Malignant Mesothelioma Recent Advances

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DM Seminar

Malignant mesothelioma

- A tumour of serosal surfaces
- Pleura, peritoneum
- Increasing incidence worldwide
- Association with asbestos exposure
- Compensation costs over 40 yrs
- $200 billion US
- $80 billion Europe

India

- 100 000 tonnes used annually
- 1/5th mined in India.
- AP,Rajasthan, Bihar
- 9th largest producer
- 6th largest user
- 13 large scale/ 673 small scale industries
- 6000 workers in direct contact

Advances

- Diagnosis
- Management
- Reviews
  - *Advances in Malignant mesothelioma*
    - *N Engl J Med 2005:353:1591-603*
  - *Malignant mesothelioma*
    - *Lancet 2005; 366;397-408*

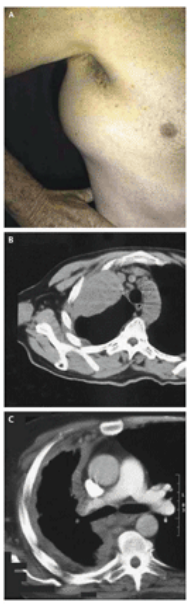
Clinical Features

- Pleura
  - 80% male
  - Effusion
  - Chest wall pain
  - Wt loss and fatigue
- Peritoneum
  - Ascites
  - Abdominal pain
  - Bowel obstruction

- Extensive at presentation (closed cavity)
- Local invasion
  - LN enlargement
  - SVCO
  - Cardiac tamponade
  - SCextensions
  - Cord compression
- Miliary spread

Signs

- Effusion/ascites
- Clubbing<1%
- Fixed chest wall
- SC masses (tracks,surg sites)
- Cancer syndrome
  - Wt loss,cachexia
  - Fever, night sweats
  - Fatigue, ESR, anaemia
  - IL-6



Causes

- Asbestos
- Amphiboles: long thin fibres/blue asbestos
- Chrysotile:feathery/white asbestos
- Parietal surface
- Repeated trauma,inflammation,repair

Simian virus 40

- Potent oncogene
- SV 40 DNA (bone/ lung tumours)
- Role unproven
- Sabin polio vaccine

- Radiation
- Zeolite (Erionite) Turkey

Epidemiology

- Rising incidence
- Peak yet to come
- 2000/year USA
- Need for controls on asbestos
- 3 cohorts:
  - Miners
  - Plumbers/carpenters/defence personnel
  - Unknown

Pathogenesis

- 2 billion cells
- Facilitate free movement;enmesh glycoproteins
- Asbestos induces mutations
- 4 mechanisms postulated

Mechanisms of Injury

- Irritate pleura (plaques, malignancy)
- Disruption of mitotic spindle
- Reactive Oxygen species (DNA damage)
- Phosphorylation of kinases; increase expression of proto-oncogenes

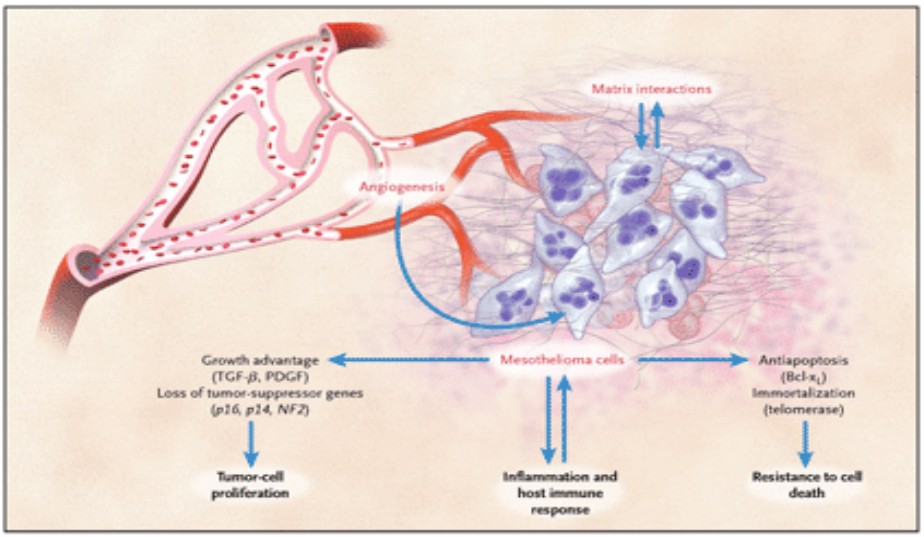
Cytogenetic abnormalities

- Loss of chromosome 22
- Rearrangement of 1p, 3p, 9p, 6q
- Animal models
  - Murine useful; respond to asbestos exposure
  - Hamsters SV-40
  - Pre clinical testing of therapies

Six characteristic features

- Increased dysregulated growth
- Immortalization (telomerase expression)
- Tumor supp genes absent (p16,p14,NF-2merlin)
- Anti-apoptosis
- Increased angiogenesis
- Matrix interactions

Biological Features



Diagnosis

- Accurate and rapid
- Therapeutic and medicolegal
- Diffrentiation from disseminated adenocarcinoma

Cytologic

- Fluid 33-84%
- FNAC tumour (no effusion)
- Immunohistochemistry
  - Calretinin
  - Wilm's tumour 1 antigen
  - Epithelial membrane antigen

HP Analysis

- Closed Biopsy <<< Thoracoscopic biopsy
- Cytokeratin
- EMA, calretinin, WT1,cytokeratin 5/6,HBME-1,mesothelin
- Absence of CEA,TTF-1,BG8
- EM microscopy

Imaging

- CXR
  - Pleural mass +effusion
  - Encircling rind
  - Lobulated masses
  - Plaques (sign of exposure)
- CT
  - Effusion 74%
  - Pl masses 92% +/- Inter lob septal thickening 86%
  - Chest wall invasion (18%)

MRI & PET

- Bony invasion
- Planning spinal RT

- Benign vs malignant
- LN involvement
- Staging and extent
- Tumor vs fibrosis

Serum markers

- Serum mesothelin related protein
  - 84% vs 2%
  - Adjunct to cyto/histopath
  - Monitoring therapy
  - Screening
- Other markers
  - CA125/CA15-3/hyaluronic acid/Osteopontin
  - Role in paired analyses (inc in sp/sens)

Other non sp tests

- Hb
- Platelets
- ESR
- Gamma globulin
- LFT
- Albumin

PFT

- Restrictive pattern
- Increased max exp flow rates
- Change in FVC reflects prog/regression provided pleural fluid constant

Prognosis & Staging

- Median survival 12 months
- Worse prognosis for:
  - Male,ext disease,perf status
  - Leucocytosis,anaemia, thrombocytosis
  - Sarcomatoid histology
  - Exp of COX 2 andVEGF
  - Vascularity
  - SV-40

*Table 1—New International TNM Staging System for Diffuse MPM According to the IMIC**

T1	
T1a	Tumor limited to the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura No involvement of the visceral pleura
T1b	Tumor involving the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura; scattered foci of tumor also involving the visceral pleura
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: Involvement of diaphragmatic muscle Confluent visceral pleural tumor (including the fissures) or extension of tumor from visceral pleura in the underlying pulmonary parenchyma
T3	Describes locally advanced but potentially resectable tumor Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: Involvement of the endothoracic fascia Extension into the mediastinal fat Solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall Nontransmural involvement of the pericardium
T4	Describes locally advanced technically unresectable tumor Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral) with at least one of the following features: Diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction Direct transdiaphragmatic extension of tumor to the peritoneum Direct extension of tumor to the contralateral pleura Direct extension of tumor to one or more mediastinal organs Direct extension of tumor into the spine Tumor extending through to the internal surface of the pericardium with or without a pericardial effusion, or tumor involving the myocardium
N, lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary nodes
N3	Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral, or contralateral supraclavicular lymph nodes
M, metastases	
MX	Presence of distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present
Stage I	
Ia	T1aNOMO
IB	T1bNOMO
Stage II	T2NOMO
Stage III	Any T3MO Any N1MO Any N2MO
Stage IV	Any T4 Any N3 Any M1

*From the IMIC, with permission.[34]

Surgery

- Useful for diagnosis (VATS,open Bx)
- Palliation (debulking, pleurodesis)
- Potentially curative (Radical resection)
- Extrapleural pneumonectomy
- Best with adjuvant chemo/radio/immuno/other treatment
- Periop mort 6%. Meidian surv 2 yrs

Chemotherapy

- Poor response rates till recently
- Decrease tumor burden
- Improve pain, breathlessness,chest wall masses

- Pemetrexed+cisplatin vs cisplatin (12.1m vs 9.3 m) 448 pts
- Inhibitor of thymidylate synthase + platinum compound
- Objective response of 41%

- Gemcitabine + cisplatin
- False nucleotide
- Objective response of 48% / 33%

- Imatinib/geftinib no response
- (PDGF/EGF)

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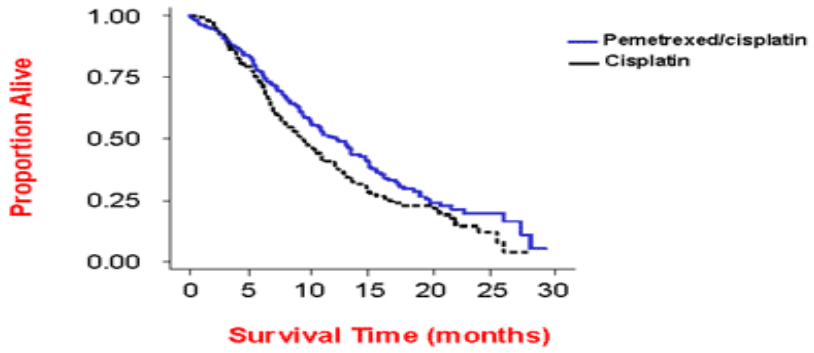

Vogelzang NJ, et al. J Clin Oncol. 2003;21:2636-2644.

Pemetrexed + cisplatin

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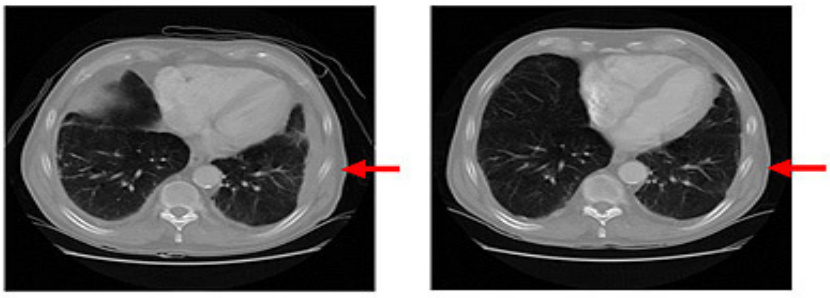

Month 0 Month 34

Courtesy of Nicholas J. Vogelzang, MD.

Radiotherapy

- Resistant to traditional RT
- Diffuse nature of tumour (pneumonitis)
- Intensity modulated
- Relief of pain
- Prevention of seeding of surgical sites
- Brachytherapy logical but disappointing

Immunotherapy

- To bolster intrinsic weak immune response
- BCG
- IFN-alpha
- IL-2
- Intratumoural GMCSF

- No results justifying widespread use.

Gene Therapy

- Intratumoral injection of vaccinia vector with IL-2 transgene.
- No major regression despite lymphocytic infiltration.

- “Suicide gene” therapy
- (Thymidine kinase + ganciclovir)
- Some response

Other therapies

- Photodynamic therapy
  - Light acts on drug
  - Produces reactive O2 species
  - Cellular necrosis
- Cytoreduction achieved
- No long term response

Antiangiogenic agents

- Target vascular VEGF pathway
- Bevacizumab,thalidomide,BAY43-9006,PTK787
- Antimesothelin monoclonal antibodies labeled with toxins
- Apoptosis inducing agent + immune therapy against APC

Palliation

- Pleurodesis (talc, surgery)
- Pain
  - Chest wall/ic nerve/organ invasion
  - NSAID/anticonvulsants/nerve block
- Dyspnea
  - Fluid/anaemia
  - Opiates
- Psychosocial factors
  - Anger, fear, worsened by MLC process

Prevention

- Vitamin A
- Vaccines directed at mesothelial proteins (risk of autoimmunity)
- Prophylactic bilateral pleurectomies!!

Conclusions

- The worst is yet to come
- Need for urgent focused research
- Enormous compensation costs may provide an economic incentive.