Managing Malignant Pleural Effusions (MPE)

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Aaargh- Happy Talk Like a Pirate Day!!!
Disclosure

• SuperDimension Inc.
  – PI for single center study
• Others: Aeris, Spiration, Broncus, CSA Medical, BI, Pfizer, Actilion, Encysive, Telacris, Asthmatx, Ethicon/J&J, Boston Scientific, Covidien
• AlphaOne Foundation Grant

Suspected MPE

1. Prove it’s malignant
   – Thoracentesis
     • US guided preferred
     • Assess for post tap symptoms and CXR improvement
   – Medical Pleuroscopy
   – VATS
   – Closed Pleural Biopsy
Proven MPE

1. Assess patient for best pathway
   1. Assess performance status
   2. Choose Management Strategy
      - VATS
        • Pleuro-peritoneal Shunt- Chylothorax
        • Decortication
        • Talc
      - Indwelling Pleural Catheter
        • (tunneled pleural catheter)
      - Chest Tube with Pleurodesis
      - Repeated Thoracentesis

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MPE

- Annual incidence:
  - 150,000-175,000 cases/year in the US
  - 40,000 cases/year in the UK

- Palliative treatment may be most compassionate

- Prognosis of patients with MPE remains poor:
  - median survival after a malignant effusion diagnosis: 4-9 months


MPE

- Performance status most accepted and may be only known predictor of survival in MPE:
  - KPS score ≥ 70: median survival of 395 days
  - KPS score ≤ 30: median survival of 34 days

- Pleurodesis after IPC and survival:
  - Median survival 2.92 months (95% CI 2.50 to 3.91)
  - No pleurodesis 1.48 months (95% CI 1.18 to 1.71)
  - Pleurodesis 9.5 months (95% CI 6.64 to 12.39)

MPE Etiology

MPE: PATHOGENESIS

- Exact mechanism: not entirely understood
- Simple presence of pleural metastasis is not enough for its pathogenesis
- Only ~ 60% of patients with proven pleural metastases develop pleural effusions

MPE: PATHOGENESIS

- Paramalignant pleural effusions

  - fail to demonstrate evidence of malignancy in the fluid and pleural surface

  - secondary to local or systemic tumor effects, cancer therapy complications or concurrent nonmalignant disease

Sahn SA, Eur Respir J 1997;10:1907-1913
MPE: DIAGNOSIS

- Clinically significant pleural effusion (>10 mm thick on US or lateral CXR): thoracentesis

- Therapeutic thoracentesis is almost always performed
  - Symptom improvement?
  - Lung reexpansion?

- Fluid analysis: usual tests to differentiate a transudate from an exudate and other “routine” tests

- At least 50 ml should be sent for cytologic analysis

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Pleural Effusion- prove it’s malignant

- Transudate MPEs: 2-5%\(^1,2\)

- The majority of these patients have a clear etiology for their transudate

- Yield of cytologic (thoracentesis) examination in establishing a diagnosis of cancer is quite variable:\(^3\):
  - sensitivity of 10% for mesothelioma
  - sensitivity of over 70% for metastatic adenocarcinomas

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Pleural Effusion- prove it’s malignant

• If lymphoma suspected: check flow cytometry¹

• Pleural fluid mesothelin²: promising tumor marker in the diagnosis of mesothelioma

• You can get mutational analysis from this type of specimen
  – ALK, K-Ras and EGFR for Adenocarcinoma- CCF data

• If cytologic examination is (-) for malignancy, AND confirming MPE important → thoracoscopy/Medical Pleuroscopy:
  - sensitivity for pleural malignancy is generally ~ 90%³,⁴

¹. Shannon V et al. In press

The semirigid pleuroscope is shown. The design, especially of the handle, is similar to that of a flexible bronchoscope. The proximal portion is stiff, with a flexible distal tip. A working channel allows for the usage of the standard instruments that are used with the flexible bronchoscope. A biopsy forceps is shown.

Figure Legend:
The semirigid pleuroscope is shown. The design, especially of the handle, is similar to that of a flexible bronchoscope. The proximal portion is stiff, with a flexible distal tip. A working channel allows for the usage of the standard instruments that are used with the flexible bronchoscope. A biopsy forceps is shown.
Effectiveness and safety of diagnostic flexi-rigid thoracoscopy in differentiating exudative pleural effusion of unknown etiology: a retrospective study of 215 patients

Bao-An Gao¹, Gang Zhou¹, Li Guan¹, Ling-Yun Zhang¹, Guang-Ming Xiang¹

J Thorac Dis 2014;6(5):418-443

- 215 Patients with undiagnosed exudative effusion
  - Non-diagnostic Thoracentesis
- 190/215- Definitive diagnosis (88.4%)
  - 97 Cancer, 91 TB
- Only complication reported was fever in 6
Medical Pleuroscopy

- Single port Thoracoscopy
- Moderate sedation
- Able to biopsy and perform talc insufflation
- Able to Guide IPC placement
- Not ideal when lung entrapped
- Not ideal with adhesions/loculations
- Less range than typical VATS

MPE: THERAPEUTIC OPTIONS

Table 1. Treatment options for malignant pleural effusions (MPEs).

<table>
<thead>
<tr>
<th></th>
<th>Repeated thoracentesis</th>
<th>Indwelling catheter</th>
<th>Tube plus slurry</th>
<th>Thoracoscopy plus pleurodrain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbidity</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Prolonged effect</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Inpatient stay</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Continuous outpatient care</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Repeat intervention required</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cost per procedure</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

 Repeat Therapeutic Thoracentesis

- Majority of patients with MPE: reaccumulation of fluid and recurrence of symptoms within 30 days
- Repeated thoracenteses:
  - “Slow” reaccumulation of fluid
  - Cancers that commonly respond to therapy (non-lung)
  - Unlikely to survive beyond 1 to 3 months or cannot tolerate other more interventional procedures
    - ECOG 3-4
- Frequent repeated thoracenteses may trigger fluid loculation

Heffner JE, Klein JS. Mayo Clinic Proceedings 2008;83:235-251
Chest Tube Chemical Pleurodesis

- Fallen out of favor in current clinical environment as first choice but helpful in some specific groups
  - ECOG 0-2-able to tolerate procedure but not willing to have VATS (medical or patient specific factors), Long Survival Times, Unable or unwilling to manage IPC
- Limited effectiveness alone
- Hospital Confinement/Cost/Discomfort

Agent

**TABLE 5: Available and Investigational Sclerosing Agents for Pleurodesis**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Reported success rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mineral Talc</td>
<td>70-100</td>
</tr>
<tr>
<td>Anesthetic</td>
<td>60-81</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>66-100</td>
</tr>
<tr>
<td>Quinacrine</td>
<td>64-100</td>
</tr>
<tr>
<td>Antiseptic</td>
<td>64-96</td>
</tr>
<tr>
<td>Iodopovidone</td>
<td>64-96</td>
</tr>
<tr>
<td>Silver nitrate</td>
<td>96-100</td>
</tr>
<tr>
<td>Antineoprotein drug</td>
<td>64-84</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>64-84</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>64-84</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>64-84</td>
</tr>
<tr>
<td>Bacterial product or component</td>
<td>65-92</td>
</tr>
<tr>
<td>Corynebacterium parvum</td>
<td>65-92</td>
</tr>
<tr>
<td>Streplococcus aureus supernagen</td>
<td>100</td>
</tr>
<tr>
<td>ONK32</td>
<td>55-79</td>
</tr>
<tr>
<td>Cytochrome</td>
<td>62-100</td>
</tr>
</tbody>
</table>

*Success rates variably reported as rate immediately after pleurodesis or rate obtained at different time points after pleurodesis.

Heffner JE, Klein JS. Mayo Clinic Proceedings 2008;83:235-251
MPE: CHEMICAL PLEURODESIS

• Pleurodesis for MPE: Cochrane review 2004

• Talc vs other sclerosants in 10 RCTs with 308 pts:
  - talc more effective sclerosant → RR for success of pleurodesis of 1.34 (95% CI 1.16 to 1.55)

• Mortality and talc (vs others): 6 studies with 186 participants
  - no significant differences based on the RR of death (RR 1.19, 95% CI 0.80 to 1.77)

Shaw PHS, Agarwal R. Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD002916

MPE: CHEMICAL PLEURODESIS

CONT.

• Thoracoscopic vs tube thoracostomy with talc as sclerosant based on 2 studies with 112 participants:
  - thoracoscopic pleurodesis more effective: RR of non-recurrence of effusion is 1.19 (95% CI 1.04 to 1.36)

Technical Issues- VATS better (even better than medical Pleuroscopy) due to getting all around the lung.

Shaw PHS, Agarwal R. Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD002916
Chest Tube Pleurodesis Management

- Stop NSAID and Steroids prior to treatment
- Hold anticoagulants
- Small bore chest tube
- Opiates, intrapleural lidocaine during the treatment
- May need to repeat if drainage is still high after 48 hours
- Fall back is IPC
- Success rates 60-90%

Indwelling tunneled pleural catheter (TPC)

MPE: IPC

Tremblay A, Michaud G. Chest 2006;129:362-368
223 patients

Symptom control at the 2-week follow-up visit:

- Complete: 97 (38.8%)
- Partial: 125 (50%)
- None: 9 (3.6%)

- SP: 103 out of 240 (42.9%)
- Median time to catheter removal in SP: 59 days (95% CI, 46 to 72 days)
- No further ipsilateral procedures needed in 90.1%
- # of failed insertions ↓'ed over 4 quartiles: 10%, 8.2%, 0%, and 2% (p=0.025)
Palliation and Pleurodesis in Malignant Pleural Effusion

The Role for Tunneled Pleural Catheters


- Median overall survival from catheter insertion was 3.7 months
- 380 (91%) did not need additional effusion-directed procedure

Use of tunneled catheters for malignant pleural effusions in patients fit for pleurodesis

A. Tremblay, C. Mason and G. Michaud

- Retrospective database analysis: 250 IPC’s insertions
- Study subgroup (109 procedures):
  - patient survival was > 90 days
  - ≤ 20% residual pleural effusion was noted following 2 weeks of drainage
Use of tunneled catheters for malignant pleural effusions in patients fit for pleurodesis

A. Tremblay, C. Mason and G. Michaud

- SP: 76 out of 109 (70%)
- SP: mean of 90 days
- Complete or partial symptom control: 100% at the 2 weeks follow-up

Eur Respir J 2007;30:759-762

MPE: IPC Spontaneous Pleurodesis (SP)

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Comparison of Large Series Studies on Tunneled Pleural Catheters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
<td>No. of Patients (Catheters)</td>
</tr>
<tr>
<td>Suzuki (current study)</td>
<td>355 (418)</td>
</tr>
<tr>
<td>Trembley (Chest 2006)</td>
<td>223 (250)</td>
</tr>
</tbody>
</table>

SP, spontaneous pleurodesis; CXR, chest x-ray.
Effect of an Indwelling Pleural Catheter vs Chest Tube and Talc Pleurodesis for Relieving Dyspnea in Patients With Malignant Pleural Effusion

The TIME2 Randomized Controlled Trial

Figure 2. Comparison of Dyspnea and Chest Pain Among Patients Treated With Indwelling Pleural Catheters (IPCs) vs Patients Treated With Chest Tube and Talc Slurry Pleurodesis (Talc) at 42 Days

Dyspnea

Chest pain

The bars represent the mean visual analog scale (VAS) score for dyspnea and pain.

Davies HE, Mishra EK, Kahan BC et al. JAMA 2012;307(22):2383-2389

- Mean IPC drainage in the first 42 days was 2x/week
- 26 out of 51 (51%) IPCs achieved “spontaneous pleurodesis”
- Further pleural procedures:
  - 12 talc patients (22%)
  - 3 (6%) in the IPC group

(OR, 0.21; 95% CI, 0.04-0.86; P=.03)

Davies HE, Mishra EK, Kahan BC et al. JAMA 2012;307(22):2383-2389
IPC: cost effectiveness

- Using an estimated survival of 6 months:\(^1\)
  - talc pleurodesis was more cost effective: $8,170
  - IPCs: $9,011

A second study did 2 assumptions:

- Using an estimated survival time of 3 months:\(^2\)
  - Lowest cost with repeat thoracentesis: $4,946
  - IPC: $6,450
  - Bedside pleurodesis: $11,224
  - Thoracoscopic pleurodesis: $18,604

- Using an estimated survival time of 12 months\(^2\)
  - IPC and bedside pleurodesis similar in cost: about $13,000

IPC in MPE

- Minimally invasive, ease of use, limited morbidity
  - Requires a system approach to longitudinal management
  - Home health care of competent family member to help manage
  - Clean environment
  - Follow-up for complications/clogging/infection management

- Outpatient procedure
  - Local practice variables
  - 23 hours obs, done with VATS/Medical Pleuroscopy

- Patients with poor PS: may not be suitable for more aggressive approaches

- IPC: rarely, if ever, interferes with ongoing active CA therapy

- Patients fit for more aggressive modalities: do they worsen PS?
  - may interfere with planned chemotherapy and/or radiation

Technical Limits: loculations, entrapped lung: where VATS still has value.

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Table 3: Complications in 400 patients with malignant pleural effusion and thoracicoscopic talc poudrage performed.

<table>
<thead>
<tr>
<th>COMPLICATIONS</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged air leak</td>
<td>26</td>
<td>(6)</td>
</tr>
<tr>
<td>Renal pain</td>
<td>10</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Subcutaneous emphysema</td>
<td>20</td>
<td>(5.0)</td>
</tr>
<tr>
<td>Air leak encumbered follow</td>
<td>3</td>
<td>(0.7)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>4</td>
<td>(1)</td>
</tr>
<tr>
<td>Lung separation</td>
<td>4</td>
<td>(1)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>4</td>
<td>(1)</td>
</tr>
<tr>
<td>Resistant pneumothorax</td>
<td>2</td>
<td>(0.5)</td>
</tr>
<tr>
<td>Tumor recurrence at port site</td>
<td>3</td>
<td>(0.5)</td>
</tr>
<tr>
<td>Mucosal infection</td>
<td>2</td>
<td>(0.5)</td>
</tr>
<tr>
<td>Empyema thoracis</td>
<td>2</td>
<td>(0.5)</td>
</tr>
<tr>
<td>Pleurisy embolism</td>
<td>2</td>
<td>(0.5)</td>
</tr>
<tr>
<td>Neoplastic pulmonary edema</td>
<td>1</td>
<td>(0.2)</td>
</tr>
</tbody>
</table>

Journal of Cardiothoracic Surgery 2010, 5:27
Rapid Pleurodesis for Malignant Pleural Effusions
A Pilot Study

30 Patients with recurrent MPE
Medical Pleuroscopy with Talc insufflation
IPC placed under direct vision
24fr chest tube placed in pleuroscopy port
-20cm
Admitted to hospital
IPC drained TID day one, BID day 2-3 then daily until <150ml/day
Removed with clinical and radiographic
Conclusions
Management of MPE

• Generally poor prognostic sign: especially in lung cancer

• Factors of significant importance:
  - Response to thoracentesis and lung re-expansion
  - Performance status
  - Patient’s life expectancy

• Based on current evidence:
  - VATS and or Chest tube directed talc pleurodesis (preferably via thoracoscopic poudrage) are reasonable first options for patients with ECOG PS 0-1, and maybe 2
  - IPC (with good medical/home support) or repeated thoracentesis probably better options for ECOG PS 3-4

Thank You!
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