

# PostScript

## LETTERS TO THE EDITOR

If you have a burning desire to respond to a paper published in *Thorax*, why not make use of our "rapid response" option?

Log on to our website ([www.thoraxjnl.com](http://www.thoraxjnl.com)), find the paper that interests you, and send your response via email by clicking on the "eLetters" option in the box at the top right hand corner.

Providing it isn't libellous or obscene, it will be posted within seven days. You can retrieve it by clicking on "read eletters" on our homepage.

The editors will decide as before whether to also publish it in a future paper issue.

### Expression of human mammaglobin gene in pleural effusions of patients with malignant mesothelioma

Human mammaglobin (hMAM) is a 10 kd protein of unknown function originally identified through a differential screening approach aimed at the isolation of breast cancer related antigens. Accordingly, hMAM overexpression was demonstrated in breast cancers compared with non-malignant breast tissue. Based on these findings, the potential role of hMAM as a breast tumour marker has been extensively investigated.<sup>1</sup> hMAM expression has recently been found in other tissues including lung cancer specimens and lung cancer cell lines.<sup>2</sup> Thus, hMAM expression is no longer considered restricted to the mammary gland and the list of normal and/or malignant tissues in which hMAM is found is likely still to be incomplete.

The aim of this study was to investigate the expression of hMAM transcripts in the pleural effusions of patients with pleural malignant mesothelioma (MM). Between June 2003 and July 2004, 26 patients with pleural effusions eventually diagnosed as MM were referred to our pulmonary unit. Our hospital is located along the seashore in an area with shipyard industries and Navy installations which, at least in part, explains

the high incidence of the disease—the highest ever reported.<sup>3</sup> Patients were enrolled in the study after giving informed consent. All patients underwent a diagnostic thoracentesis through a Pleuromed catheter (N G C Medical SpA, Novedrate, CO, Italy) and histological specimens were then obtained by medical thoracoscopy.<sup>4</sup> Diagnosis was established according to standard criteria. Cytological examination of all effusions was performed by haematoxylin-eosin and Papanicolaou staining. We have previously developed an ultrasensitive nested RT-PCR protocol for hMAM gene detection that has been described elsewhere,<sup>5</sup> and this was applied to the cells obtained from the pleural effusions.

hMAM transcripts were found in six of the 26 patients (23%). Five patients were of the epithelioid type while one was sarcomatoid. Eleven patients had positive cytology for malignant cells (42%), all of the epithelioid subtype. When hMAM analysis and cytology were compared, four patients were hMAM positive and cytology positive, two were hMAM positive and cytology negative, seven were hMAM negative and cytology positive, and the remaining 13 patients were hMAM negative and cytology negative. The PCR product from one patient was sequenced and confirmed to be hMAM. Figure 1 shows a representative agarose gel of RT-PCR amplified hMAM mRNA from one positive and one negative patient. To the best of our knowledge, this is the first demonstration of hMAM expression in the pleural fluid of patients with MM.

The diagnosis of pleural mesothelioma is challenging. While thoracoscopy usually yields adequate diagnostic material, it is a relatively cumbersome procedure that must be performed by well trained chest physicians. Not all patients with pleural effusions are candidates for thoracoscopy. Based on our observation, thoracoscopy should not be withheld in patients with an hMAM positive pleural effusion of unknown origin on the assumption that such positivity is suggestive of metastatic breast cancer.

The potential diagnostic role of hMAM detection in patients with a pleural effusion is unknown. In MM patients we found no correlation between hMAM positivity and cytology. This observation indicates that these two non-invasive diagnostic tools are

non-redundant and have the potential to yield independent information. Further studies with larger samples—which include non-malignant effusions as well as effusions secondary to malignancies of different origin—will be necessary to investigate the potential role of hMAM analysis in the work up of patients with a pleural effusion of unknown origin.

**A M Carletti**

U O Pneumologia, Ospedale S. Bartolomeo, Sarzana (SP), Italy

**S Roncella**

U O Istopatologia e Citopatologia, Ospedale S. Andrea, La Spezia (SP), Italy

**P A Canessa, L Praticò, R Maggiani**

U O Pneumologia, Ospedale S. Bartolomeo, Sarzana (SP), Italy

**B Bacigalupo, P Ferro, F Fedeli**

U O Istopatologia e Citopatologia, Ospedale S. Andrea, La Spezia (SP), Italy

Correspondence to: Dr A M Carletti, U O di Pneumologia, Ospedale S. Bartolomeo, Sarzana (SP), Italy; [annamaria.carletti@asls.liguria.it](mailto:annamaria.carletti@asls.liguria.it)

doi: 10.1136/thx.2005.049270

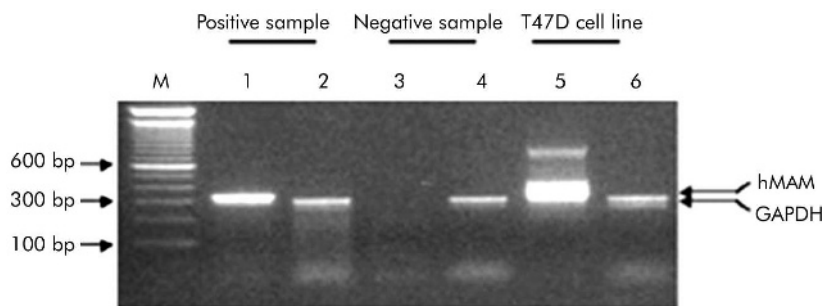
### References

- 1 Fleming TP, Watson MA. Mamaglobin, a breast-specific gene, and its utility as a marker for breast cancer. *Ann NY Acad Sci* 2000;**923**:78–9.
- 2 Sjodin A, Guo D, Sorhaug S, et al. Dysregulated secretoglobulin expression in human lung cancers. *Lung Cancer* 2003;**41**:49–56.
- 3 Gennaro V, Montanaro F, Lazzarotto A, et al. Mesothelioma Registry of the Liguria Region (Italy). Incidence and occupational etiology in a high risk area. *Epidemiologia e Prevenzione* 2000;**24**:213–8.
- 4 Boutin C. Thoracoscopy in malignant mesothelioma. *Pneumologie* 1989;**43**:61–5.
- 5 Roncella S, Ferro P, Bacigalupo B, et al. Human mamaglobin mRNA is a reliable molecular marker for detecting occult breast cancer cells in peripheral blood. *J Exp Clin Cancer Res* 2005;**24**:265–71.

### HIV testing in TB clinics: a problem in practice?

The London Regional Office of the Communicable Disease Surveillance Centre (CDSC) has stated that all patients diagnosed with tuberculosis (TB) should be offered an HIV test.<sup>1</sup> We sought to implement this by introducing a programme within two central London hospitals with high rates of TB, where TB specialist nurses saw all patients early in their treatment course and discussed HIV testing. A standard protocol was used which covered the reasons for offering a test, the "pros and cons" of testing, and the actual process involved (including how the results would be given). Staff training and support was supplied by local HIV psychologists. Pretest discussion took an average of 10–15 minutes per patient and was usually performed within the first month of treatment.

Between July 2002 and July 2003 there were 247 new cases of TB. The median age was 43 years and 60% were male. The main ethnic groups were black African (40%), white (22%), and Indian (11%). Eleven (4%) were already



**Figure 1** Example of ethidium bromide stained 1.5% agarose gel of RT-PCR amplified hMAM mRNA and GAPDH mRNA. hMAM positive samples (lanes 1 and 2), hMAM negative samples (lanes 3 and 4), and hMAM positive T47D breast cancer cell line (lanes 5 and 6) are shown. Molecular weight markers 100 bp (lane M); primers hMAM (lanes 1, 3, 5); primers GAPDH (lanes 2, 4, 6).

**Table 1** Numbers of outpatients and inpatients with active tuberculosis and unknown HIV status offered and accepting an HIV antibody test, and numbers found to be positive

	Outpatients (N = 178)	Inpatients (N = 58)	p value
Offered HIV test	88 (49%)	43 (74%)	0.001*
Accepted HIV test	61/88 (69%)	42/43 (98%)	<0.0001†
HIV positive	1/61 (2%)	17/42 (40%)	<0.0001†

\* $\chi^2$  test; †Fisher's exact test.

known to be HIV positive and were excluded from further analysis. Of the remaining 236, 131 (56%) were offered an HIV test. 109 (83% of those offered) took this up and 18 (17% of sample tested, 8% of all TB patients) were found to be HIV positive.

When subjects were divided on the basis of where the diagnosis of TB was made, striking differences in HIV rates were noted (table 1). Inpatients were much more likely to be offered, to accept, and to test positive on HIV testing. There was no difference in the demographic parameters between inpatients and outpatients, although inpatients tended to have more symptoms and to be smear positive (data not shown). Where no HIV test was offered, we found common themes in patient care. The most important of these was a lack of TB nurses to offer testing, and patients being diagnosed outside the focused TB service. A problem specific to the outpatient setting was the lack of appropriate clinic space in which to discuss HIV testing.

The most common reason given by patients who declined to undergo testing was a perceived inability to cope with the dual diagnosis (46% of cases), especially if the initial diagnosis of TB itself had been difficult to deal with. Such individuals would rarely agree to further discussion on HIV testing at a later date. Other reasons—such as patients regarding themselves to be at low risk of HIV infection—were much less frequently reported (10%).

The overall high rate of HIV co-infection is in line with other metropolitan studies.<sup>2</sup> Our data, as well as that of others,<sup>3</sup> may appear to suggest that we should predominantly target inpatients (in whom the rates of HIV were 20 times greater than in outpatients). However, given the increasing HIV/TB rates in the UK, we feel that this is a short sighted approach as we would expect that more individuals will present with TB as their first HIV related illness in an outpatient setting.<sup>4</sup>

HIV testing was unacceptable to some patients. There is need for in-depth qualitative analysis to explore issues such as the timing of the discussion on HIV testing and the belief systems and coping mechanisms of individuals.<sup>5</sup>

Despite attempts to provide a focused HIV testing service within our TB clinics, we find low rates of uptake. Much of this stems from an apparent failure to offer testing to almost half our patients. This may be an overestimate as it is conceivable that other healthcare workers might have discussed testing but not documented it in the patient's notes. Data systems need to be implemented which can accurately capture this information.

Achieving HIV testing targets will require dedicated resources as well as improvements in both staff and patient education. This would argue for a greater interaction between local TB and HIV services.

**S Dart, D Alder**

Royal Free Hospital, London, UK

**M Mamdani**

Whittington Hospital, London, UK

**A Solamalai, A Evans**

Royal Free Hospital, London, UK

**N Johnson**

Whittington Hospital, London, UK

**I Cropley, M Lipman**

Royal Free Hospital, London, UK

Correspondence to: Ms S M Dart, Chest Clinic, North Middlesex Hospital, London N19 1QX, UK; susan.dart@nrmh.nhs.uk

doi: 10.1136/thx.2005.048066

## References

- 1 Iskander R, Wass T, Jones J, et al. *Communicable Disease Surveillance Centre Annual Report 2001*. London: London Regional Office, 2001.
- 2 Bowen EF, Rice PS, Cooke NT, et al. HIV seroprevalence by anonymous testing in patients with *Mycobacterium tuberculosis* and in tuberculosis contacts. *Lancet* 2000;**356**:1488–99.
- 3 M, Warley A, Milburn H, et al. Tuberculosis and HIV seroprevalence in Lambeth, Southwark and Lewisham, an area of South London. *Respir Med* 2003;**97**:167–72.
- 4 Delphech V, Forde J, Lipman M, et al. Under-reporting of tuberculosis among HIV infected individuals diagnosed in the United Kingdom. *HIV Med* 2005;**6**:41.
- 5 Fylkesnes K, Siziya S. A randomized trial on acceptability of voluntary HIV counselling and testing. *Trop Med Int Health* 2004;**9**:566–72.

## Suppression of HPA axis in adults taking inhaled corticosteroids

Fluticasone propionate, a frequently prescribed potent inhaled corticosteroid, is an effective and generally safe treatment for chronic asthma. However, rare cases of dose related systemic absorption of inhaled corticosteroids leading to suppression of the hypothalamic-pituitary-adrenal (HPA) axis have been reported, particularly in children.<sup>1,2</sup> Using the insulin tolerance test (ITT), we report two cases of symptomatic adrenocortical suppression in asthmatic adults taking inhaled fluticasone. The two patients reported here were selected from a review of 59 patients undergoing ITTs for investigation of suspected HPA dysfunction.<sup>3</sup>

Patient 1, a 38 year old woman (weight 49.9 kg) with a history of chronic asthma and allergic rhinitis, was referred for investigation of a 2 year history of fatigue, presyncope, and reduced libido. She denied symptoms of neuroglycopenia, thyroid dysfunction, headaches, arthralgia, myalgia, weight change, constipation, and diarrhoea. Past history

included depression (in remission, on no current treatment) and bulimia nervosa. Menses were regular. There was no history of postpartum haemorrhage. Medications included fluticasone propionate/salmeterol xinafoate (Seretide) 250/25 µg one inhalation twice daily and mometasone furoate monohydrate (Nasonex) nasal spray 50 µg each nostril twice daily. However, adherence and dosing were variable. Of note, the patient reported that her presenting symptoms improved significantly whenever she had received oral steroids for asthma exacerbations in the past. Initial blood results are shown in table 1. Given low early morning cortisol levels in the absence of increased levels of adrenocorticotropin hormone (ACTH), an ITT was performed which revealed HPA axis suppression (table 1). Magnetic resonance imaging (MRI) demonstrated loss of upper concavity of the pituitary gland. Prednisone 2.5 mg/day was commenced and the dose of fluticasone propionate/salmeterol xinafoate was reduced to 125/25 µg one inhalation twice daily, with good symptomatic response. The patient was concurrently diagnosed with celiac disease following small bowel biopsy.

Patient 2, a 61 year old woman (weight 55 kg) with chronic asthma, treatment resistant osteoporosis, Hashimoto's hypothyroidism and celiac disease, reported fatigue, presyncope, neuroglycopenia, adrenergic symptoms of hypoglycaemia, anorexia and weight loss. Menopause was premature at age 45 years. There was no history of significant haemorrhage. Medications included inhaled fluticasone propionate (Flixotide) 250 µg and salmeterol xinafoate (Serevent) 50 µg one inhalation of each twice daily (for 12 months prior to presentation). As morning cortisol levels were low and the ACTH level was normal, an ITT was undertaken which demonstrated suppression of the HPA and growth hormone axes (table 1). Pituitary MRI scan was unremarkable. Prednisone 2 mg/day was commenced with symptomatic improvement. The dose of prednisone was reduced to 1 mg after 4 months without recurrence of presenting symptoms.

Using the ITT, we detected HPA suppression in two adult asthmatic patients taking inhaled/intranasal corticosteroids. The variable and unpredictable absorption of inhaled corticosteroids, low body weight, and intermittent adherence and dosing in patient 1 may have contributed to the patients' symptoms of adrenal insufficiency. The high lipophilicity of fluticasone, which results in an increased volume of distribution and prolonged elimination half life, is thought to account for the greater frequency of adrenal insufficiency in patients taking fluticasone compared with other inhaled corticosteroids.<sup>2</sup>

Adrenal suppression in asthmatic adults taking inhaled fluticasone is thought to occur less frequently than in children, particularly in patients taking <800 µg/day,<sup>4</sup> due to a lower effective steroid dose per unit body surface area.<sup>2</sup> However, previous studies have used relatively insensitive discriminators of HPA dysfunction such as early morning serum and salivary cortisol levels, 24 hour urinary free cortisol, and the 250 µg cosyntropin stimulation test to examine the integrity of the HPA axis in adult asthma patients taking inhaled corticosteroids.<sup>4,5</sup> We are aware of no previous study that has used the ITT, the current "gold standard" test of HPA function,<sup>1</sup> in this patient group. Although potentially dangerous in patients with seizure