Case 1

Clinical Summary

- A 65 year-old gentleman presented with a 7-month history of multiple erythematous nodules on the face, neck, chest and extremities
- The nodules started on his chest and progressed to involve head, neck, trunk and extremities

Clinical Pictures

- Multiple erythematous/brown/purpuric nodules on the face, neck and chest
- Dense diffuse dermal infiltrate
No epidermal involvement

Medium to large atypical cells with hyperchromatic nuclei, irregular nuclear membranes and blastoid appearance

No expression of CD8 or CD20 in the lesional cells

The differential diagnosis includes:

A. Leukemia cutis
B. Mycosis fungoides, tumor stage
C. Primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoproliferative disorder
D. Blastic plasmacytoid dendritic cell neoplasm (BPDCN)

The most likely diagnosis is?

A. Leukemia cutis
B. Mycosis fungoides, tumor stage
C. Primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoproliferative disorder
D. Blastic plasmacytoid dendritic cell neoplasm (BPDCN)
Case Summary

- At presentation, he had BPDCN with involvement of skin, lymph nodes and bone marrow confirmed by skin and bone marrow biopsy as well as radiology studies (PET/CT).

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

Outline
- Introduction
- Clinico-pathological features
- General management
- SL-401/anti-CD123 therapy
- Treatment response

History

- Rare, clinically aggressive, hematologic malignant tumor (OS: 1–2yrs)
- Recognized as a distinct clinical entity, but unknown lineage
- Previously called:
  - blastic natural killer cell lymphoma
  - agranular CD4+ natural killer cell leukemia
  - agranular CD4+CD56+ hematodermic neoplasm
- WHO 2008: Named and classified as a neoplasm derived from precursors of plasmacytoid dendritic cells and grouped with acute myeloid related precursor neoplasms

Clinical Presentation

- Predominantly affects elderly males
  - Mean age of 61-67 years (M:F = ~3.3:1)
- Often presents with cutaneous lesions, progress to BM and LN involvement with leukemic dissemination
- Up to 20% of patients have concomitant BM involvement by another phenotypically distinct process, usually AML
- Skin lesions: usually present with asymptomatic solitary or multiple nodules, plaques or bruise-like areas

Histophenotypic Features

- Predominantly dermal diffuse atypical monocytic infiltrate with no epidermal involvement
- The lesional cells are medium to large with irregular nuclear membranes and vesicular chromatin (i.e., blastoid appearance)
- The lesional cells are:
  - Positive: CD123, CD4, CD56, and TCL1
  - Negative: CD3, CD8, CD20, and other lineage-specific myeloid or lymphoid markers

Management

- The optimal therapeutic approach to patients with BPDCN remains unclear, and most patients die of their disease despite intense therapeutic approaches
- Typical treatment is a combination of treatment regimens for acute leukemias
  - multi-agent chemotherapy (CHOP/hyperCVAD)
  - radiation therapy
  - stem cell transplantation
  - central nervous system prophylaxis
  - skin-directed treatment
- Our patient was treated with clinical trial SL-401 (anti-CD123 targeted therapy) #NCT00397579
New Targeted Therapy (Anti-CD123)

- **CD123 (interleukin-3 receptor):**
  - A cell-surface protein involved in the proliferation and differentiation of hematopoietic cells

- **SL-401 (anti-CD123):**
  - A recombinant fusion protein comprised of a diphtheria toxin with interleukin-3 (IL-3)
  - A promising new biologic targeted therapy
  - Directed at IL-3 receptor alpha subunit or CD123

### Before anti-CD123 treatment

### 5 months after anti-CD123 treatment

### Expression of CD123

- **Before treatment**
- **After anti-CD123 treatment**

### Response to SL-401 (anti-CD123)

- In a multicenter pilot trial of SL-401, five of nine patients with recurrent or chemotherapy-refractory BPDCN had a complete response and two had a partial response after just one cycle of SL-401

- The median response duration was 5 months (range, 1–20+ months)
Skin lesions before and after 4 months of treatment with SL-401

PET/CT scans before and after 6 months of treatment with SL-401 show shrinkage of involved inguinal lymph nodes (arrows)


Summary of SL-401

• Partial loss of CD123 expression in BPDCN after SL-401 therapy
• Most likely due to therapy effect (similar to loss of CD20 after Rituximab in DLBCL)
• Awareness of this immunohistochemical findings may prevent a misdiagnosis of this disease
• Follow up of these patients is ongoing to determine whether partial loss of CD123 is associated with prognosis

Patient Outcome

• Approximately 1 year after the initial treatment response, he developed recurrence of skin lesions and AML
• One year later, he developed widespread BPDCN including CNS involvement and passed away

Learning Points

• BPDCN is very aggressive
• Poor prognosis (overall survival 1–2 years)
• No standard therapy
• Systemic chemotherapy (Anti-CD123)
• Short remission
• Frequent recurrences
• High mortality

Case 2

Clinical Summary

• A 63-year-old man presented with a lesion on his right middle digit
• No known history of malignant neoplasm
• The clinical differential diagnosis included
  • Basal cell carcinoma
  • Melanoma in situ, lentigo maligna type
• Brown et al., Am J Dermatopathol, 2000
Predominantly intraepidermal basophilic tumor cells; distributed in nests and single units at all levels of the epidermis

Round to oval cells with basophilic scant cytoplasm, hyperchromatic nuclei and nuclear molding

The differential diagnosis includes:

A. Melanoma in situ  
B. Squamous cell carcinoma in situ  
C. Extramammary Paget disease  
D. Merkel cell carcinoma in situ  
E. Mycosis fungoides

The best diagnosis is:

A. Melanoma in situ  
B. Squamous cell carcinoma in situ  
C. Extramammary Paget disease  
D. Merkel cell carcinoma in situ  
E. Mycosis fungoides

Merkel Cell Carcinoma (MCC)

- First described in 1972 by Toker and was named “trabecular carcinoma” because of solid trabeculae arrangement of tumor cells
- The annual incidence of MCC in U.S. is increasing, with an estimated 1,600 new cases per year
- Elderly and immunocompromised patients with male predominance (age 62-84, M:F = 8:1)
- Most common primary sites: sun-damaged skin in head, neck, and extremities
Merkel Cell Carcinoma (MCC)
• A rare but aggressive primary cutaneous neuroendocrine carcinoma
• Exact cell of origin is still controversial
• Local recurrences and regional lymph node and/or distant metastases develop in ~33% of patients

Pathogenesis of MCC
• Main risk factors: Immunosuppression, UV radiation exposure, Merkel cell Polyomavirus (MCV) infection (~80%)
• MCV: a small, circular, non-enveloped, double-stranded DNA virus
• Patients with MCV-negative MCC have worse outcomes than those with MCV-associated MCC

Clinical presentation: non-specific
AEIOU
• A: asymptomatic/lack of tenderness
• E: expanding rapidly
• I: immune suppression
• O: older than 50 years &
• U: ultraviolet-exposed site on a person with fair skin

Histologic Features of MCC
• Predominantly dermal-based tumor
• Solid sheets and nests
• Small-medium, round to ovoid cells with hyperchromatic nuclei
• Multiple small nucleoli
• Scant amphophilic cytoplasm
• Numerous mitotic figures
• Apoptotic bodies

Phenotypic Features of MCC
• Positive:
  • Cytokeratin (CK20 dot-like, CK7: ~30%)
  • Neuroendocrine markers (Synaptophysin, Chrom)
  • Merkel cell polyoma virus (MCV)
• Differential diagnosis: metastatic small cell carcinoma of lung
  • Positive TTF-1 (exceptionally positive in MCC)
  • Negative CK20 (33% may express CK20 but exceptional in metastatic lesions)

Presence of Second Malignancy in Patients with MCC
• MCC: frequently associated with cutaneous and hematological malignancies, chiefly SCC and chronic lymphocytic leukemia (CLL)
• The presence of any second neoplasm, whether concurrent or not, conferred a poor prognosis
• Patients with both MCC and CLL have a dismal prognosis, with >50% overall mortality within the first 1.5 year after MCC diagnosis
• The role of MCV in CLL is still controversial although it was detected in ~27% of purified leukemic cells of CLL cases
Interesting case

- 65 year old male with history of CLL presented with a single 2 cm subcutaneous nodule near medial epicondyle
- Clinical Dx: adenopathy related to progressive CLL and treated with 2 cycles of fludarabine/cyclophosphamide/rituximab with no improvement

Take home message

- Merkel Cell carcinoma with partial B-cell blastic immunophenotype; a potential mimic of transformed CLL (diffuse large B-cell/Richter’s transformation) in the patients with known history of CLL (especially after treatment with rituximab)

Merkel Cell Carcinoma in situ (MCCIS)

- ≤18% of MCC have minor epidermal involvement in addition to the dermal tumor
- Strictly intraepidermal MCC (MCCIS) is extremely rare
- Mostly as an incidental histopathological finding in other cutaneous lesions
- SCC, actinic keratosis, seborrheic keratosis
- MCCIS, frequently present in the upper extremity (~55%)

Summary of Three Cases of Merkel Cell Carcinoma In Situ at MDACC

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Tumor Site</th>
<th>Clinical Presentation</th>
<th>Tumor Size, cm</th>
<th>CK20</th>
<th>EMA</th>
<th>Synaptophysin</th>
<th>Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74</td>
<td>M</td>
<td>Right side of nose</td>
<td>Rapidly growing nodule</td>
<td>0.6</td>
<td>perinuclear dot like</td>
<td>++</td>
<td></td>
<td>WLE, SLN</td>
<td>NED at 19 mo.</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>M</td>
<td>Right eyelid</td>
<td>Slow-growing nodule</td>
<td>0.7</td>
<td>perinuclear dot like</td>
<td>++</td>
<td></td>
<td>WLE</td>
<td>NED at 13 mo.</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>M</td>
<td>Right digit</td>
<td>Slow-growing nodule</td>
<td>0.8</td>
<td>cytoplasmic</td>
<td>N/A</td>
<td>+</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

EMA, epithelial membrane antigen; M, male; NA, not available; NED, no evidence of disease; SLN, sentinel lymph node biopsy; RT, radiation therapy; WLE, wide local excision.

Differential Diagnosis

- The distinction between MCCIS and other diseases can be difficult, especially on small biopsy samples with no invasive component
- Attention to the presence of the characteristic nuclear features associated with MCC cells and the use of immunohistochemical markers should lead to the correct diagnosis
Differential Diagnosis of Merkel Cell Carcinoma with Epidermal involvement

- Melanoma
- Extramammary Paget disease (EMPD)
- Pagetoid squamous cell carcinoma
- Sebaceous carcinoma
- Basal cell carcinoma
- Cutaneous T-cell lymphomas
- Epidermotropic metastases
- Langerhans cell histiocytosis
- Benign conditions, such as pagetoid dyskeratosis, clear cell papulosis

Melanoma in situ (MIS)

- More abundant cytoplasm containing melanin pigment and intranuclear cytoplasmic pseudo-inclusions
- Expression of melanocytic markers such as S-100 protein, Melan-A, HMB45, SOX10

Extramammary Paget Disease (EMPD)

- Abundant basophilic cytoplasm (highlighted with mucin and PASD)
- Positive CK7, and variable EMA and CEA staining

Squamous Cell Carcinoma in situ (SCCIS)

- Presence of desmosomes between the tumor cells
- Expression of high-molecular-weight keratin and p63, but lack of expression of neuroendocrine markers or labeling for CK20

Sebaceous Neoplasms

- Multivacuolated cytoplasm with intracytoplasmic lipid droplets and nuclear scalloping
- Expression of adipophilin, and lack of neuroendocrine markers or labeling for CK20

Basal Cell Carcinoma

- Atypical basaloid cells with peripheral palisading and peri-tumoral clefting
- Lack of expression of neuroendocrine markers or labeling for CK20
2 months later…

Moh's surgery

Forehead

55 y/o female

Biopsy

Key Points

- Merkel cell carcinoma in situ exists
- Can present in the absence of associated cutaneous neoplasms

1 month later…

• Recurrence of nodules in the frontal midline scalp
• PET-CT: nodal metastasis to cervical and parotid lymph nodes

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