PATHOLOGY OF THE PLEURA:
Mesothelioma and mimickers
Necessity of Immunohistochemistry

M. Praet
Pathology of the Pleura

• Normal serosa: visceral and parietal layers
• Inflammation
• Neoplasia:
  – Primary: mesothelioma
  – Secondary: direct invasion from the lung, indirect (lymphatic invasion)
Normal anatomy
REPARATIVE CHANGES in the PLEURA

POSSIBLE ORIGINS OF RENEWING CELLS IN HEALING OF MESOTHELIUM.
Mesothelioma Registry

- In ‘86 (6), ‘87 (2), ‘88 (22), ‘89 (17), ’90 (17), ’91 (22)
- Since 1992 - monthly meetings
- Provides diagnostic service to pathologists and to the Fund of Occupational Diseases with validation of diagnoses
Presented cases to the registry

incidence

Presented cases to the registry
LONGVLIESKANKER IN VLAANDEREN

Het aantal gevallen van longvlieskanker tussen 1997-2001 per gemeente (bij mannen in verhouding tot het verwachte aantal, rekening houdend met de leeftijd). In de gemeenten die in het rood zijn ingekleurd, is de incidentie hoger dan verwacht. In Kapelle-op-den-Bos (zwart) zijn er elf keer meer gevallen van longvlieskanker dan normaal.

(Bron: Stichting Kankerregister)
Untraceable ubiquitous exposure to asbestos preceedes problems in the collection of adequate epidemiological data: latency of 20 years.
Amiante
Un poison lent

Crocidolyte

CRYSOTYLE
PREVIOUS WORKSHOPS
PATHOLOGY of MESOTHELIOMA

Problems in the diagnosis of Mesothelioma
- sample size of the biopsy is crucial for the diagnosis
- heterogeneity of the tumor, diagnosis may change after deeper sections
- extensive panel of adequate immunohistochemical antibodies is mandatory: often not applied in private practice
- metastases mimick meso’s, meso’s mimick other neoplasms
CHALLENGE OF MESONEOPLASMS

- Identification of the pleural cell identity
- Taking into account the possibility of dedifferentiation and transdifferentiation

- Be aware that secondary neoplasms are extremely good in adopting a “mesothelioma-look”.
Subtypes of mesothelioma

- EPI
- DESMO
- BIPH
- SARCO
EPITHELOID MESOTHELIOMA

- Tubulo-papillary
- Acinar
- Microcystic (adenomatoid)
- Deciduoid
- Small cell type
- Pleomorphic
- Signet ring
- Clear cell
- Lymphohistiocytic
- Mucin+ mesothelioma
EPITHELOID MESOTHELIOMA

DIFFERENTIAL DIAGNOSIS:
- hyperplasia
- hyperplasia secondary to metastatic invasion
- metastatic invasion
BIPHASIC MESOTHELIOMA

DIFFERENTIAL DIAGNOSIS

- synoviosarcoma: biphasic subtype
SARCOMATOID MESOTHELIOMA

DIFFERENTIAL DIAGNOSIS:
- monophasic synoviosarcoma
- sarcomatoid carcinoma
- sarcoma: leiomyo, angiosarcoma (epitheloid), SFT malignant subtype
DESMOPLASTIC MESOTHELIOMA

DIFFERENTIAL DIAGNOSIS
- hyaline plaque: cellular subtype
- chronic fibrous pleurisy
- subacute pleuritis
Cellular hyaline plaque

- Reactive?
- Desmoplastic Meso?
VARIABILITY in 1 meso case: EPPE
Extra Pleural PneumoEctomy: EPPE
MESOTHELIOMA presents with a heterogeneous spectrum
Subtypes of mesothelioma in REGISTRY

- 75%
- 14.85%
- 9.4%
How to treat a case of mesothelial pathology

• Is this case reactive or neoplastic?
• What is the causing neoplasm?
• Mesothelioma: what immunostains are necessary?
• No- mesothelioma: what immunostains are needed for detection of the secondary neoplasm?
Panel of Immunostains

Choice of antibodies: sensitivity, specificity > 80%
Cut off: > 10%
Panel applied in most mesotheliomapanel:
- Cal, CK5.6, WT1 = antibodies with the highest sensitivity and specificity
- D2-40, mesothelin
- EMA m
- TTF1, CEApol, CD15, BER EP4, B72.3, MOC 31
- CK: AE1-AE3, MNF 116
Reactive versus neoplastic mesothelium?

- Most important criterium is invasion in the subserosal layers/fat
- Criterium of ZONATION with horizontal layering of the reactive mesothelial cells
- Invasion means PERPENDICULAR growth in the depth
- Atypical hyperplasia: papillary growth, nuclear atypism
Reactive versus neoplastic mesothelium

Important immunostainings are:
- CKBS: growth pattern of mesothelial cells: zonation, perpendicular growth
- EMA staining: cell membrane staining: negative in benign lesions
Epitheloid mesothelioma

Panel immunostains:
- pro mesocell identification:
  calretinine, WT-1, EMA cell membrane, CK5.6, D2-40, mesotheline
- pro- non- mesocell identification/detection:
  CEApol, TTF-1, CD15, BER EP4
Calretinine: high sensitivity

• Mesothelioma: Epit/Biph: 98%
• Synoviosarcoma
• Serous adenoca of the ovary

• Staining properties: nuclear and cytoplasmic staining
EMA staining in mesothelioma

• Located at the cell membrane
• Reflects microvillous surface of the mesothelial cell
• In biopies: often only positive at the surface of the biopsy.
• Mainly to be expected in epithelial parts of the tumor
Mesothelioma and cytokeratins

Depends on the type of mesothelioma:
- Normal mesothelium:
  CK7/CK20
- Epitheloid mesothelioma:
  looses epithope CK7/CK20:
  therefore: CKBS

Main value: detection of growth pattern, differentiation of the mesotype
WT-1 (Wilm’s Factor 1)

• **Specificity:**
  - Epi meso 92.9 %
  - BUT:
    - 100% papillary carcinoma of ovary
    - 100% RCC

**Staining properties:**
- nuclear stain with aspecific vessel staining
BIPHASIC MESOTHELIOMA

Calretinin will stain the better differentiated areas of the tumor: epithelial differentiation, less staining in the sarcomatous areas.
WT-1 in Biphasic Meso

- WT-1 stain positive in epithelial and sarcomatous pats of the tumor
DESMOPLASTIC MESOTHELIOMA
DESMOPLASTIC MESOTHELIOMA

CRITERIA:
- Cellular nodules
- Absence of zonation
- Bland necrosis
- Cellular atypie
- Infiltration into the fat by CK + tumorcells
DESMOPLASTIC MESOTHELIOMA

RELATION TO FAT
DESMOPLASTIC MESOTHELIOMA

CKBS: illustration of invasion of neoplastic cells into the fat
SARCOMATOUS MESOTHELIOMA

CKBS: % of staining cells depends on the degree of anaplasia of the tumor
Calretinin: rare neoplastic cells are positive: <10%
WT-1 stain: ADDED value: 30-60% often only a few nuclei
WT-1 in sarcomatous mesothelioma
METASTATIC INVASION

• Adenocarcinoma of the lung:
  – TTF1 ++ (82%)
  – CEA pol (90%)
  – Ber EP 4 (70%)
  – EMA: CM + Cytoplasmic stain
  – PAS/DIASTASE ++
Papillary neoplasm of the peritoneum or pleura in a woman?

Biopsy: meso

Resection: metastasis
METASTATIC INVASION

• OVARIAN NEOPLASM:
  – Calretinine/ WT-1 pos
  – Add ER/PR in the panel!
ER/PR in mesoneoplasms in women
## DD ovarian neoplasm/SSPC

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mesothelioma</td>
<td>Serous PapillaryCarcinoma</td>
</tr>
<tr>
<td>CKBs (AE1-3)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CK7</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Calret</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CK5/6</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>WT1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>EMA</td>
<td>+ CM</td>
<td>+CM/cytoplasm</td>
</tr>
<tr>
<td>CD15</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CEA p</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ER/PR- p53</td>
<td>-</td>
<td>Pos (cfr differentiation)</td>
</tr>
</tbody>
</table>
METASTATIC INVASION: other epithelial neoplasms
SYNOVIOSARCOMA

- **Monophasic pattern:**
  - Sarcomatoid mesothelioma: WT1+, AE1-AE3 +, (CK5.6+, CAL +)
  - SFT: CD34 +, CK-, EMA -
  - Fibrosarcoma: CK-, EMA-
  - Leiomyosarcoma: CK+/-, desmin+, SMA+, BCL2-
  - MPNST: Coll IV +, BMP +, CD 99+, CD56-, CK-
  - Sarcomatoid carcinoma: p63
  - Thymoma: CK19+(CD5+), EMA+, TdT
SYNOVIOSARCOMA

Immunohistochemistry
AE1/AE+, calretinin+, EMA+
CD56: 100% ++
BCL2: 96% ++

Molecular analysis:
RT-PCR revealing the SYT-SSX transcripts manifestation of
t(X-18)(p11;q11) : in > 90%
SFT

- Microscopical features:
  - low to moderate cellularity
  - loosely arranged spindle-shaped or oval cells scattered randomly among strands of collagen
  - in a pattern-less, storiform or hemangiopericytoma-like fashion

CD34 ++/CK neg
Epitheloid HemangioEndothelioma

Microscopical features:
variable, morphologic spectrum resembling hemangioma, spindle cell sarcoma, carcinoma, biphasic mesothelioma with presence of vacuolated and epitheloid cells in 75%!
Arrangement in cords and nests

CD31/ CK +
Reference

- Guidelines for Pathologic Diagnosis of Malignant Mesothelioma: a consensus statement from the International mesothelioma Interest group

Husain et al Arch pathol Lab med Vol 133, 1317-1331, 2009