Management of malignant pleural effusion

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Introduction
and outline of this thesis
Pleural Effusion

Pleural effusion is fluid that accumulates between the parietal and visceral pleura. In a physiologic balance, this fluid is ‘produced’ by the parietal and visceral pleura and absorbed by the parietal pleura. Increased production, decreased breakdown and a combination of both disturbs this equilibrium.

Pleural effusion can be a manifestation of a variety of diseases. Differentiation between those causes can be made on past medical history, radiologic examination and fluid analysis. In 1972, doctor Richard Light demonstrated that a combination of LDH and protein levels in both pleural and serum samples differentiated more accurately between transudate and exudate (Table 1) than these values individually. Pleural fluid is not likely to be caused by malignancy in patients without a medical history of cancer; in a large study reviewing almost 6000 pleural effusions, less than 10 percent of effusions were caused by malignancy. Differentiation between transudate and exudate contributes to the diagnosis even without a history of malignancy, since most MPEs are exudates. It must be emphasized that differential diagnosis for exudative pleural effusion is broader than MPE alone.

<table>
<thead>
<tr>
<th></th>
<th>Protein PF/serum ratio</th>
<th>LDH PF/serum ratio</th>
<th>LDH ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transudate</td>
<td>&lt; 0.5</td>
<td>&lt; 0.6</td>
<td>&lt; 2/3</td>
</tr>
<tr>
<td>Exudate</td>
<td>≥ 0.5</td>
<td>≥ 0.6</td>
<td>≥ 2/3</td>
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**TABLE 1 - Light’s criteria**
PF= pleural fluid; ULN= upper limit of normal; LDH= lactate Dehydrogenase

Symptoms

MPE can cause a variety of symptoms. Most common complaint is dyspnea, followed by coughing and chest discomfort. The differential diagnosis of dyspnea in end-stage cancer patients is more diverse than in healthy people and fluid aspiration helps to assess the impact of MPE on dyspnea. Pleural involvement of (metastasized) malignancy means that curation is no longer an option. The presence of malignant pleural effusion has a negative impact on the quality of life of patients with metastasized malignancy. Treatment of malignant pleural effusion should therefore focus on symptom relief rather than survival improvement. More than other endpoints, patient reported outcomes should be used to monitor treatment effect of pleural interventions.
Diagnosis

The sensitivity of cytopathologic examination increases with the number of pleural taps. (8,9,10) Thoracoscopy is often performed when pleural fluid recurs and no malignant cause is demonstrated. An alternative for a thoracoscopy is a closed pleural biopsy, which can also identify the nature of the origin of the effusion. 8 There is an on-going debate on the optimal volume of pleural fluid needed for cytopathologic examination, 10-12 More importantly, the sensitivity of cytopathologic examination varies by tumor type. 9;13 It is clear that the probability that a pleural effusion is of malignant origin rises when patients suffer from any malignancy. In a post-mortem series of patients with malignancy, 28% of patients had pleural metastases and approximately half of them (15%) presented with MPE. 14 MPE is most frequently seen in patients suffering from malignant mesothelioma, lung cancer or breast cancer and lymphoma. 15

Both special radiology and nuclear medicine are not standard of care in diagnosing MPE and their role might be underestimated. Pleural involvement can be demonstrated by a Chest X-ray (CXR), Computed Tomography (CT-scan) and 18-FluoroDeoxyGlucose-Positron Emission Tomography (18FDG-PET). 16;17 Ultrasonography enables the pulmonologist to diagnose malignant pleuritis and to perform pleural interventions safely simultaneously. 18-21 Ultrasound examination of the thorax has now become standard in most countries to facilitate the examination of MPE.

Prognosis

Patients with malignant pleural effusion have a poor prognosis. 15 Moreover, patients with metastasized malignancy due to pleural involvement have even worse prognosis than patients with metastases to other organs. 22;23 Since 2007, NSCLC with pleural involvement is considered as metastasized disease. Predicting overall survival is hard, as was illustrated by the largest study on talc pleurodesis comparing thoracoscopic talc instillation with bedside administration of talc sludge by chest drain. 24 Despite the inclusion criteria of an estimated life expectancy of at least 2 months, approximately half of patients died within those 2 months making MPE a symptom of a grave prognosis.
Treatment

Malignant pleural effusion can be treated by either local or systemic treatment. Some primary tumors and their pleural metastases respond very well to systemic treatment, preventing patients from repeat pleural interventions. Recurrence rates of MPE are determined by a number of factors. One of them is the tumor type. MPE in chemo-sensitive tumors like small cell lung cancer (SCLC), ovarian cancer or lymphoma is mostly responsive to systemic treatment. Patients with these malignancies in particular can be treated with systemic antitumor therapy.

Therapeutic thoracenteses were traditionally limited to drain 1-1.5 L in order to prevent re-expansion pulmonary edema (RPE). However, RPE in MPE is a rare phenomenon, but has been reported in the literature. To avoid RPE, pleural manometry might be of additional value in predicting lung expansion and pleurodesis success. Therapeutic drainages can be performed repetitively, necessitating the patients to visit the hospital regularly on an outpatient basis. The down side of this approach is that each single thoracentesis is an invasive intervention with risk of bleeding, infection, pneumothorax or the development of a tract metastasis.

More definitive pleural treatments are talc pleurodesis (via either bedside chest drain, or thoracoscopy) and insertion of an indwelling pleural catheter (IPC, Figure 1A). According to most guidelines, talc pleurodesis can be performed when the lung can still expand and patient’s life expectancy is at least one month. The physician’s assessment of lung expansion and survival guides decisions on talc administration.

Talc pleurodesis vs indwelling pleural catheter

In general, patients who undergo pleurodesis are admitted to the hospital for 5-7 days. Results of a Dutch multicenter study show that talc was injected in only 75% of patients. In approximately 15% of patients no talc was instilled due to poor lung expansion. Other reasons for withholding talc were: persisting high fluid production (n=3), rapid clinical deterioration (n=3), absence of malignant cells in pleural effusion (n=3), technical drain problems (n=2), chylothorax and empyema (both n=1). Success rate in an intention-to-treat analysis was 32 percent. Success rate in this study increased when patients in whom no talc was instilled were omitted from analysis. Regarding only patients who were alive at 6 weeks after performed talc instillation, pleurodesis success increased further to 71%. The reported success rates of pleurodesis are also influenced by the elastance of the lung, the pH, tumor type and possible systemic treatment, and performance status.
Fluid recurrence following pleurodesis can be invasively treated by repetitive aspirations, repeat talc pleurodesis, insertion of an indwelling pleural catheter. Those drains are also called tunneled pleural catheters (TPCs), but will be consequently named IPCs in this thesis. Vacuum bottles (Figure 1B) can be connected to these IPCs. These catheters enable the patient and caregivers to drain the fluid themselves on an ‘as needed’ basis. Since an IPC is an effective MPE treatment following failed pleurodesis or in patients with a trapped lung syndrome, 35-37 studies have been initiated to investigate whether IPCs would adequately manage MPE in a frontline setting as well.

**Outline of this thesis**

*The first part of this thesis* focuses on IPCs in MPE management. In an invited review, the (dis)advantages and prejudices of IPCs are described (*Chapter 1.1*). Since costs and reimbursement issues are the main reasons in the Netherlands to withhold patients from IPCs, we performed a retrospective analysis of a prospectively collected database. In this database, we registered patient characteristics (gender, tumor type), survival data and IPC supplies. Material costs of IPC treatment were calculated and are presented in *Chapter 1.2*. Results of a multicenter randomized controlled trial comparing talc pleurodesis (TP) with IPC as first line treatment in The Netherlands are presented in *Chapter 1.3*.

*In part two of this thesis* therapeutic thoracenteses are evaluated. Since lung expansion is one of the most important predictors for lung expansion, we focused on lung expansion. Results of a survey on the interpretation of Chest X-rays (CXRs) are discussed in *Chapter 2.1*. Chest physicians of The Netherlands and Belgium were asked to review 50 CXRs from consecutive patients previously treated for MPE. For each CXR, they were asked whether they considered the lung to be expanded; whether they would instill talc and to estimate the success rate. In the next chapter (*Chapter 2.2*), pleural manometry was used for early recognition of lung expansion or trapped lung. In contrast to more frequently used methods, we used software to monitor/record pleural pressure with a high frequency. We observed pleural pressure swings during respiration. In *Chapter 2.3* we show patient reported outcomes (PROs) after therapeutic thoracentesis and correlate these scores to re-interventions. Finally, in a letter-to-the-editor we comment on a predictor study for definitive MPE treatment. (*Chapter 2.4*)
**FIGURE 1A - Inwelling pleural catheter**
An IPC with drainage holes (visible on the right side of the picture). The subcutaneous tunneled cuff (1) provides fixation. A vacuum bottle (Figure 2B) can be attached to a valve (2) at the end of the external part.

**FIGURE 1B - Vacuum bottle**
A vacuum bottle with an access tip (1) which can be inserted into the valve. The flow of pleural fluid can be controlled by the blue button. Full flow can be generated when the slider (2) is pushed over the button.