Primary or Metastatic?

I. Melanocytic Neoplasms
II. Neuroendocrine Neoplasms
III. Sweat Gland Carcinomas

I. Melanocytic Neoplasms – Primary vs Metastatic
1. Primary Dermal (Nodular) Melanoma vs Metastasis
2. Epidermotropic Metastatic Melanoma vs Primary
3. Nevus/Melanocytoma vs Metastatic Melanoma
4. Nodal Nevus vs Metastatic Melanoma
5. Metastatic Melanoma vs Primary Soft Tissue Tumor
I.1 Metastatic vs Primary Nodular Melanoma

Melanoma Metastatic to Skin

Metastatic Melanoma?

Pathology:
- Mass in subcutis
- Multinodular growth
- Necrosis
- No nevus or melanoma in situ

Primary or Metastatic?
Staging of Melanoma: Clinical Context Matters

- Prior history of melanoma
- Clinical history of tumor
- Evidence from other clinical studies and follow-up
- Evidence from ancillary, especially molecular studies

Primary Dermal Melanoma – Original Report

- 11 of 1800 melanoma patients presented with solitary nodule and no associated precursor
- Initially thought to be metastatic
- Unusual high survival rate suggests that they may be primary tumors

Primary Dermal Melanoma

Definition:
- Melanoma in dermis and/or subcutis
- No associated in situ melanoma or nevus

Study:
- 7 cases with mean thickness of 7 mm
- 100% survival (mean FU of 41 months)
Melanoma Metastases to Skin

- Cutaneous metastases in the setting of prior melanoma are common
- A solitary dermal metastasis without a prior history of melanoma is exceedingly rare

Pathologic Clues for Metastatic Melanoma

- Odd silhouette
- Small diameter of lesion
- Collarette
- Associated LVI
I.2. Epidermotropic Metastatic Melanoma

• Melanoma metastatic to dermis may colonize epidermis

• Epidermal involvement is usually focal and does not extends beyond periphery of dermal nodule

• The metastatic tumor usually displays uniform high grade atypia

Primary or Metastatic Melanoma?

Epidermotropic Metastatic Melanoma
I.3. Melanocytic Nevus vs Metastatic Melanoma

- Blue nevus-like melanoma metastasis
- De novo proliferative nodule or melanocytoma vs metastasis
What is Your Diagnosis?

Blue Nevus-like Metastasis

BN-Like Metastasis
I.4: Nodal Nevus vs Metastatic Melanoma

- Features typical of nodal nevus
  - Located in fibrous tissue
  - Cytologically bland
  - Negative for HMB-45 and PRAME

- Features typical of metastatic melanoma
  - Located in nodal parenchyma
  - Cytologically atypical
  - Positive for HMB-45 and/or PRAME
Trabecular Nodal Nevus

What do these cells mean?

Capsular and Subcapsular Nodal Nevus
I.5: Metastatic Melanoma vs Soft Tissue Tumor

- Metastatic melanoma vs benign soft tissue tumor
- Metastatic melanoma vs sarcoma
- Metastatic melanoma vs neurocristic neoplasm
  - Clear cell sarcoma
  - Melanotic schwannian neoplasm
  - Other neurocristic tumors

Metastatic Melanoma or Not?
Clinical History

• Dermal nodule, biopsied to r/o DF
• No h/o prior or concurrent melanoma

Metastatic Melanoma or Not?

Reported in 2016
“Neurocristic tumor of uncertain malignant potential”

Molecular Analysis in 2019
• CRTCL-TRIM11 Fusion
What is your diagnosis?

44 yo man reported to have metastatic melanoma

Mutation Analysis

POSITIVE FOR THE FOLLOWING SOMATIC ALTEATIONS IN THE INVESTIGATIONAL PANEL:
1. BRIIT (NRAS) (p.T257K)
2. BRIIT (NRAS) (p.Q61R)
3. BRIIT (NRAS) (p.Q61K)
4. BRIIT (NRAS) (p.Q61L)
5. BRIIT (NRAS) (p.Q61P)
6. BRIIT (NRAS) (p.Q61S)
7. BRAF (V600E)
8. BRAF (V600K)
9. BRAF (V600L)
10. BRAF (V600M)
11. BRAF (V600N)
12. BRAF (V600Q)
13. BRAF (V600R)
14. BRAF (V600S)
15. BRAF (V600T)
16. BRAF (V600V)
17. BRAF (V600W)
18. BRAF (V600X)
19. BRAF (V600Y)
20. BRAF (V600Z)
21. BRAF (V600AA)
22. BRAF (V600AB)
23. BRAF (V600AC)
24. BRAF (V600AD)
25. BRAF (V600AE)
26. BRAF (V600AF)
27. BRAF (V600AG)
28. BRAF (V600AH)
29. BRAF (V600AI)
30. BRAF (V600AJ)
31. BRAF (V600AK)
32. BRAF (V600AL)
33. BRAF (V600AM)
34. BRAF (V600AN)
35. BRAF (V600AO)
36. BRAF (V600AP)
37. BRAF (V600AQ)
38. BRAF (V600AR)
39. BRAF (V600AS)
40. BRAF (V600AT)
41. BRAF (V600AU)
42. BRAF (V600AV)
43. BRAF (V600AW)
44. BRAF (V600AX)
45. BRAF (V600AY)
46. BRAF (V600AZ)
47. BRAF (V600BA)
48. BRAF (V600BB)
49. BRAF (V600BC)
50. BRAF (V600BD)
51. BRAF (V600BE)
52. BRAF (V600BF)
53. BRAF (V600BG)
54. BRAF (V600BH)
55. BRAF (V600BI)
56. BRAF (V600BJ)
57. BRAF (V600BK)
58. BRAF (V600BL)
59. BRAF (V600BM)
60. BRAF (V600BN)
61. BRAF (V600BO)
62. BRAF (V600BP)
63. BRAF (V600BQ)
64. BRAF (V600BR)
65. BRAF (V600BS)
66. BRAF (V600BT)
67. BRAF (V600BU)
68. BRAF (V600BV)
69. BRAF (V600BW)
70. BRAF (V600BX)
71. BRAF (V600BY)
72. BRAF (V600BZ)
73. BRAF (V600CA)
74. BRAF (V600CB)
75. BRAF (V600CC)
76. BRAF (V600CD)
77. BRAF (V600CE)
78. BRAF (V600CF)
79. BRAF (V600CG)
80. BRAF (V600CH)
81. BRAF (V600CI)
82. BRAF (V600CJ)
83. BRAF (V600CK)
84. BRAF (V600CL)
85. BRAF (V600CM)
86. BRAF (V600CN)
87. BRAF (V600CO)
88. BRAF (V600CP)
89. BRAF (V600CQ)
90. BRAF (V600CR)
91. BRAF (V600CS)
92. BRAF (V600CT)
93. BRAF (V600CU)
94. BRAF (V600CV)
95. BRAF (V600CW)
96. BRAF (V600CX)
97. BRAF (V600CY)
98. BRAF (V600CZ)
99. BRAF (V600DA)
100. BRAF (V600DB)
101. BRAF (V600DC)
102. BRAF (V600DD)
103. BRAF (V600DE)
104. BRAF (V600DF)
105. BRAF (V600DG)
106. BRAF (V600DH)
107. BRAF (V600DI)
108. BRAF (V600DJ)
109. BRAF (V600DK)
110. BRAF (V600DL)
111. BRAF (V600DM)
112. BRAF (V600DN)
113. BRAF (V600DO)
114. BRAF (V600DP)
115. BRAF (V600DQ)
116. BRAF (V600DR)
117. BRAF (V600DS)
118. BRAF (V600DT)
119. BRAF (V600DU)
120. BRAF (V600DV)
121. BRAF (V600DW)
122. BRAF (V600DX)
123. BRAF (V600DY)
124. BRAF (V600DZ)
125. BRAF (V600EA)
126. BRAF (V600EB)
127. BRAF (V600EC)
128. BRAF (V600ED)
129. BRAF (V600EE)
130. BRAF (V600EF)
131. BRAF (V600EG)
132. BRAF (V600EH)
133. BRAF (V600EI)
134. BRAF (V600EJ)
135. BRAF (V600EK)
136. BRAF (V600EL)
137. BRAF (V600EM)
138. BRAF (V600EN)
139. BRAF (V600EO)
140. BRAF (V600EP)
141. BRAF (V600EQ)
142. BRAF (V600ER)
143. BRAF (V600ES)
144. BRAF (V600ET)
145. BRAF (V600EU)
146. BRAF (V600EV)
147. BRAF (V600EW)
148. BRAF (V600EX)
149. BRAF (V600EY)
150. BRAF (V600EZ)
151. BRAF (V600FA)
152. BRAF (V600FB)
153. BRAF (V600FC)
154. BRAF (V600FD)
155. BRAF (V600FE)
156. BRAF (V600FF)
157. BRAF (V600FG)
158. BRAF (V600FH)
159. BRAF (V600FI)
160. BRAF (V600FJ)
161. BRAF (V600FK)
162. BRAF (V600FL)
163. BRAF (V600FM)
164. BRAF (V600FN)
165. BRAF (V600FO)
166. BRAF (V600FP)
167. BRAF (V600FQ)
168. BRAF (V600FR)
169. BRAF (V600FS)
170. BRAF (V600FT)
171. BRAF (V600FU)
172. BRAF (V600FV)
173. BRAF (V600FW)
174. BRAF (V600FX)
175. BRAF (V600FY)
176. BRAF (V600FZ)
177. BRAF (V600GA)
178. BRAF (V600GB)
179. BRAF (V600GC)
180. BRAF (V600GD)
181. BRAF (V600GE)
182. BRAF (V600GF)
183. BRAF (V600GG)
184. BRAF (V600GH)
185. BRAF (V600GI)
186. BRAF (V600GJ)
187. BRAF (V600GK)
188. BRAF (V600GL)
189. BRAF (V600GM)
190. BRAF (V600GN)
191. BRAF (V600GO)
192. BRAF (V600GQ)
193. BRAF (V600GR)
194.
I.5: Consider Primary Soft Tissue Tumor

- **Clinical context:**
  - Absence of clinical history of prior or concurrent melanoma
  - Tumor in soft tissue (not lymph node); solitary
  - Young patient

- **Pathology**
  - Absence of marked nuclear pleomorphism
  - Lack of numerous mitoses
  - Misc clues (wreath like giant cells, psammomatous calcifications, Verocay)

- **Molecular Studies**
  - Translocations/fusions
  - Distinct mutations

II. Neuroendocrine Neoplasms

- Merkel cell carcinoma

- Carcinoid-like tumors
Merkel Cell Carcinoma - Pathology

MCC vs Metastatic Small Cell Carcinoma

MCC:
- Negative for TTF1
- Positive for NF
- Positive for CM2B4

Metastatic Small Cell Ca:
- Positive for TTF1
- Negative for NF
- Negative for CM2B4

Merkel cell carcinoma

Which is primary and which is metastatic?
Primary vs Metastatic MCC to Skin

- Clinical history/context is essential
- Histologic features favoring a primary tumor
  - Associated intraepidermal MCC
  - Associated SCC or other tumor
  - Associated dense inflammation
- CGH/Mutation analysis may help

Primary Cutaneous Neuroendocrine Carcinoma (NEC)

Epidermotropic MCC | SCC in situ and NEC | Combined SCC and NEC
Multiple primary MCCs?
II.2: Carcinoid-like Neoplasm

Positive for
- Cytokeratins
- Chromogranin

Metastatic Neuroendocrine Tumor

Metastasis to Skin

Primary Gastrointestinal NET

III. Adenocarcinoma: Primary vs Metastasis

- Microscopic evidence in support of a primary neoplasm
  - Associated adenoma (e.g., spiradenocarcinoma)
  - Distinct pathologic findings of the carcinoma itself (e.g., EMP5GCA)

- Microscopic evidence in support of a metastasis
  - Distinct microscopic features of the carcinoma itself (e.g., cilia)
  - Distinct immunophenotype (e.g., positive for TTF1)
III. Adenocarcinoma: Primary vs Metastasis

- Tumors not distinguishable by morphology
  - Ductal carcinoma, NOS
  - Carcinoma with mucinous features
  - Basaloid adenocarcinoma
  - Poorly differentiated adenocarcinoma

- Diagnosable with ancillary studies
- Diagnosable with clinical context

Adenocarcinoma associated with adenoma

Spiradenoma  Spiradenocarcinoma

Porocarcinoma (Carcinoma ex Poroma)
Distinct Primary Cutaneous Adenocarcinomas

- Microcystic adnexal carcinoma
- Cribriform carcinoma
- Endocrine mucin-producing sweat gland carcinoma
- Hyalinizing clear cell carcinoma
- Secretory carcinoma
- Adenoid Cystic Carcinoma

Microcystic Adnexal Carcinoma
Sclerosing Sweat Duct Carcinoma

Clinical
- Firm nodule or plaque with predilection for nasolabial and periorbital skin
- Local recurrences common

Pathology
- Syringoma-like
- Keratocystic and ductal
- Sclerosing duct

Differential Dx
- DTE, BCC
- SCC

Microcystic Adnexal Carcinoma

Clinical
- Firm nodule or plaque with predilection for nasolabial and periorbital skin
- Local recurrences common

Pathology
- Syringoma-like
- Keratocystic and ductal
- Sclerosing duct

Differential Dx
- DTE, BCC
- SCC
Desmoplastic (Adeno) SCC

Primary Cutaneous Cribriform Carcinoma

- First described by Requena in 1998
- Clinical Findings
  - Middle aged adults
  - Extremities
  - Low-grade behavior
- Pathology
  - Dermal proliferation of cords, tubules, cribiform and solid nests – sieve like
  - Low-grade nuclear features
  - Stromal desmoplasia
  - IHC: CK7, CK5/6, S100P, CD117
### Primary vs Metastatic Cribriform Carcinoma

<table>
<thead>
<tr>
<th>Primary Cribriform</th>
<th>Metastatic Adenocarcinoma with Cribriform Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>• Isolated small papule, no h/o prior</td>
<td>• History of carcinoma</td>
</tr>
<tr>
<td></td>
<td>or concurrent adenocarcinoma</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td><strong>Pathology</strong></td>
</tr>
<tr>
<td>• Low grade nuclei</td>
<td>• High grade nuclei</td>
</tr>
<tr>
<td>• Mitoses are rare</td>
<td>• Mitoses common</td>
</tr>
<tr>
<td>• Necrosis absent</td>
<td>• Apoptosis common</td>
</tr>
<tr>
<td>• No LVI</td>
<td>• LVI may be present</td>
</tr>
</tbody>
</table>

### Endocrine Mucin-Producing Sweat Gland Carcinoma

<table>
<thead>
<tr>
<th><strong>Clinical</strong></th>
<th><strong>Histology</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Typically periocular</td>
<td>• Intra- and peritumoral mucin</td>
</tr>
<tr>
<td>• Low grade neoplasm</td>
<td>• Solid and cribriform growth</td>
</tr>
<tr>
<td><strong>IHC</strong></td>
<td><strong>IHC</strong></td>
</tr>
<tr>
<td>• CK7, ER, PR, INSM1, chromo, synaptophysin</td>
<td>• CK7, ER, PR, INSM1, chromo, synaptophysin</td>
</tr>
</tbody>
</table>
Hyalinizing Clear Cell Carcinoma

72M, nose

Hyalinizing Clear Cell Carcinoma

Hyalinizing Stroma
Molecular: EWSR1-ATF1
Clear Cells

Diagnosis: Hyalinizing Clear Cell Carcinoma

- Infiltrative growth of clear and basaloid cells with hyalinized stroma
- EWSR1 – ATF1 fusion
- Typically low grade neoplasms
- Most report cases are of salivary gland origin
Secretory Carcinoma

Variant of apocrine carcinoma
- Breast
- Salivary Gland
- Skin
- Other

Usually low grade neoplasm

Typically associated with a Gene Fusion
- ETV6 - NTRK

Secretory Carcinoma

Secretory Carcinoma – Gene Fusions


Secretory Carcinoma of the Skin Harboring ETV6 Gene Fusions: A Genealogic Analogue to Secretory Carcinomas of the Breast and Salivary Glands

Primary Cutaneous Adenoid Cystic Carcinoma

- Clinical
  - Slow growing neoplasm with indistinct features
  - Middle aged to elderly people; predilection for scalp
  - Usually low grade neoplasm

- Pathology
  - Cribriform growth of basaloid epithelial and myoepithelial cells
  - Hyaline material, mucin
  - IHC: CD117, EMA
  - Molecular: MYB Alterations

Distant Metastases from Cutaneous ACC
Salivary Gland ACC Metastatic to Skin

Extracutaneous Adenoid Cystic Carcinoma (ACC)

- Multiple possible sites of origin; most often salivary glands
- PNI and local recurrences common
- Distant metastases may occur
- Persson et al PNAS 2009;106:18740-4: MYB-NFIB Fusions
MYB Alternations in Cutaneous ACC

Prognostic Features of ACC

ACC in the Dermis: Primary or Metastatic?

- History of prior or concurrent ACC
- Beware of anatomic site (cheek, breast)
- Small, confined to the dermis or large, involving subcutis?
- Uniform low grade appearance with tubular and cribriform growth vs high grade histology (solid growth, atypia, necrosis, mitoses)
Metastatic Carcinomas with Distinct Features

- Renal cell carcinoma
- Pulmonary adenocarcinoma
- Thyroid carcinoma

Metastasis with Distinct Features

![Metastatic Renal Cell Carcinoma](image)

Primary neoplasm or metastatic?

![Primary neoplasm or metastatic?](image)
Metastasis with Distinct IHC

Tumors with indistinct features and IHC: “Adenocarcinoma, poorly differentiated”
Mucinous Carcinoma

Primary Cutaneous Mucinous Carcinoma

Mucinous Carcinoma - Cytology
Mucinous Carcinoma


- Requena & Sangueza (Cutaneous Adnexal Neoplasms; Springer, 2017):
  - Reviewed 287 cases of reported mucinous carcinoma
  - 80% of patients are between 50-60 yrs of age
  - Predilection for head and neck area, especially eyelids
  - Low grade neoplasm
    - 21/287 with regional LN mets
    - 9/287 with distant mets

Mixed Mucinous Carcinoma

Stroma-Rich, Cell-Poor

Stroma-Poor, Cell-Rich
Mucinous (Colloid) Mammary Carcinoma

MSKCC Experience
- 849 patients with mucinous mammary carcinoma
- 120 metastasized (15%)
- Most common sites of metastasis
  - Lung
  - Lymph node
- Not a single case of first cutaneous metastasis

Metastasizing Mucinous Mammary Carcinoma

Mixed Mucinous Carcinoma

More tumor than stroma stroma
More mucinous stroma than tumor
Metastasis from Mammary Mucinous Ca

![Image 1](image1.jpg)

FIG. 1. Mucinous carcinoma of eccrine glands showing nests of tumor cells floating in mucin lakes (hematoxylin and eosin x 100).

Metastasizing Cutaneous Mucinous Carcinoma

![Image 2](image2.jpg)

FIG. 2. Mucinous carcinoma of eccrine glands. Nests in a solid area show uniform cells with vesicular nuclei and glandular pattern in areas (hematoxylin and eosin x 400).

Mucinous Carcinoma — Primary vs Metastatic

- Requena & Sangueza in Cutaneous Adnexal Neoplasms, 2017; p326:
  - “The majority of the mucinous carcinomas involving the skin are metastatic”
  - “In any patient with mucinous ca of the skin, it is important to r/o metastasis”

- MSKCC Experience
  - All pure mucinous carcinomas seen in the skin have been primary
  - Metastatic carcinomas to the skin are mixed mucinous carcinomas or misc. adenocarcinomas with mucinous features

Mucinous Signet Ring Cell Carcinoma

- Colorectal Signet Ring Cell Mucinous Carcinoma Metastatic to Skin

Metastatic AdenoCA with Mucinous Features

- [Imagery]
Metastasizing Gastric Carcinoma

Basaloid Adenocarcinoma - Pathology

Immunophenotype

Positive for
- CK7
- EMA
- CD117

Negative for
- ER
- PR
- HER2Neu
- Gata3
Clinical History

Pathology of Bone Lesion

Pathology of Prior Breast Biopsy
Final Diagnosis: Metastatic Breast Cancer

What is Your Diagnosis?

What is Your Diagnosis?
Original Pathology Interpretation

CLINICAL INFORMATION:
A skin lesion arose on the back of the right arm of a patient with hepatozellulare carcinoma and was excised. Microscopy revealed a subcutaneous lesion with ill-defined borders and areas of necrosis. The lesion was composed of pleomorphic cells with abundant cytoplasm and hyperchromatic nuclei. The findings are consistent with a malignant neoplasm.

DIAGNOSIS:
Metastatic Cholangiocarcinoma

Work-up of Adenocarcinoma in Dermis

- Clinical history is paramount
- Review of entire tumor may provide clues (e.g., associated adenoma)
- Ancillary studies can help, but not always
- Tumors with features that do not fit a known entity may be metastases
- Comparative pathology (H&E, IHC, molecular) is important