1. Asbestos Lung Disease and Malignant Mesothelioma – Diagnostic Challenges

Dr Sameer Kaul (Respiratory Physician)

Asbestos

- Naturally occurring fibres of hydrated magnesium silicates
- Tensile strength and properties well suited for construction and insulation
- Serpentine
  - Chrysotile
- Amphibole
  - Crocidolite/amosite/tremolite

Asbestos exposure

- Mining/milling of fibres
- Textiles/cement/shipbuilding/insulation industries
- Non-occupational exposure to airborne asbestos (regular exposure to soiled work clothes brought home by an asbestos worker, renovation or demolition, environmental exposure of industrial sources, natural environmental exposure to geological sources)
- Environmental exposure – industrial emissions – low level – more likely in mesothelioma not asbestosis

Asbestos related diseases

- Pleural diseases
  - Plaques
  - Pleural thickening
  - Benign effusions
  - Malignant effusions
- Lung (asbestosis)
- Malignancies
  - NSCLC
  - SCC
  - Mesothelioma

History

- Asymptomatic usually 20-30 years post-exposure
- Latency period inverse to degree of exposure
- Insidious onset of breathlessness with exertion
- Progress despite no further asbestos exposure

Examination

- Bibasal end inspiratory crackles – 32-64%
- Clubbing – 32-42%
- Cor Pulmonale in advanced disease

Tests

- Lung function tests – early decrease in DLCO, later decreased FVC, SVC, TLC
- No airflow obstruction FEV1/FVC>70
- Chest XRAY – Lower zones with mid zone plaques, usually no lymphadenopathy
- Gallium lung scan – still experimental
- HRCT chest

Pathological diagnosis (rarely required)

- Uncoated/coated asbestos fibres with interstitial fibrosis changes of UIP
- Asbestos Bodies – asbestos fibres with coating of iron and protein
- Open Lung Bx or BAL fluid

Pleural plaques

- Hylanised collagen fibres in parietal pleura
- 20+ years post asbestos exposure
- Inflammation in response to asbestos fibres sent to pleural surface
- Adjacent to ribs 6-9
- Also diaphragmatic pleura
- Less likely in visceral pleura, intercostal spaces and absent in region of costophrenic sulci and lung apices
- Don't have further disease potential
- Marker for asbestos exposure
- Considered independent risk factor for pleural mesothelioma

Diagnosis

- CXR – 20%
- CT Chest 50%
- Path 80%
- CT helps to distinguish from extrapleural fat and endothoracic fascia

Benign pleural effusions

- Early manifestation within 10 years of exposure
- Typically small unilateral
- Asymptomatic
- Pain, fever, dyspnoea
- Can happen after minimal exposure – no clear dose correlation
- Usually resolve over months some recur

Diagnosis

- History
- Pleural tap – usually exudate, blood stained
- Needs follow up to resolution or biopsy

Diffuse pleural thickening

- Starts as fibrosis or visceral pleura
- Secondary thickening of Parietal pleura
- Obliteration of costophrenic sulci

CT Scan

- Smooth uninterrupted pleural opacity
- At least 25% of chest wall
- >8cm cranio caudal direction
- >5cm of chest wall in cross section
- Thickness>3mm

Rounded Atelectasis

- Folded lung/Blesovsky's syndrome
- Subpleural mass out of which emanates a swirl of vessels and bronchi that curve like a comet tail as they connect the atelectatic lung parenchyma to the hilum
- Lower lobes/lingual/right middle lobe
- If characteristic comet tail is not identified biopsy recommended
- Characteristic rounded atelectasis with all of the above-mentioned findings does not have to be biopsied
- Rounded atelectasis can persist for years, can clear spontaneously, or, in rare cases, can grow
- Approximately 70 percent of cases of rounded atelectasis are associated with previous asbestos exposure

CT Scan

- Pleural thickening
- Round, oval or triangular shaped mass adjacent to the pleura
- Comet tail sign – vessels converge into the mass in a curvilinear fashion

Mesothelioma

- Neoplasm arising from mesothelial surfaces of the pleural and peritoneal cavities, the tunica vaginalis, or the pericardium
- 80% pleural origin
- 70 percent cases associated with documented asbestos exposure

Exposures – History

- Occupational
- Non-occupational
- Radiation
- Viral Oncogenes
- Genetic factors

Diagnosis
- History
- Imaging
- Tissue

History (non specific)
- Gradual onset
- Breathlessness
- Chest pain
- Loss of weight

Imaging
- CT Chest – can detect invasion, chest wall and lymph node involvement
- PET – uptake may help distinguish benign from malignant
- MRI – useful to define local extent of disease
- Blood tests – mesothelin, osteopontin, fibulin-3 – Non specific

Diagnosis
- Pleural fluid cytology +26%
- CT guided pleural biopsy +39%
- Medical Pleuroscopy 98%
- Surgical biopsy

Difficulties
- History not helpful
- CT not always confirmatory
- Recurrent pleural effusions common, mesothelioma less common
- Making diagnosis even with tissue not easy

Conclusions
- Mesothelioma is difficult to diagnose
- Keep high index of suspicion
- History and timelines important
- Recurrent pleural effusions are a red flag
- Negative tissue does not mean negative for mesothelioma
- More tissue is usually better
- Thoracoscopy/surgery for best tissue

2) Therapeutic Advances and Treatment of Malignant Mesothelioma

Dr Muhammad Alamgeer (Medical Oncologist)

Mesothelioma in Australia

Number of new cases in 2014 was: 641

- Deaths = 607
- 518 (81%) were male
- Male : Female = 4:1
- >80% aged 65-84 (largest number in 70-74)

Asbestos Containing Materials (ACMs)

- 95% of Mesothelioma cases are asbestos related
- Only 7% of asbestos workers will develop the disease
- 50% of non-occupational asbestos related MM are females
- Non Asbestos causes:
  - Carbon Nanotubes
  - Radiation
  - ?Virus

Mesothelioma: Germline mutations and asbestos exposure

- Mesothelioma relatively uncommon insidious and potentially lethal disease linked to asbestos, erionite exposure and, potentially, radiation
- Cappadocia, Turkey: genetics influences risk of mesothelioma in persons exposed to erionite
- BAP1 germline mutatations can predispose patients to familial and sporadic Mesothelioma and uveal melanoma
  - Tumour suppressor gene located on chromosome
  - Somatic mutations or 3p21.1 loss lead to BAP1 inactivation
  - In these individuals, asbestos exposure may predispose mesothelioma

Frontline systemic therapy for advanced mesothelioma

- Mesothelioma was largely chemoresistant with response rate $\leq$ 15%
- Combination regimens improved response rate
- Historically, the most efficacious agents incombination included: doxorubicin, epirubicin, mitomycin, cyclophosphamide, ifosfamide, and platinum agents

Current standard of care in Australia

- Cisplatin 75mg/mg2 + pemetrexed 500mg/m2 every 3 weeks
- Carboplatin + pemetrexed can be used in patients who cannot tolerate cisplatin

VEGF in Mesothelioma

- Mesothelioma patients have highest VEGF levels
- VEGF expression coorelated with microvascular density and poor survival
- VEGF is a paracrine growth factor for mesothelioma cells
- Thus VEGF may be an appropriate Target for Therapy in mesothelioma

MAPS: randomized trial of Cis/Pem ± Bev in unresectable mesothelioma

Results

- Improvement in Median Survival (16.1 to 18.8 months, p=0.0167)
- Higher adverse effects (grade 3/4)
- High serum VEGF levels associated with worse prognosis
- Not available in Australia yet

Nantadenib: An oral VEGF inhibitor

- A small molecule Tyrosine Kinase inhibitor of VEGFR, pDGFR & FGFR
- Double blind, multicentre, randomized phase II/III trial

Immunotherapy

CTLA4 – Tremilimumab

- Phase II study
- 29 patients
- DCR 31%
- Median survival 10.7 months

- Phase II study
- 29 patients
- DCR 51%
- Median survival 11.3 months

PD-1: Pembrolizumab

- Single agent phase I/II study
- Reported in abstract
- 28/38 PDL-1 positive
- 20% response rates
- 72% disease control rates
- Low toxicity
- Some very long/durable responses
- Randomized phase II study underway

Mesothelin-based approach

- Mesothelin is a protein present on normal mesothelial cells and overexpressed in several human tumours, including mesothelioma
- Adoptive immune therapy: T cells, subtypes of immune cells, are taken out and modified in a way that they target a specific protein on cancer cells, and then injected back in

Conclusions

- Multiple challenges in the management of MPM
- Recent improvement in survival seen in MPM
- Areas being improved upon:
  - Diagnostic work-up
  - Accurate staging methodologies
  - Treatment response monitoring
  - Understanding of biology
  - Clinical trial design
- Supportive/palliative care

3) Surgical Management of Malignant Mesothelioma

Mr Adrian Pick (Cardiothoracic Surgeon)

Surgery for Mesothelioma

- Diagnostic
- Palliative
- Cytoreduction
- ?Preventative

Pleurectomy vs. Extrapleural Pneumectomy (Pros and Cons)

Pleurectomy

- Higher local recurrence (70-100%)
- Less cytoreductive
- Lower mortality
- Lower morbidity
- Adjuvant radiation difficult

Extrapleural Pneumonectomy

- Lower local recurrence (13 – 30%)
- More cytoreductive
- Higher mortality
- Higher morbidity
- Adjuvant radiation easy

Multimodality Cytoreducation

Pleurectomy and decortication

- Aim to fully expand lung
- Aim to remove disease from chest wall
- De-bulk tumour (Cytoreductive Surgery)

Diaphragm and pericardium rarely resected.
Radiotherapy to drain site
Pre and post-operative chemotherapy

Conclusions

- Radical surgery can be performed safely with an acceptable mortality and morbidity
- Patients appear to get symptom relief from the operation in terms of chest wall pain and shortness of breath
- Disease free interval lengthened

4) Legal Perspectives for Asbestos Disease Sufferers

Margaret Kent (partner at Slater and Gordon)

What is a compensable asbestos-related condition?

- Mesothelioma
- Lung Cancer – dose related/competing causes/synergy
- Asbestosis – once diagnosis established
- Pleural plaques – usually not compensable
- Other asbestos related diseases (for example, sometimes pleural thickening)

Types of compensation

- Common Law negligence claims
- Statutory schemes, including no fault – i.e Workers Compensation, Comcare
- *In Victoria, time limits apply to the bringing of a claim. It is important that people seek advice **early**, so that they can make informed decisions*

Common law negligence claims

To bring a successful claim, the plaintiff must prove the following:

- Duty of care
  - That a duty of care exists and is owed by a defendant to a plaintiff. Relationships that give rise to duty of care most often relevant to asbestos claims are those between an employer and employee, a manufacturer and a consumer and an occupier and a person who enters onto the property
- Breach
  - That there was a breach of duty of care
  - That the defendant did something or failed to do something that resulted in a failure to meet the required standard of care
- Causation
  - That in breaching its duty of care, the defendant's act or omission was a cause or contributing factor to the plaintiff's injury

In Common Law cases the plaintiff is entitled to claim damages (compensation) for the following:

- Pain and suffering
- Loss of expectation of life
- Past and future medical expenses
- Past and future economic loss
- Voluntary care – compensation for the extra care that family or friends provide to the plaintiff
- Repayments – General principle of an award of damages is to restore the plaintiff to the position that he or she would have been in had the injury not occurred. The plaintiff should recover damages generally no more or less than they actual loss. Accordingly where someone else has met a cost created by the injury, they must be repaid (for example, Private Health insurers, Medicare, Department of Veteran's Affairs)

Common Law litigation process

- Confirming diagnosis
- Establishing the contribution of the asbestos related disease to symptoms (primarily non malignant asbestos related conditions)
- Identifying the source of the exposure
- Identifying the Defendans
- Issuing Supreme Court proceedings in most cases
- Speedy trial application if the condition is terminal
- Interlocutory procedures
- Application for a de bene esse hearing where necessary
- Pre-trial conference – most cases resolve at around this stage
- Trial

Survivorship – Estate Claims

- A person with an asbestos related injury MUST issue proceedings in Court prior to their death, in order to protect their entitlements to damages for pain and siffering
- Accordingly it is critical that people with asbestos related diseases receive timely legal advice so that those entitlements are not lost
- One a claim is issued in court, should a person die before the conclusion of the legal proceedings the Executor of the estate can be substituted as the plaintiff and the claim may be continued after the person's death