Quick Review: Mesothelioma
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Citation

Abstract
This article reviews briefly the main points of mesotheliomas.

DEFINITION AND HISTORY
The term was first used in 1921 by Eastwood & Martin to describe primary tumors of the pleura

- At that time, the diagnosis was extremely controversial (required autopsy examination)
- Today, the diagnosis is still problematic
  - 15% of cases cannot be differentiated from adenocarcinoma
- Wagner, South African miners [Br J Ind Med]
  - first evidence implicating asbestos in the pathogenesis
  - landmark paper, began widespread investigation
- Incidence has reached “Epidemic”
  - European Experience: Expected Peak, 2010 - 2020 (2,700 - 9,000 deaths/yr.)
  - U.S. Experience: Peaked in the 1970's & since 1980 the incidence has been decreasing

The increase in general incidence has been attributed to the widespread use of asbestos in the post-World War II period [McDonald 1987]

- Precautions were first taken in the U.S.
- Europe was “slow” to respond
- Effect on third-world countries
- Industrialized Countries

- 2 per million in females
- 10 - 30 per million in males regional differences are due to the level of industrial activity
- Areas with shipyards are at the highest risk
- Type is also a Factor: Crocidolite & Amosite > Chrysotile

The occurrence of mesothelioma is related to an Occupational Exposure to Asbestos.

Non-occupational environmental exposure leading to it’s development is uncommon

- Only 7.2% of asbestos workers, will develop the disease
- Up to 50% of patients, do not have any history of exposure

Cases due to exposure in buildings with asbestos insulation are extremely rare!

THE RISK
[Hughes et al. 1986: “quantitative risk”]
[Lilienfield 1991: “four cases in school teachers”]

There has never been prospective evidence to support the widespread removal of asbestos insulation...

3 Main Groups:

- Benign Localized Mesothelioma
  - “pleural fibroma”
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- Unassociated with asbestos exposure
- Paraneoplastic syndromes occur in 1/3
  - Migrating Thrombosis
  - Thrombocytosis
  - Hemolytic Anemia
  - Hypoglycemia
  - Hypercalcemia
  - Pulmonary Hypertrophic Osteoarthropathy [Boutin 1998]
  - Arise from the visceral pleura
  - Unless incomplete, surgical resection is curative

- Malignant Localized Mesothelioma
  - 20% of all primary malignant pleural tumors are localized
  - Present as Symptomatic Masses
  - Difficult to differentiate from Chest Wall Neoplasms
  - Treatment
    - Wide enbloc excision of all involved tissue
    - Lung, Chest Wall, Soft Tissues, & Skin
    - With incomplete excision, the prognosis approaches MDM
    - External beam radiation is of little benefit

- Malignant Diffuse Mesothelioma
  - Classical form
  - Related to exposure
  - Latent Period of 20 years
  - Smoking is an associated factor
    - not for mesothelioma, but for overall survival rate

TYPICAL SCENARIO
Middle-aged man with pleuritic chest pain, shortness of breath, & a clear history of asbestos exposure

3 CELL TYPES:
- Epithelial Type: 50% of cases
  - most often confused with adenocarcinoma
- Mesenchymal Type: 16% of cases
- Mixed Type: 34% of cases

PATHOGENECITY:
Benign pleural plaques are the most common manifestation of asbestos exposure
- usually develop on the parietal or diaphragmatic pleura
- malignant mesothelioma is thought to originate from the parietal pleura
- high concentrations of asbestos fibers in the lung are associated with bronchial carcinoma [Antilla 1993]

CLINICAL POINTS:
- Mean Age of Patients: 60
  - has been reported in children (unrelated to asbestos) [Fraire 1988]
- Clinical signs/symptoms depend on the stage
  - TNM Classification
  - Early-Stage Disease: Symptoms are Rare
    - Late-Stage Disease: Pain, Dyspnea, Moderate Effusion
The initial chest radiograph leading to a diagnosis of mesothelioma reveals a pleural effusion 92% of the time
- 7% of the time, a Multinodular Pleural Tumor was found
- 0.5% of the time, an Empyema
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- 0.5% of the time, a Spontaneous Pneumothorax [Boutin 1993]

On thoracentesis, the pleural fluid is an Exudate with little evidence of inflammation & a high number of mesothelial cells

- Cytology of the fluid is 30% sensitive! [Renshaw 1997]
- Removal of the pleural fluid improves the possibility of establishing the diagnosis

DIAGNOSTIC WORK-UP
- CXR (with thoracentesis)
- Chest C.T.
  - irregular, nodular pleural thickening
  - spread into the diaphragm, pericardium, chest wall, or mediastinal lymph nodes is difficult to assess [Masilta 1991]
- Thoracoscopy with Biopsy
- MRI

STAGING
- Stage I: tumor isolated to ipsilateral pleura or lung
- Stage II: tumor invades chest wall, mediastinum, pericardium, or contralateral pleura
- Stage III: tumor involves both thorax & abdomen
- Stage IV: distant blood-borne metastases

EXPECTED SURVIVAL:
- Stage I: 16 months
- Stage II: 9 months
- Stage III: 5 months [Cohen 1995]

ESTABLISHING THE DIAGNOSIS
Thoracoscopy is indicated in any patient without a precise histopathological diagnosis in whom clinical & laboratory findings raise the suspicion of mesothelioma

- Cardinal Characteristics
  - Age between 55 – 65
  - Previous occupational exposure to asbestos
  - Pleural Effusion
  - C.T. / MRI (with nodular lesions of the parietal pleura) [Boutin 1998]
  - VATS
    - Mesothelioma takes on a “grape-like” appearance
      - patches of closely-spaced, smooth, translucent, poorly-vascularized nodules with a clear to yellowish color
        - not unique to mesothelioma
        - also seen with metastatic cancer of the pleura
          - Unlike benign inflammation (pleurisy), the pleura becomes hard & non-elastic - with biopsy, the cut edges do not bleed
      - 10 - 15% of cases, the observed lesions are nonspecific
        - path report: “benign pleural inflammation”
      - The more unimpressive the picture, the more biopsies should be taken (up to 20)
      - Look for involvement of the Lung or Visceral Pleura
      - 98% sensitive in establishing the diagnosis
      - Mortality is 1:8000
      - Complications are minimal
        - Subcutaneous Emphysema
        - Localized Infection
Minor Bleeding (< 100 cc) [Viallat 1991]

1 Problem with VATS: Seeding of the Trocar Path

- unknown incidence but can occur
- has been documented after thoracentesis & blind pleural biopsy

Can be prevented by performing Prophylactic Radiotherapy after healing to the point of entry [Rey 1995]

**NATURAL HISTORY**

- Median Survival: 12 - 17 months
- 5-year Survival: < 5%
- Mesothelioma is a Local Disease
  - Invasion usually first involves the Lung & Diaphragm
  - Progressive Retraction of the hemithorax leading to a “trapped lung”
  - Peritoneal Infiltration - through the diaphragm or it’s posterior openings with secondary ascites

- Spread to the Endothoracic Fascia (T2) or Intercostal Spaces (T3) is common
  - Found in 30 - 50% of patients at the time of biopsy [Chahinian 1983]
  - Parietal involvement can be “massive”
  - UNCOMMON:
    - Clinically-detectable lesions in bone, tissue, or brain
    - Involvement of the contralateral lung

However, at the time of autopsy, 50% of patients will have metastatic spread [Antman 1981]. Death is usually due to progressive dyspnea & respiratory insufficiency with extensive weight loss & muscle wasting

**THERE IS NO SINGLE TREATMENT WHICH HAS PROVEN EFFECTIVE...**

**TREATMENT: SURGERY**

To ensure that surgery will be as curative as possible, resection must include:

- the Pleura: Stage Ia
- the Lung: Stages Ib, II, and III

Many cases will require resection of the diaphragm, pericardium, & chest wall; but does surgery improve survival?

- Worn 1974, 248 Patients
  - 62 Patients with Radical Pneumonectomy
    - 2-yr. Survival, 37% 5-yr. Survival, 10%
  - Conservative Treatment
    - 2-yr. Survival, 12.5% 5-yr. Survival, 0%
- Probst 1990, 111 cases
  - Median survival was longer after pneumonectomy than any other method (1.4 months)

Operative mortality for radical pneumonectomy, across the board, is 25%

A current review of all surgical series suggests that treatment protocols including surgery do extend survival...

- Pleurectomy (2-yr. Survival): 11-35%
- Radical Pneumonectomy: 10-37% [Boutin 1998] [Aisner 1995]
  - The only prospective study
  - Pneumonectomy, w/o post-operative treatment
    - 2-yr. Survival: 33%
    - Median Survival: 10 months
A prospective, randomized, phase III trial is required to find the appropriate role of surgery.

**TREATMENT: RADIATION**

Despite in-vivo success against mesothelial cells, this mode has not been proven successful in the clinical setting

- Problem: size of the target area
- Post-radiation fibrosis can further aggravate pain
  - via compression of the chest wall & intercostal nerves
- Is effective to prevent “seeding”

**TREATMENT: CHEMOTHERAPY**

RESPONSES SEEN IN 20 -30 % OF PATIENTS, BUT WITHOUT IMPROVEMENT IN OVERALL MORTALITY

- Doxorubicin
- Cisplatin
- Methotrexate
- Combined Protocols : 33 - 66 % response

**TREATMENT: IMMUNOTHERAPY**

- Intrapleural delivery of cytokines are currently being tested
  - Interferon-Gamma
  - Interleukin-2
- Studies began in 1987 (150 patients)
  - Response Rates: 6 - 44 %
  - Effect on Survival is unknown at present
    [Dreisen 1992]

**TREATMENT: GENE THERAPY**

trials have begun to evaluate the genetic transfer of thymidine kinase (from herpes virus to adenovirus)

** too early to judge effect or outcome...[Smythe 1995]

**SUMMARY**

Mesothelioma kills - slowly & effectively...

- Early-stage disease: most important predictor of outcome
- To find “early-stage disease”, remember the risk factors
  - Age between 55 – 65
  - Previous occupational exposure to asbestos
  - Pleural Effusion
  - C.T. / MRI (with nodular lesions of the parietal pleura)
- Diagnosis is best established by V.A.T.S.
  - Following invasive procedures, “seeding” will occur & should be treated by radiotherapy
- Treatment: “it is currently, the clinician's choice”
  - Multimodal approach including radical surgery
  - “Limited-Role for Limited-Surgery”
    - Palliative
    - Relief of symptoms

south african miners -
 european industrialists -
 american manufacturers -
 slowly but effectively...

**References**
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