Challenging Cases in Endocrine/Neuroendocrine Pathology
(Catarina said…. “a lung case”)

Marco Volante

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Clinical history

- Female patient, aged 53
- Moderate smoker
Clinical history

✓ March 2018:

mild fever and cough; CT imaging revealed a single lung parenchymal lesion in the left upper lobe, 27 mm in size, associated with mediastinal lymph node involvement and liver metastasis

TRU-CUT 18G lung biopsy performed (slide #1)
Microscopic findings (sample #1)
Microscopic findings (sample #1)
Microscopic findings (sample #1)
Immunophenotype (sample #1)
Immunophenotype (sample #1)

TTF-1
Immunophenotype (sample #1)

Ki-67: heterogeneous, up to 20% in hot spots
Summary of pathological findings (sample #1)

✓ small cells
✓ uniform, no significant cytological atypia, rare nucleoli
✓ no mitotic figures
✓ no necrosis
✓ nesting arrangement in a fibrotic stroma
✓ CgA diffusely positive
✓ “moderate” (high?) proliferation index
Neuroendocrine neoplasm with well-differentiated morphology (carcinoid-type) and moderate/high proliferation index
Discussion
(sample #1)

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Smoking Status</th>
<th>Location</th>
<th>Size (mm)</th>
<th>Mitotic Count (10 HPF)</th>
<th>Margin Status</th>
<th>Stage</th>
<th>Chemotherapy for Metastasis</th>
<th>Outcome (Follow-up Period)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>Never-smoker</td>
<td>Central (EB)</td>
<td>50</td>
<td>47</td>
<td>R0</td>
<td>1B</td>
<td>No</td>
<td>DOD, mediastinal metastasis (84 mo)</td>
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<tr>
<td>2</td>
<td>M</td>
<td>Smoker</td>
<td>Central (EB)</td>
<td>40</td>
<td>61</td>
<td>R0</td>
<td>1B</td>
<td>Platinum based (no response)</td>
<td>DOD, liver metastasis (16 mo)</td>
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<tr>
<td>3</td>
<td>M</td>
<td>Smoker</td>
<td>Peripheral</td>
<td>20</td>
<td>23</td>
<td>R0</td>
<td>1B</td>
<td>No</td>
<td>DOD, liver metastasis (22 mo)</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>Never-smoker</td>
<td>Peripheral</td>
<td>14</td>
<td>16</td>
<td>R0</td>
<td>2A</td>
<td>Platinum based (no response)</td>
<td>DOD, mediastinal metastasis (44 mo)</td>
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<tr>
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<td>Central (EB)</td>
<td>20</td>
<td>17</td>
<td>R0</td>
<td>1B</td>
<td>No</td>
<td>AWD, liver metastasis (77 mo)</td>
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<tr>
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<td>Peripheral</td>
<td>24</td>
<td>27</td>
<td>R0</td>
<td>1A</td>
<td>N/A</td>
<td>DOD, no recurrence (46 mo)</td>
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<tr>
<td>7</td>
<td>F</td>
<td>Never-smoker</td>
<td>Peripheral</td>
<td>12</td>
<td>15</td>
<td>R0</td>
<td>1A</td>
<td>CAPTEM (response)</td>
<td>AWD, liver metastasis (62 mo)</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>Smoker</td>
<td>Central</td>
<td>37</td>
<td>13</td>
<td>R0</td>
<td>3A</td>
<td>No</td>
<td>DOD, intraperitoneal met (22 mo)</td>
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<tr>
<td>9</td>
<td>M</td>
<td>Ex-smoker</td>
<td>Peripheral</td>
<td>68</td>
<td>11</td>
<td>R0</td>
<td>2B</td>
<td>CAPTEM (no response)</td>
<td>AWD, liver and bone metastasis (38 mo)</td>
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<tr>
<td>10</td>
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<td>Ex-smoker</td>
<td>Peripheral</td>
<td>15</td>
<td>15</td>
<td>R0</td>
<td>4</td>
<td>CAPTEM (response)</td>
<td>AWD, liver metastasis (39 mo)</td>
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<td>Peripheral</td>
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<td>41</td>
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<td>3A</td>
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<td>Smoker</td>
<td>Peripheral</td>
<td>20</td>
<td>14</td>
<td>R1</td>
<td>4</td>
<td>Platinum based (no response)</td>
<td>DOD, bone metastasis (81 mo)</td>
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</table>

High-grade Neuroendocrine Carcinoma of the Lung With Carcinoid Morphology

Discussion

**(Sample #1)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ki-67 &lt; 4% (#147)</th>
<th>Ki-67 4–9% (#60)</th>
<th>Ki-67 ≥10% (#32)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M</td>
<td>66</td>
<td>18</td>
<td>16</td>
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<tr>
<td></td>
<td>F</td>
<td>81</td>
<td>42</td>
<td>16</td>
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<tr>
<td>Age</td>
<td>Median</td>
<td>56</td>
<td>55</td>
<td>64</td>
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<tr>
<td>Histological type</td>
<td>TC</td>
<td>122</td>
<td>41</td>
<td>8</td>
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<td></td>
<td>AC</td>
<td>25</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>pT</td>
<td>pT1–2</td>
<td>133</td>
<td>56</td>
<td>26</td>
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<tr>
<td></td>
<td>pT3–4</td>
<td>14</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>pN</td>
<td>pN0</td>
<td>113</td>
<td>49</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>pN+</td>
<td>28</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Ki-67 pattern</td>
<td>Homogeneous</td>
<td>80</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Heterogeneous</td>
<td>13</td>
<td>8</td>
<td>11</td>
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<tr>
<td>Vascular invasion</td>
<td>Present</td>
<td>34</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>101</td>
<td>33</td>
<td>11</td>
</tr>
<tr>
<td>Pleura</td>
<td>PL0</td>
<td>100</td>
<td>28</td>
<td>20</td>
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<tr>
<td></td>
<td>PL+</td>
<td>3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Patient status</td>
<td>NED/DOC</td>
<td>127</td>
<td>51</td>
<td>20</td>
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<tr>
<td></td>
<td>AWD/DOD</td>
<td>11</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Survival data</td>
<td>Median TTP (months)</td>
<td>Undefined</td>
<td>Undefined</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td>Median OS (months)</td>
<td>244</td>
<td>Undefined</td>
<td>122</td>
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</tbody>
</table>

Caterina Marchiò¹,², Gaia Gatti³, Federica Massa², Luca Bertero¹,², Pierluigi Filoso⁴, Giuseppe Pelosi⁵,⁶, Paola Cassoni¹,², Marco Volante⁵,⁷, Mauro Papotti²,⁷

Distinctive pathological and clinical features of lung carcinoids with high proliferation index.
Discussion (sample #1)

<table>
<thead>
<tr>
<th></th>
<th>Total, n (%)</th>
<th>WD-NEN, n (%)</th>
<th>PD-NEN, n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ki67 ≤20%</td>
<td>Ki67 &gt;20%</td>
<td>WD-NEN Ki67 ≤20% vs. Ki67 &gt;20%</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>Months</td>
<td>68</td>
<td>108</td>
<td>68</td>
</tr>
<tr>
<td>At 2 years</td>
<td>%</td>
<td>59</td>
<td>96</td>
<td>71</td>
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<tr>
<td>At 5 years</td>
<td>%</td>
<td>50</td>
<td>91</td>
<td>54</td>
</tr>
<tr>
<td>Overall survival</td>
<td>Mean</td>
<td>Months</td>
<td>85</td>
<td>75</td>
</tr>
<tr>
<td>At 2 years</td>
<td>%</td>
<td>73</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>At 5 years</td>
<td>%</td>
<td>57</td>
<td>91</td>
<td>50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Total, n (%)</th>
<th>WD-NEN, n (%)</th>
<th>PD-NEN, n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ki67 ≤20%</td>
<td>Ki67 &gt;20%</td>
<td>WD-NEN Ki67 ≤20% vs. Ki67 &gt;20%</td>
</tr>
<tr>
<td>Total n (%)</td>
<td>244 (100)</td>
<td>52 (22)</td>
<td>7 (3)</td>
<td></td>
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<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>39 (16)</td>
<td>39 (75)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>20 (8)</td>
<td>13 (25)</td>
<td>7 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Clinicopathological Profiling of Lung Carcinoids with a Ki67 Index >20%

Atsuko Kasajima* c  Björn Konukiewitz*  Naomi Oka* d  Hiroyoshi Suzuki* d  
Akira Sakurada*  Yoshinori Okada*  Toru Kameya*  Yuichi Ishikawa*  
Hironobu Sasano*  Wilko Weichert* b  Günter Klöppel*
Discussion (sample #1)

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Ki67</th>
<th>3.3 (0.2–16)</th>
<th>29 (24–37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homogenous</td>
<td>58 (0.2–99)</td>
<td>3 (43)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneous</td>
<td>217 (89)</td>
<td>4 (57)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ki-67</th>
<th>Ki-67 &lt;4</th>
<th>Ki-67 4–9</th>
<th>Ki-67 &gt;/=10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>heterogeneous</td>
<td>homogeneous</td>
<td></td>
</tr>
<tr>
<td>p=0.011</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
June 2018: diagnostic mediastinoscopy for sub-staging purposes with multiple sampling of sub-aortic lymph nodes (slide #2).
Microscopic findings (sample #2)
Microscopic findings (sample #2)
Microscopic findings (sample #2)
Immunophenotype (sample #2)
Immunophenotype (sample #2)
Immunophenotype (sample #2)

CgA
Immunophenotype (sample #2)
Immunophenotype (sample #2)

Ki-67: heterogeneous, up to 15% in hot spots
Summary of pathological findings (sample #2)

- small to intermediate cells
- mild cytological atypia in some areas with rare nucleoli
- small nests in a fibrotic stroma
- CgA diffusely positive
- “moderate” proliferation index
Lymph node involvement from a neuroendocrine neoplasm with well-differentiated morphology and moderate proliferation index coexistent with acinar adenocarcinoma
SPECTRUM OF LUNG NEUROENDOCRINE NEOPLASMS

CARCINOID
(TC)AC
with high
Ki-67

(LC)NEC
With carcinoid
morphol.

NEC
(small/large
cell types)

NSCLC

COMBINED
Olofson AM, Tafe LJ. 
A case of a primary lung cancer comprised of adenocarcinoma and atypical carcinoid tumor with both components harboring BRAF p.V600E mutation. 
Exp Mol Pathol. 2018;104:26-28

Nilforoshan M, Matus IA. 
Combined Typical Carcinoid-Adenocarcinoma Lung Tumor. 
Clinical history

Molecular testing performed because of the ADCA component:
PD-L1: negative (TPS score 0)
EGFR, ALK, ROS1: negative

Chemotherapy followed with no surgery because of the advanced disease stage
Clinical history

✓ May 2019:

disease progression with the left upper lobe lung lesion increasing in size up to 65 mm, increase in the number of liver lesions and onset of adrenal metastases.

TRU-CUT 18G biopsy performed for a new tissue evaluation of the lung lesion (same site of previous biopsy) (slide #3).
Microscopic findings (sample #3)
Microscopic findings (sample #3)
Microscopic findings (sample #3)
Immunophenotype (sample #3)

TTF-1
Ki-67: heterogeneous, up to 60% in hot spots
Summary of pathological findings (sample #3)

- large cells
- presence of cytological atypia and nucleoli
- larger nests with organoid pattern
- mitotic/apoptotic figures and focal necrosis
- CgA positive, but less diffuse
- high proliferation index
Microscopic findings (sample #1 vs #3)
Diagnosis (sample #3)

High grade lung neuroendocrine neoplasm (large cell neuroendocrine carcinoma) progressing from a highly proliferative lung carcinoid (secondary?)
Next-Generation Sequencing of Pulmonary Large Cell Neuroendocrine Carcinoma Reveals Small Cell Carcinoma-like and Non-Small Cell Carcinoma-like Subsets

Natasha Rekhtman¹, Maria C. Pietanza², Matthew D. Hellmann³, Jarushka Naidoo⁴, Arshi Arora³, Helen Won⁴, Darragh F. Halpenny⁵, Hangjun Wang⁶, Shaozhou K. Tian¹, Anya M. Litvak⁷, Paul K. Paik², Alexander E. Drilon⁸, Nicholas Socci⁹, John T. Poirier², Ronglai Shen², Michael F. Berger¹, Andre L. Moreira¹, William D. Travis¹, Charles M. Rudin², and Marc Ladanyi¹,²

Clin Cancer Res; 22(14) July 15, 2016
Most high-grade neuroendocrine tumours of the lung are likely to secondarily develop from pre-existing carcinoids: innovative findings skipping the current pathogenesis paradigm.

Discussion (sample #3)

High-grade neuroendocrine lung tumors

LCNEC

Type I LCNECs

Type II LCNECs

SCLC

Genomic profile

TP53mut + STK11/KEAP1mut

TP53mut + RB1mut

TP53mut + RB1mut

Transcriptional profile

ASCL1high

DLL3high

NOTCHlow

ASCL1low

DLL3low

NOTCHhigh

ASCL1high

DLL3high

NOTCHlow

NATURE COMMUNICATIONS | (2018)9:1048

Immunophenotype (sample #3)

hASH-1
Immunophenotype (samples #1 and #2)
New Insights into the Molecular Characteristics of Pulmonary Carcinoids and Large Cell Neuroendocrine Carcinomas, and the Impact on Their Clinical Management

Jules L Derks, MD, a Noëmie Leblay, b Sylvie Lantuejoul, MD, PhD, c,d Anne-Marie C. Dingemans, MD, PhD, a Ernst-Jan M Speel, PhD, e Lynnette Fernandez-Cuesta, PhD b,∗

Journal of Thoracic Oncology Vol. 13 No. 6

June 2018

Molecular alterations related to the development of neuroendocrine tumors

- Typical carcinoid
- Atypical carcinoid
- SCLC (occasional LCNEC)
- LCNEC or SCLC (trans-differentiation by TKI∗)
- LCNEC

Alterations likely related to metastasis

- Carcinoid with increased proliferative capabilities
- Carcinoid with increased proliferative capabilities

Neuroendocrine cell lineage. The disease is often located in the larger airways

Non-neuroendocrine cell lineage. The disease is often located in the peripheral (small) airways / alveoli