Examination of Pleural Effusions

Pleural effusion may be induced by congestion, trauma, inflammation, infection and neoplasia affecting pleura, lungs, heart or mediastinum.
The **clinical signs** of pleural effusion are variable (dyspnoea, thoracic pain, coughing).
A diagnose of pleural effusion is mostly made radiographicly. Fluid can be identified between the lungs and thorax wall and/or within pleural fissures of the lung lobes.
For identifying the cause of the effusion a macroscopic, physical/chemical and cytological examination of a thoracic aspiration is helpful.

Macroscopic findings

Fluid from thorax may appear watery clear (hydrothorax), purulent (pyothorax), milky (chylus) or haemorrhagic (haemothorax). However, the aetiology of the effusion cannot be determined in most cases (fig. 1).

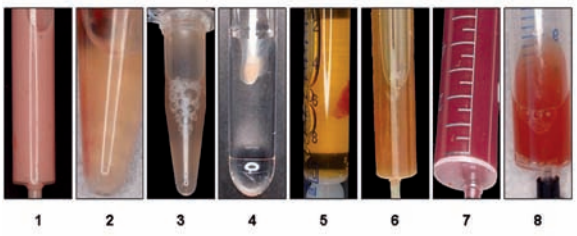

Fig.1 Macroscopic findings of different pleural effusions:
1) Chylothorax, 2) Traumatic effusion, 3) Lymphoma,
4) Positive Rivalta test, 5) FIP, 6) Pulmonary carcinoma,
7) Pulmonary carcinoma, 8) Traumatic effusion

Physical / chemical findings

Physical/chemical examinations of pleural effusions are mostly used to differentiate transudate, modified transudate, exudate and chylus. In most cases an additional cytology is needed to narrow down the aetiology.
For cell count and cytology the fluid should be send in an EDTA-tube.

For chemical analyses (protein, cholesterol and triglyceride) a plain tube or serum tube is recommended.
The LDH value in pleural effusion is used as an inflammation parameter, as LDH indeed a granulocyte enzyme is. But also decay of neoplastic or mesothelial cells releases LDH. LDH values > 200 IU/l are considered as markers for exudative processes.
pH values < 7.4 speak for an inflammatory non-neoplastic process. Are the pH values < 7.4 plus a glucose value < 30 mg/dl (normal 70-100 mg/dl) together with > 85% neutrophils then a septic effusion is present.
Pleural effusions caused by malignant tumours are also often exudative but they have normal or high pH values (< 7.4), glucose values between 10-80 mg/dl and less than 30% neutrophils.
Slight varying reference values are found in the literature. In **Table 1** reference values with the highest accordance are shown.

Cytology findings

By the cytological examination the numbers of cells are assessed followed by the identification of the different cell types.
It is recommended to submit air-dried smears made from effusion or its sediment (centrifuge 5 min by 165-365G / 1000-1500 rpm) depending on the density of cells in the effusion.
It is important to note that a „normal“ pleural effusion cytology do not exist, as each clinical/radiological detected effusion is per se always pathological.
Due to the number and kind of cells (fig. 2) found in an effusion a conclusion on pathogenesis can be made in many cases **(Table 2)**.

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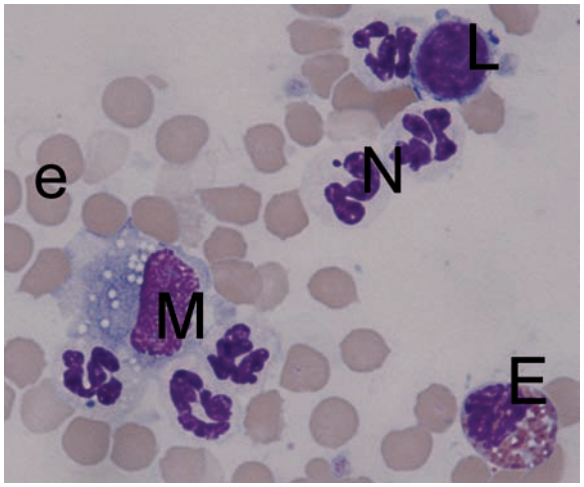

Fig. 2: Neutrophil granulocytes (N), macrophage (M), eosinophil granulocyte (E), activated lymphocyte (L) and multiple erythrocytes (e) in a pleural effusion

Mesothelial cells may contain one, two or multiple round nuclei. Various amounts of homogenous cytoplasm are present. The frequently observed coronas are artefacts.

Macrophages are present in most effusions. Their cytoplasm is with varying degree highly vacuolated and they contain a bean shaped hypo-chromatic nucleus.

The differentiation between macrophages, mesothelial cells and carcinoma cells is not always possible.

Neutrophilic granulocytes can be found in low numbers in almost every effusion. It is possible to distinguish degenerated (infection) from non-degenerated neutrophils. Intracellular infectious agents may be recognized.

Lymphocytes can be seen in low numbers in nearly all effusions. An increased number is found in chylus. In lymphomas the lymphoid cells show evidence of malignancy.

Mast cells are rarely found in pleural effusions, but seen in low numbers during inflammations and in high numbers by intra-thoracic mast cell tumours.

Eosinophilic granulocytes may be found in cases of pneumothorax, heart worm disease or hypersensitivity reactions.

Erythrocytes are induced by trauma, increased vascular permeability or coagulation diseases, or they are mechanical induced during thoracocentesis.

Thrombocytes indicate acute haemorrhage or a contamination during thoracocentesis.

All kinds of neoplastic cells (Fig. 3) deriving from various primary tumours could in principle be found in pleural effusion (see below).

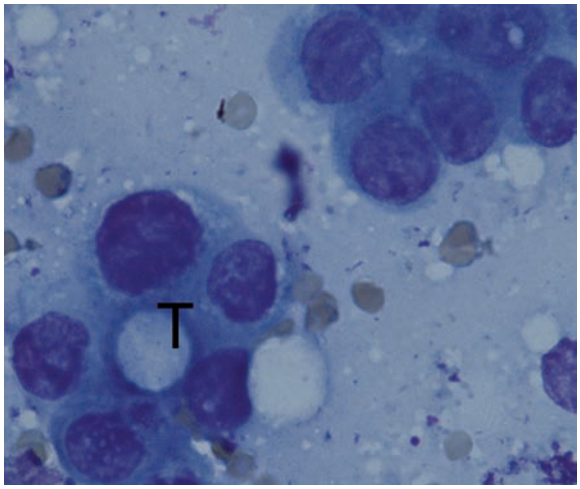

Fig. 3: Tubular epithelial formation (T) in pleural effusion from a cat with lung carcinoma.

Haemothorax (hemorrhagic effusion) are caused by trauma, ruptured neoplasms or coagulation diseases (e.g. rodenticides poisoning). Macroscopically it is a watery red fluid, but biochemically the effusion values mimic the ones found in peripheral blood. Cytologically high numbers of erythrocytes are found. After 2 days erythrophagocytosis by macrophages can be observed and after 5 days haemosiderin.

By a **transudate / modified transudate** the effusion is caused by an increased hydrostatic or oncotic pressure. The fluid is macroscopically colourless or light yellow (hydrothorax). The biochemical examinations, especially the proteins, serve as a differentiator between a hydrostatic (cardiac) and an oncotic (hypoproteinemic) transudate.

Cytological only few lymphocytes, mesothelial cells, macrophages or neutrophils may be found. The term “modified transudate” is exclusively

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used in veterinary medicine to describe the broad overlapping of findings in transudate and exudate.

Chylothorax is caused by rupture of the ductus thoracicus or due to permeability disorders of the lymphatic system. In cats chylothorax is often seen by hypertrophic or restrictive cardiomyopathy. In dog neoplasms, hernia or cardiac disease are possible causes of chylothorax.

Macroscopically chylus is milky white or light pink. Chylothorax belongs formally to the modified transudates and is characterized by a high increase of triglycerides (>100 mg/dl) together with almost normal cholesterol values. Cytologically multiple lymphocytes, macrophages, a few neutrophils and mesothelial cells are found, together with the typically small fat drops.

Exudate arises from inflammatory induced increased vessel permeability. These effusions are often cloudy and red-brown in colour (pyothorax). Cytologically exudate is characterized by degenerated and non-degenerated neutrophils, macrophages and activated mesothelial cells.

By septic effusions (e.g. streptotrichosis) both intra- and/or extracellular pathogen structures may be found.

One of the classical forms of inflammatory pleural effusions is the humid form of feline infectious peritonitis **(FIP)**. Here the effusion is yellow and partly viscid. Clinically the FIP-effusion is characterized by a specific gravity > 1030 and a positive Rivalta test caused by the high protein level (> 35-45 g/l). An additionally performed electrophoresis shows an albumin/globulin-ratio of < 0.8. Cytologically only few cells are found (1500-2000 cells/μl) as non-degenerated neutrophils, macrophages, lymphocytes and plasma cells as few mesothelial cells embedded in protein rich fluid. In rare cases also cell rich effusions (up to 6000 cells/μl) may be seen in FIP.

Pleural effusions in neoplastic diseases are caused by the blockade of lymphatic drainage of the serosa and secondary inflammation. Macroscopically these effusions cannot be distinguished from effusions of other aetiologies. They may have characteristics of transudates to exudates, when a secondary inflammatory reaction is present. Both cell count and protein concentration can vary widely.

The primary neoplasm may be located both within the thorax or extra-thoracic.

Intra-thoracic neoplasms are primary lung carcinomas, pulmonary metastases, mediastinal carcinomas, lymphomas, thymic lymphosarcoma and rarely thymomas and mesotheliomas. Diagnosis of mesotheliomas is only possible histologically or immunohistochemically.

If the primary neoplasm is located extra-thoracic the neoplastic cells reach the pleural cavity by pulmonary metastases or the lymphatic system.

Cytological findings vary depending on the type of neoplasm.

Negative findings of neoplastic cells in the pleural effusion do not rule out a possible neoplasia!

The cytological criteria of malignancy are: firstly altered nucleus structures as un-rounding of the nuclei, granulated chromatin, nucleoli and a changed nucleus-plasma ratio. Secondly the appearance of cell clusters (e.g. carcinomas or mesotheliomas). However, no cell clusters are formed by lymphomas and only very small clusters may be build by macrophages and activated mesothelial cells.

Conclusion is that pleural effusion cytology is very helpful as a diagnostic tool, when the clinical results and macroscopical and biochemical findings are taken into account.

A meaningful interpretation is therefore only possible when the clinical and radiological results are known. A final diagnosis or the cause of the effusion cannot be given in each case. Here re-testing or other diagnostics (e.g. thoracoscopy, biopsy) are needed.

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Table 1: Biochemical parameters useful in differentiating pleural effusions

	Specif. gravity	Protein g/l	Cell count /µl	Cholesterol/ Triglyceride ratio	LDH IU/l	pH	Glucose mg/dl
Transudate	< 1018	< 25 Rivalta negative	< 1000	> 1	< 200	~ 7,4	70-100
Mod. Transudate	1018-1025	25-75 Rivalta negative / low positive	1000-7000	> 1		~ 7,4	70-100
Exudate	> 1025	> 30 Rivalta positive	> 7000	> 1	> 200	< 7	< 30
Chylus	> 1018	> 25	variable	< 1 Triglyceride > 100 mg/dl		~ 7,4	70-100
FIP	> 1030	> 35-45 Rivalta positive Albumin:Globulin < 0,8	1500-2000		> 300	~ 7,4	< 70
Neoplastic effusion	> 1018	> 25	variable	> 1	200-1600	≥ 7,4	10-80
Hemorrhagic effusion	> 1025	> 30	> 1000	> 1		~ 7,4	-

Table 2: Cytological findings in different types of pleural effusions

	Lympho-cytes	Mesothelial cells	Macro-phages	Deg. Neutrophils	Non-deg. Neutrophils	Erythro-phils	Neoplastic cells
Transudate	(+)	+	+	-	(+)	-	-
Mod. Transudate	++	+	+	-	+	(+)	-/+
Exudate							
Infectious	+	+	+/++	+++	+	(+)	-
Non- infectious	+	+	+/++	-	++	(+)	-/+
Chylus	+++	+	+/++	-	+	-	-
Pseudo-chylus	++	++	++	+	++	(+)	-
FIP	+	-	+	-	+	-	-
Hemorrhagic effusion	(+)	+/++	+	(+)	(+)	+++	-
Neoplastic effusion	+	+	+	-	+	(+)	++/-

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