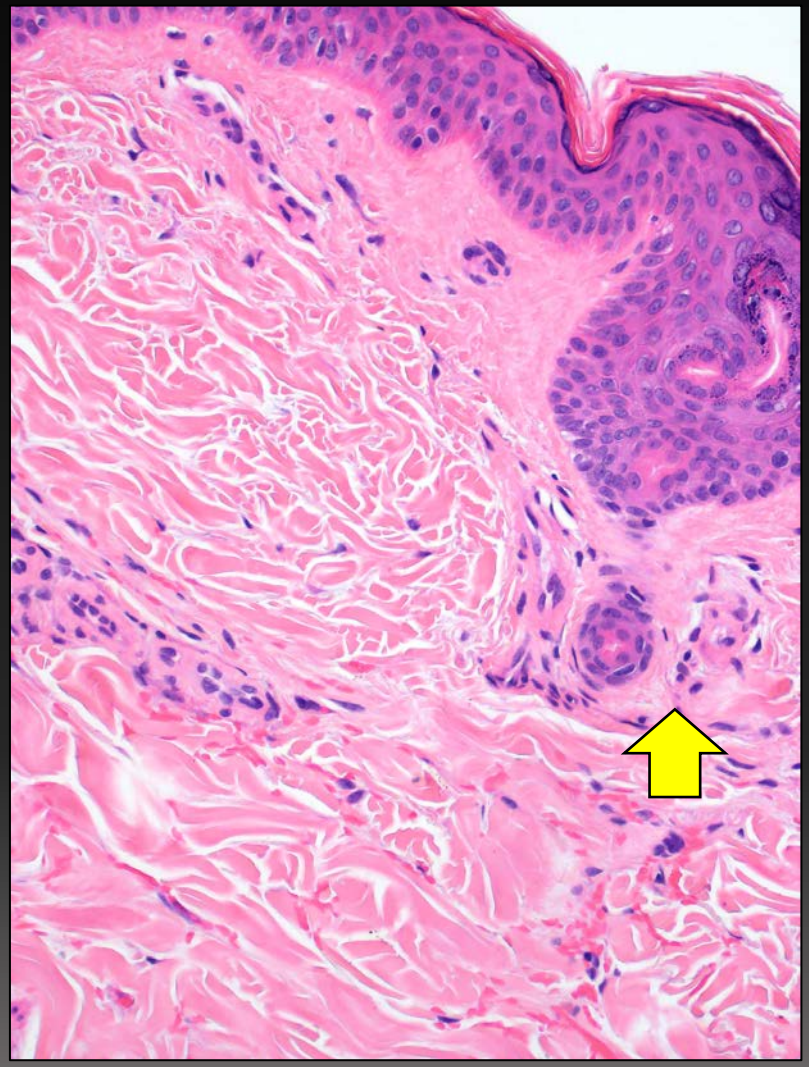
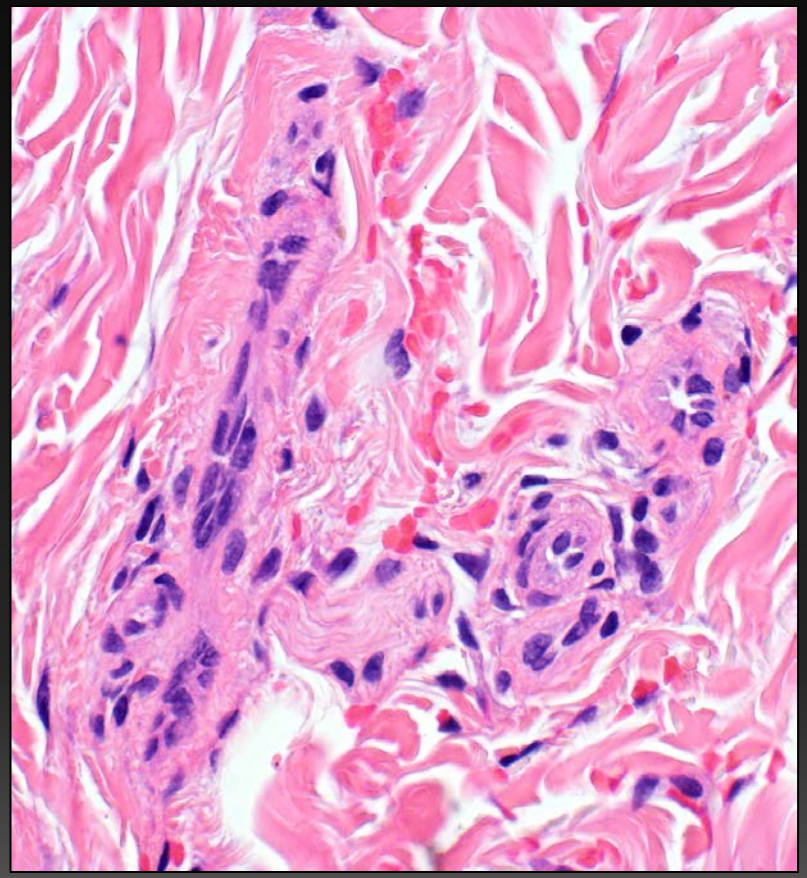
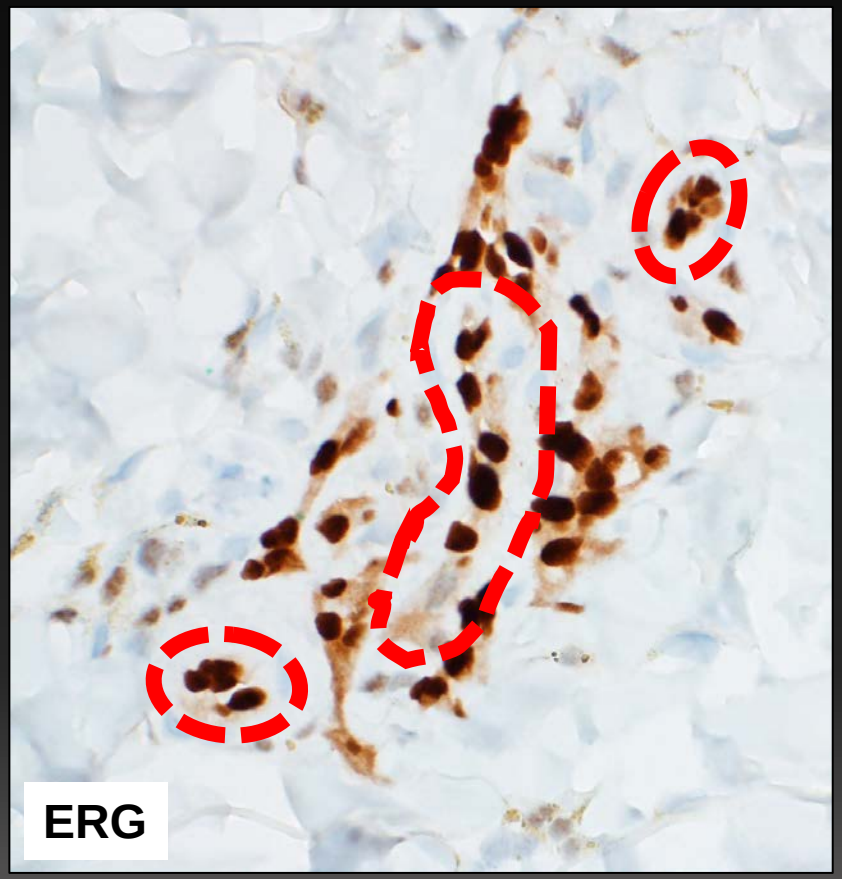
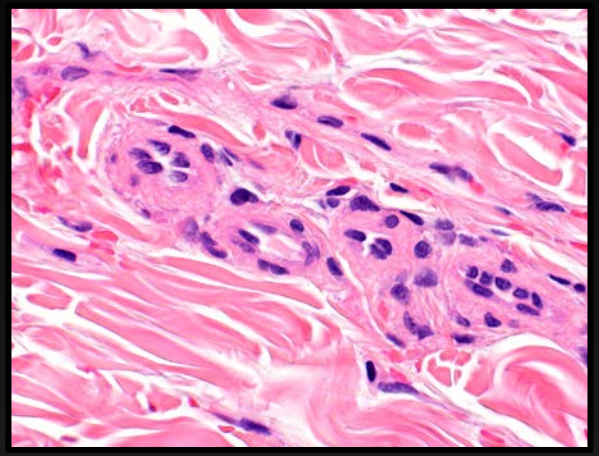


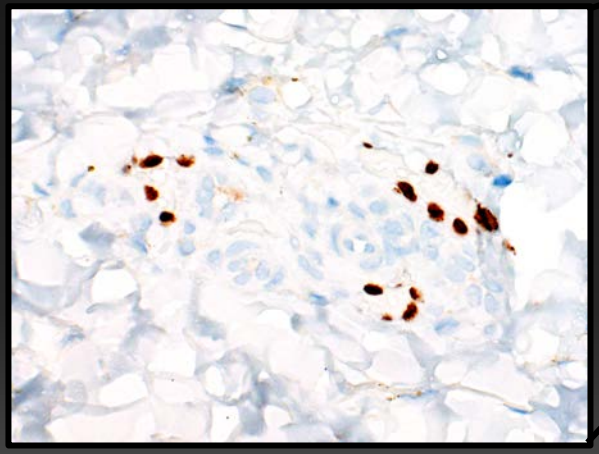
Case #1: Immunohistochemistry

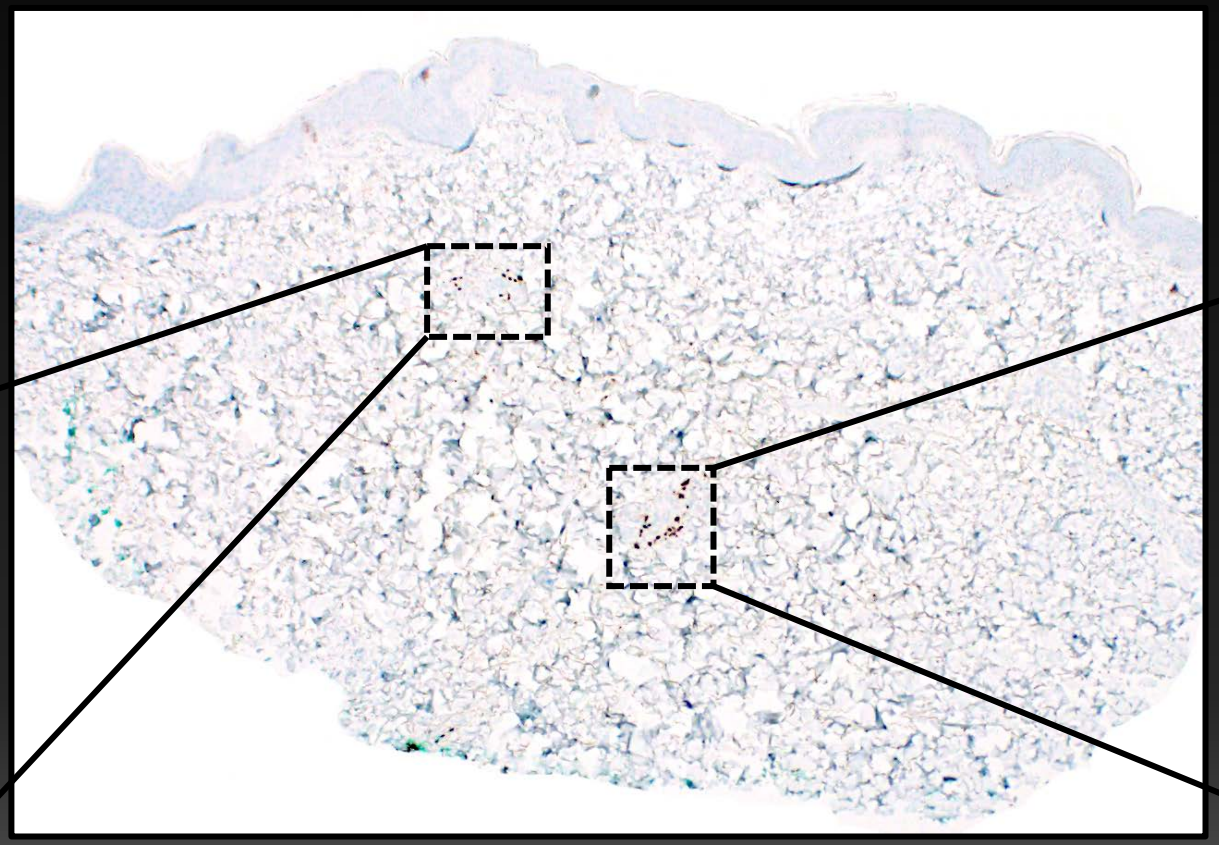


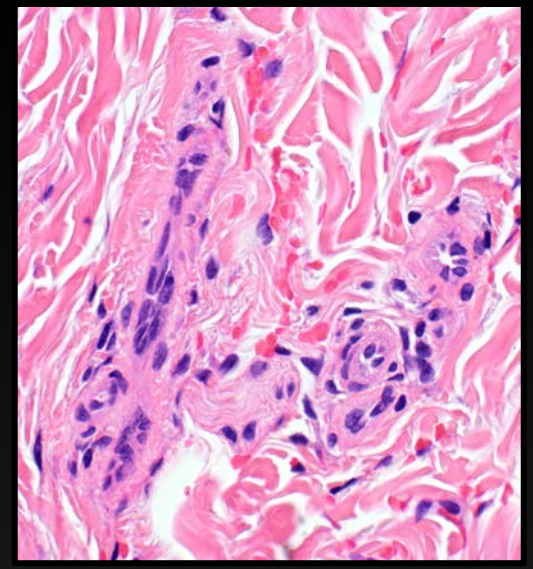


Case #1: HHV8









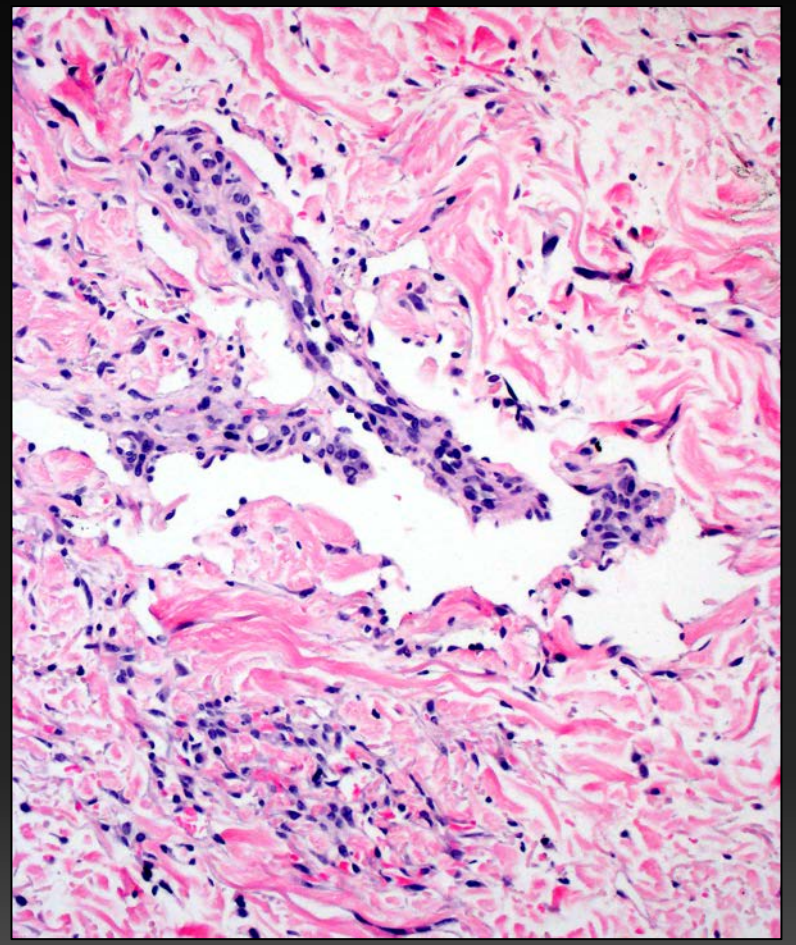
Diagnosis:
Kaposi sarcoma

Kaposi Sarcoma: Clinical Features

- 4 populations
  - elderly men (classic)
  - sub-Saharan African children and young men and women (endemic)
  - immune suppressed individuals (iatrogenic)
  - HIV (epidemic)
- May involve skin, lymph nodes, or internal organs.
- Associated with DNA virus KS-associated herpesvirus (KSHV, or HHV8).
  - Viral gene product LNA-1 can be detected by immunohistochemistry

Kaposi Sarcoma: Diagnosis

- Patch stage
  - Subtle infiltration of irregular thin vessels around existing structures
  - Clues
    - Promontory sign
    - Dilated spaces in dermis
    - Extravasated RBCs, hemosiderin, plasma cells
- Plaque stage
  - Similar to patch stage, but more overt vascular proliferation
- Nodular stage
  - Intracytoplasmic spaces containing RBC fragments (hyaline globules)
  - Lacks high-grade cytologic atypia



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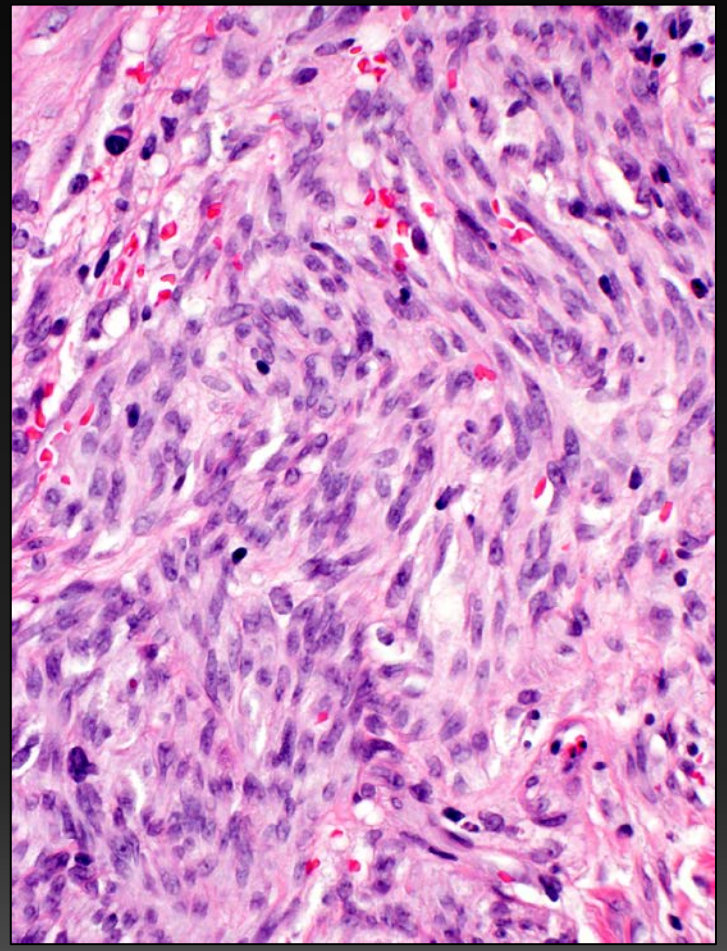


Patch Stage KS: Differential Diagnosis

Reactive processes

Pigmented purpuric dermatosis
Telangiectasia
Acroangiodermatitis (pseudo-Kaposi)
Diffuse dermal angiomatosis/
Reactive angioendotheliomatosis
Chronic lymphedema

Low grade angiosarcoma
Post-rad AVL

Fibrous/fibrohistiocytic lesion

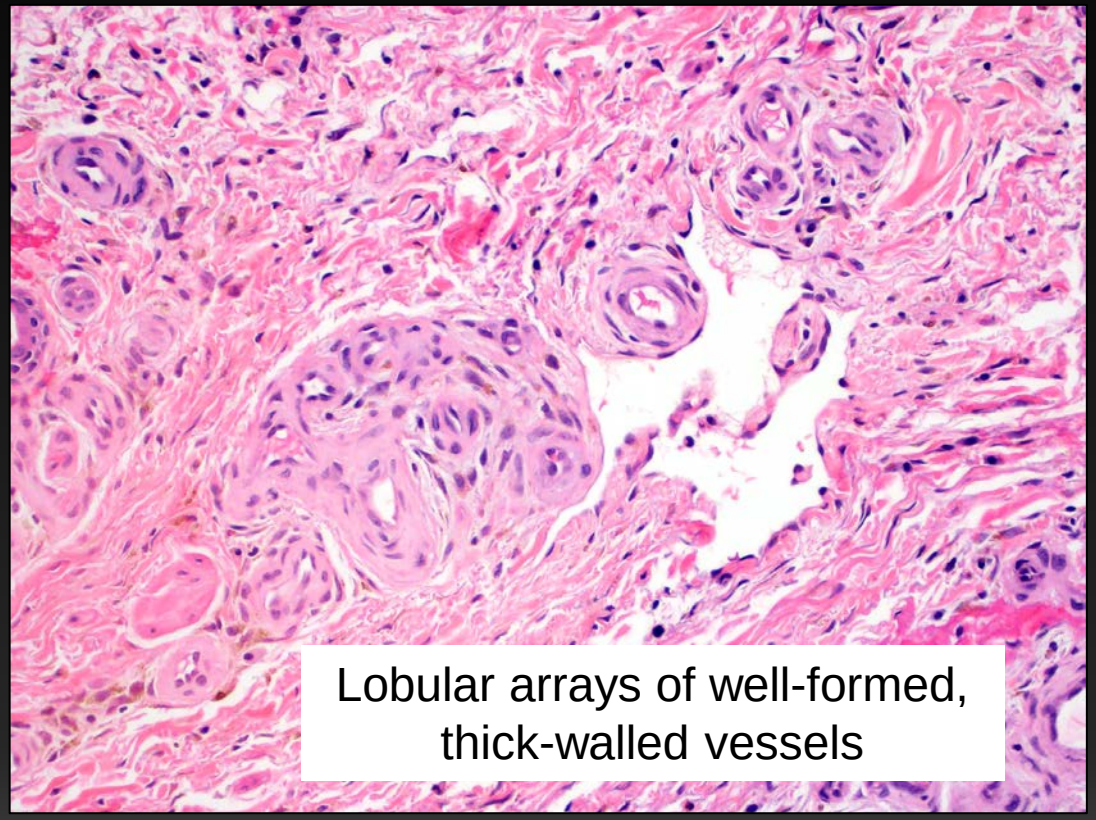
Key diagnostic clues for KS
Plasma cells
Branching/slit-like vessels
Promontory sign
Limited atypia (unlike AS)

HHV8 IHC may be critical

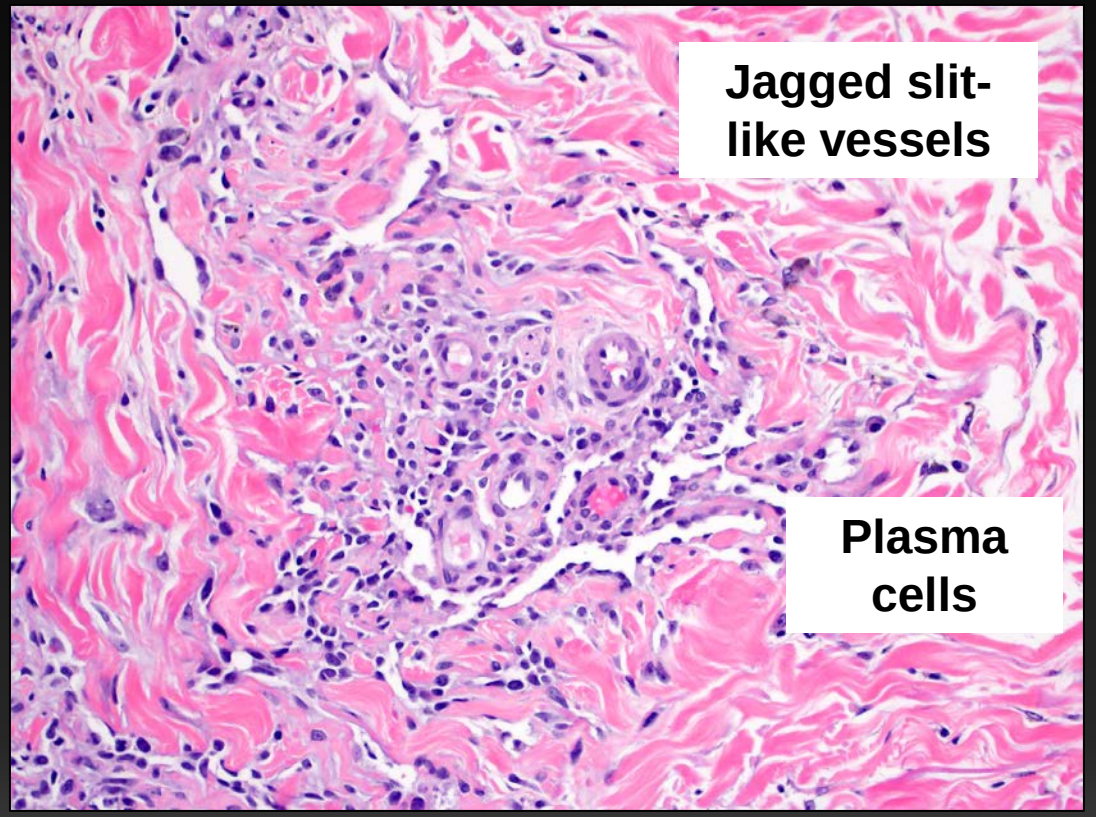
Angiomas

Acquired progressive lymphangioma
Targetoid hemosiderotic hemangioma
Acquired tufted hemangioma
Microvenular hemangioma

Acroangiodermatitis vs. KS

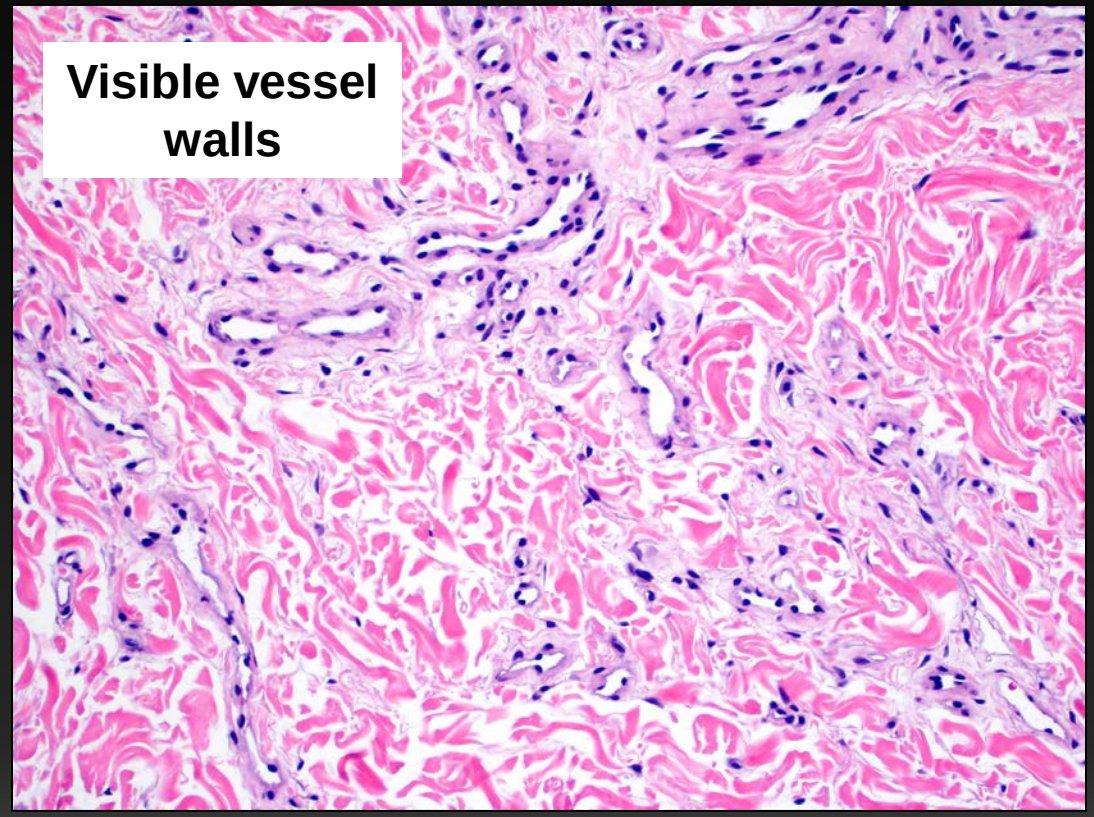


Acroangiodermatitis

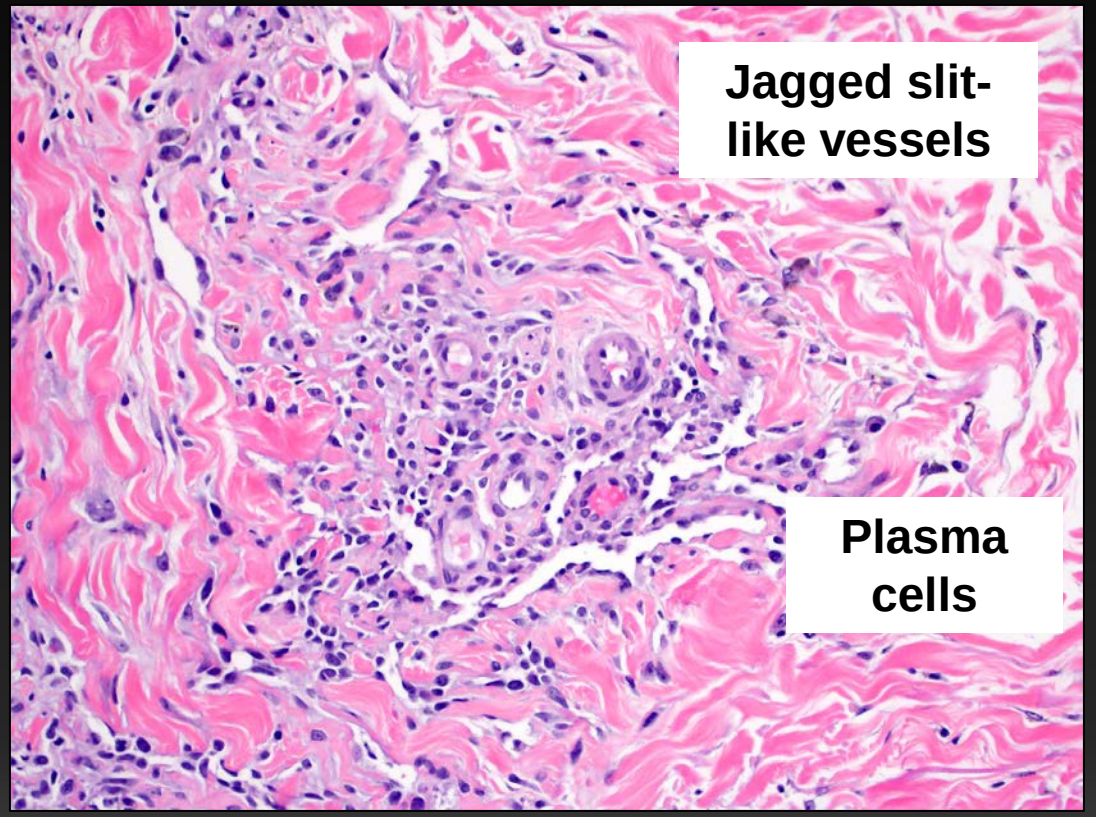


KS

Microvenular Hemangioma vs. KS

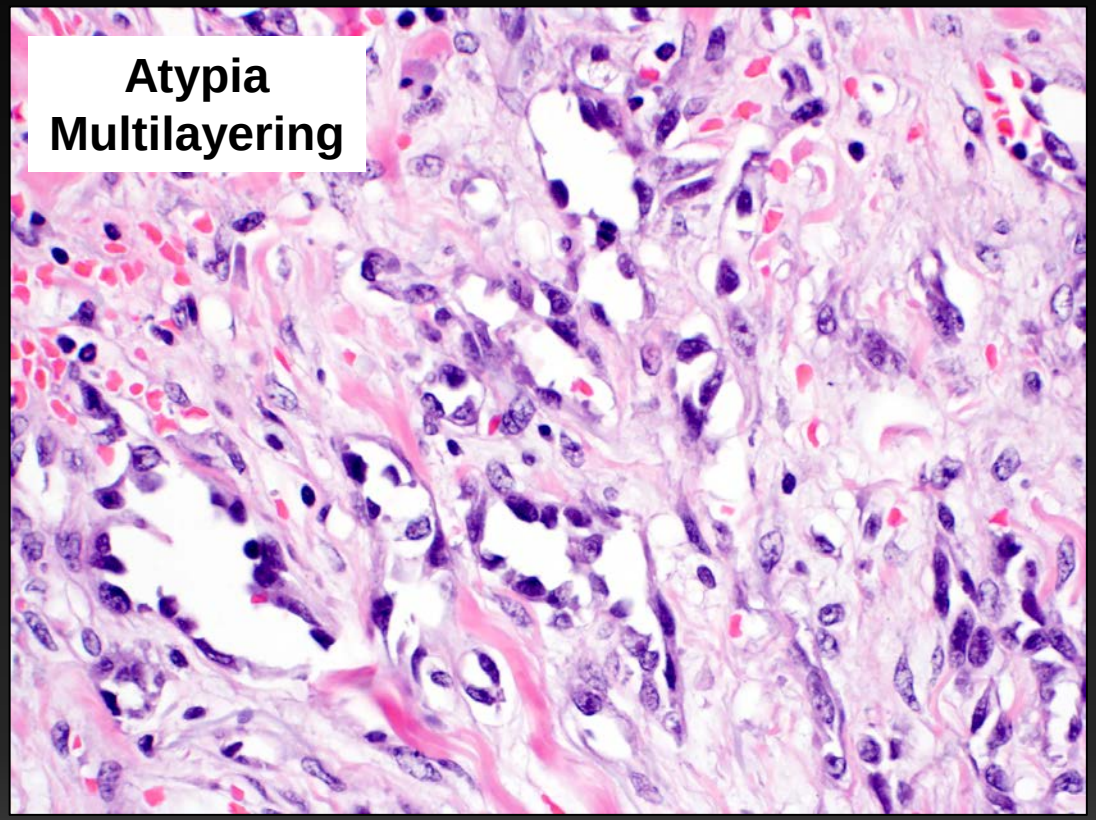


MVH

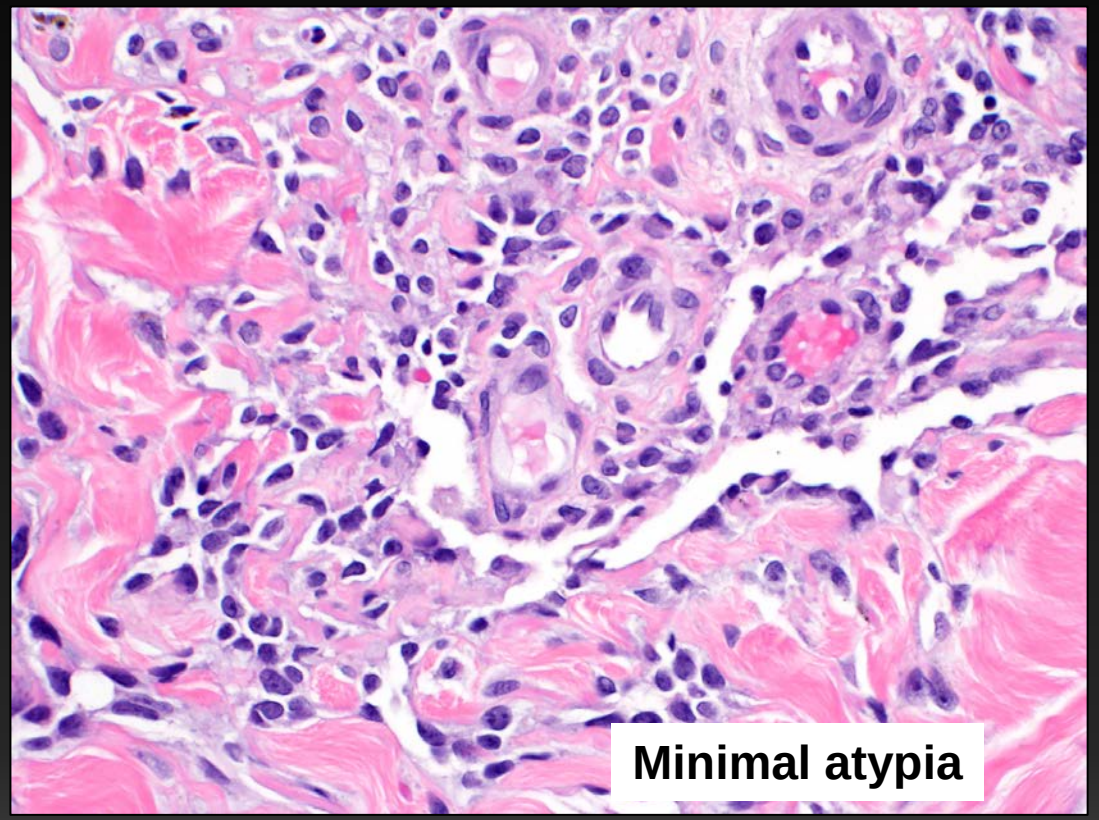


KS

Angiosarcoma vs. KS



AS



KS

Case #1: Summary

- Kaposi sarcoma should be included in the “normal skin” differential for patients in at-risk populations

- Diagnostic clues to subtle patch-stage KS include extravasated RBCs, empty spaces in dermis, and subtle vessels around dermal structures

Case 2

Case #2 History

- A women in her 70s with stage IVA1 Sezary syndrome presented with persistent rash and a scaly-appearing plaque on the elbow

- Punch biopsy was performed

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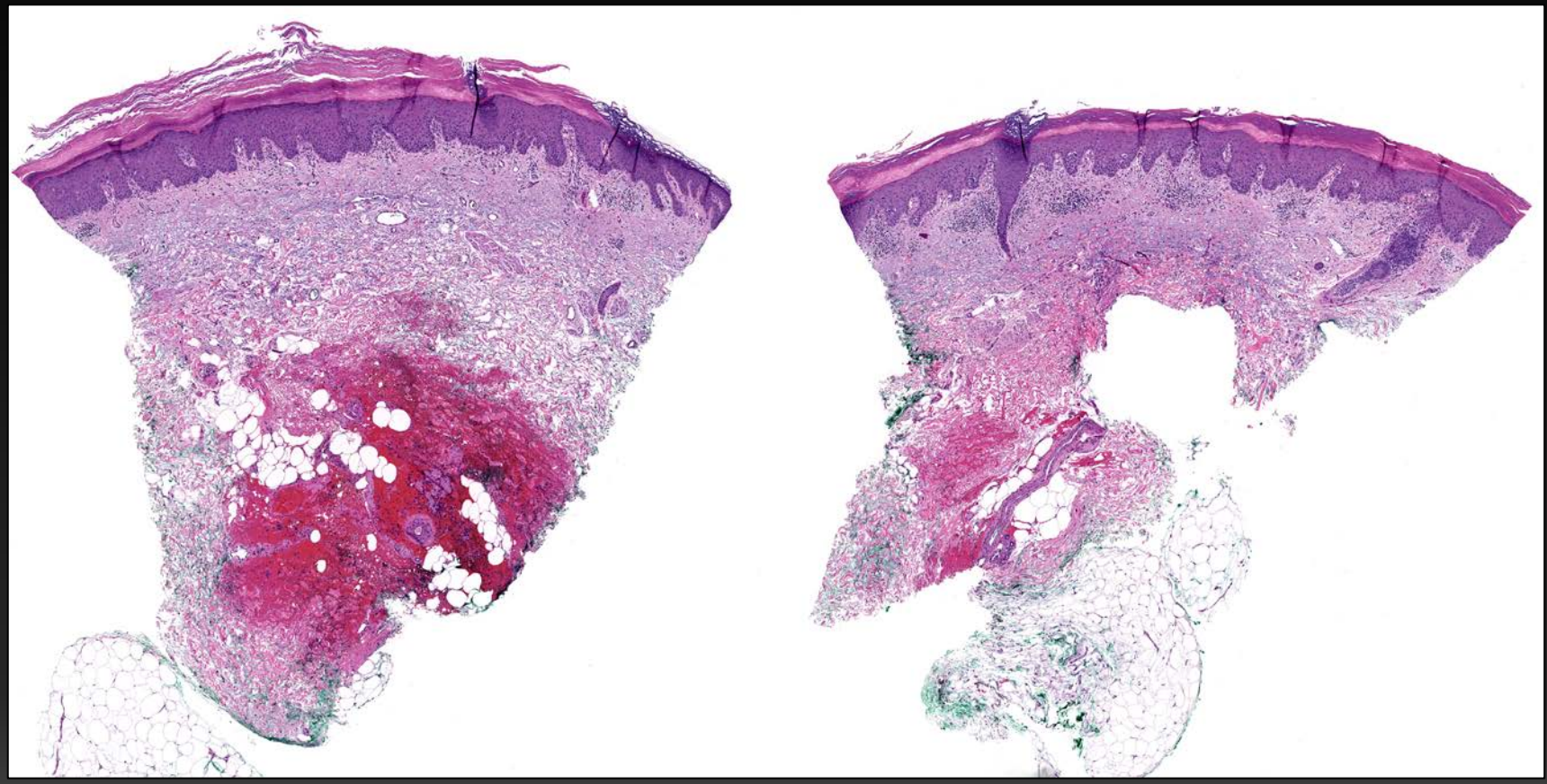
Case #2 H&E

Scaly patch on arm of 70yoF with Sezary syndrome



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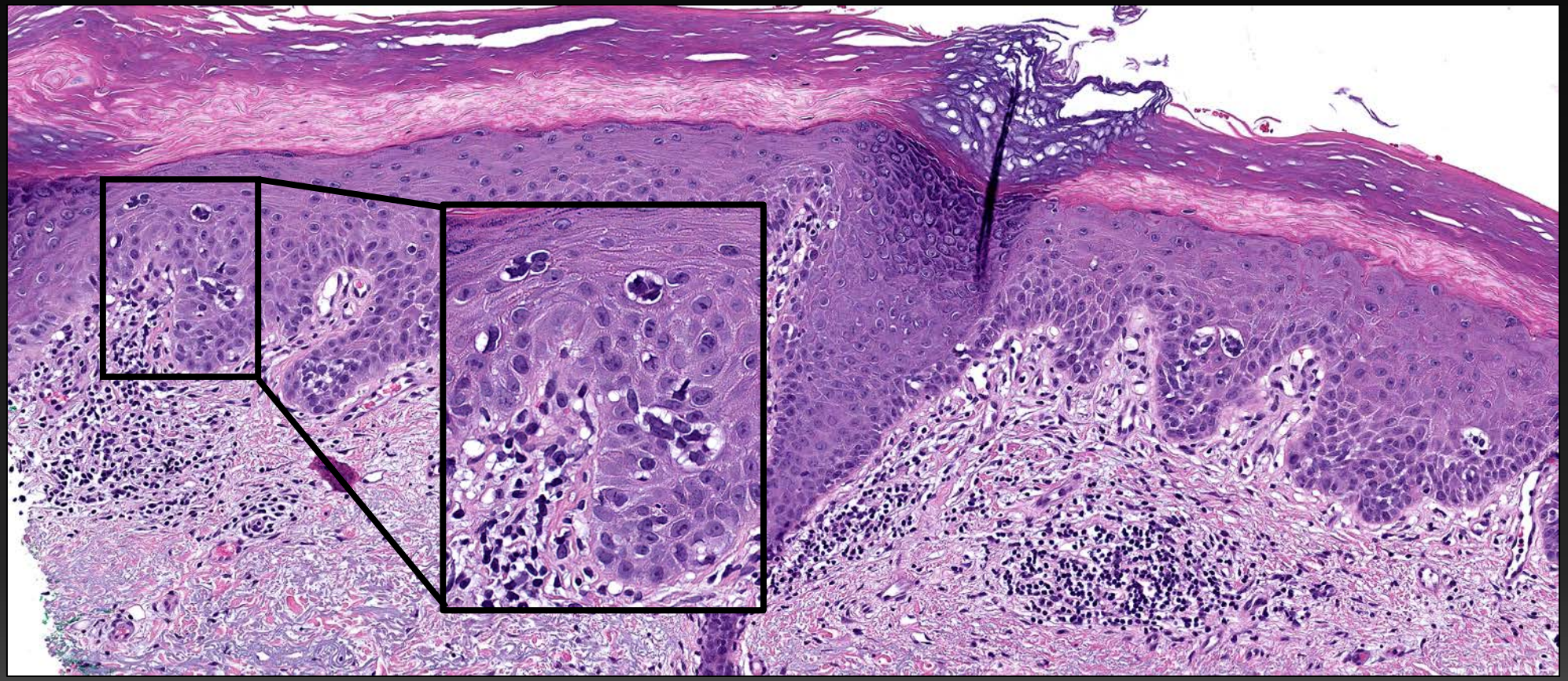
Case #2 H&E



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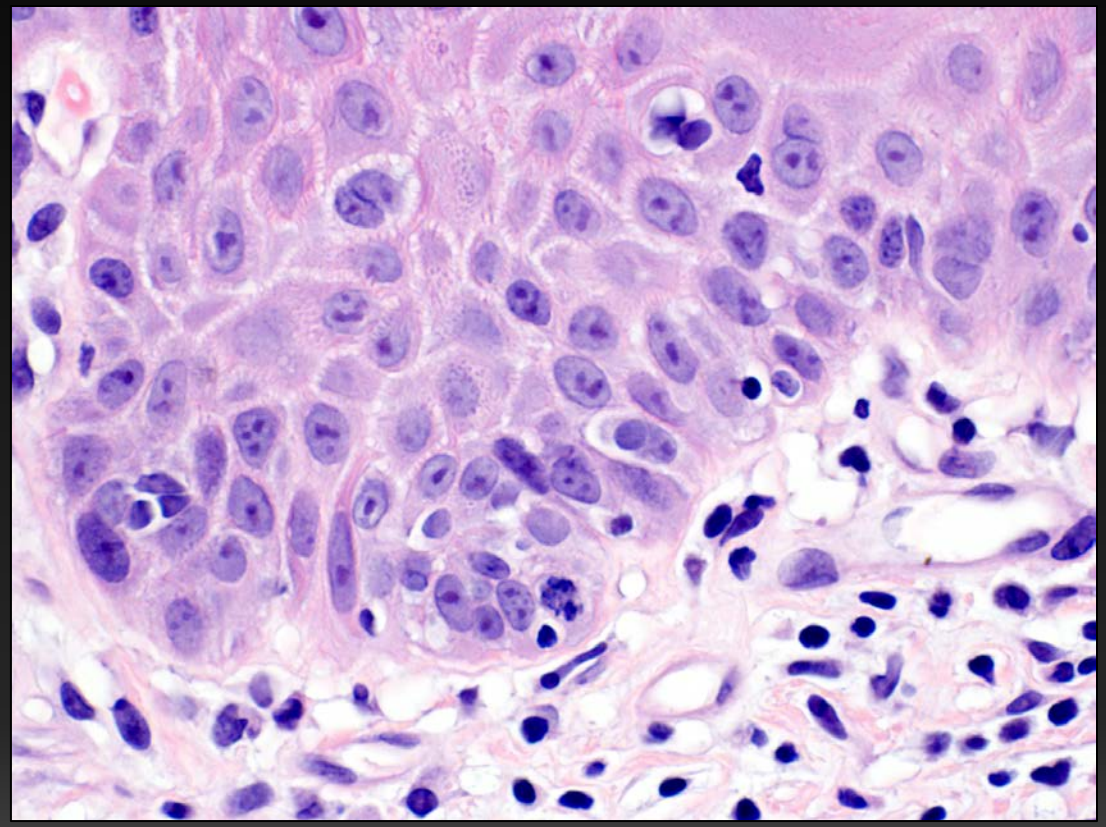
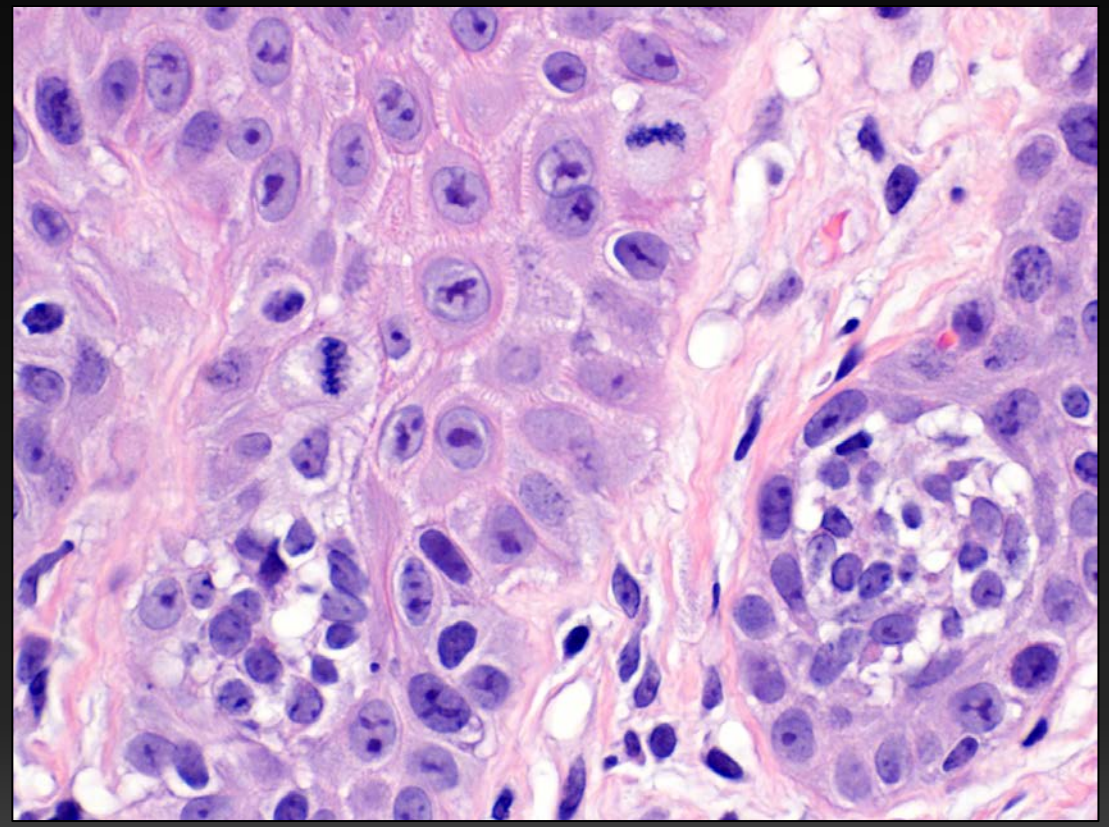
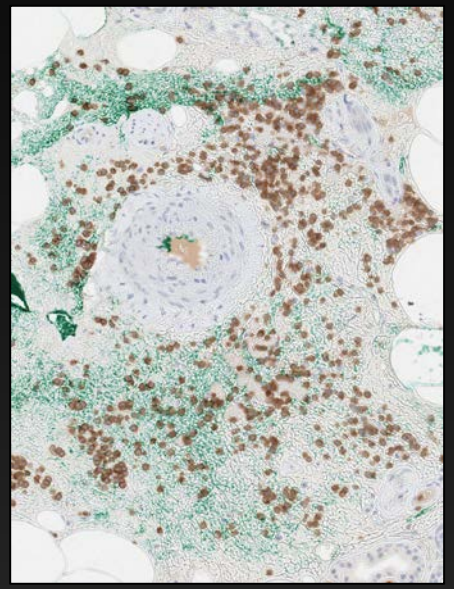
Case #2 H&E

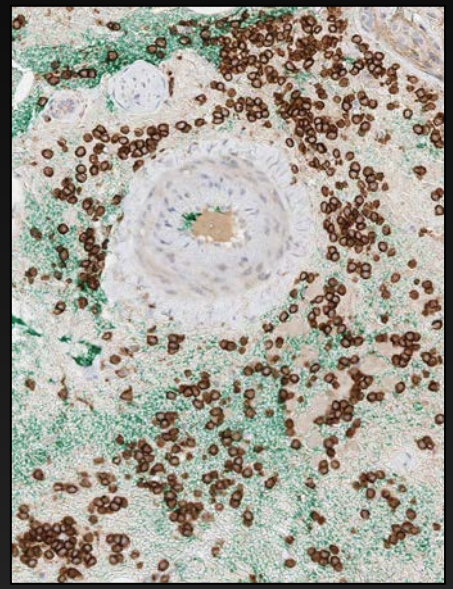




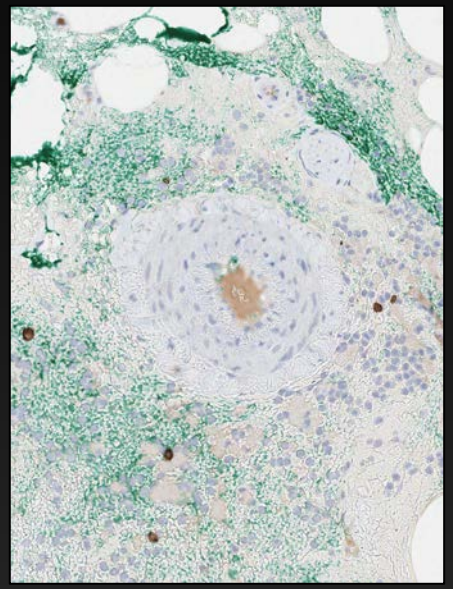
Case #2: Immunohistochemistry



CD3



CD4

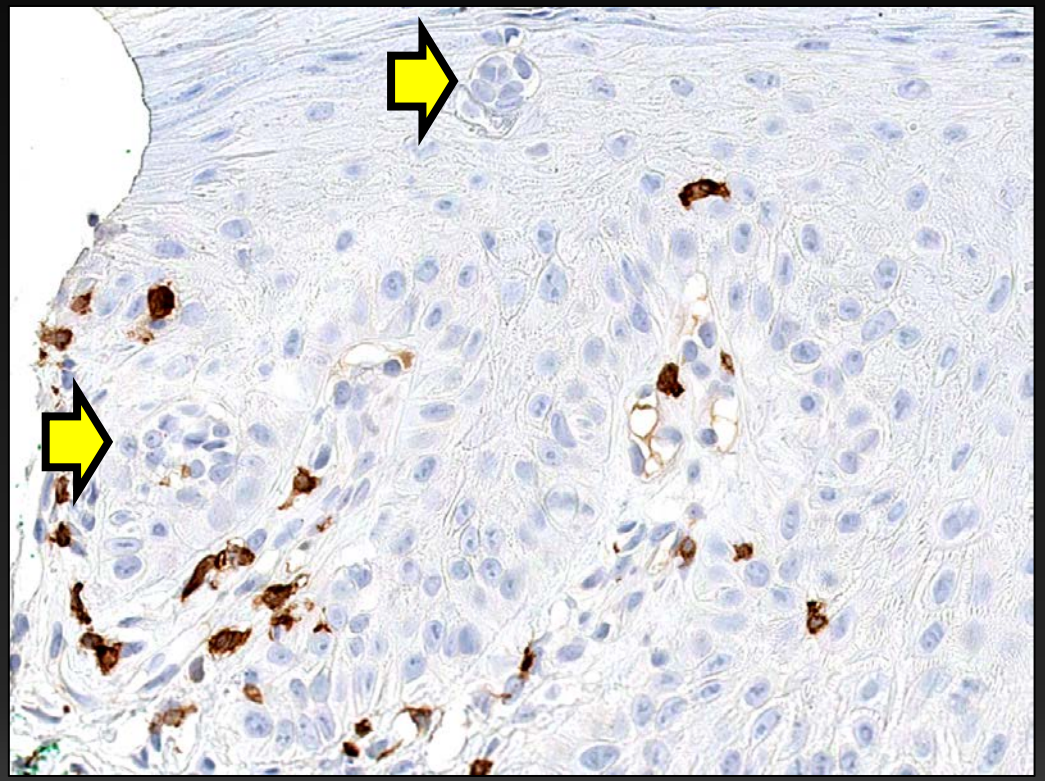


CD8

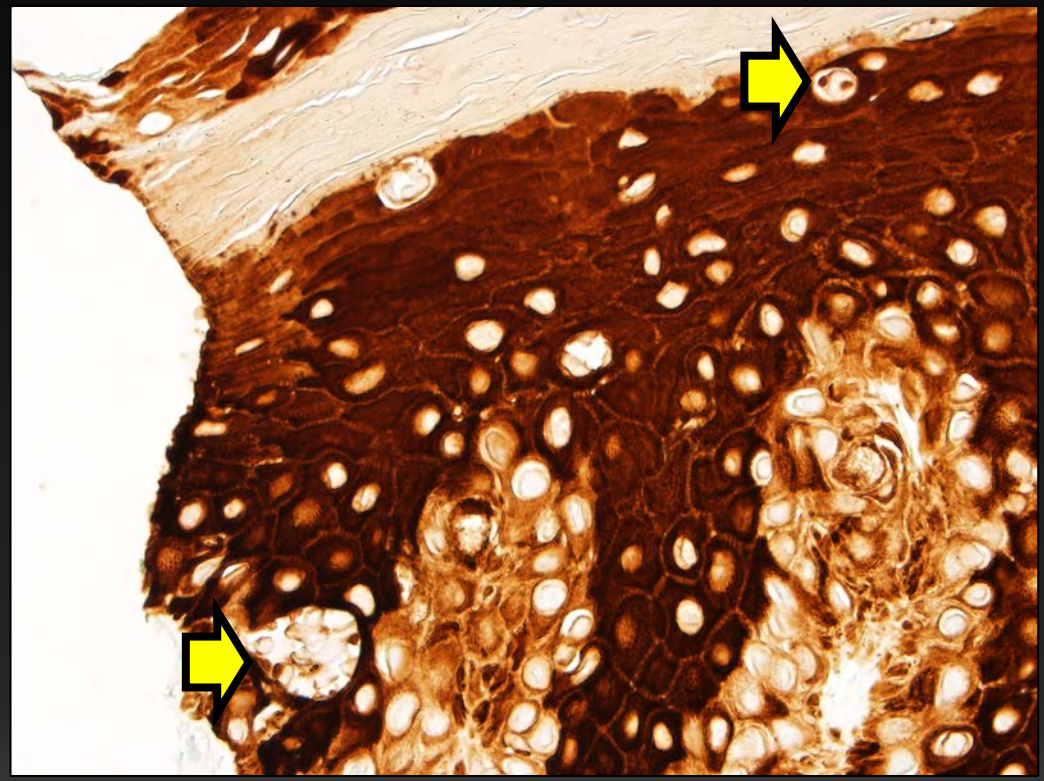
Atypical T-cell infiltrate
CD3+
CD4+
CD7-
CD8-

Consistent with involvement by Sezary Syndrome

Case #2: Immunohistochemistry



CD3



AE1/AE3/CAM5.2

2nd population
CD3-
CD4-
CD8-
Pan-T marker-

CK weak+

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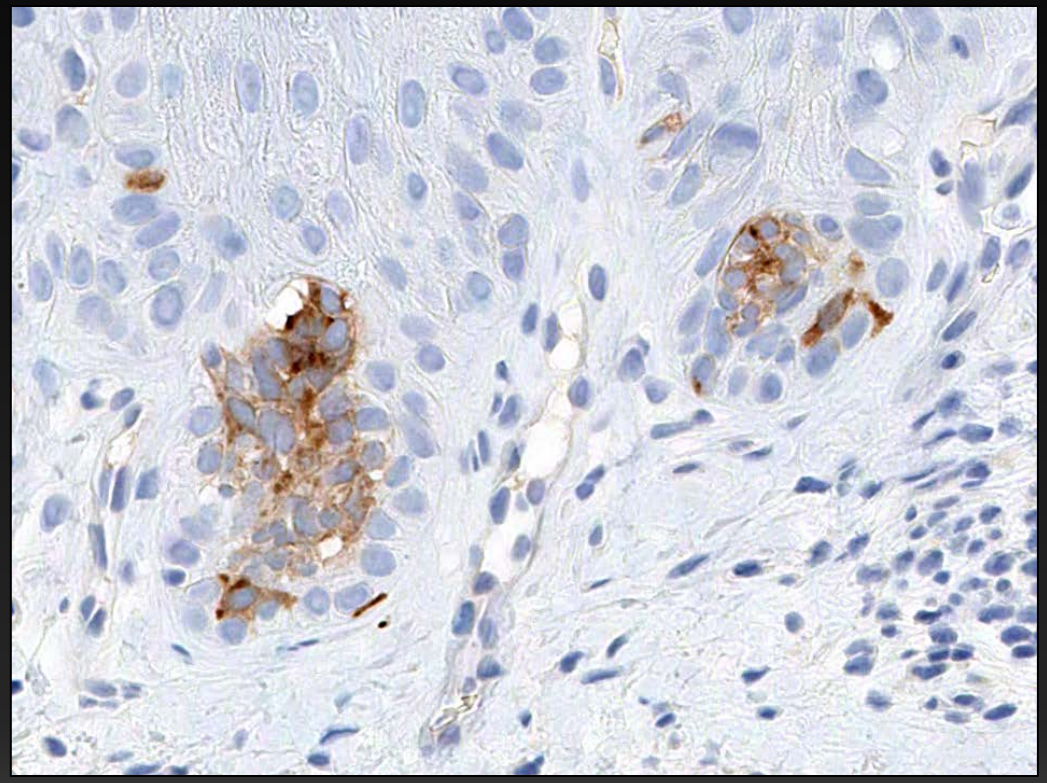
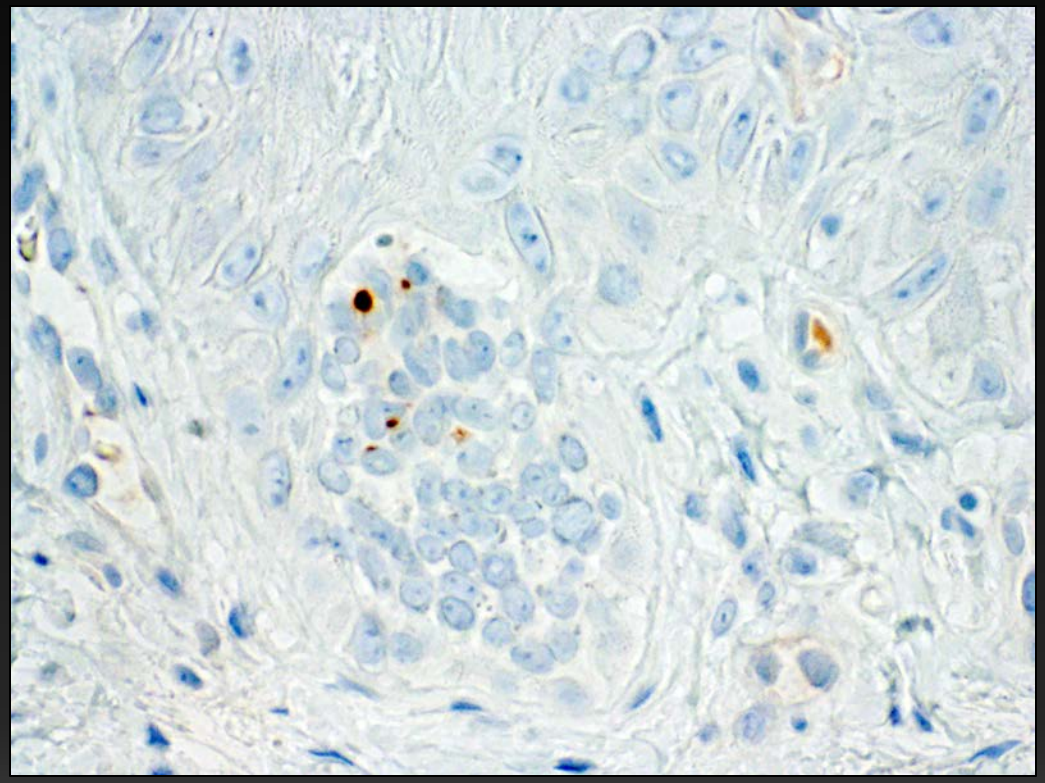
Case #2: Immunohistochemistry



Synaptophysin



Neurofilament

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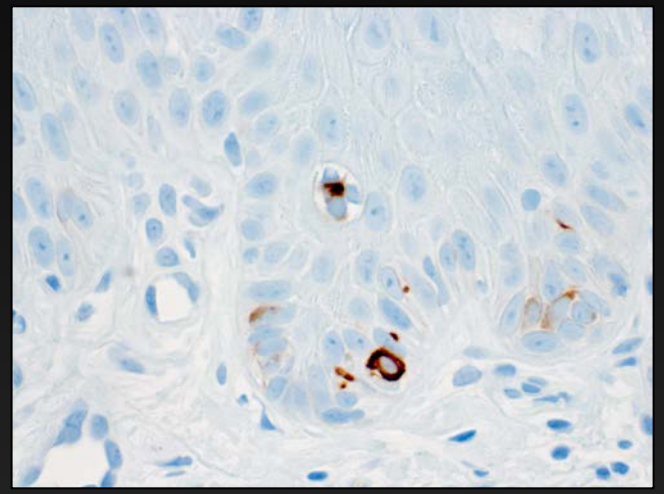
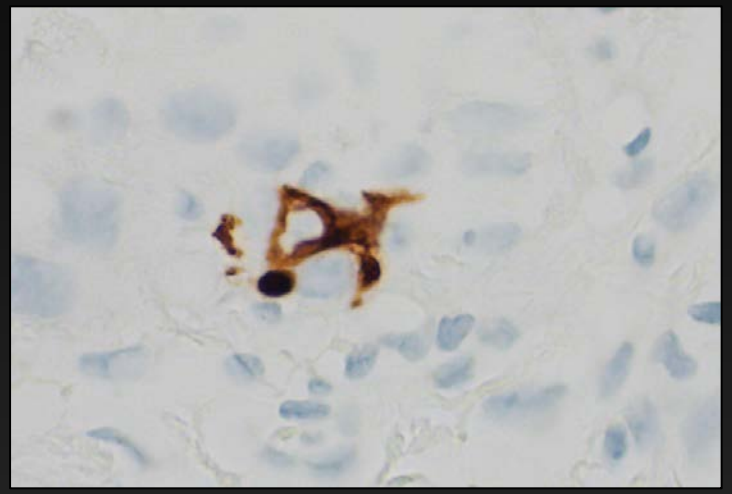
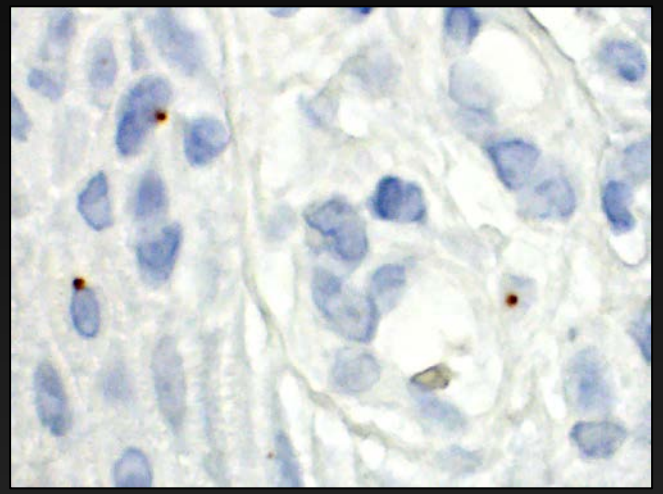


CK19



CK20



MCPyV RNA-ISH

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Case 2 Diagnosis

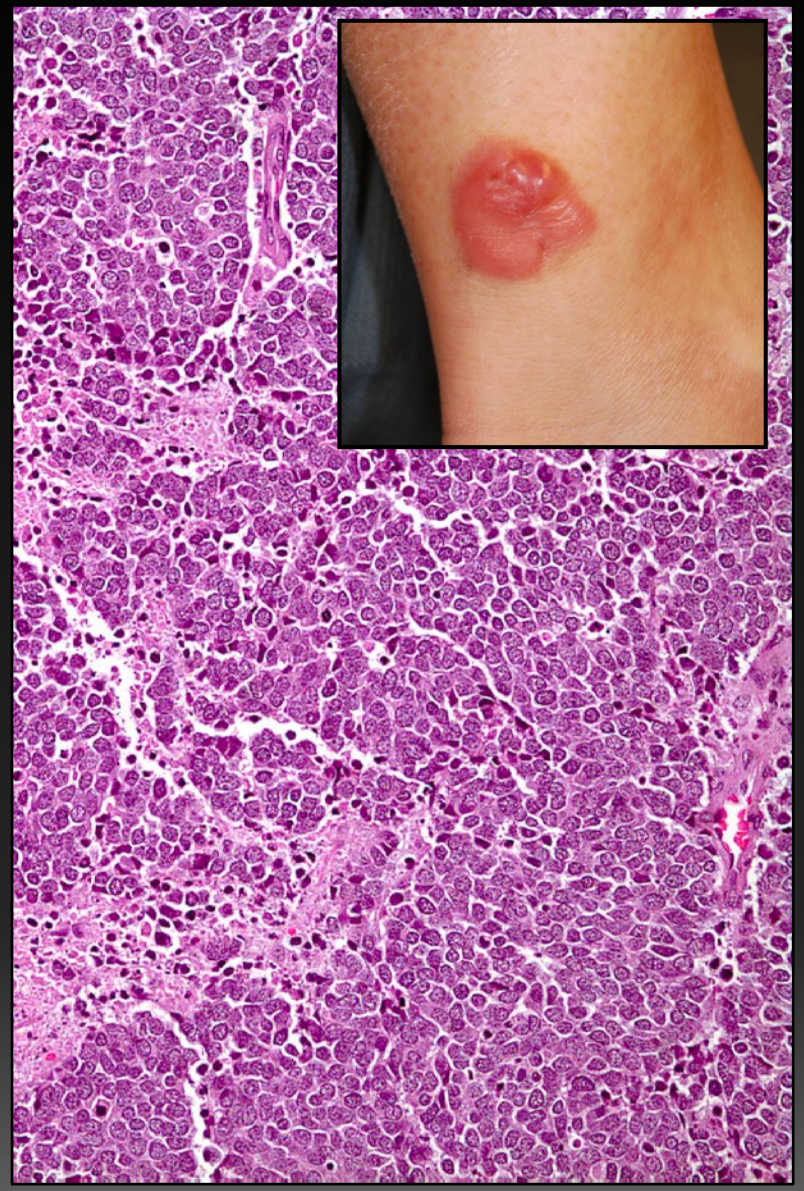
Merkel cell carcinoma in situ

Case 2: Management and Outcome

- Wide local excision showed residual MCCIS with negative margins and no dermal involvement
- No sentinel lymph node mapping
- 3 years after diagnosis: no recurrence of MCCIS; persistent Sezary syndrome

Merkel Cell Carcinoma

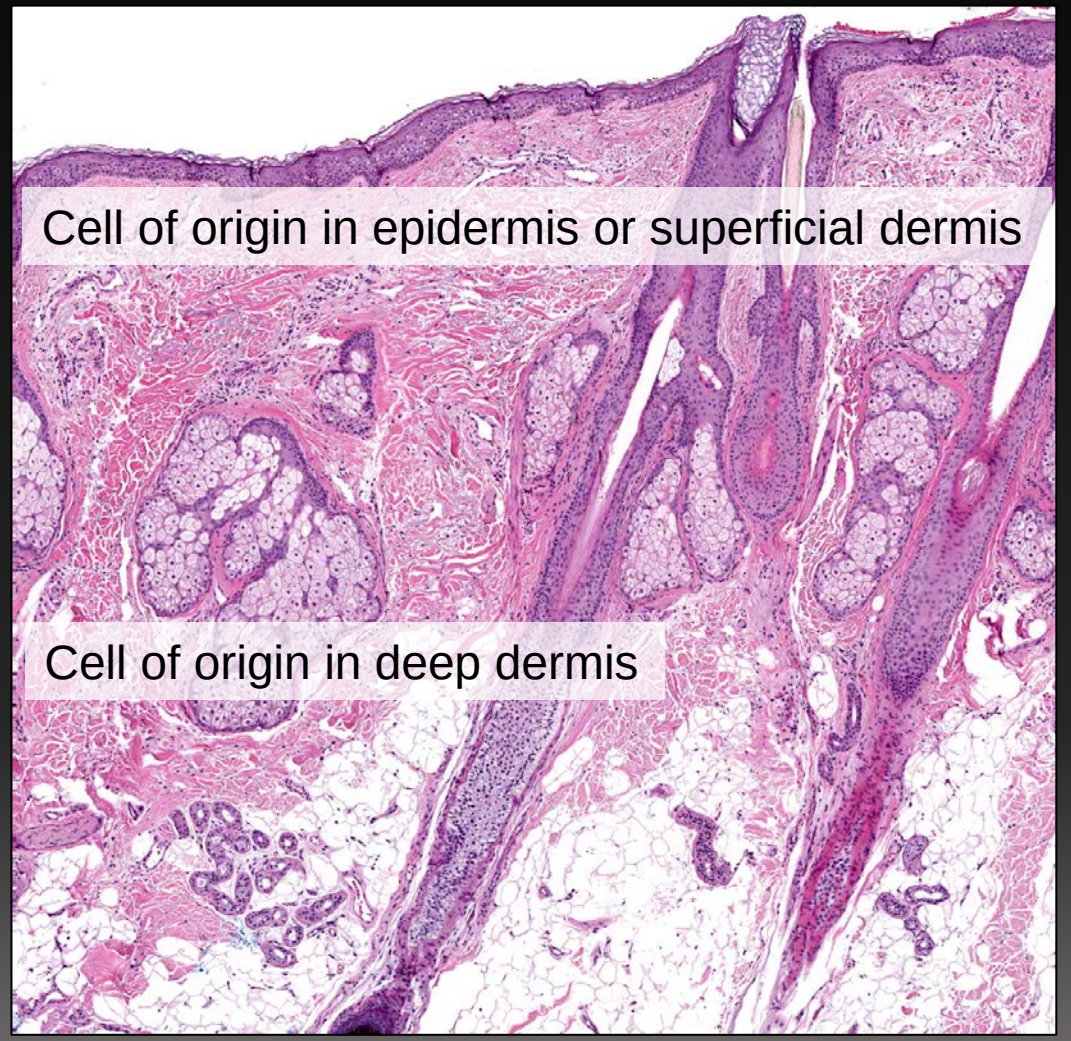
- Cutaneous neuroendocrine tumor
- Highly aggressive
- Increased incidence in individuals with immune dysfunction, including B-cell lymphoma
- DNA virus (Merkel cell polyomavirus) identified in ~75% of MCC



Model for Origin of MCC

MCPyV-Negative MCC
High UV mutation burden

MCPyV-Positive MCC
Very low mutation burden



MCC and Lymphoma

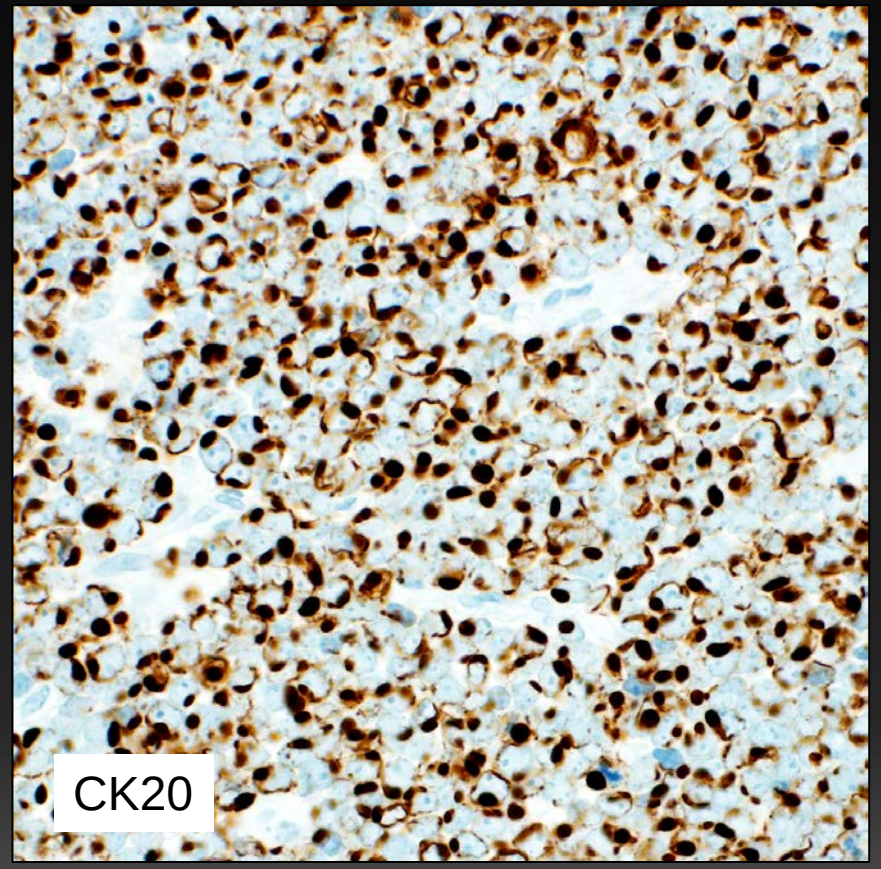
- Well-documented association between MCC and B-cell lymphoma (especially CLL)
- MCC arising in setting of CTCL is rare
- Immune dysfunction related to advanced CTCL may increase risk for MCC

Merkel Cell Carcinoma: Diagnosis

- Immunohistochemistry
  - CK20: Paranuclear dot or cytoplasmic (most cases)
  - NE markers
  - +/-MCPyV

- Differential diagnosis
  - Metastatic SCLC
  - Small cell melanoma
  - Lymphoma
  - Other poorly differentiated carcinoma

  Most common misdiagnosis is likely BCC



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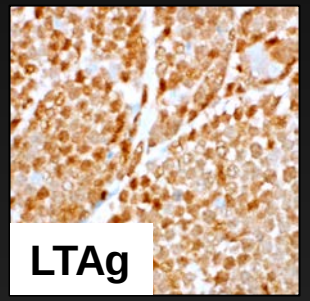

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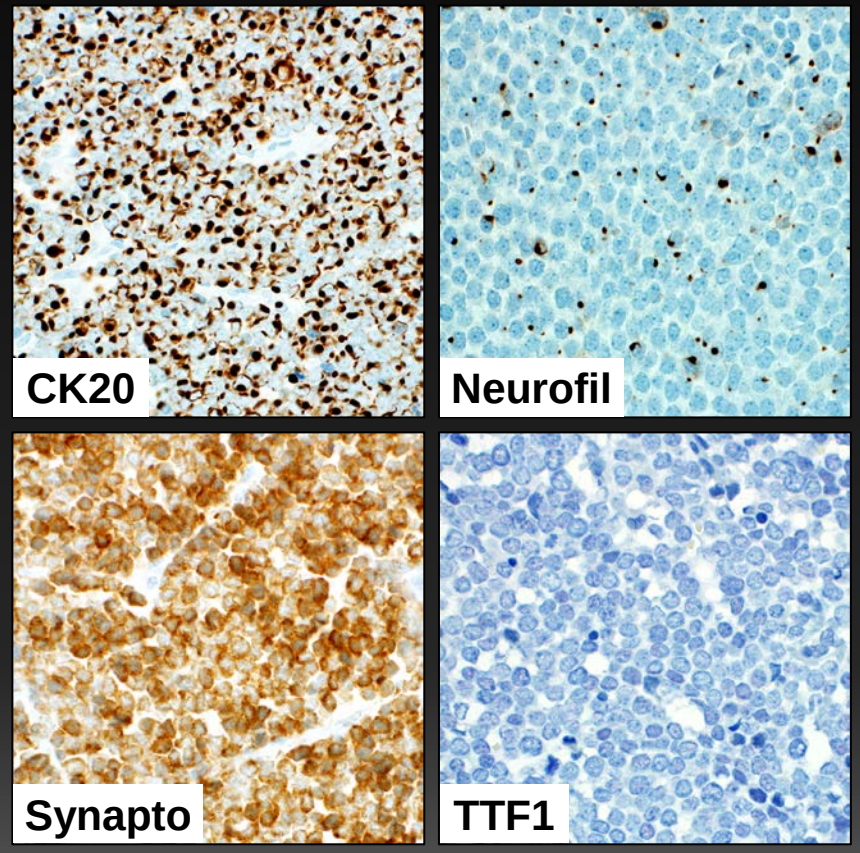


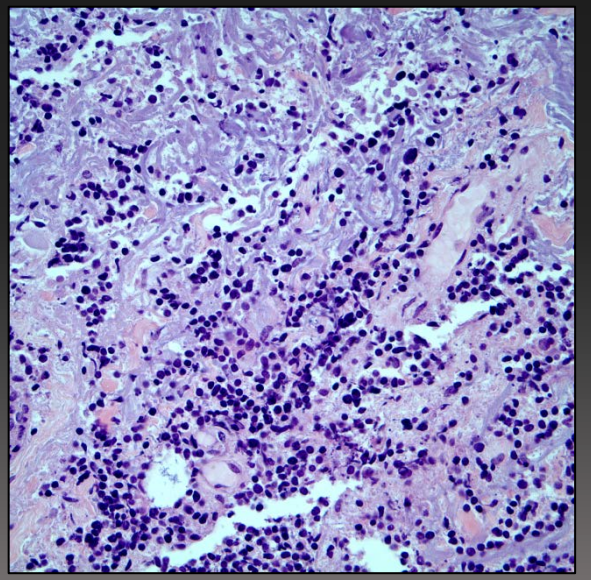
MCC Vs. Lymphoma

Small cell variant MCC may resemble lymphoid process

MCC may express TdT, PAX5, Ig

Negative for other lymphoid markers (LCA, CD20, CD3, etc.)

MCC
Small cell variant



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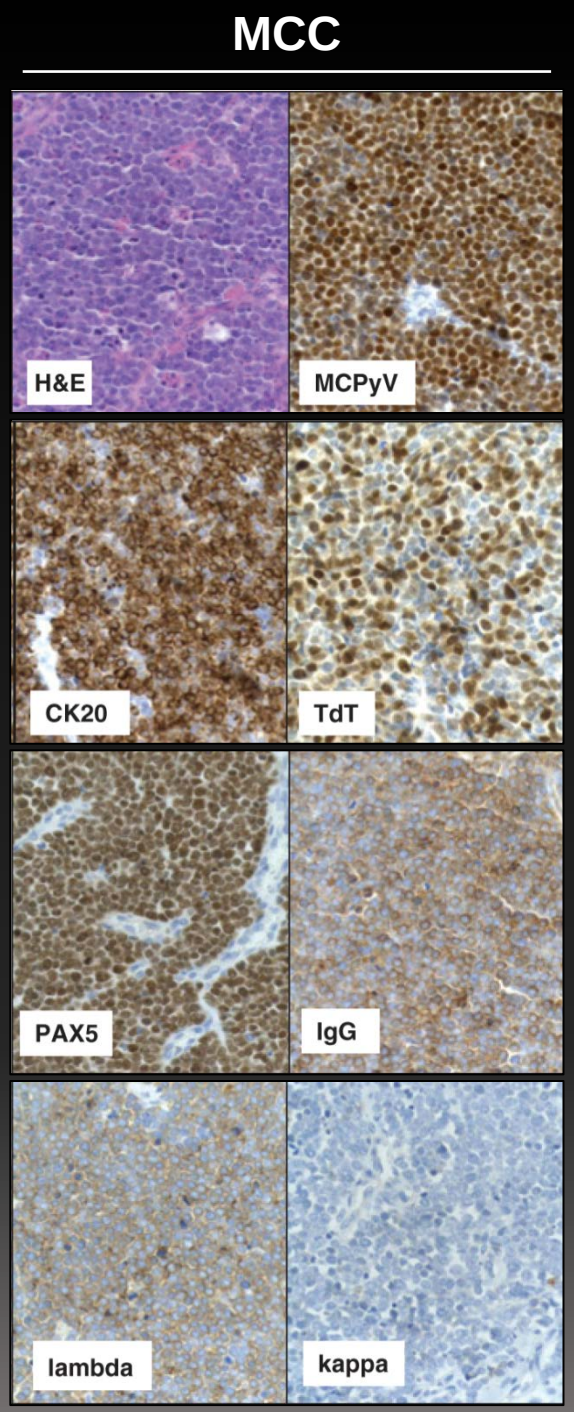


zur Hausen et al 2013

Merkel Cell Carcinoma In Situ

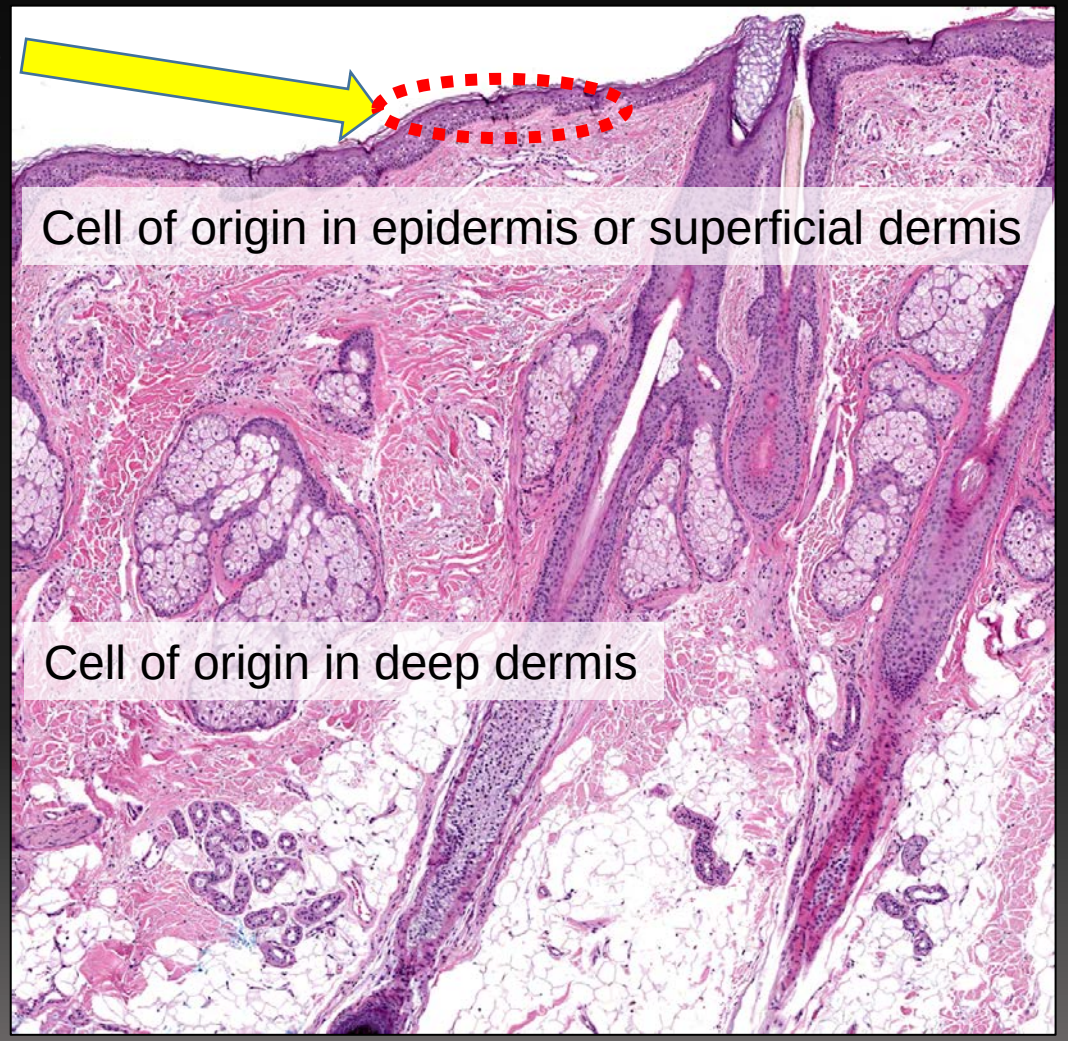
- MCC in situ (without dermal component) is exceedingly rare
- Although recurrence with progression to dermal involvement and metastatic disease has been reported in one case of MCCIS, all other cases have had an uneventful course following excision
- In partial sampling, critical to exclude dermal involvement

Model for Origin of MCC

Current Case: MCPyV-Positive MCC in Epidermis

MCPyV-Negative MCC
High UV mutation burden

MCPyV-Positive MCC
Very low mutation burden



Case #3

Case 3: History

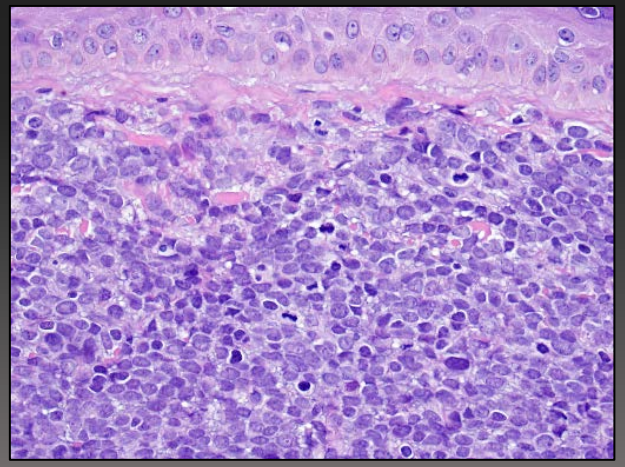
- 84-year-old man presented to the Department of Dermatology at the University of Puerto Rico with a new lesion of concern.
- History of multiple NMSCs, including SCC of the left zygoma that had been diagnosed by biopsy 6 months prior to the current visit but not yet excised
- At the current visit, a new, ill-defined erythematous scaly plaque on the left upper forehead was identified

Falto Aizpurua *et al.* JAADCR 2018

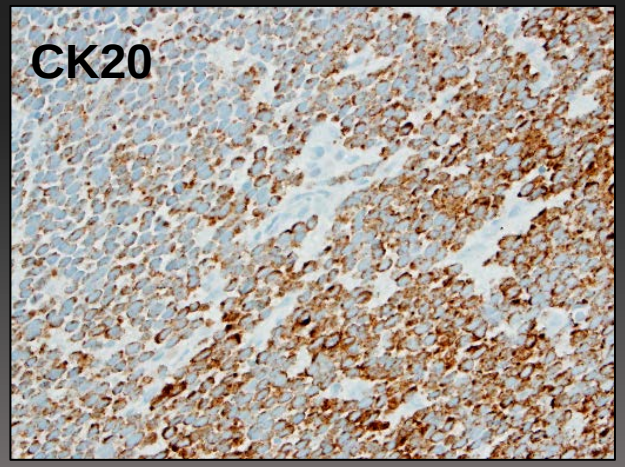
Case 3: Microscopic Findings

- Small blue cell tumor

- Numerous mitoses



- Immunohistochemistry
  - Dot-like CK20
  - Neuroendocrine markers

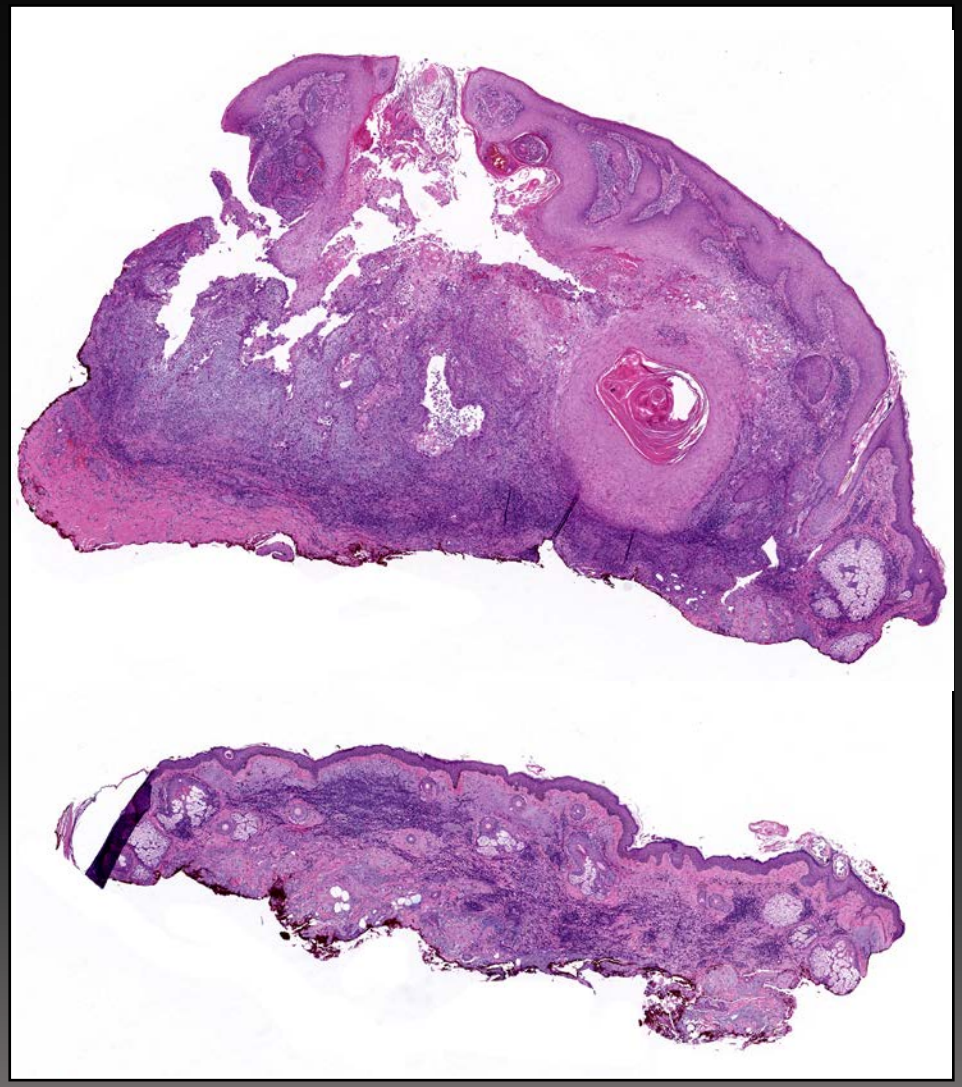


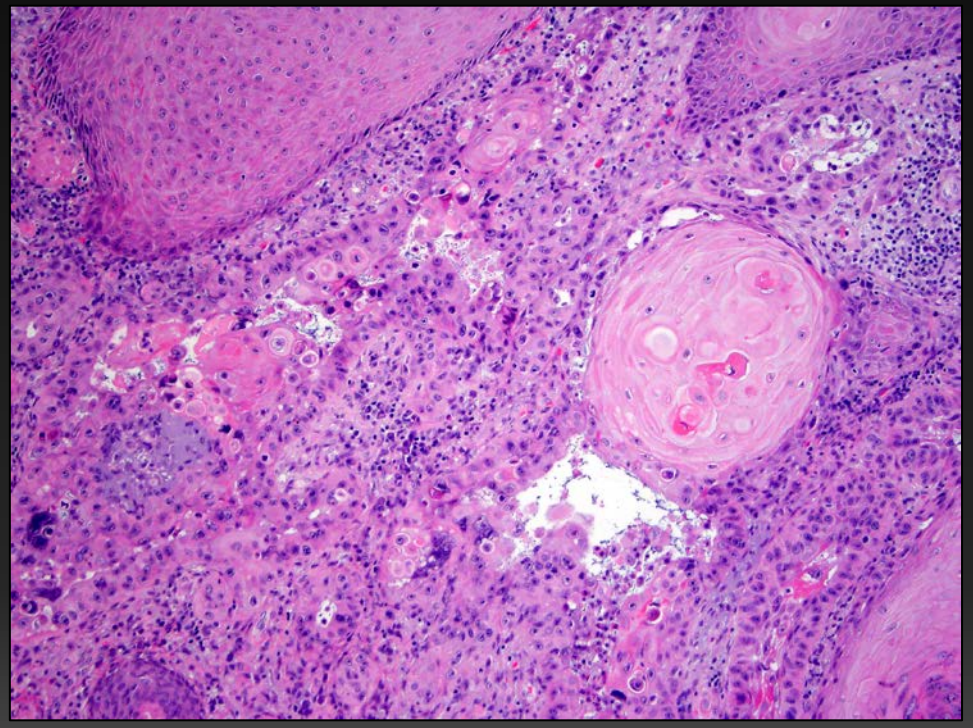
Case 3: History (continued)

- Three months after the initial diagnosis of MCC, the previously biopsied SCC on the left zygomatic area was removed by Mohs micrographic surgery.
- Mohs surgeons became concerned about atypical infiltrate that was not SCC.

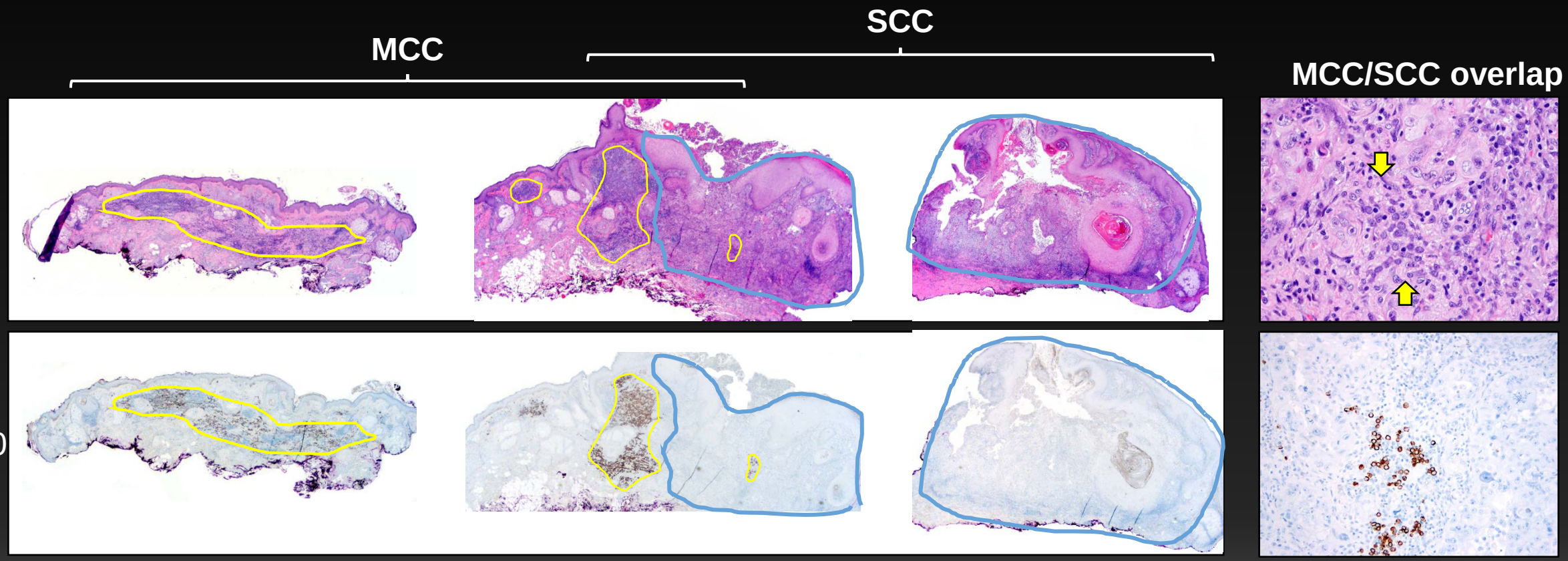
Falto Aizpurua *et al.* JAADCR 2018

Case 3, Tumor 2: Microscopic Findings



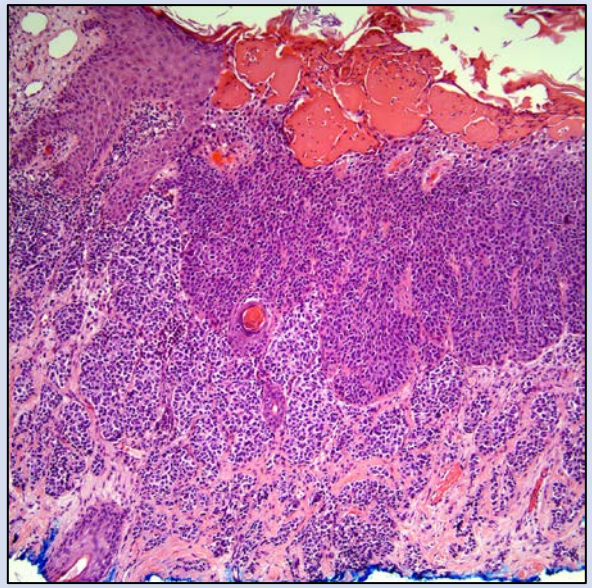


Case 3, Tumor 2

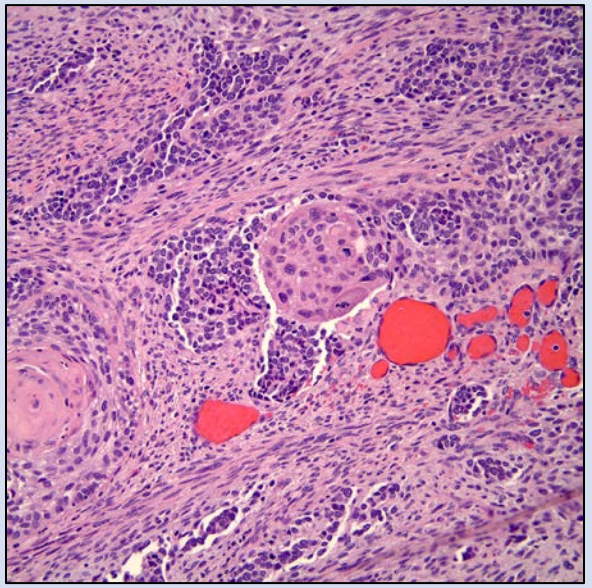


Falto Aizpurua *et al.* JAADCR 2018

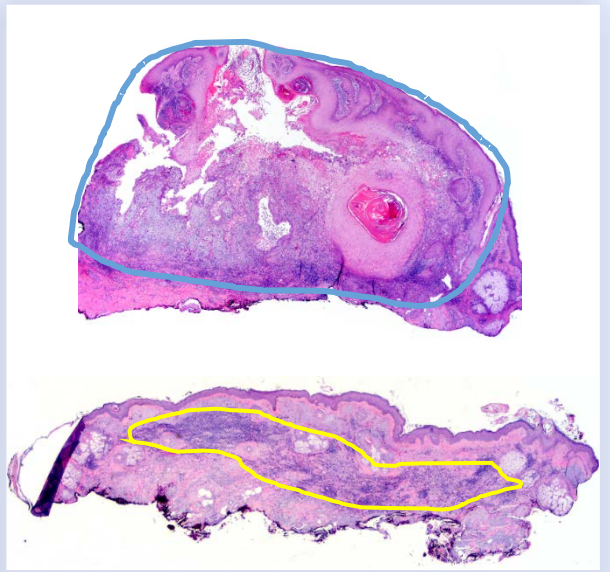
MCC with Concurrent SCC vs. MCC with Squamous Differentiation



MCC with concurrent SCC: distinct zones of MCC, SCC

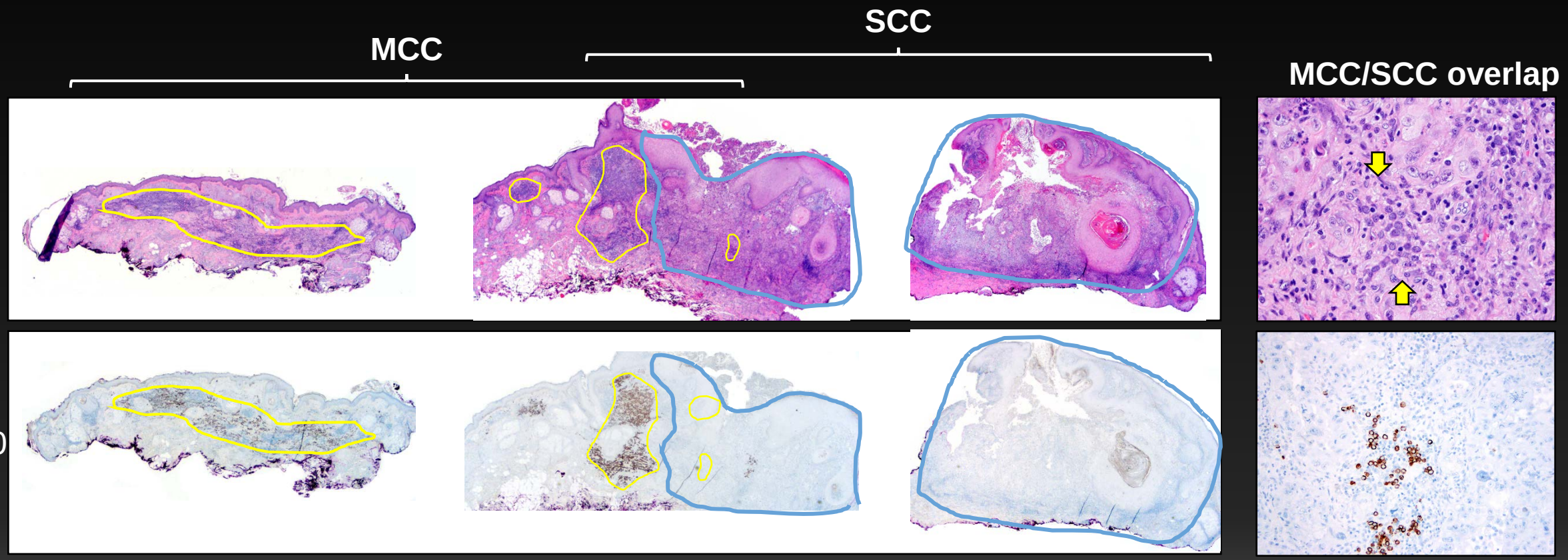


MCC with squamous differentiation: interspersed foci of squamous cells



Case 3

Case 3, Tumor 2



Combined tumor (MCC-SCC) or collision?

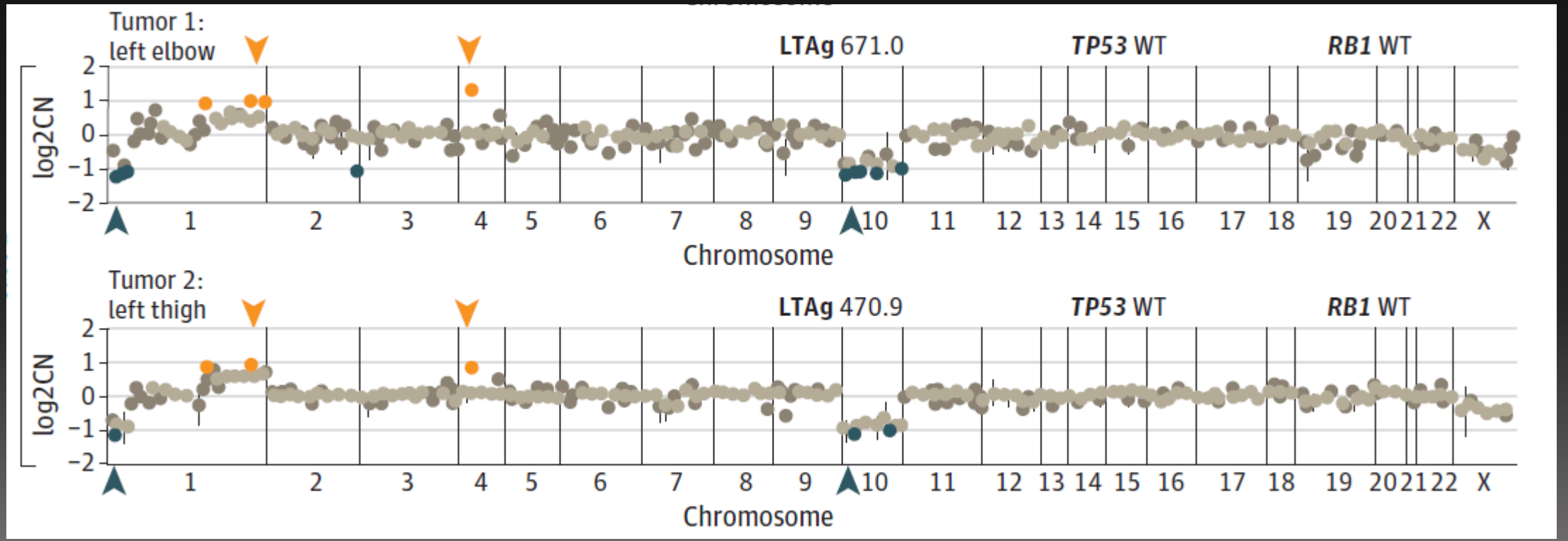
Regional metastasis or new primary?

Falto Aizpurua *et al.* JAADCR 2018

JAMA Dermatology | Original Investigation

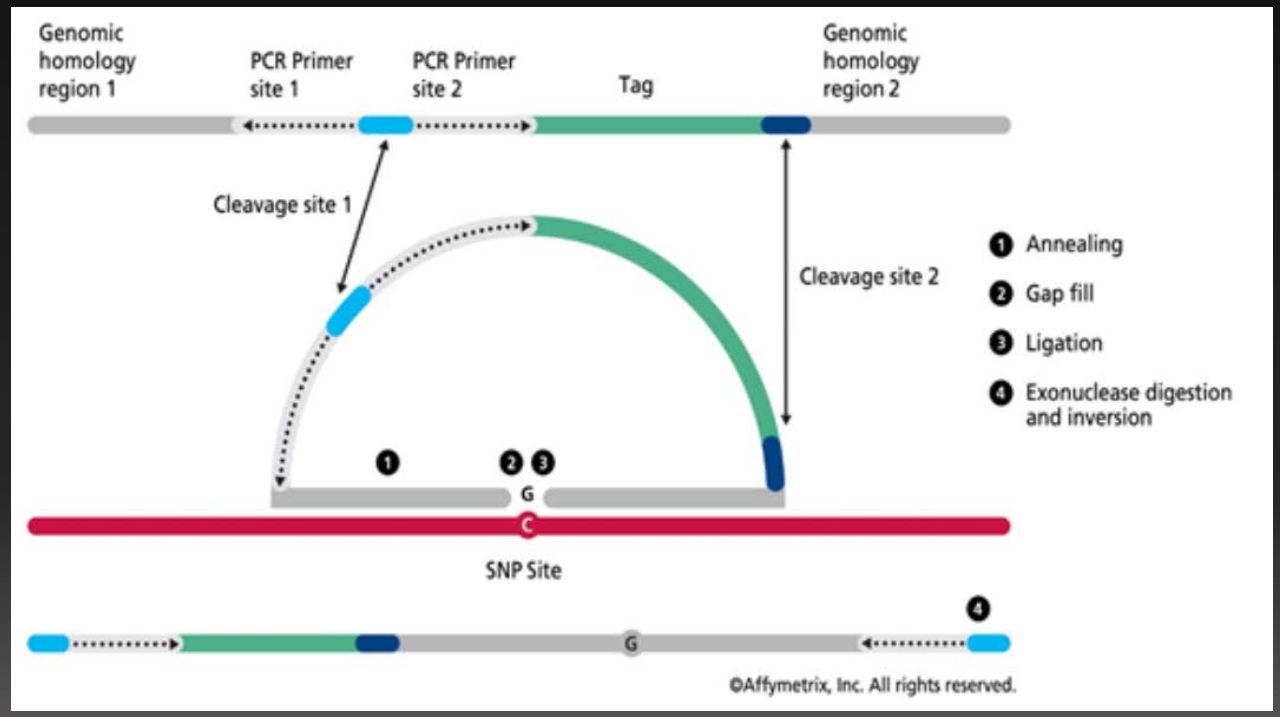
Molecular Profiling of Multiple Primary Merkel Cell Carcinoma to Distinguish Genetically Distinct Tumors From Clonally Related Metastases

Kelly L. Harms, MD, PhD; Lorena Lazo de la Vega, BS; Daniel H. Hovelson, MS; Samantha Rahrig; Andi K. Cani, MS; Chia-Jen Liu, MS; Douglas R. Fullen, MD; Min Wang, PhD; Aleodor A. Andea, MD; Christopher K. Bichakjian, MD; Timothy M. Johnson, MD; Scott A. Tomlins, MD, PhD; Paul W. Harms, MD, PhD

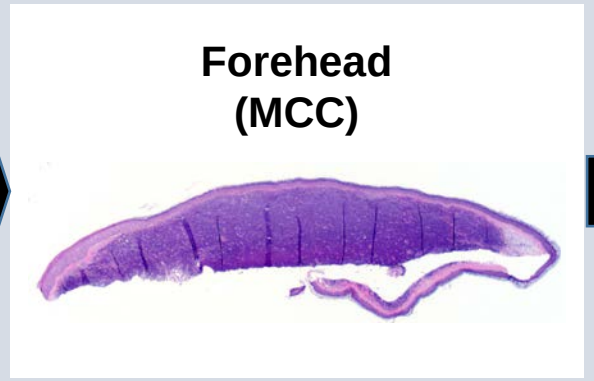


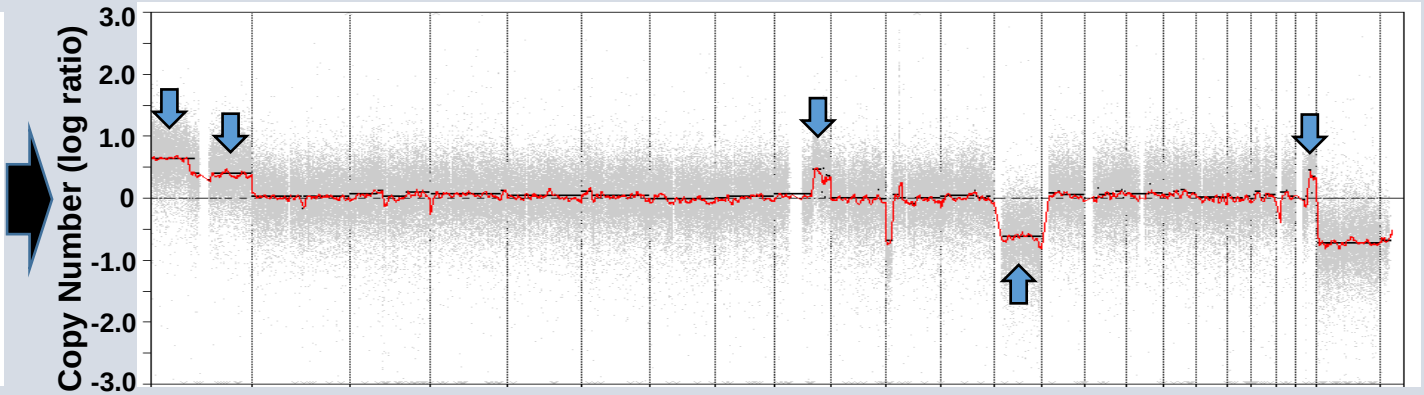
Aleodor Andea

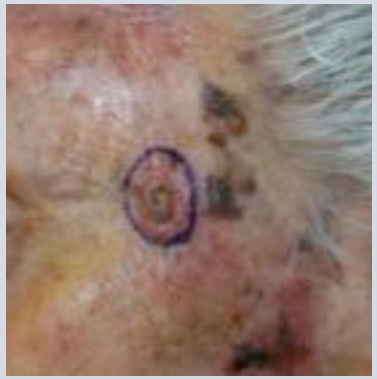
CGH Analysis of FFPE Tumor by Molecular Inversion Probes

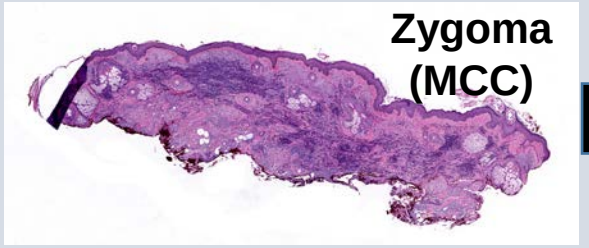


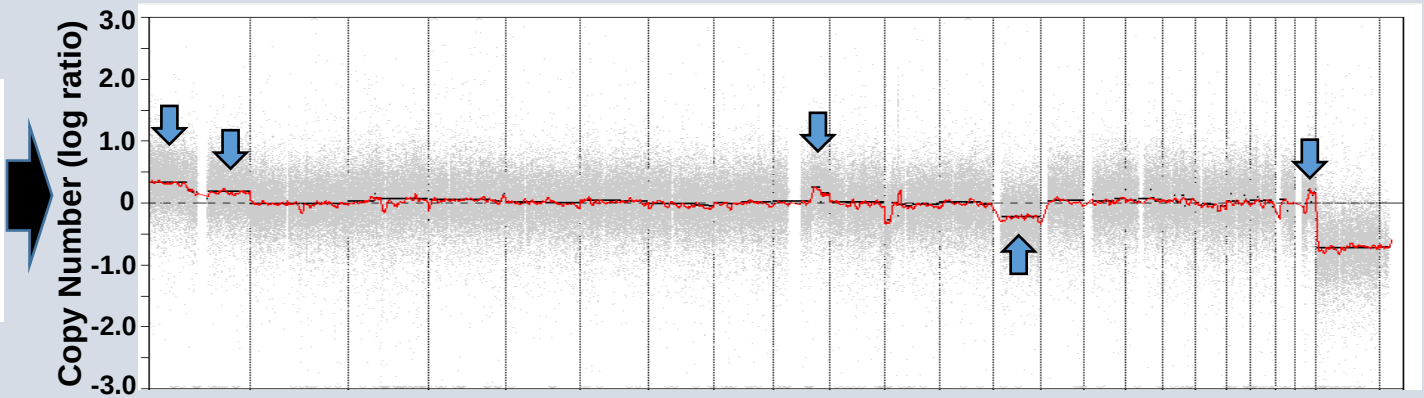
- 50–100 kb copy number resolution in cancer genes
- 300 kb genome-wide copy number resolution outside of cancer genes
- LOH detection
- Hotspot mutation calling

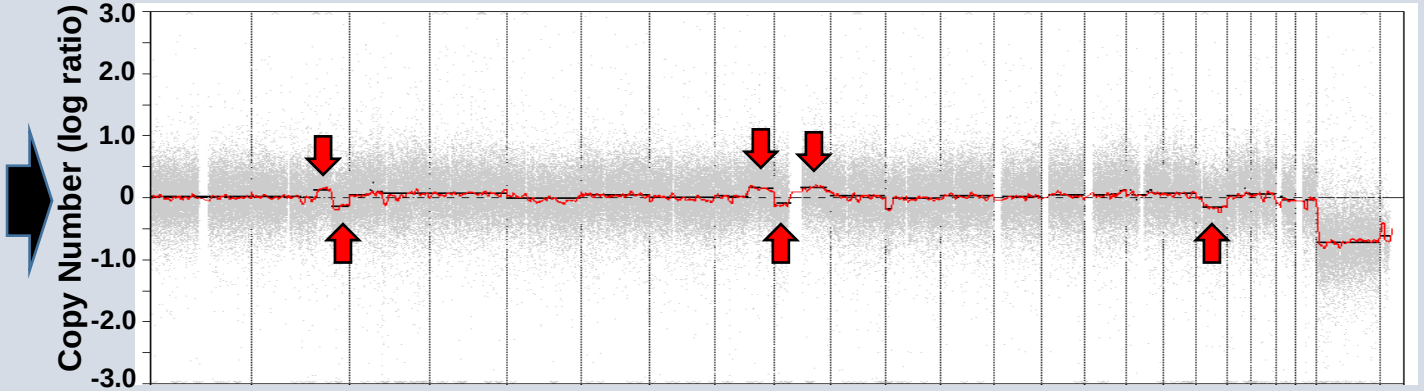










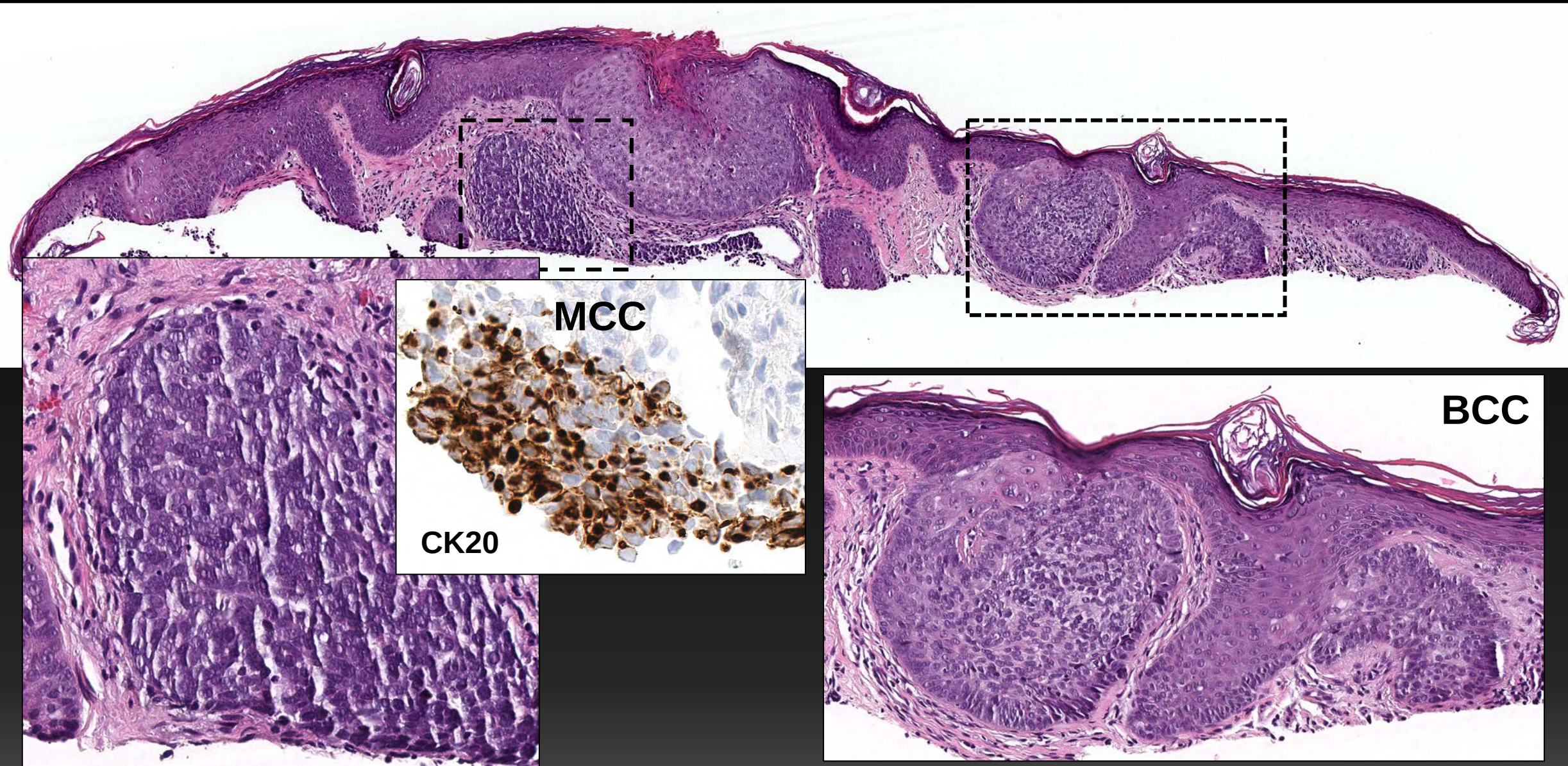


Shared copy gain or loss

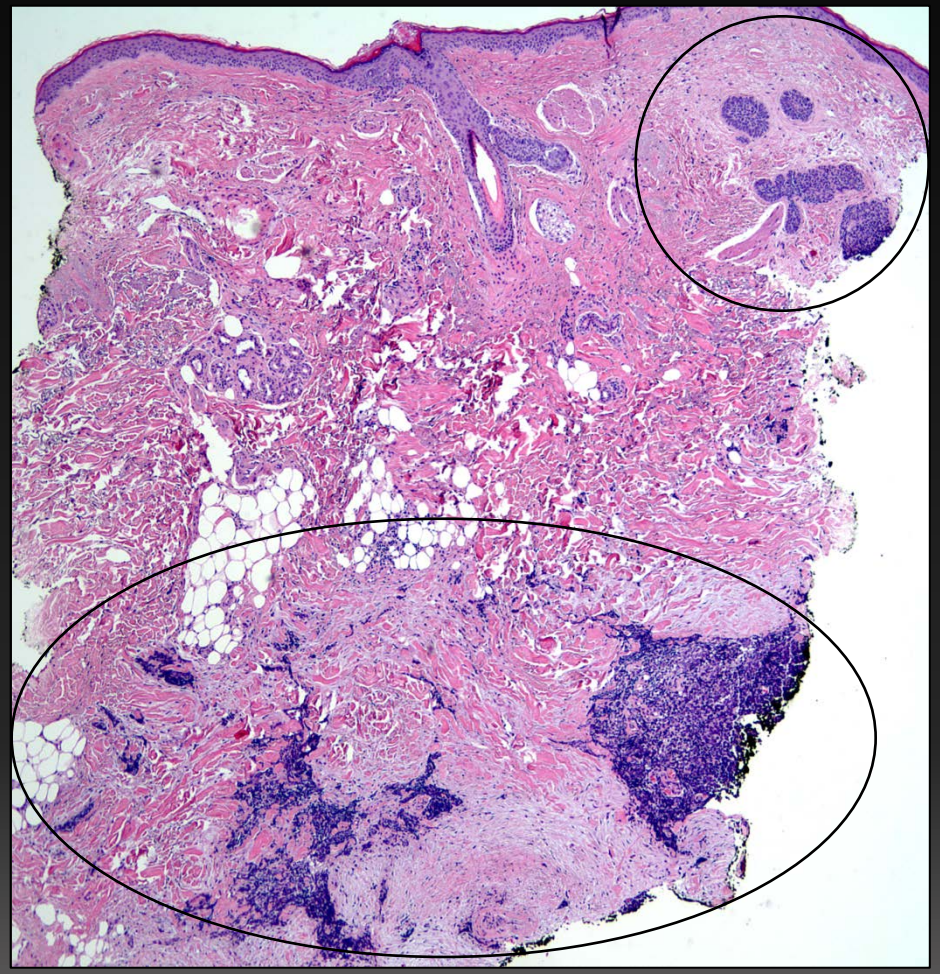
Case 3 Diagnosis

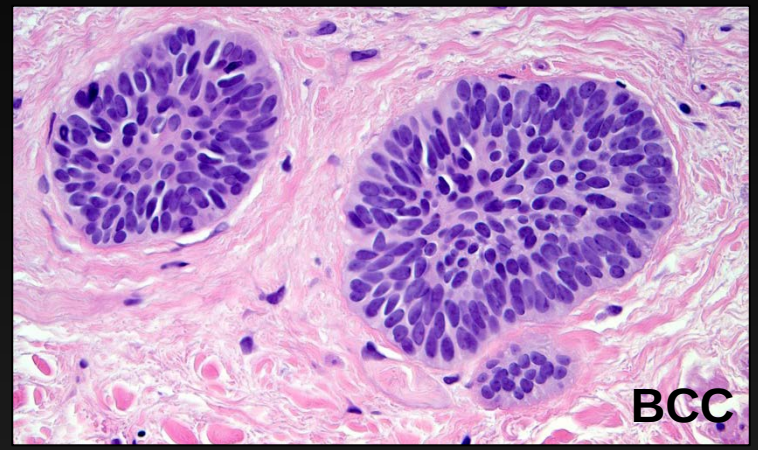
MCC metastasis to site of SCC

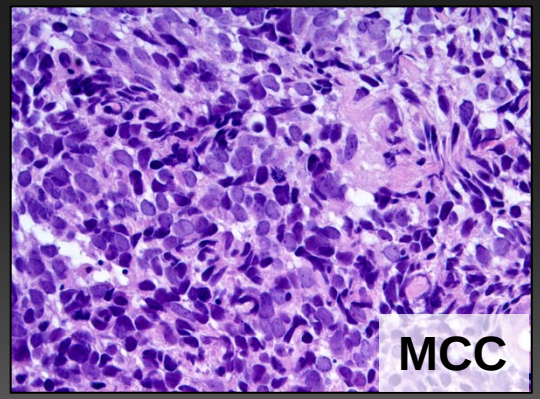
Merkel Cell Carcinoma as a Second Diagnosis


MCC
CK20
BCC

MCC Vs. BCC

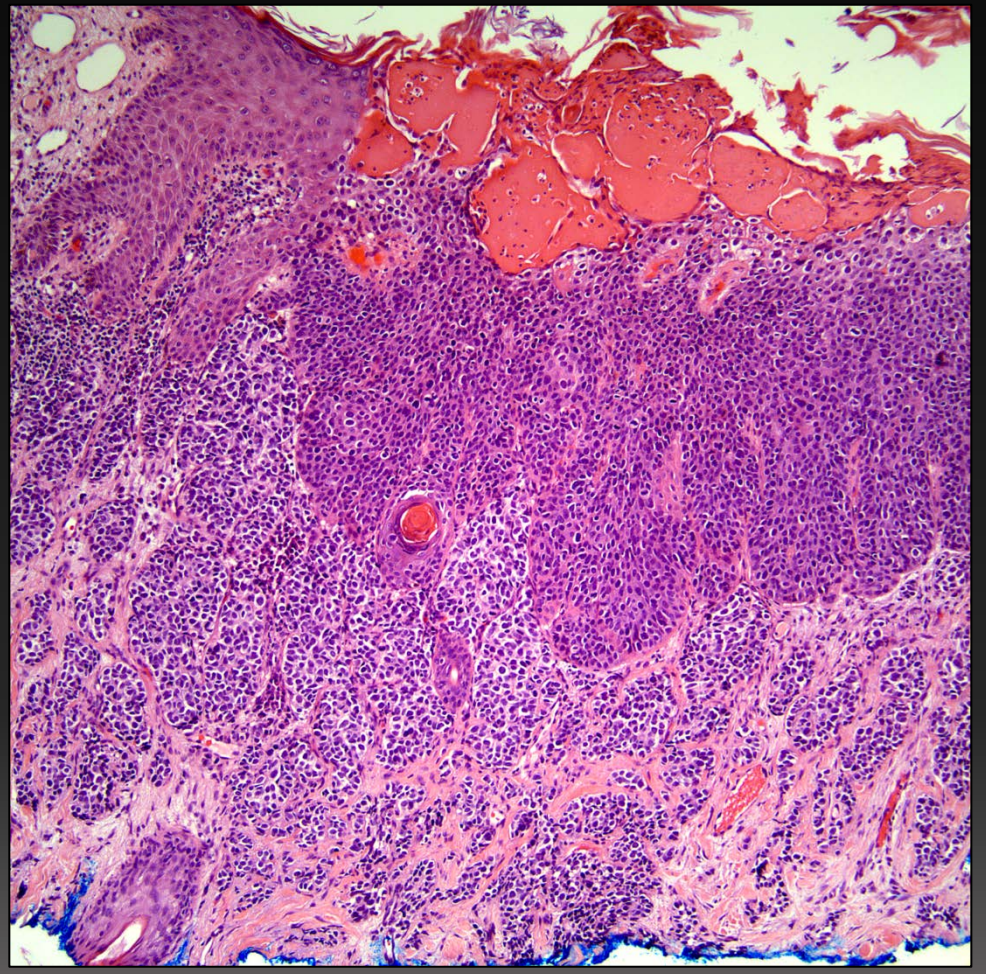






MCC with SCCIS

Minority of MCC associated with SCC (in situ or invasive) or other epithelial lesion



Cases 2 and 3: Summary

- MCC arises in the elderly and immunodeficient populations
- In a minority of cases, MCC occurs alongside other neoplasms including NMSC and lymphoma
- Index of suspicion is essential for diagnosing MCC with limited sampling, challenging morphology, or concurrent second neoplasm
- Sezary syndrome/mycosis fungoides patients should undergo careful skin checks given a higher risk for NMSC
- In patients with history of MCC, consider the possibility of concurrent MCC metastasis when regional NMSCs are excised

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- Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sézary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model. Scarisbrick JJ, et al. J Clin Oncol. 2015 Nov 10;33(32):3766-73

- Merkel cell carcinoma arising in association with cutaneous T-cell lymphoma: A potential diagnostic pitfall. Zoumberos NA, McMullen E, Wang L, Wang X, Harms KL, Tejasvi T, Chan MP, Fullen DR, Hristov AC, Harms PW. J Cutan Pathol. 2019 Mar;46(3):199-203.

- A case of combined Merkel cell carcinoma and squamous cell carcinoma: Molecular insights and diagnostic pitfalls. Falto Aizpurua LA, Wang M, Ruiz HA, Sánchez JL, Chan MP, Andea AA, Harms PW. JAAD Case Rep. 2018 Nov 3;4(10):996-999.

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- Dermatology, 4th edition. Bolognia, Schaffer, and Cerroni, eds. 2018, Elsevier Limited.

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Douglas Fullen

Rajiv Patel

Lori Lowe

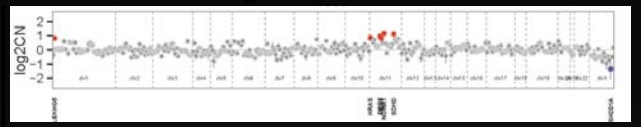
Alexandra Hristov

Scott Bresler

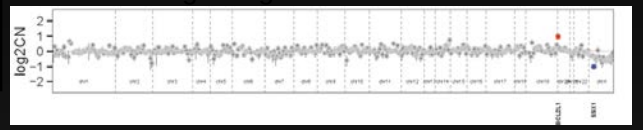

QUESTIONS?

Patient 1

Tumor 1: Left finger

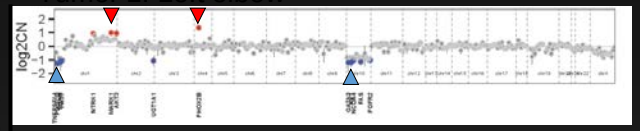


Tumor 2: Right finger

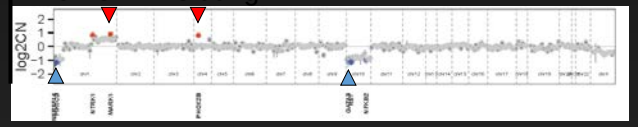


Patient 2

Tumor 1: Left elbow

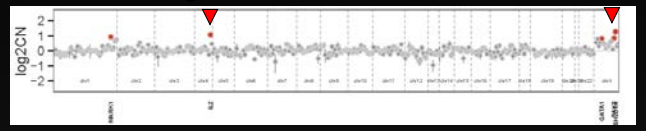


Tumor 2: Left thigh

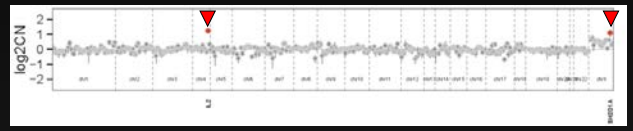


Patient 3

Tumor 1: Right Nose

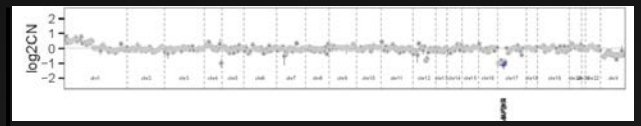


Tumor 2: Left nose

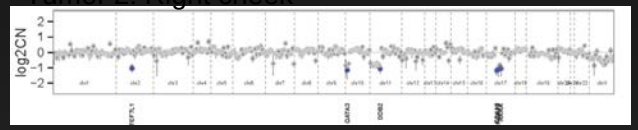


Patient 4

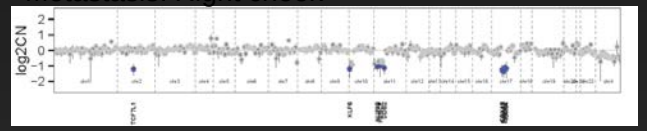
Tumor 1: Left cheek

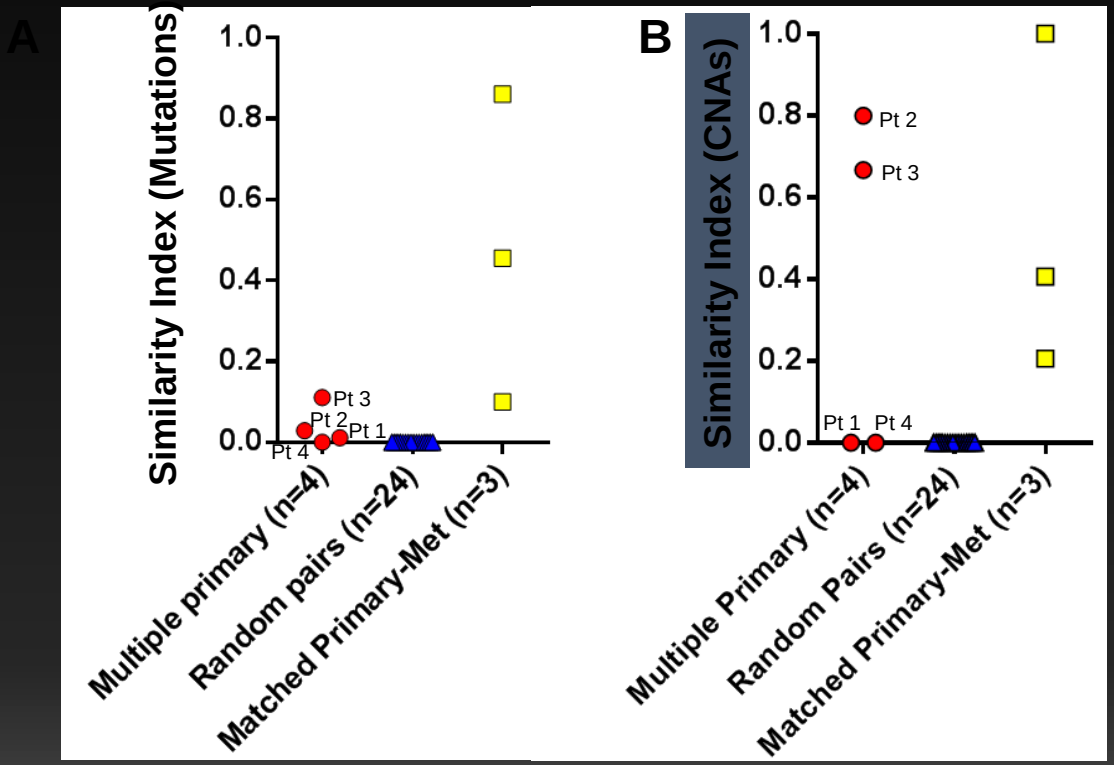


Tumor 2: Right cheek

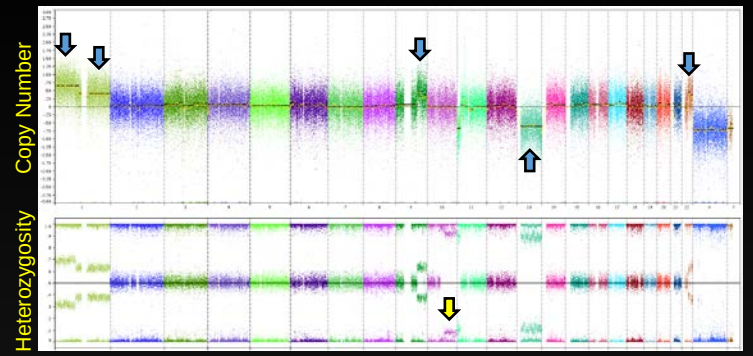


Metastasis: Right cheek

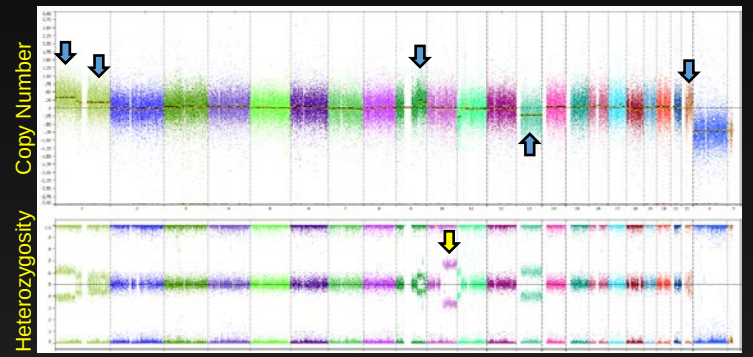



A
Similarity Index (Mutations)
1.0
0.8
0.6
0.4
0.2
0.0
Pt 3
Pt 2
Pt 1
Pt 4
Multiple primary (n=4)
Random pairs (n=24)
Matched Primary-Met (n=3)
B
Similarity Index (CNAs)
1.0
0.8
0.6
0.4
0.2
0.0
Pt 2
Pt 3
Pt 1
Pt 4
Multiple Primary (n=4)
Random Pairs (n=24)
Matched Primary-Met (n=3)

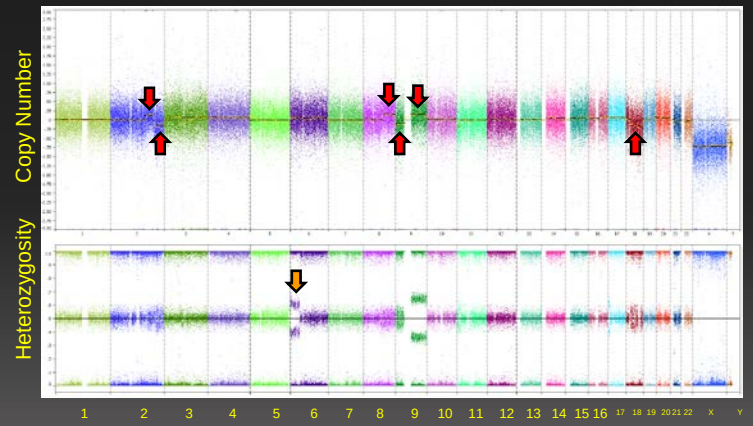
Scalp (MCC)



Zygoma (MCC)



Zygoma (SCC)



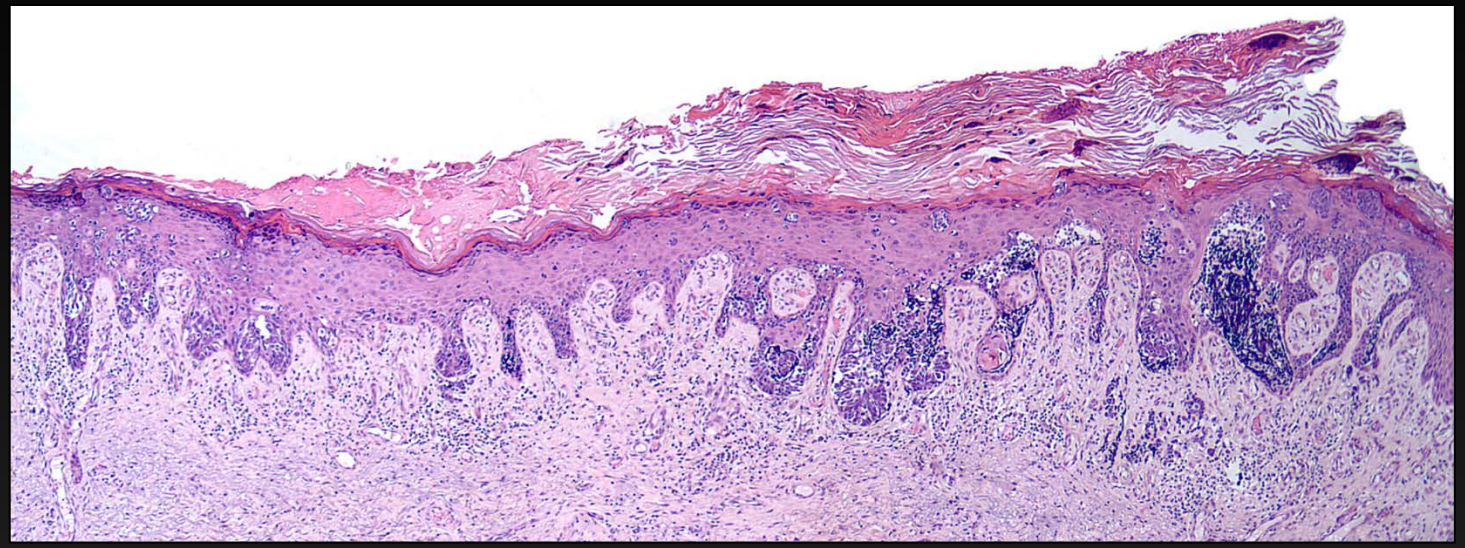
Shared copy gain or loss

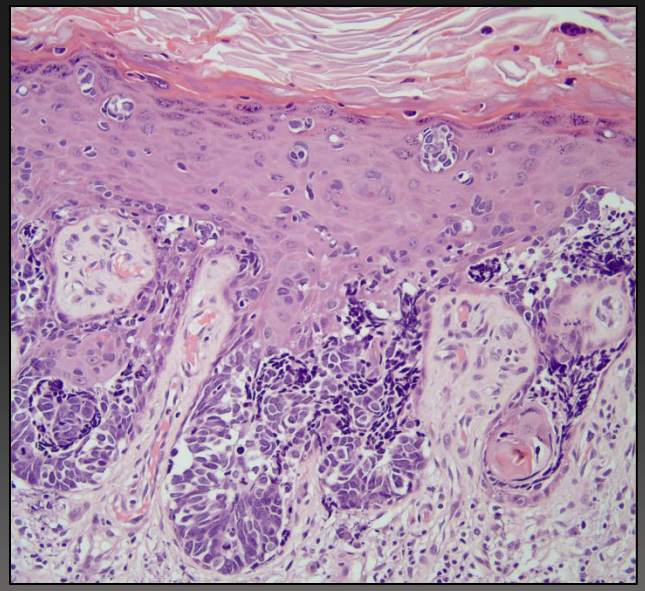
Shared copy neutral LOH

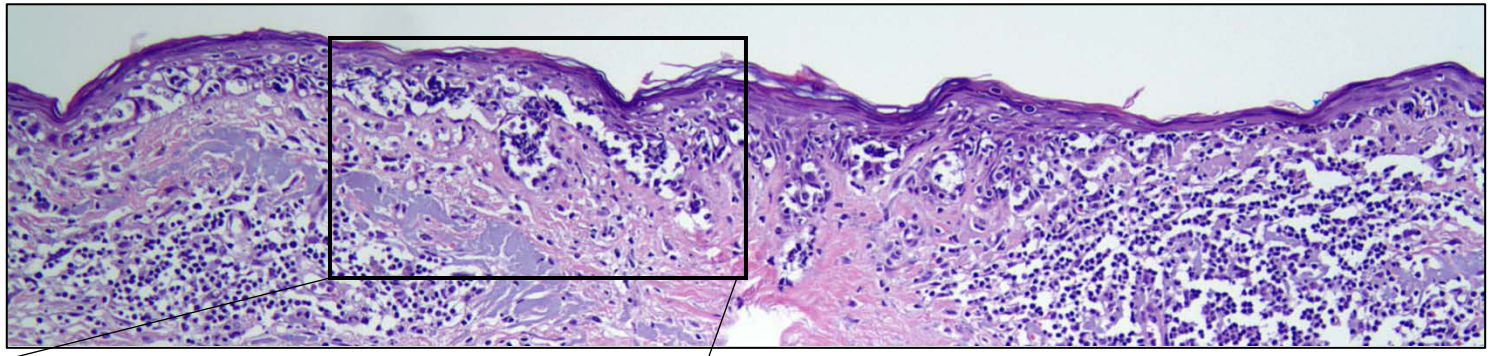
Distinct copy gain or loss

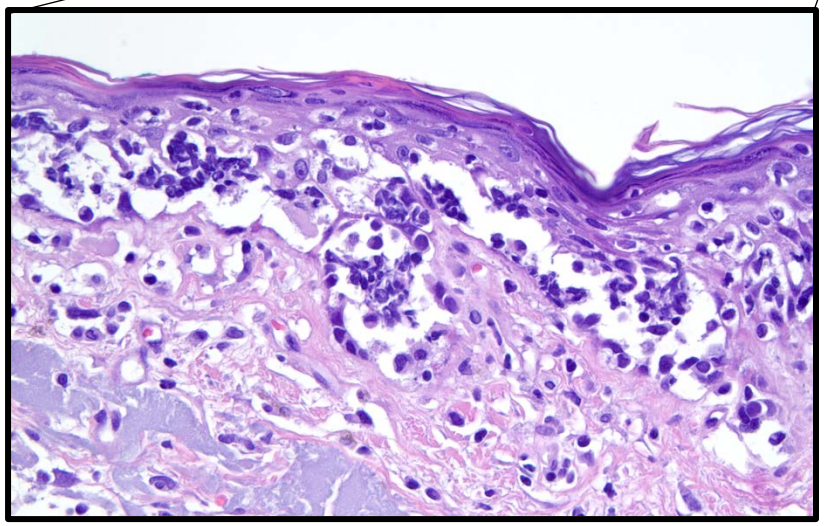
Distinct copy neutral LOH

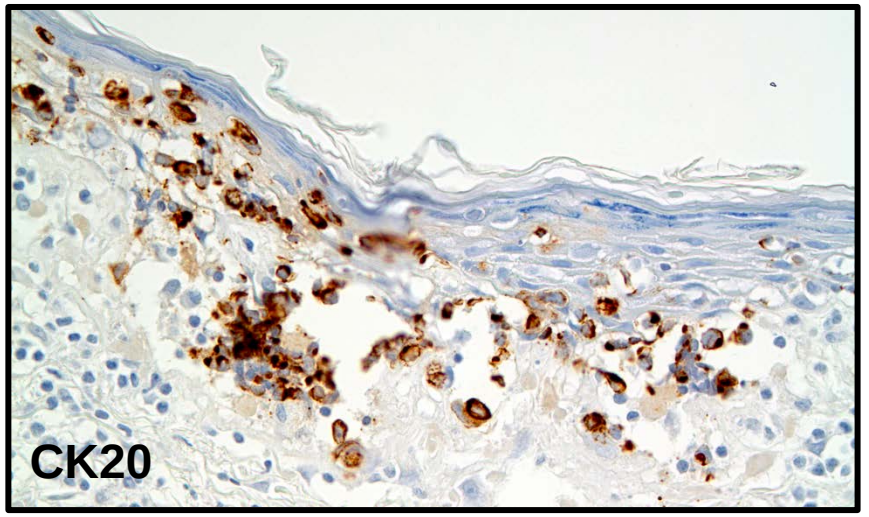
Epidermal Involvement by MCC

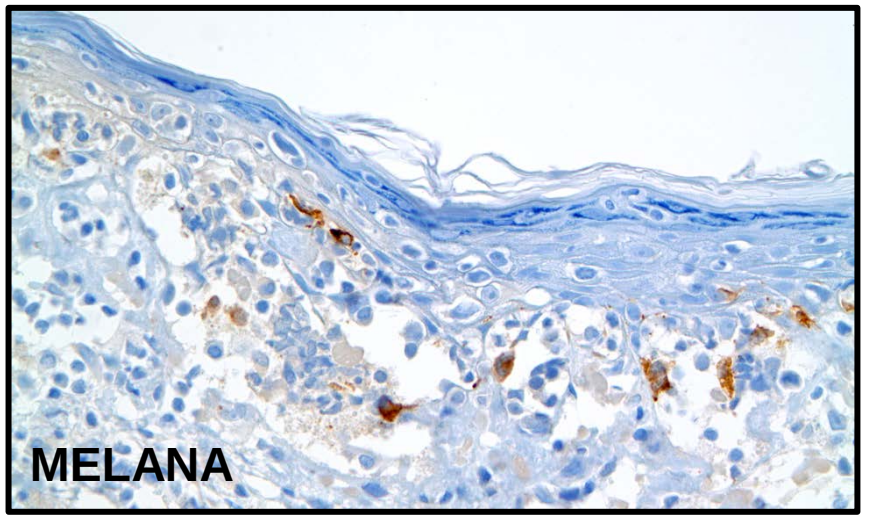












Intraepidermal MCC may mimic melanoma in situ