Effusions of the Serous Cavities

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The serous cavities

- Pleura
- Peritoneum
- Pericardium

The visceral space is normally 5-10 microm wide and holds a minimal amount of fluid.

An effusion is any abnormal accumulation of fluid.
There are two types of effusions

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<tr>
<th>Transudates</th>
<th>Exudates</th>
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<td>– increased hydrostatic pressure and/or</td>
<td>– always inflammation, tissue damage, increased capillary permeability</td>
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<td>– decreased colloid osmotic pressure</td>
<td>– high protein content</td>
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<td>– low protein content</td>
<td>– may be blood-stained, cloudy, yellow, chylous</td>
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<td>– clear</td>
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<td>– sparse cellularity</td>
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<td>– Causes: Heart failure, liver cirrhosis, nephrotic syndrome, etc</td>
<td>– Causes: Malignancy, infection (pneumonia, pancreatitis, etc), systemic disease, trauma, medication, radiation therapy, heart surgery, embolism, lung infarction, etc</td>
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<td>– Seldom sent for cytological examination</td>
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Effusions of the serous cavities

What makes serous effusions different from other exfoliative cytology?

They are always pathological
There is no place for "normal cytology" in effusion cytology diagnosis
Ambitions of cytological diagnosis in effusions

- As exact as possible
- Explain the cause of the effusion
- A clinically relevant conclusion
- The ambition for effusion cytology should be as high as for fine needle aspirates
What can be diagnosed?

- Metastatic disease
  - Adenocarcinoma
  - Origin?
  - Other metastatic tumour
  - Type? Classification?
- Lymphoma
What can be diagnosed?

- Mesothelial cells
  - Benign proliferation
  - Mesothelioma
- Other primary tumours of the serosa (rare)
- Specific benign diagnoses in some cases
  - Empyema, rheumatoid arthritis, etc
And apart from diagnosis……

- Prognosis
  - Although an effusion is a late stage cancer manifestation survival time may vary considerably

- Prediction of therapy response
What modalities should be used?

- Macroscopic appearance
- Microscopic morphology
- Ancillary methods
  - Static immunocytochemistry
  - Flow cytometry
  - FISH, CISH
  - DNA analysis – amplification status, mutation status
The importance of using all available information

Get clinical information!
- Clinical information of paramount importance
- If the information on the referral sheet is not sufficient - call the clinician and ask!

Don't forget previous specimens!
- Always compare with previous cytologic and/or histologic specimens if available
Check subsequent histology!

- Use histology as quality control
- BUT remember: discrepancies don't always mean that cytology was wrong
- The correlate to the cytological finding must always be identified in the corresponding histologic specimen
- If you have good reasons to believe in your diagnosis, stick to it
Why is this so important?

- It improves the accuracy of your diagnosis
- It helps you avoid mistake
- It makes you keep learning
The macroscopic appearance!

- Amount?
- Appearance
  - Blood stained?
  - Colour? (light or dark yellow)
  - Viscous, foamy?
  - Cloudy?
  - Milky?
  - Purulent?
Look and shake!
Microscopic morphology
The mesothelial cell – a challenge in effusions

The serous cavities are lined with a single layer of mesothelial cells

Mesothelial cells are of mesenchymal origin but often display epithelial features

Various amounts of mesothelial cells are usually shed into effusions regardless of their causes

Mesothelial cells are not to be trusted morphologically - reactive cells may be highly atypical with high mitotic activity
The basic problem in effusion cytology

Benign proliferative mesothelial cells

?  

Mesothelioma

Adenocarcinoma
(and other metastatic tumours, especially if poorly differentiated)
The differentiation between mesothelioma, benign mesothelial hyperplasia, and adenocarcinoma metastasis may be extremely difficult.
Mesothelial hyperplasia

Mesothelioma

Adenocarcinoma (lung)
Unspecific reactive effusions

- Regular mesothelial cells
- Mixture of von macrophages, lymphocytes, lymphocytes, and neutrophils
Hyperplastistic, atypical mesothelial cells

- Uremic
- Chronic liver disease
- Peritonitis
- Chronic heart failure
- Pleuritis after pulmonary infarction and embolus
- Trauma
Proliferative mesothelial cells

Pleural effusion from a patient with a small cell lung carcinoma. No cancer cells in effusion.
Avoid "atypia" in effusions

Try to characterise the cells further

"Epithelial-like" cells

- Mesothelial cells
  - Benign proliferation
  - Mesothelioma
- Alien cells
  - Metastatic tumour growth
  - CAVE superficial benign ovarian tumours
Avoid "no malignant cells"

- Mesothelial proliferations and mesotheliomas cannot always be differentiated morphologically.
- Mesotheliomas can shed cells into effusions that don't have malignant features but they can nevertheless be diagnostic with ancillary techniques.
- More specific diagnoses can be made in effusions.
- Often misunderstood by clinicians.
Mesothelioma

- A rare tumour
- Originates from pluripotent submesothelial cell
- Divided into epithelial, mesenchymal and biphasic types
- Grows diffusely in the serous cavities
- 80% occur in the pleural cavity
- Prognosis dismal
- Predominating etiology: asbestos
- Incidence increases in spite of ban on asbestos
- Mesothelioma cells shed into effusions show epithelial features
Fibrous, epithelial, and biphasic mesotheliomas
Effusions in mesothelioma I

Most malignant mesotheliomas give rise to an effusion and most effusions contain malignant cells.

The malignant cells may not show obvious malignant features.

Some mesotheliomas cause an effusion with predominance of lymphocytes and macrophages, and few or no "diagnostic cells."

Thus, don't rule out mesothelioma if there is a clinical suspicion.
Effusions in mesothelioma II

Don’t forget mesothelioma in cases of relapsing unilateral effusions without explanation

Clinical information? Imaging techniques? Exposure to asbestos?

Use hyaluronan analysis liberally!
Adenocarcinoma

The most common malignancy in effusions
Often the primary tumour is not known
Morphology may give some hints regarding primary organ
  – Papillary clusters, psammoma bodies, intracytoplasmic vacuoles, cell balls, clusters with peripheral palissading, background necrosis, etc
But adenocarcinomas in effusions may look pretty much the same regardless of origin!
Use immunocytochemistry to narrow down the alternatives!
Serous papillary carcinoma of ovary
Breast carcinoma

- Papillary clusters, dense cell balls
Squamous carcinoma

- Squamous carcinoma cells seldom found in effusions
- Late stage lung cancer
- Often dispersed cells, no distinct keratinisation
- Squamous metaplasia in pleural cavity – broncho-pulmonary fistula
- Never report "squamous atypia" in effusions
Squamous carcinoma
Lymphocytic proliferations

- Reactive populations are often monotonous – T-cells
- Diff diagnosis lymphocytic lymphoma!

- Use immunocytochemistry generously
  - Static
  - Flow cytometry
Lymphatic proliferations in effusions

- Tuberculosis – no giant cells if no granulomas in the serosa!
- Viral infections
- Lung carcinoma
- Autoimmune diseases
- Chemotherapy
- Radiation therapy
Lymphoma diagnosis in effusions

- Never lymphoma diagnosis/suspicion based on morphology only
- When in doubt flow cytometry or static immunocytochemistry
Ancillary techniques

- Immunocytochemistry is often needed to arrive at a correct diagnosis and should be used liberally in effusions

- A mesothelioma diagnosis requires immunocytochemical confirmation
Special aspects of immunocytochemistry on effusions

- Effusions pose problems different from those found in specimens containing a pure cell population.
- In a mixed population it may be difficult to be sure in which type of cells the reactivity is seen.
- Often weak unspecific cytoplasmic reactivity in macrophages.
Special aspects of immunocytochemistry on effusions

- Immunoreactivity usually does not differentiate between benign and malignant mesothelial cells (exceptions: desmin and EMA)
- Antibodies that prove mesothelial origin unsuitable to detect a few adenocarcinoma cells hidden among benign mesothelial cells in effusions
Interpretation of immunocytochemistry

- Results from the literature usually based on histology
- Fixation, preparation technique, staining method and protocol affect the result
- Clone important
A myriad of antibodies have been tested, recommended or disregarded.

........so what shall we do??

Remember that a new antibody is of no value if it does not add information – regardless of its specificity and sensitivity

Get familiar a small panel of antibodies
Antibody selection in effusions

A limited panel is sufficient to differentiate between
- Mesothelial proliferations
- Mesothelioma
- Metastatic adenocarcinoma

CEA, BerEp4, EMA, CK5, desmin, TTF-1

Add organ- and tissue "specific" antibodies to narrow down diagnostic alternatives in adenoarcinomas (primary site) and in poorly differentiated malignant tumours
EMA in the differentiation between adenocarcinoma and mesothelioma

Mesothelioma

Adenocarcinoma

EMA with membranous distribution

EMA with cytoplasmic distribution
Serous papillary ovary carcinoma

CA 125

Sialyl

CEA

HBME-1
Squamous carcinoma

CK 14

CAM5.2
Benign lymphocytes in effusions

CD 3

CD20

Ki 67
Hyaluronan analysis I

- HPLC-based method
- Specificity and sensitivity suitable for clinical practice
- Ca 10 ml of the supernatant after centrifugation
- >75 g uron acid/L specific for mesothelioma
- Sensitivity 60%
Hyaluronan analysis II

- Adds information in cases when immunocytochemistry does not give conclusive information
- Hyaluronan/mesothelin ratio (evaluation in progress)
Take home messages - summary

- Don’t forget the macroscopic appearance
- Compare with previous cytology specimens
- Use ancillary techniques liberally
- Get clinical information
- Check subsequent histology but don’t forget that cytology may be right if there is a discrepancy
- Stick to your diagnosis if you feel sure that it is well founded
- Be cautious with mesothelial cells
- Avoid ”no malignant cells” and ”atypia” – because you can do better than that!!!
Final remark

- Effusion cytology is difficult, challenging, exciting and rewarding
- Thank you for your attention – see you again in a while!