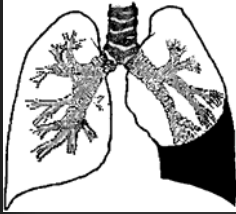


# International Pleural Newsletter



A Publication of the International Pleural Network

Volume 2 Issue 3  
July 2004

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## Advances in Mesothelioma Research Report of the IMIG Meeting



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Research in mesothelioma has taken encouraging strides, as was made clear at the 7th meeting of the International Mesothelioma Interest Group (IMIG) in Brescia, Italy in June, 2004. The meeting, hosted by Dr Luciano Mutti, attracted about 350 attendees and an international group of speakers. Advances in several areas appear likely, in the near future, to alter our approaches for screening, diagnosis, prognosis and treatment. Investigators and clinicians stressed the importance of referring patients with mesothelioma to centers with expertise so patients can receive the best available treatment and can be offered entry into clinical trials of new and promising agents.

The epidemiology presentations reminded us of the growing problem. While the peak incidence of mesothelioma may have been reached in the US due to asbestos control measures, the peak of mesothelioma in Europe is still 10-20 years away and increased use of asbestos in some countries, especially in Asia, may portend a further increase of mesothelioma in future decades. While asbestos is clearly the major risk, genetic predisposition may explain why fewer than 5% of asbestos-exposed individuals develop mesothelioma. The role of genetic predisposition is strongly supported by evidence reported from Turkey that, although much of the population is exposed to erionite, a non-asbestos carcinogenic fiber, only some families within only three villages develop mesothelioma. Genetic linkage studies are ongoing to explore the genetic contributions to mesothelioma in this population. Another possible risk factor is the simian virus 40 (SV40), which contaminated polio vaccines between 1954-1963. Indeed, SV40 was a major topic of discussion, with data presented both from animal experiments and case-control studies suggesting that the virus may act as a cofactor

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with asbestos. The role of SV40 is still highly controversial and it is unclear why SV40 has not yet been associated with a shorter latency period for development of mesothelioma.

One major story of the conference was the growing clinical and research utility of the mesothelial cell glycoprotein, mesothelin, and related proteins termed soluble mesothelin-related proteins (SMRP). As discussed later in this newsletter, SMRP in serum may serve as a useful screening test for mesothelioma in asbestos-exposed, high risk populations; SMRP in pleural fluid and serum may assist in diagnosing mesothelioma. In addition, an immunotoxin targeted to mesothelin has been developed and appears to show activity against mesothelioma in phase I clinical trials. Finally, a transgenic mouse has been developed in which the mesothelin promoter is used to target expression of SV40 to mesothelial tissues, for studying the possible role of SV40 in mesothelioma.

Other highlights included updates on treatments that have already reached patients via clinical trials and on those that may soon reach patients. The current status of available modes of treatment such as surgery (extrapleural pneumonectomy and pleurectomy/decortication) and chemotherapy using the newly reported active folate antagonists were presented from the major centers. Also, newer therapeutic approaches in clinical trials included conformal radiotherapy to maximize local control after surgery, immunotherapy via tumor vaccination or interferon beta intrapleural gene therapy, and anti-angiogenesis. Preclinical approaches that could be promising include induction of apoptosis, tyrosine kinase inhibition to interrupt several growth factor pathways, and blockade of the immunosuppressive effects of TGF-beta.

The etiology and biology of mesothelioma appears to be coming into clearer focus with several speakers highlighting the importance of frequently deleted genes (NF2 and p16/p14ARF) and the overactivity of specific signaling pathways (ERK and Akt). Global gene expression data are starting to identify informative genes or gene ratios that can offer diagnostic and prognostic information in mesothelioma.

For a detailed account of the meeting proceedings, please refer to the IMIG website, [www.imig.org](http://www.imig.org), by Aug-Sept 2004. At that website, you can learn more about IMIG, the international organization for those interested in understanding and treating mesothelioma, and can join at no charge. The next IMIG meeting will take place in the USA in 2006 (details at [www.imig.org](http://www.imig.org) by Dec. 2004).

## **Serum Mesothelin-Related Protein** **– a new serum marker for mesothelioma**

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Serum markers are frequently used to confirm the diagnosis of different cancers and can be used to monitor treatment response. Serum markers for cancers of the prostate (prostate specific antigen) and ovary (CA125), for example, are in regular clinical use<sup>1</sup>. However malignant mesothelioma (MM), an aggressive tumor, typically presenting at an advanced stage, has no such marker. The median life expectancy is <12 months for mesothelioma patients and treatment options are limited. Therapy might be more effective if given early, but until now there has been no reliable, validated serum marker for mesothelioma that might facilitate an early diagnosis.

We recently reported on a potential new serum marker for malignant mesothelioma<sup>2</sup> - Serum Mesothelin-Related Protein, SMRP. Mesothelin, the archetypal SMR family member is a 40 kDa glycoprotein located on the surface of normal mesothelial cells. It is believed to have a role in cell-adhesion and possibly in cell-to-cell recognition and signaling. In addition to mesothelioma, mesothelin is also over-expressed in cancers of the ovary, pancreas, stomach, lung and endometrium. It is not yet clear how SMRP reaches the circulation.

Using a simple ELISA, we showed that SMRP levels were elevated in the serum of 37 of 44 mesothelioma patients. In 75% of patients the levels were elevated within a 2-month period of diagnosis. Importantly, none of 19 patients presenting with non-mesothelioma pleural effusions, and only 2% of patients with non-mesothelioma lung or pleural diseases had elevated SMRP levels. In our study, SMRP was not elevated in patients presenting with clinical profiles similar to that of mesothelioma, and the overall specificity was >90% for patients with other pleural effusions and pleural masses. It should be noted that in women where metastases from the ovary is in the differential diagnoses, this test will be of little value as mesothelin is over-expressed in ovarian cancers<sup>3</sup>.

Our most important finding was that in archival serum samples we found that SMRP levels were elevated in three subjects, who were healthy at the time of serum collection but went on to develop MM 1 to 5 years later. Given that in some instances SMRP levels were raised well before diagnosis, it is probable that serum SMRP levels may be useful for screening asbestos-exposed populations for early mesothelioma. Animal models suggest that early therapy for mesothelioma is more effective, but the effect on humans can only be studied when individuals with early disease can be identified with the aid of new markers, such as SMRP. It is expected that SMRP will also be a useful adjunct in the clinical diagnosis of mesothelioma when it becomes commercially available later this year.

<sup>1</sup> Thomas CM, Sweep CG. *Int J Biol Markers* 2001;16:73-86.

<sup>2</sup> Robinson BW, Creaney J, Lake R, et al. *Lancet* 2003;362:1612-6.

<sup>3</sup> Scholler N, Fu N, Yang Y, et al. *Proc Natl Acad Sci USA* 1999;96:11531-6.

## Quantifying Non-Malignant Asbestos Pleural Disease: *A new CT Score System*

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Accurate quantification of the extent of non-malignant pleural disease is important for two reasons. Firstly, it allows quantification of the proportion of pulmonary function impairment due to pleural disease in patients with concurrent parenchymal and pleural involvement (eg connective tissue disease and asbestosis). Secondly, compensation is often sought by individuals with asbestos-related non-malignant pleural disease: correlations between structure and function may be used to determine whether functional impairment is ascribable to pleural disease in individual patients.

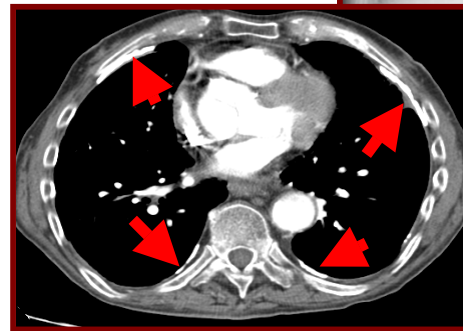
Historically, chest radiography has been the mainstay of assessment of pleural disease extent, particularly in pleural thickening from asbestos exposure. However, CT offers several advantages. Differentiating diffuse pleural thickening from pleural plaques on chest radiography may be problematic<sup>1</sup>, whereas CT is more specific for the type of pleural involvement (Fig 1). Furthermore, observer agreement is greater with CT, particularly for pleural plaques<sup>2</sup>. Also, axial CT sections have obvious advantages when the underlying lung parenchyma is obscured by pleural disease on chest radiography, as interstitial fibrosis may also contribute to a restrictive defect.

In asbestos-exposed individuals, a CT method with good functional correlation and observer agreement is particularly desirable for the assessment of pleural disease, as a variety of co-existing disease processes may each independently contribute to a deficit in pulmonary function (eg. interstitial fibrosis, diffuse pleural thickening, emphysema and small airways disease). In order to deconstruct and analyze the complex relationships in these individuals, a robust system for quantifying each individual component is required. The CT extent of non-malignant asbestos-induced pleural disease has been correlated with pulmonary function with varying success in the past<sup>3-6</sup>. However, our recent publication has identified a simple 'user-friendly' CT system for the quantification of pleural thickening, with an acceptable level of interobserver variation and good functional correlation<sup>2</sup>.

The CT score system was developed for use in clinical practice (Prof. A. W. Musk, personal communication) before formal evaluation. Five levels of the thorax were scored. At each level, the mean thickness of diffuse pleural disease, the percentage circumference of the thorax involved (combining the left and right hemithoraces and excluding the mediastinal surface) and the presence and number of areas of rounded atelectasis were recorded. Diffuse pleural thickening was

defined as pleural thickening with tapering margins as opposed to pleural plaques which were defined as areas of circumscribed pleural thickening with well-demarcated or defined borders.

Fig 1 showing bilateral calcified pleural plaques due to asbestos exposure on chest radiography and CT. Note how the plaques in the paravertebral regions and under the anterior ends of the ribs (arrows) are better demonstrated by CT.



The main functional determinant of the CT scoring system was the proportion of the thoracic circumference with diffuse pleural thickening (Fig 2). Logically, it might be expected that bilateral diffuse pleural thickening should result in greater decrements in lung volumes than unilateral diffuse pleural thickening (in which the unaffected side may be able to compensate). Surprisingly, for a given total extent of diffuse pleural thickening, there was no significant difference between unilateral and bilateral disease<sup>2</sup>.

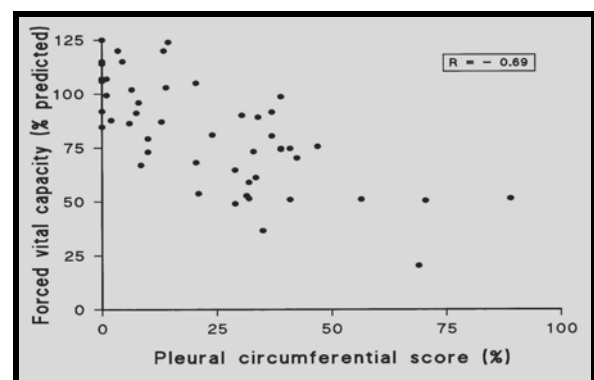


Fig 2. Univariate relationships between FVC (% predicted) and circumference score of diffuse pleural thickening for the simple CT scoring system ( $r=0.69$ ;  $p<0.00005$ ). Similar good correlations were shown between lung volumes and the easily applied simple CT system. (Reproduced with permission from *Radiology R.S.N.A publications*, ref 2.)

In summary, a straightforward and reliable CT visual scoring system for the accurate quantification of pleural disease has been identified, which may be of particular relevance in asbestos-exposed individuals.

<sup>1</sup> Bourbeau J, Ernst P. *Between and within-reader variability in the assessment of pleural abnormality using the ILO 1980 international classification of pneumoconioses*. Am J Ind Med 1988; 14:537-43.

<sup>2</sup> Copley SJ, Wells AU, Rubens MB, et al. *Functional consequences of pleural disease evaluated with chest radiography and CT*. Radiology 2001; 220:237-43.

<sup>3</sup> Aberle DR, Gamsu G, Ray CS. *High-resolution CT of benign asbestos-related diseases: clinical and radiographic correlation*. AJR 1988; 151:883-91.

<sup>4</sup> Jarad NA, Wilkinson P, Pearson MC, et al. *A new high resolution computed tomography scoring system for pulmonary fibrosis, pleural disease, and emphysema in patients with asbestos related disease*. Br J Ind Med 1992; 49:73-84.

<sup>5</sup> Al Jarad N, Poulakis N, Pearson MC, et al. *Assessment of asbestos-induced pleural disease by computed tomography - correlation with chest radiograph and lung function*. Respir Med 1991; 85:203-8.

<sup>6</sup> Schwartz DA, Galvin JR, Yagla SJ, et al. *Restrictive lung function and asbestos-induced pleural fibrosis. A quantitative approach*. J Clin Invest 1993; 91:2685-92.

resolve spontaneously in the first weeks post-transplant and require no further investigation. Pneumothoraces in the early post-transplant period are usually small but, in rare cases, can be massive due to bronchial rupture, which will require emergency thoracotomy<sup>5</sup>.

The influence of acute pleural complications on postoperative morbidity and mortality has been recently evaluated. Using a multivariate model, both hemothorax and persistent air leak are significantly associated with increased postoperative mortality<sup>4</sup>.

**Late pleural complications** are also frequent in lung transplant recipients. These complications are usually secondary to the many post-transplant pulmonary problems in these patients. Pleural effusion, iatrogenic pneumothorax following transbronchial biopsy and persistent air leak are the most frequent complications<sup>3,4</sup>. Patients transplanted for cystic fibrosis and obstructive lung diseases have higher risks of respiratory infections such as pneumonia. As a result, these patients may develop parapneumonic pleural effusions and empyemas, which are the only late pleural complications reported to be associated with death<sup>2</sup>. Pleural tuberculosis can also develop in lung allograft recipients, but its frequency depends on the local prevalence of tuberculosis infection. Pleural effusions appearing in the late postoperative period should be managed according to established clinical guidelines. However, the etiology of the effusion in many cases remains unclear. These undiagnosed effusions usually resolve by 12 months with residual pleural thickening seen in CT scans in 83% of the cases. Pneumothorax complicating transbronchial biopsies should be conservatively managed, as most patients will not require pleural drainage. Patients with persistent air leak usually need pleural drainage<sup>4</sup>.

In conclusion, physicians attending patients with lung transplants should be aware that pleural complications are frequent, and should be up-to-date with their management.

<sup>1</sup> Trulock EP. *Lung transplantation*. Am J Respir Crit Care Med 1997; 155: 789-818.

<sup>2</sup> Herridge MS, de Hoyos AL, Chaparro C, et al. *Pleural complications in lung transplant recipients*. J Thorac Cardiovasc Surg 1995; 110: 22-6.

<sup>3</sup> Judson MA, Sahn SA. *The pleural space and organ transplantation*. Am J Respir Crit Care Med 1996; 153: 1153-65.

<sup>4</sup> Ferrer J, Roldán J, Román A, et al. *Acute and chronic pleural complications in lung transplantation*. J Heart Lung Transplant 2003; 22: 1217-25.

<sup>5</sup> Judson MA, Handy JR, Sahn SA. *Pleural effusions following lung transplantation. Time course, characteristics and clinical implications*. Chest 1996; 109: 1190-4.

<sup>6</sup> Judson MA, Sahn SA, Hahn AB. *Origin of pleural cells after lung transplantation. From donor or recipient?* Chest 1997; 112: 426-9.

## ***Pleural Involvement After Lung Transplant***

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Lung transplantation has become the main therapeutic alternative for end-stage lung disease<sup>1</sup>. Pleural diseases are common after lung transplantation, occurring in 22 to 34% of the patients<sup>2</sup>. Pleural complications may be classified into two main groups depending on the time of presentation<sup>3</sup>.

**Early pleural complications** are those developing in the first two weeks after surgery, and include hemothorax, pneumothorax, transient or persistent air leak and pleural effusion. Pleural effusion on the same side of the transplanted lung is detected in all patients postoperatively<sup>4,5</sup>. These effusions are usually small to moderate in size, and usually resolve spontaneously within 3 weeks<sup>3,4</sup>. The pleural fluid of these early effusions is initially bloody, exudative and neutrophilic, but over the first 7 days the percentage of neutrophils and the levels of LDH and protein decrease<sup>6</sup>. The etiology and pathogenesis of these effusions are unknown. Possible explanations include increased permeability of alveolar capillaries secondary to allograft ischemia, denervation and subsequent reperfusion, postoperative lymphatic flow disruption or acute rejection. Most air leaks

If you have any interesting case of pleural disease to share, or any comment on the Newsletter, contact:  
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