Insulinoma-associated protein (INSM1) is a sensitive and specific marker for lung neuroendocrine tumors in cytologic and surgical specimens.

Kartik Viswanathan, M.D., Ph.D
New York Presbyterian - Weill Cornell Medicine
Department of Pathology and Laboratory Medicine
New York, NY-10021, USA
September 11th, 2018
Disclosure Information

I hereby declare that I have had business or personal interests in the following industrial enterprises since 1 September 2017:

Name of the enterprise / Nature of the interest

<table>
<thead>
<tr>
<th>Enterprise</th>
<th>Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Fine needle aspiration is useful in the initial workup of a lung mass

- Minimally invasive

- Can help provide a definitive diagnosis

- Sensitivity: 91.5%, Specificity: 72.5% (Modi M.B et al. 2016)

- Cytology samples can be used for molecular testing
Neuroendocrine differentiation alters management of lung cancer

Image courtesy Dr. David Lam, CME (January 2015)
Current immunohistochemical markers for neuroendocrine differentiation

<table>
<thead>
<tr>
<th>CD56</th>
<th>Synaptophysin</th>
<th>Chromogranin A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membranous</td>
<td>Cytoplasmic</td>
<td>Cytoplasmic</td>
</tr>
<tr>
<td>Sensitivity: 79.4-90.5%</td>
<td>Sensitivity: 86.2-94%</td>
<td>Sensitivity: 49-82.3%</td>
</tr>
<tr>
<td>Specificity: 95%</td>
<td>Specificity: 95%</td>
<td>Specificity: 100%</td>
</tr>
</tbody>
</table>

- can be negative in up to 10-25% of high grade neuroendocrine carcinomas
- Need for additional sensitive and specific neuroendocrine markers
**Insulinoma-associated protein 1 (INSM1) is a novel neuroendocrine marker**

- Nuclear transcription factor identified in 1992
- Plays a role in neuronal differentiation
- Promotes endocrine differentiation in organs – e.g. pancreas, pituitary etc.
- Can be highly expressed in neuroendocrine tumors
Insulinoma-associated protein 1 (INSM1) is a useful neuroendocrine marker

Middle ear adenoma

Olfactory neuroblastoma

Small cell carcinoma-cervix

Small cell carcinoma-prostate

GI neuroendocrine

Merkel cell carcinoma
INSM1 is a useful neuroendocrine marker in lung biopsy and surgical specimens

Small cell carcinoma

Images courtesy Rooper et al. AJSP 2017
INSM1 is a useful neuroendocrine marker in pulmonary cytology

Small cell carcinoma

Adenocarcinoma

Images courtesy Doxtader et al. Cancer Cytopathology 2018
What is not known?

- INSM1 staining in atypical carcinoids was not assessed in cytology.
- Doxtader et al. only had one large cell neuroendocrine carcinoma in their cytology cohort.
- INSM1 specificity among other lung tumor types has not been extensively characterized.
Assessment of INSM1 in cytologic and surgical specimens

- Retrieval of cytology cell blocks with corresponding surgical resections between 2007-2018
  - Typical carcinoids (TC) – 12
  - Atypical carcinoids (AC) – 11
  - Small cell neuroendocrine carcinoma (SCLC) – 10
  - Large cell neuroendocrine carcinoma (LCNEC) – 9
  - Squamous cell carcinoma (SCC) – 10
  - Adenocarcinoma (ADC) – 12
Assessment of INSM1 in cytologic and surgical specimens

- Tissue microarrays
  - Adenocarcinoma – 428 cases
  - Squamous cell carcinoma – 10 cases
  - Large cell carcinoma (LCC) – 17 cases
  - Other subtypes – 24 cases
    - Adenosquamous carcinoma (10 cases)
    - Sarcomatoid carcinoma (11 cases)
    - Solitary fibrous tumor (2 cases)
    - Inflammatory myofibroblastic tumor (1 case)
Assessment of INSM1 in cytologic and surgical specimens

- INSM1 (SantaCruz Biotech, C-8 clone, 1:100) was used for immunohistochemistry

- Grading:
  - Positive if at least 1+ and staining >5%
Clinicopathologic parameters

- N = 60 patients
- Average age: 67 years (Range: 32-86 years)
- M:F ratio: 1.1:1
- Tumor size: 3 cm (Range: 0.7-9.5 cm)
- Tumor source: All cases were of pulmonary origin
  - 78.3% cases were primary
  - 21.7% cases were secondary metastases to liver and lymph nodes
INSM1 IHC in Cytologic specimens

Typical carcinoid

Atypical carcinoid
Squamous cell carcinoma

Adenocarcinoma
INSM1 IHC in Surgical Specimens

Typical carcinoid

Atypical carcinoid

H&E

INSM1 IHC

weill.cornell.edu
Small cell carcinoma

Large cell neuroendocrine carcinoma
Squamous cell carcinoma

Adenocarcinoma

H&E

INSM1 IHC
## INSM1 performance summary in cytology specimens

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Negative</th>
<th>Positive</th>
<th>Total</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical carcinoid</td>
<td>0</td>
<td>11</td>
<td>11</td>
<td>100%</td>
</tr>
<tr>
<td>Atypical carcinoid</td>
<td>0</td>
<td>12</td>
<td>12</td>
<td>100%</td>
</tr>
<tr>
<td>Small cell neuroendocrine carcinoma</td>
<td>2</td>
<td>8</td>
<td>10</td>
<td>80%</td>
</tr>
<tr>
<td>Large cell neuroendocrine carcinoma</td>
<td>2</td>
<td>7</td>
<td>9</td>
<td>78%</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>10</td>
<td>0</td>
<td>10</td>
<td>0%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>20</strong></td>
<td><strong>38</strong></td>
<td><strong>58</strong></td>
<td></td>
</tr>
</tbody>
</table>
## INSM1 performance summary in surgical resections and tissue microarrays

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Negative</th>
<th>Positive</th>
<th>Total</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical carcinoid</td>
<td>1</td>
<td>17</td>
<td>18</td>
<td>94.4%</td>
</tr>
<tr>
<td>Atypical carcinoid</td>
<td>1</td>
<td>14</td>
<td>15</td>
<td>93.3%</td>
</tr>
<tr>
<td>Small cell neuroendocrine carcinoma</td>
<td>0</td>
<td>11</td>
<td>11</td>
<td>100%</td>
</tr>
<tr>
<td>Large cell neuroendocrine carcinoma</td>
<td>2</td>
<td>10</td>
<td>12</td>
<td>83.3%</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>57</td>
<td>1</td>
<td>58</td>
<td>1.7%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>424</td>
<td>6</td>
<td>430</td>
<td>1.4%</td>
</tr>
<tr>
<td>Large cell non-neuroendocrine carcinoma</td>
<td>14</td>
<td>3</td>
<td>17</td>
<td>17.6%</td>
</tr>
<tr>
<td>Other subtypes</td>
<td>23</td>
<td>1</td>
<td>24</td>
<td>4.2%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>522</td>
<td>63</td>
<td>585</td>
<td><strong>5.49%</strong></td>
</tr>
</tbody>
</table>
## Overall performance for INSM1

<table>
<thead>
<tr>
<th></th>
<th>INSM1 Cytology</th>
<th>INSM1 surgical specimens</th>
<th>CD56*</th>
<th>Synaptophysin*</th>
<th>Chromogranin A*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>90.5%</td>
<td>92.9%</td>
<td>79.4-100%</td>
<td>86.2-94%</td>
<td>49-82.3%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>100%</td>
<td>97.9%</td>
<td>95%</td>
<td>95%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Positive Predictive Value</strong></td>
<td>100%</td>
<td>92.9%</td>
<td>98%</td>
<td>98%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Negative Predictive Value</strong></td>
<td>80%</td>
<td>97.9%</td>
<td>100%</td>
<td>88%</td>
<td>46%</td>
</tr>
</tbody>
</table>

Advantages of INSM1 IHC

- High sensitivity and high specificity
- Nuclear staining
- Useful in cases of extensive necrosis — non-specific background staining can occur with Chromogranin A, Synaptophysin, CD56
Limitations of INSM1 IHC

• INSM1 can show focal false-positive staining in NSCLC cases

• False-negative cases can also occur with INSM1

• Small number of cytology cases
Conclusions

• INSM1 is a sensitive and specific marker for neuroendocrine differentiation in pulmonary tumors

• Comparable to CD56, Synaptophysin and Chromogranin A

• Will INSM1 replace the traditional markers CD56, Chromogranin A, Synaptophysin?
Acknowledgements

Mentors
- Dr. Alain C. Borczuk
- Dr. Momin T. Siddiqui

Translational Research Program at Weill Cornell Medicine
- Bing He
- Yifang Lu
References

1. Travis W, Brambila E, Burke AP et al. WHO Classification of Tumors of the Lung, Pleura, Thymus and Heart. 4th ed. 2015, Lyon, France: IARC.


