Non-neoplastic

Mesothelial markers: D2-40, Calretinin, WT-1, CK5/6 (Not entirely specific)
Pancytokeratin can be helpful to

Reactive Mesothelial Hyperplasia

“Activated” reactive mesothelial cells, often responding to inflammation/irritation, can look very scary and mimic mesothelioma/carcinoma.

Common scary findings: High cellularity, mitotic figures, cytologic atypia, papillary groups, and entrapment of mesothelial cells in fibrous tissue mimicking invasion.

Can see “layering” as additional layers of mesothelium and fibrous tissue organize over one another. Think: sedimentary rock

Reactive Mesothelial Hyperplasia

<table>
<thead>
<tr>
<th>Reactive Mesothelial Hyperplasia</th>
<th>Mesothelioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of stromal invasion (be aware of entrapment and tangential sectioning)</td>
<td>Stromal invasion usually apparent (highlight with pancytokeratin staining)</td>
</tr>
<tr>
<td>Cellularity may be prominent but is confined to the mesothelial surface/pleural space and is not in the stroma</td>
<td>Dense cellularity, including cells surrounded by stroma</td>
</tr>
<tr>
<td>Simple papillae; single cell layers</td>
<td>Complex papillae; tubules and cellular stratification</td>
</tr>
<tr>
<td>Loose sheets of cells without stroma</td>
<td>Cells surrounded by stroma (“bulky tumor” may involve the mesothelial space without obvious invasion)</td>
</tr>
<tr>
<td>Necrosis rare</td>
<td>Necrosis occasionally present</td>
</tr>
<tr>
<td>Inflammation common</td>
<td>Minimal inflammation (usually)</td>
</tr>
<tr>
<td>Uniform growth (highlighted with cytokeratin staining)</td>
<td>Expansile nodules; disorganized growth (highlighted on cytokeratin staining)</td>
</tr>
</tbody>
</table>

Usually Not Helpful: Mitotic activity, Mild to moderate cellular atypia

**Fibrous pleurisy**
aka “Diffuse Pleural Fibrosis” or “Chronic fibrosing pleuritis”

*Deposition of bland, hypocellular fibrous tissue in the pleura.*

Often involves the visceral pleura and may produce apical fibrous “capping.” Severe cases can obliterate pleural space.

May be associated with connective tissue disorders, such as lupus erythematosus or rheumatoid arthritis, as well as chronic infections and asbestos exposure.

May mimic desmoplastic mesothelioma

<table>
<thead>
<tr>
<th>Fibrous Pleurisy</th>
<th>Desmoplastic Mesothelioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storiform pattern not prominent</td>
<td>Storiform pattern often prominent</td>
</tr>
<tr>
<td>Absence of stromal invasion</td>
<td>Stromal invasion present (highlight with pancytokeratin staining)</td>
</tr>
<tr>
<td>Uniform thickness of the process</td>
<td>Disorganized growth, with uneven thickness, expansile nodules, and abrupt changes in cellularity</td>
</tr>
<tr>
<td>Perpendicularly oriented vessels</td>
<td>Paucity of vessels. No orientation.</td>
</tr>
<tr>
<td>Hypercellularity at the surface with maturation and decreased cellularity deep (so-called zonation)</td>
<td>Lack of maturation from the surface to the depths of the process</td>
</tr>
<tr>
<td>Necrosis, if present, is at the surface epithelioid mesothelial cells (where there is often associated acute inflammation)</td>
<td>Bland necrosis of paucicellular, collagenized tissue</td>
</tr>
</tbody>
</table>

*Not helpful: Cellularity, Atypia (unless severe), Mitotic activity (unless numerous atypical mitotic figures)*


**Pleural Plaque**
aka “hyaline pleural plaque”

*Hypocellular, dense bundles of hyalinized collagen,* often with a “basket weave” arrangement. Often dystrophic *calcifications.* Variable chronic inflammation.

Often on parietal pleura, particularly on diaphragm

Often a marker of asbestos exposure, but can be seen with other sources of chronic pleural irritation.
Peritoneal Inclusion Cyst
Often discovered incidentally. More common in women
Single or multiple, small, thin-walled, translucent, unilocular cysts attached or free in the peritoneal cavity.
Lined by a single layer of flattened, benign-appearing mesothelial cells

Benign Multicystic Peritoneal Mesothelioma
aka “multilocular peritoneal inclusion cysts” (better name!)
Occurs most frequently in young to middle-aged women in the peritoneum/pelvis.
Likely a hyperplastic reactive lesion (vs. a benign neoplasm).
Associated with previous abdominal surgery, pelvic inflammatory disease, and endometriosis.
It has a strong tendency to recur.
Grossly: often large, multiple small, thin-walled, translucent, unilocular cysts that may be attached or free floating. Often fibrous tissue in septae with sparse inflammation.
Cysts are lined by a single layer of flattened to cuboidal mesothelial cells which occasionally have a “hob-nail” appearance.

Sclerosing Peritonitis
“Cocoon abdomen”
Rare. Encasement of the bowel by fibrous tissue causes bowel obstruction.
Can be idiopathic, or seen with intraperitoneal dialysis, VP shunts, and fibrothecomas of the ovary.

Sclerosing Mesenteritis
Rare. Idiopathic.
Varying degrees of fat necrosis, chronic inflammation, and fibrosis, usually involving the mesentery of the small bowel forms a distinct mass

Other lesions:
Splenosis
Melanosisis
Infarcted epiploicae
Keratin granulomas
Adenomatoid Tumor

Irregularly shaped gland-like microcystic spaces composed of flattened or cuboidal cells with associated fibrous stroma. Bland cytologic features.

**Helpful feature:** "thread-like bridging strands“ (→)

Sometimes signet ring-like vacuolated cells.

Solitary, localized.

Most commonly in the **female genital tract** (e.g., uterine or adnexal surface) or **genitourinary tract** (e.g., paratesticular), but can be pleural.

Well-Differentiated Papillary Mesothelioma

Rare. Grossly **velvety** appearance.

**Prominent papillary architecture with myxoid cores covered by a single layer of flattened to cuboidal bland epithelioid cells.**

Nuclei are **bland**, round, and small without atypia.

Generally NO invasion.

**Indolent** tumors. Most cases cured by excision. Very long survival. May recur.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Well-differentiated Papillary Mesothelioma</th>
<th>Malignant Mesothelioma with a Papillary Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth feature- bulk of disease</td>
<td>Often incidental, solitary, focal area of velvety appearance</td>
<td>Diffuse or multinodular, grossly apparent</td>
</tr>
<tr>
<td>Morphology of papillae</td>
<td>Fibrous and stout cores, single-cell layer</td>
<td>Fibrous cores, lined by cells with stratification</td>
</tr>
<tr>
<td>Cytology</td>
<td>Flat cuboidal, no anisocytosis</td>
<td>Cuboidal cells with nucleoli and variable anisocytosis</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Other growth patterns</td>
<td>Absent</td>
<td>Tubular, solid, cribriform, complex papillae</td>
</tr>
<tr>
<td>Stroma invasion</td>
<td>Predominantly exophytic growth, Invasion usually absent or very focal/superficial</td>
<td>Present</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Good, with local recurrence</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Adapted from: WHO Classification of tumors of the lung, pleura, thymus, and heart. 2015.
Epithelioid Mesothelioma

Malignant proliferation of mesothelial cells with epithelioid morphology.

Usually **diffuse** (circumferential, rind-like) → **Poor prognosis**.
Rarely, localized (solitary, well-circumscribed) → Better prognosis

Most common in elderly, often male. Often unilateral at first.
Most common cause is asbestos exposure.
Often insidious onset with chest pain and/or dyspnea

Clinical information (either from imaging or intraoperative findings) can be very helpful with Dx: Circumferential pleural thickening is highly suggestive of malignancy, Nodular pleural thickening is also often malignant.

Often relatively bland cytologically (but can be pleomorphic) with eosinophilic cytoplasm in vesicular nuclei.

Demonstration of **tissue invasion** (e.g., into chest wall or lung) is often key for diagnosis (see next page). However, when a substantial amount of solid, malignant tumor (i.e., a mass) is identified, the presence of invasion is not required for diagnosis.

**Common histologic patterns:** solid, tubulopapillary, trabecular.
Rare patterns: micropapillary, clear cell, deciduoid, adenomatoid, transitional, small cell, lymphohistiocytoid, etc.

Can see psammoma bodies.

Special studies: Can serve several purposes
1) Use IHC to confirm mesothelial (and not metastatic carcinoma) (see tables →) Always use a panel!
2) After mesothelial origin is confirmed, special studies can support the diagnosis of malignancy (if necessary)

**Special Studies that support the diagnosis of mesothelioma with good specificity (not fantastic sensitivity though):**

**IHC:** BAP1 or MTAP **loss**
**FISH:** CDKN2A (p16) **deletion**
Multigene expression profiling panels

Molecular: Often multiple chromosomal alterations. Frequent loss of tumor suppressors CDKN2A, BAP1, and NF2.

---

<table>
<thead>
<tr>
<th>Metastatic Adenocarcinoma</th>
<th>Mesothelial cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>BerEP4</td>
<td>Calretinin</td>
</tr>
<tr>
<td>MOC31</td>
<td>D2-40</td>
</tr>
<tr>
<td>B72.3</td>
<td>WT-1</td>
</tr>
<tr>
<td>Claudin-4</td>
<td>CK5/6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Squamous cell carcinoma</th>
<th>Mesothelial cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>p40 &amp; p63</td>
<td>Calretinin</td>
</tr>
<tr>
<td>MOC31</td>
<td>D2-40</td>
</tr>
<tr>
<td>Claudin-4</td>
<td>WT-1</td>
</tr>
</tbody>
</table>

Adeno stains that can also get mesos: PAX8, CK7, GATA-3, AE1/AE3
Meso stains that can also get carcinomas: WT-1, CK5/6
Stains that get both mesos and SCC: CK5/6
Is it really invasive?

Given that reactive mesothelial processes can look so atypical, demonstrating tissue invasion is often required for the diagnosis of mesothelioma, unless there is a significant solid tumor mass.

Tip: Use of IHC stains (e.g., Pancytokeratin or Calretinin) can highlight infiltrative cells, helping confirm invasion.

Look for cytokeratin-positive malignant cells in regions in which they would not normally be present: adipose tissue, skeletal muscle deep to the parietal pleura, or lung tissue (or other extrapleural structures).

Caution: Sometimes the biopsy process can create fake empty fat-like spaces. When in doubt, do an S100 to see if it is real fat. Also, vimentin will be negative as this fake fat does not have any cellular lining.

Benign processes ➔ Tend to be well-circumscribed (only a few glands evident beneath the pleural surface, or a sharp line beyond which no mesothelial cells are found)

Malignant processes ➔ Poorly-circumscribed, invasive

Warning: On small biopsies, it can be very hard to evaluate for invasion. In such cases where invasion is not definite, it is recommended that you simply say “atypical mesothelial hyperplasia” or “atypical mesothelial proliferation,” with a comment that another larger biopsy (likely surgical), may be appropriate if the clinician is suspicious for mesothelioma.

<table>
<thead>
<tr>
<th>Mesothelial Hyperplasia</th>
<th>Mesothelioma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major criteria</strong></td>
<td></td>
</tr>
<tr>
<td>Stromal invasion</td>
<td>Absent</td>
</tr>
<tr>
<td>Cellularity</td>
<td>Confined to the pleural surface</td>
</tr>
<tr>
<td>Papillae</td>
<td>Simple, lined by a single layer of cells</td>
</tr>
<tr>
<td>Growth Pattern</td>
<td>Surface growth</td>
</tr>
<tr>
<td>Zonation</td>
<td>Process becomes less cellular towards chest wall</td>
</tr>
<tr>
<td>Vascularity</td>
<td>Capillaries perpendicular to surface</td>
</tr>
<tr>
<td></td>
<td>Present (the deeper the more definitive)</td>
</tr>
<tr>
<td></td>
<td>Dense, with stromal reaction</td>
</tr>
<tr>
<td></td>
<td>Complex, with cell stratification</td>
</tr>
<tr>
<td></td>
<td>Expansile nodules, complex, disorganized</td>
</tr>
<tr>
<td></td>
<td>No zonation of process, often more cellular away from effusion</td>
</tr>
<tr>
<td></td>
<td>Irregular, haphazard</td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
<td></td>
</tr>
<tr>
<td>Cytologic atypia</td>
<td>Confined to areas of organizing effusion</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Rare</td>
</tr>
<tr>
<td>Mitoses</td>
<td>May be plentiful</td>
</tr>
<tr>
<td></td>
<td>Present in any area, but often deceptively bland</td>
</tr>
<tr>
<td></td>
<td>More common</td>
</tr>
<tr>
<td></td>
<td>Often rare (but atypical favors malignancy)</td>
</tr>
</tbody>
</table>

Adapted from: WHO Classification of tumors of the lung, pleura, thymus, and heart. 2015.
**Sarcomatoid mesothelioma**: Spindle cell appearance. Arranged in fascicles or haphazard. Can see heterologous elements (e.g., rhabdomyosarcoma).

**Desmoplastic mesothelioma**: Dense collagenized tissue with malignant mesothelial cells. Either patternless or storiform pattern. Must be ≥50% of tumor. Invasion into fat is most helpful feature to differentiate from organizing pleuritis.

**Biphasic mesothelioma**: Contains BOTH epithelioid and sarcomatoid patterns, each ≥10%.

Stromal invasion is often more difficult to recognize in these spindle cell proliferations as the invasive malignant cells are often deceptively bland → Use IHC liberally.

IHC: Usually stain, at least focally, with a broad spectrum pancytokeratin (can also help demonstrate invasion). Loss of BAP1 is very uncommon in these types.

Poorer prognosis than epithelioid mesotheliomas. Desmoplastic mesothelioma has a particularly dismal prognosis (often <6 months).

Hmm... that looks pretty bland, but the clinician said it’s a mass.

Yikes! A cytokeratin stain shows that all of those bland spindled cells are actually invasion!
Other Tumors

Synovial Sarcoma
Malignant. Usually young adults.
- **Monophasic SS** → Just spindled component.
- **Biphasic SS** → Spindled and epithelioid components.

Fairly uniform spindled cells with relatively little cytoplasm. Ovoid, “stubby,” nuclei with hyperchromatic granular chromatin and small nucleoli. Can see “Stag-horn” vessels. Epithelial cells arranged in nests and glands with paler cytoplasm and vesicular nuclei.

IHC: Patchy EMA and CK (particularly strong in epithelial areas). Usu. CD99 (+). TLE-1 (+)

Molecular: **SS18-SSX gene fusions t(X;18)**

Solitary Fibrous Tumor (“SFT”)
Usually benign.

“Patternless pattern” of varying cellularity of bland spindled cells with varying amounts of collagenized stroma. Prominent “Staghorn vessels” (dilated, thin-walled, branching vessels). Can be hyalinized or myxoid.

IHC: **STAT6 (+)**. Also, CD34, CD99 (+, but variable).

Molecular: **NAB2/STAT6 gene fusion**

Factors associated with malignant behavior:
Numerous mitoses (esp. >4/10 HPF), Large size (esp. >15 cm), and tumor necrosis.

Desmoplastic Small Round Cell Tumor
Malignant tumor of uncertain histogenesis often found in the peritoneal cavity; often in young men.

Basaloid nests of small, round, uniform tumor cells that are surrounded by desmoplastic stroma. Tumor cells have hyperchromatic nuclei and scant cytoplasm. Mitoses and apoptoses are frequent.

IHC: Express **Cytokeratins**, EMA, **Desmin** (perinuclear dot-like pattern), WT-1 (but C-terminus—opposite of the WT-1 in Wilms!), and NSE

Molecular: Characteristic **EWSR1-WT-1 translocation**

**Poor prognosis** (although may respond at first)
Calcifying Fibrous Tumor

Rare. **Benign.** Occurs on visceral pleura/peritoneum. More common in **women,** often **younger.**

**Paucicellular collagenized fibrous tissue with associated psammomatous or dystrophic calcifications.**
Scattered chronic inflammation. **Circumscribed,** but not encapsulated.

Confined to pleura and does **not** invade underlying tissue.

**IHC:** CD34(+). STAT6, ALK1, β-catenin (-)

Desmoid-type Fibromatosis

**Benign (never metastasize), but infiltrative with high-recurrence rate (>50%).**

Infiltrative growth into surrounding structures (esp. skeletal muscle).

**Broad, sweeping fascicles.**

Uniform spindled cells with small, pale nuclei with pinpoint nucleoli.

Moderate amounts of collagen, surrounding cells, in slightly myxoid background.

**IHC:** Nuclear β-catenin. Some actin (+)

**Molecular:** Associated with FAP and mutations in the APC/β-catenin (CTNNB1) pathway

Angiosarcoma

**Malignant. Very aggressive.** Typically elderly.

**Variable degrees of vascular differentiation.**

Some areas show well-formed anastomosing vessels, while other areas may show solid sheets of high-grade cells. Can be epithelioid or spindled.

Often extensive hemorrhage.

Unlike benign lesions: **significant cytologic atypia, necrosis, endothelial cells piling up, and mitotic figures** (although mitoses can be seen in some benign tumors)

**IHC:** CD31, ERG, FLI1, often CD34

**Malignant.** Very aggressive. Typically elderly.

Variable degrees of vascular differentiation.

Some areas show well-formed anastomosing vessels, while other areas may show solid sheets of high-grade cells. Can be epithelioid or spindled.

Often extensive hemorrhage.

Unlike benign lesions: **significant cytologic atypia, necrosis, endothelial cells piling up, and mitotic figures** (although mitoses can be seen in some benign tumors)

**IHC:** CD31, ERG, FLI1, often CD34

**Lymphoproliferative Disorders**

**Primary Effusion Lymphoma:**

Rare. Presents as an effusion without solid tumor masses. Usually in **immunocompromised** patients (e.g., HIV-positive). Proliferation of large, atypical B cells with an immunoblastic appearance. Positive for HHV8, often with coinfection with EBV. **IHC:** CD45(+), but usually lack pan-B-cell markers like CD20, CD19, PAX5, CD79a. Usually express CD30 CD138, CD38, EMA. **Poor prognosis.**

**Diffuse Large B Cell Lymphoma associated with chronic inflammation:**

Occurs in patients with long-standing pyothorax or other chronic inflammatory processes, usually in body cavities. **EBV-associated.** Morphologically resembles other forms of DLBCL with large vesicular nuclei with prominent nucleoli. Express B-cell markers. **Aggressive.**
Müllerian Lesions

The pelvic and lower abdominal mesothelium can be primarily or secondarily involved by many Müllerian lesions.

Müllerianosis

Endosalpingiosis: Glands lined by benign tubal-type (ciliated) epithelium involving the peritoneum or pelvic or para-aortic lymph nodes. Likely secondary as associated with salpingitis. Can have associated psammoma bodies.


Endocervicosis: Benign endocervical-type epithelium.

Deciduosis

Ectopic decidual cells (epithelioid cells with abundant pale pink granular cytoplasm and bland nuclei) arranged individually, in nodules, or in plaques. Seen during pregnancy. May have associated hemorrhage/inflammation.

Primary Peritoneal Serous Borderline Tumors

Morphologically identical to the noninvasive peritoneal implants of ovarian serous borderline tumors. Diagnosis of exclusion: only when the ovaries are uninvolved or there only minimal surface involvement. Likely arises from endosalpingiosis. Generally good prognosis. Can get primary peritoneal low-grade serous carcinomas, so sample well!

Primary Peritoneal High-Grade Serous Carcinoma

Morphologically identical to the primary tuboovarian high-grade serous carcinoma. Diagnosis of exclusion: Both tubes and both ovaries grossly and microscopically uninvolved (when examined entirely). Dx can only be made at primary surgery prior to any chemotherapy. Otherwise, looks and behaves like peritoneal carcinomatosis from high-grade serous carcinoma.

Other lesions:

Walthard rests
Peritoneal leiomyomatosis
(and pretty much anything arising from Müllerianosis!)