

# International Pleural Newsletter

A Publication of the International Pleural Network

Volume 1 Issue 2  
April 2003

## Editors:

**Richard W Light** Nashville, TN, USA  
**Y.C. Gary Lee** Oxford, UK

## Co-Editors:

**Michael H. Baumann** Jackson, MS, USA  
**Robert J.O. Davies** Oxford, UK  
**John E. Heffner** Charleston, SC, USA

## International Advisors:

**Phillipe Astoul** France  
**Demosthenes Bouros** Greece  
**V Courtney Broaddus** USA  
**Tam E Eaton** New Zealand  
**Fergus V Gleeson** United Kingdom  
**Gunnar Hillerdal** Sweden  
**T K Lim** Singapore  
**Robert Loddenkemper** Germany  
**Marc Noppen** Belgium  
**F Rodriguez-Panadero** Spain  
**Steven A Sahn** USA  
**Lisete R Teixeira** Brazil  
**Francisco S Vargas** Brazil  
**Nai-San Wang** Taiwan  
**Canmao Xie** China  
**Anthony P C Yim** Hong Kong

## CLINICAL VALUE OF PLEURAL FLUID pH

**Steven A. Sahn MD**

Professor of Medicine and Director,  
Division of Pulmonary and Critical Care Medicine,  
Allergy and Clinical Immunology  
Medical University of South Carolina  
Charleston, U.S.A.

Normal pleural fluid pH is alkaline (7.60-7.66) in animals and man. Transudative effusions have a pH range of about 7.45-7.55 and most exudates have a pH of 7.30-7.45. However, there are a select number of exudative effusions with a pH of <7.30, representing a substantial accumulation of hydrogen ions in the pleural space; these effusions are also associated with low glucose concentrations (<60 mg/dl or PF/S <0.5). These low pH-low glucose effusions include: 1) complicated parapneumonic effusion (CPE) and empyema (pus); 2) rheumatoid pleurisy; 3) esophageal rupture (anaerobic empyema); 4) malignant pleural effusion; 5) tuberculous pleural effusion; and 6) lupus pleuritis<sup>1</sup>. There are rare reports of hemothorax, pulmonary infarction, and infarcted herniated bowel into the chest as causing pleural fluid acidosis. The only transudative effusion with a pH <7.30 is urinothorax due to the acidic urine that has exuded through the capsule of the obstructed kidney and moved through ipsilateral diaphragmatic defects into the pleural space.

Pleural fluid pH has been shown to be of clinical value in the management of parapneumonic effusions and malignant pleural effusions. However, the only accurate measurement of pleural fluid pH is with a radiometer system, as with an arterial blood pH. There is no clinical value in measuring the pH of a purulent effusion, as these empyemas always require pleural space drainage for resolution of pleural sepsis.

Pleural fluid acidosis occurs in CPE and empyemas because of increased metabolic activity of pleural fluid (neutrophilic phagocytosis and bacterial metabolism) with glucose end products, CO<sub>2</sub> and lactic acid, accumulating due to an inflamed pleura<sup>2</sup>. A pleural fluid pH <7.30 in a parapneumonic effusion makes it highly unlikely that the

## From the Editors

In January, the first issue of the International Pleural Newsletter was successfully distributed electronically to the clinical network members of the American College of Chest Physicians (ACCP), European Respiratory Society and Thoracic Society of Australia & New Zealand. The current and past issues of the Newsletter are now posted on the websites of the ACCP ([www.chestnet.org/networks](http://www.chestnet.org/networks)) and the British Thoracic Society ([www.brit-thoracic.org.uk](http://www.brit-thoracic.org.uk)). Recognizing the education value of the Newsletter, the ACCP will provide CME points to its members on reading the Newsletter.

We are encouraged by these developments and by the many positive feedbacks from readers of different countries. In the coming months, we will seek to further expand the distribution volume of the Newsletter, while working towards producing a periodical of the highest quality.

**Y. C. Gary Lee** Oxford, U.K.  
**Richard W. Light** Nashville, U.S.A.

effusion will resolve without pleural sepsis or pleural space sequelae unless drainage is instituted. In contrast, if the effusion is free-flowing and occupies less than 40% of the hemithorax, a pleural fluid pH of  $\geq 7.30$  predicts with high likelihood that the effusion will resolve without clinically important pleural sequelae with antibiotics alone<sup>3,4</sup>. As with any diagnostic test, borderline measurements should not affect the clinician's decision whether or not to drain the pleural space; the ultimate decision should depend on the global assessment of the patient, age of the pneumonia, virulence of the organism, and co-morbid disease.

Pleural fluid acidosis in malignancy results from marked tumor involvement of the pleura inhibiting the efflux of glucose end products from the pleural space<sup>5</sup>. Therefore, a low pleural fluid pH in a malignant pleural effusion is typically found with far-advanced disease of the pleura and is associated with a poorer survival, a higher sensitivity on initial pleural fluid cytology, and a poorer response to chemical pleurodesis than in patients with malignant pleural effusions who have a pleural fluid pH of  $\geq 7.30$ <sup>6</sup>. However, the clinician should not use pleural fluid pH as the sole criterion for deciding on whether or not to palliate with chemical pleurodesis<sup>7</sup>. Pleural fluid pH should be considered as adjunctive information in the context of the patient's expected survival, general health, performance status, tumor type, pulmonary status, and other co-morbid disease.

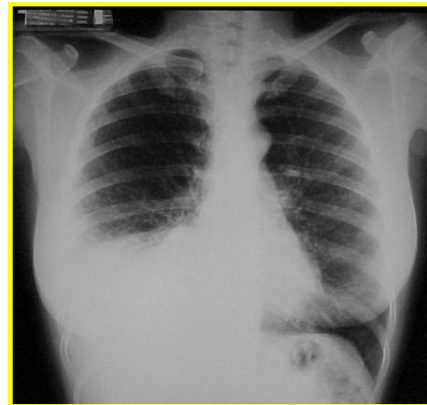
Many clinicians relate that their hospital laboratories refuse to measure pleural fluid pH because it is not a CLIA-approved test. I recommend that they discuss the pleural fluid pH literature with the Director of the Clinical Laboratory. Following a discussion at my institution, we now have routine radiometer measurement of pleural fluid pH on all pleural effusions.

#### References

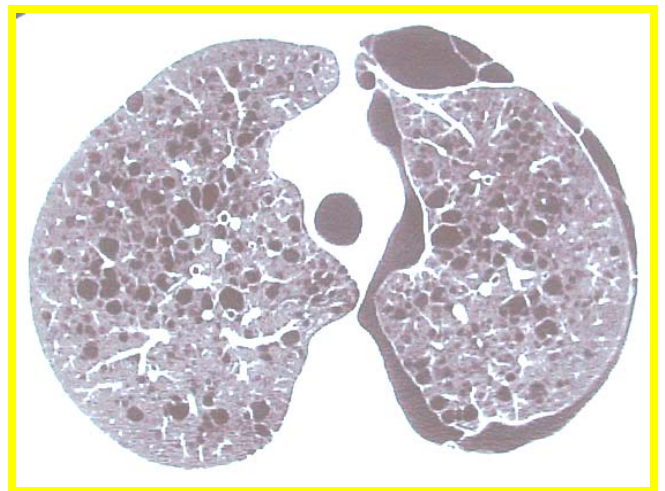
- 1 Good JT, Jr, Tayle DA, Maulitz RM, Kaplan RL, Sahn SA. The diagnostic value of pleural fluid pH. *Chest* 1980;78:55-9.
- 2 Sahn SA, Reller LB, Tayle DA, Antony VB, Good JT, Jr. The contribution of leukocytes and bacteria to the low pH of empyema fluid. *Am Rev Respir Dis* 1983;128:811-5.
- 3 Potts DE, Levin DC, Sahn SA. Pleural fluid pH in parapneumonic effusions. *Chest* 1976;70:328-31.
- 4 Heffner JE, Brown LK, Barbieri C, DeLeo JM. Pleural fluid chemical analysis in parapneumonic effusions. A meta-analysis. *Am J Respir Crit Care Med* 1995;151:1700-8.
- 5 Good JT, Jr, Tayle DA, Sahn SA. The pathogenesis of low glucose-low pH malignant effusions. *Am Rev Respir Dis* 1985;131:737-41.
- 6 Sahn SA, Good JT, Jr. Pleural fluid pH in malignant effusions: diagnostic, prognostic, and therapeutic implications. *Ann Intern Med* 1988;108:345-9.
- 7 Heffner JE, Nietert PJ, Barbieri C. Pleural fluid pH as a predictor of pleurodesis failure. *Chest* 2000;117:87-95.

## WHAT IS THE DIAGNOSIS?

A 39-year-old woman presented with a 3-month history of dyspnea. A chest radiograph showed a moderate right-sided pleural effusion and bilateral parenchymal infiltrates. Thoracentesis yielded 1000ml of milky fluid, which was an exudate (protein 4.4g/dl, LDH 500IU). The pleural fluid showed a striking lymphocytosis (96% of all WBCs), of which 84% were T-lymphocytes with a CD4/CD8 ratio of 1.8. The lymphocytes were mature and polyclonal, compatible with a reactive process. The pleural fluid analysis showed 86mg/dl of cholesterol and 1799mg/dl of triglyceride. No evidence of malignancy was seen in the pleural fluid and pleural biopsy.



Two weeks after this procedure the patient had acute chest pain and dyspnea. CT scan of the thorax revealed a left pneumothorax, interstitial fibrosis and numerous thin-walled cysts.



*For the diagnosis, go to page 6.*

**Lisete R. Teixeira**

**Sao Paulo, Brazil.**

## IN REVIEW:

Selected Recent Publications on Pleural Diseases

### Yield of Sputum Induction in the Diagnosis of Pleural Tuberculosis

Conde MB, Loivos AC, Rezende VM, Soares SLM, Mello FCQ, Reingold AL, Daley CL and Kritski AL.

**Am J Respir Crit Care Med 2003; 167:723-5**

In tuberculous (TB) pleuritis, pleural fluid develops from a delayed hypersensitivity reaction to the mycobacteria. Often, the bacterial load in the pleural cavity is low, and mycobacterial cultures are usually unrewarding. It is believed that TB pleuritis develops when subpleural foci of mycobacterial infection erupt into the pleura. Such foci are small and pleuritis is often the only clinical manifestation of TB.

Conde *et al* performed induced sputum in 113 patients who presented with a lymphocytic effusion in Brazil, 84 of which had TB pleuritis. In keeping with the literature, pleural biopsy (showing granulomatous inflammation) provided the best yield (78%) for the diagnosis of TB pleuritis, whereas pleural fluid culture was positive in only 12% of patients. Interestingly in 52% of the patients, induced sputum was culture-positive for TB, even if no parenchymal abnormalities were present on chest radiographs. Sputum induction was well tolerated.

One limitation of diagnosing TB pleuritis from pleural histology alone is the lack of bacteriological culture (and anti-microbial sensitivity) results. In 13 (15%) patients, induced sputum yielded a positive mycobacterial culture, not otherwise obtained from pleural tissue or pleural fluid cultures. This may be of importance in regions with high incidence of resistant organisms.

While the results of this study await confirmation in larger series, the potential additional benefits of sputum induction in the diagnosis of TB pleural effusions should be further explored.



### Peritoneal Dialysis and Epithelial-to-Mesenchymal Transition of Mesothelial Cells

Yanez-Mo M, Lara-Pezzi E, Seigas R, *et al*.

**New Engl J Med 2003; 348:403-413**

Pleural fibrosis can be undesirable (*eg* in asbestos pleural thickening or TB fibrothorax), but can also be of therapeutic value (as in pleurodesis). While fibroblasts are

responsible for fibrotic diseases in other organs, it remains uncertain which is the principle cellular source of the collagen and matrix proteins that constitute pleural fibrosis. Mesothelial cells outnumber the fibroblasts in the pleura, and pleural mesothelial cells have been shown to produce collagen (Lee *et al*. Eur Respir J; in press).

This study showed that human peritoneal mesothelial cells can undergo transformation to become fibroblast-like cells phenotypically. With the transition, the mesothelial cells lost their cytokeratin reactivity, and reduced their E-cadherin expression. The fibroblast-like cells had higher  $\alpha_2$  integrin expression and stronger migratory capacity. This epithelial-mesenchymal transition (EMT) is more prominent with longer duration of peritoneal dialysis, and following peritonitis. *In vitro*, transforming growth factor-beta (TGF $\beta$ ) and interleukin (IL)-1 $\beta$  can induce EMT. The authors believed that TGF $\beta$ , known to be present in peritoneal fluid, induces the EMT of mesothelial cells, which then adopt the functional role of fibroblasts to produce fibrosis.

These observations on peritoneal cells are likely to apply to pleural mesothelial cells. Human pleural effusions of various pathological causes are known to contain large quantities of TGF $\beta_1$  and TGF $\beta_2$ , as well as IL-1. Similar EMT phenomenon also occurs in pleural mesothelial cells. These findings would strengthen the belief that pleural fibrosis is mediated by cells of mesothelial origin.

Y. C. Gary Lee *Oxford, U.K.*

## WHAT IS THE DIAGNOSIS?

-continued from page 5

*DIAGNOSIS:*

**Lymphangiomyomatosis (LAM)**

This reported case illustrated a typical presentation of LAM in a young female who developed a chylothorax and pneumothorax.

The diagnosis was confirmed with characteristic CT appearances, and in this case, also on open lung biopsy. Hormonal treatment with medroxyprogesterone was initiated. In this patient, the pneumothorax recurred, but was treated successfully with talc pleurodesis with no further recurrence after one year.

## ***A BIT OF HISTORY***

While Giovanni Maria Lancini (1654-1720) from Italy first described percussion of the chest bone, it was an Austrian physician, Josef Leopold Auenbrugger (1722-1809), who was given the credit of conceiving the method of percussion of the lungs, especially to identify a pleural effusion.

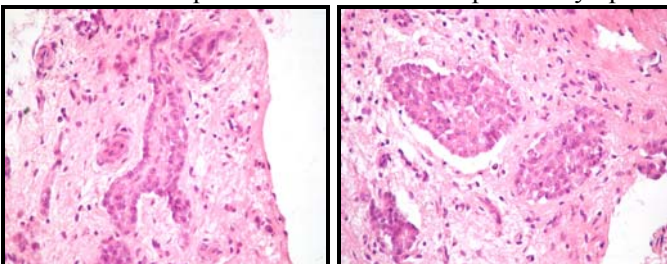
Interestingly, Auenbrugger was the son of a wealthy innkeeper, and learned medicine at the University of Vienna. It is widely believed that young Auenbrugger was strongly influenced by observing his father tapping on wine barrels to find out the level of wine left. Indeed Auenbrugger used to demonstrate his theories of sound muffling by knocking on barrels, which he filled up to various levels. The art of percussion was furthered by a Paris surgeon Raphael Bienvenu Sabatier (1732-1811) who advocated its use for diagnosing empyema.

References: <http://www.whonamedit.com>  
<http://www.umanitoba.ca/faculties/medicine/units/history/notes/>

## **AN UNUSUAL CASE OF MESOTHELIOMA**

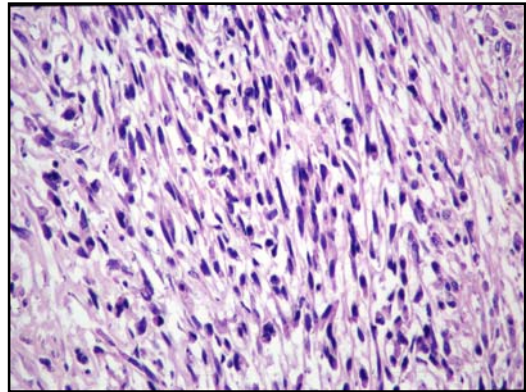
Histologically, malignant mesothelioma (MM) are commonly classified as epithelioid or sarcomatoid, or mixed (with both components). We report a case of MM initially epithelioid in type with delayed progression and an accelerated phase related to evolution into sarcomatoid mesothelioma.

A 54 year old man with a history of occupational exposure to asbestos presented with dyspnea and a painless left pleural effusion. Pleural biopsies showed an epithelioid type of MM. The malignant cells were lining cleft-like spaces and present as nests of regular cells with prominent nucleoli and quite abundant eosinophilic cytoplasm.

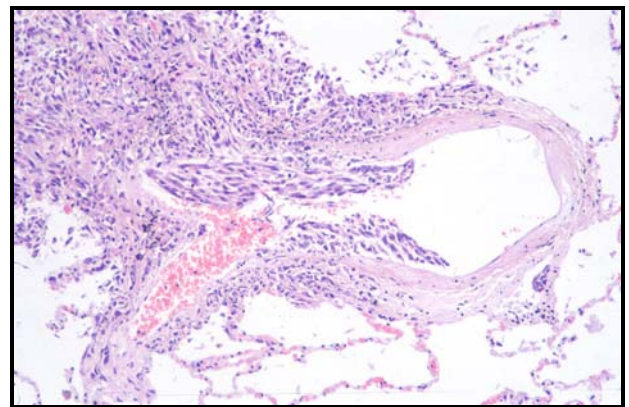


No sarcomatoid spindle cell population was identified. Immunostains confirmed that the tumor cells were not epithelial (BerEP4 and CEA negative) and carcinoma was excluded.

In spite of the usually poor prognosis of MM, the patient remained well for four years when he developed gastric symptoms. A gastric biopsy showed infiltration of the gastric mucosa by sarcomatoid mesothelioma.



There was then a rapid decline in the patient's condition and within a few months he died. At autopsy there was metastatic MM in the bones and vascular invasion in the lungs (below).



**Colin Clelland** *Oxford, U.K.*

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

**Dr Y C Gary Lee**  
**[garylee@well.ox.ac.uk](mailto:garylee@well.ox.ac.uk)**  
**Fax: +44-1865-287578**