Small Blue Cell Tumors of the Lung, Mediastinum & Pleura

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Objectives

- Discuss the differential diagnosis of small blue cell tumors of lungs, mediastinum & pleura
- Review the diagnostic features of each of these entities and the role of ancillary studies
- Discuss the role of electron microscopy in the differential diagnosis of small blue cell tumors

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Drs. Pavlisko and Roggli declare they have no conflict(s) of interest to disclose.
Small Blue Cell Tumors of the Lungs

- Small cell carcinoma
- Large cell neuroendocrine carcinoma
- Typical and atypical carcinoid tumors
- Ewing family of tumors
- Basaloid squamous cell carcinoma
- MALT lymphoma

Histology: Small Cell Carcinoma
Histology: Small Cell Carcinoma

Small Cell Carcinoma and Giant Cell Carcinoma

Ultrastructure: Small Cell Carcinoma
- Oval or spindle shaped cells variably with polar processes
- Diffuse noninsular arrangement of cells
- High nuclear to cytoplasmic ratio
- Intercellular junctions
- Dense core granules
Distinction Between SCLC and Basaloid Squamous Cell Ca.

<table>
<thead>
<tr>
<th>Small cell carcinoma</th>
<th>Basaloid sq. cell ca.</th>
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<tbody>
<tr>
<td>TTF-1 (N)</td>
<td>p63(p40) (N)</td>
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<tr>
<td>Pankeratin (rim &amp; dot)</td>
<td>CK 5/6</td>
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<td>CD56</td>
<td>CK903</td>
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<tr>
<td>Synaptophysin</td>
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<td>Chromogranin</td>
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Histology: Basaloid Squamous Cell Carcinoma

Ultrastructure: Basaloid Squamous Cell Carcinoma

- High nuclear to cytoplasmic ratio
- Perinuclear tonofibrillar bundles
- Well-formed desmosomes
- Widened intercellular spaces
- Replicated basal lamina
Distinction Between SCLC and MALT Lymphoma

**Small cell carcinoma**
- TTF-1 (N)
- Pankeratin (rim & dot)
- CD56
- Synaptophysin
- Chromogranin
- Ki-67 (50-100%)

**MALT Lymphoma**
- Keratin negative
- CD45
- CD20
- CD79a
- Ki-67 (< 20%)

**Ultrastructure: MALT Lymphoma**
- Abundant heterochromatin especially along the nuclear envelope
- Cytoplasm composed predominantly of free polyribosomes
- Absence of intercellular junctions
Small Blue Cell Tumors of the Mediastinum

- Thymomas
- Thymic basaloid carcinoma
- Thymic neuroendocrine tumors
- Lymphomas
- Metastatic small cell carcinoma
- Soft tissue sarcomas
- Neuroblastoma

Distinction Between Thymoma and Lymphoma

**Thymoma**
- Keratin positive
- p63 (N)
- PAX8 (N)

**Lymphomas**
- Keratin negative
- CD20, CD79a (B-cell)
- CD3, CD4, CD8 (T-cell)
- Gene rearrangement
Small Blue Cell Tumors of the Pleura

- Small cell mesothelioma
- Desmoplastic small round cell tumor
- Metastatic small cell carcinoma
- Lymphoma (CLL/SLL)
- Intrapleural thymoma
- Ewing family of tumors

Distinction Between Small Cell Mesothelioma and Metastatic Small Cell Carcinoma

Small Cell Meso. | Metastatic SCLC
---|---
WT-1 (N) | TTF-1 (N)
D2-40 (M) | CD56
Calretinin (N/C) | Synaptophysin
Small Blue Cell Tumors of the Pleura

- Small cell mesothelioma
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Distinction Between DSRCT and Small Cell Mesothelioma

**DSRCT**
- *EWSR1-WT1* gene fusion
- Desmin (perinuclear dot-like pattern)
- NSE, CD56

**Mesothelioma**
- p16/CDKNN2A homozygous deletion

Ultrastructure: Desmoplastic Small Round Cell Tumor

- Closely apposed round and oval cells separated by fibroblastic stromal bands
- Discontinuous basal lamina
- Intermediate filaments with paranuclear whorls
- Diminutive and intermediate junctions
- Occasional polar processes with microtubules
- ± dense core granules, ± focal glycogen
Illustrative Case Studies

Case 1: Clinical History

- 61 year old man
- Presented with dyspnea, chest pain and left pleural effusion
- Patient worked for General Electric
- Smoking history is unknown
- Radiographic studies showed encasement of lung by rind of tumor

Left Pleural Biopsy

- Smoking history is unknown
- Radiographic studies showed encasement of lung by rind of tumor
- A pleural biopsy was performed
Case 1: Clinical History

- Biopsy interpreted as small cell carcinoma
- No response to first line therapy for small cell lung cancer
- An extrapleural pneumonectomy was performed
Cytokeratin IHC

Calretinin IHC

D2-40 IHC

WT-1 IHC
Case 2: Clinical History

- 56 year-old male
- Works as a minister
- Non-smoker
- Presents with large mediastinal mass
- Craniotomy for meningioma 9 mos. previously

Chest X-ray: 9 mos. prior to presentation
Case 2: Clinical History

- Pre-operative diagnosis:
  - thymoma versus lymphoma
- Frozen section: small blue cell malignancy

Large Mediastinal Mass

Embryonal Rhabdomyosarcoma

Rhabdomyoblasts
Ultrastructure: Rhabdomyoblast

Ultrastructure: Thick and Thin Cytoplasmic Filaments

Ultrastructure: Thick and Thin Filaments in Register

Mediastinal Embryonal Rhabdomyosarcoma
- Grisner reported a case in 1962
- Lloyd et al. described 7 cases arising in thorax, abdomen, or retroperitoneum in adults from MSK (1983)
- Suster et al. reported a case in anterior mediastinum in a male (1994)
Adult Embryonal Rhabdomyosarcoma
- Mean age 40 years
- 60% in males
- 79% mortality 17 mos. post diagnosis
- Only one case from thorax, abdomen, or retroperitoneum survived 5 years

Conclusions
- Dense core granules favor small cell carcinoma in small blue cell tumors
- Absence of intercellular junctions favors lymphoma
- Perinuclear tonofilaments and well-formed desmosomes favor basaloid carcinoma
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Conclusions

- Dense core granules favor small cell carcinoma in small blue cell tumors
- Absence of intercellular junctions favors lymphoma
- Perinuclear tonofilaments and well-formed desmosomes favor basaloid carcinoma
- Myosin and actin filaments in register favor rhabdomyosarcoma
- Long sinuous surface MV favor mesothelioma
- Paranuclear whorls of intermediate filaments favor DSRCT