Intrathoracic extramedullary haematopoiesis (EMH) is a rare entity that is usually asymptomatic. A 44 year old man with alpha-thalassaemia is described who developed dyspnoea and massive left sided haemothorax. The haemoglobin disorder was established by Hgb H staining and haemoglobin electrophoretic studies. The DNA analysis revealed it to be a case of double heterozygous terminal codon mutation with the genotype \( \alpha^4/\alpha^a \). Computed tomographic scanning and magnetic resonance imaging of the thorax showed multiple paravertebral masses which were found by thoracoscopic biopsy to be extramedullary haematopoiesis. Although no additional sclerosing pleurodesis or low dose radiation therapy was given, the lung expanded well and there has been no recurrence of haemothorax to date.

Keywords: extramedullary haematopoiesis; haemothorax; thalassaemia

Extramedullary haematopoiesis (EMH) occurs as a compensatory phenomenon to several haematological diseases including thalassaemia, myelofibrosis, and hereditary spherocytosis. Intrathoracic EMH is a rare entity which is often located in the lower thoracic paraspinal area and is usually asymptomatic. We describe the case history of a patient who presented with alpha-thalassaemia complicated by haemothorax.

Case report

The patient, a 44 year old man, had a history of alpha-thalassaemia for some years. The disorder was diagnosed by positive haemoglobin H staining and haemoglobin electrophoretic studies (Hgb H 10.3%). DNA analysis showed a double heterozygous terminal codon mutation with genotype \( \omega^{CS}/\omega^a \) (CS = constant spring; \( T = \) terminal codon mutation other than CS). Bone marrow aspiration cytology revealed erythroid hyperplasia. He was admitted in February 1996 with left sided chest pain and dyspnoea for several days. There was no history of trauma. We were unable to obtain a family history of haematological disorder.

Physical examination revealed a blood pressure of 146/76 mm Hg, pulse rate of 95/min, respiratory rate of 19/min, pale conjunctiva, icteric sclera, diminished left sided breathing sounds, and marked hepatosplenomegaly. Initial haematological examination showed a haemoglobin level of 6.8 g/dl, haemocrit value of 27.1%, mean corpuscular volume (MCV) of 71.9 fl, mean corpuscular haemoglobin concentration (MCHC) of 25.1 g/dl, total iron binding capacity (TIBC) 187 \( \mu g/dl \), and total bilirubin 4.6 mg/dl. Serum biochemical analysis gave the following values: iron 140 \( \mu g/dl \), ferritin 374 ng/ml, total iron binding capacity (TIBC) 187 \( \mu g/dl \), and total bilirubin 4.6 mg/dl. Chest radiography showed a massive left sided pleural effusion and posterior mediastinal masses (fig 1). Computed tomographic scanning of the chest revealed multiple lobulated paravertebral masses over the T spine with good contrast enhancement (fig 2). Magnetic resonance imaging of the thorax showed elongated lobulated paraspinal masses with isointensity to muscle on T1-weighted images and hyperintensity on T2-weighted images. Thoracocentesis revealed a bloody effusion with a protein level of 6500 mg/dl, sugar 5 mg/dl, red blood cell count 3.4 \( \times \) 10\(^6\)/mm\(^3\), white blood cell count 2 \( \times \) 10\(^3\)/mm\(^3\), and negative cytological results. Video-assisted
Intrathoracic extramedullary haematopoiesis with massive haemothorax in α-thalassaemia

Discussion

α-thalassaemia is caused by deletion or mutation of α-globin genes. In order of increasing severity they are α-thalassaemia-2 trait (−α/αα), α-thalassaemia-1 trait (−α/αα), Hb H disease (−α/−α), and Hb Barts (−/−). Haemoglobin constant spring (HbCS), Hb H disease (−/–/–) and Hb Bart (−/−) are highly radiosensitive, low dose radiation has been suggested as an effective method for controlling symptomatic spinal cord compression and haemothorax.²⁻⁶ In our patient, because it was the first episode of haemothorax and there was good expansion of the lung after tube thoracostomy, we did not apply local radiation therapy. To date there has been no evidence of recurrent haemothorax.

In conclusion, based on the characteristic radiographic findings and radionuclide marrow scanning, it is important to recognise the possibility of intrathoracic EMH as a differential diagnosis of non-traumatic haemothorax, especially in patients with bone marrow insufficiency or chronic haemolytic anaemia. Although radiation therapy or sclerosing pleurodesis is suggested for recurrent haemothorax,
FEV, and PEF in COPD management

Chronic obstructive pulmonary disease (COPD) is a common disease usually treated in general practice, especially in the early stages. The recently published British Thoracic Society guidelines encourage a systematic approach to the management of COPD as is widely used in asthma. Lung function measurements are regarded as central to the correct implementation of the guidelines. The guidelines are unequivocal in advising the use of forced expiratory volume in one second (FEV₁) rather than peak expiratory flow (PEF) in the management of COPD. In COPD the relationship between PEF and FEV₁ is poor and it is not possible to predict FEV₁ from the PEF or vice versa. This is a key issue for GPs who have to decide whether or not to purchase a spirometer, and whether they have the organisational capacity to cope with the maintenance, calibration, and interpretation demands of modern spirometers.

We have investigated the literature examining the relationship between FEV₁ and PEF in COPD. We have been unable to find substantive evidence to support the statement in the BTS guidelines regarding the superiority of FEV₁ over PEF. The only citation among the 171 references offered in the guidelines to support their position is a paper by Kelly and Gibson. In fact, Kelly and Gibson state the opposite view and report a very strong correlation between FEV₁ and PEF with an r value of 0.95 (p < 0.001). A similarly strong relationship between the two parameters has been reported by others.

The close relationship between FEV₁ and PEF is reassuring to us because the arguments put forward by the COPD guidelines seem counter-intuitive to GPs working daily with PEF in asthma. We recognise the role of spirometry as a whole in the diagnosis of COPD, especially in distinguishing primarily restrictive from obstructive disease. In the continuing management of COPD, however, we suspect that spirometry has limited additional value to offer over PEF, but considerable practical disadvantages.

LETTERS TO THE EDITOR

FEV₁ and PEF in COPD

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Health effects of passive smoking

Cook and Strachan are to be congratulated on their series of meta-analyses on the health effects of passive smoking. However, in their analysis of parental smoking and spirometric indices they gave as the main reason for excluding many studies using different definitions of parental smoking and different measures of mid expiratory flow. We invite Cook et al to update their estimates accordingly.

SUSAN CHINN
ROBERTO J RONA
Department of Public Health Sciences, King's College London, London SE1 3QD, UK

AUTHORS' REPLY We welcome Dr Simpson's interesting comments. He describes a group of patients which appears to be rather different from the patients reported in our study. Firstly, our patient group had been troubled by cough do not have heartburn. The approximation in assuming FEV1 percentage deficits can be achieved in most patients without duration was 18.8 months (range one month to 20 years). Initial treatment was given on the basis of history and routine clinical examination with investigations reserved for patients not responding after one month. Thirty four patients failed to return after their initial appointment. Twenty were contacted by phone and all reported complete resolution of their symptoms. Clinical diagnoses in the 14 others were similar and they probably defauted because of improvement, but none specifically withdrew from analysis. Investigations performed included radiology of the sinuses in 8%, bronchial provocation testing in 16%, and investigation for gastro-oesophageal reflux in 19%. The final diagnoses (table 1) were based on successful response to treatment. Asthma was uncommon (7%) but, as there were few treatment failures, it seems unlikely that asthma was missed. The awareness of asthma by GPs is high in Australia and it had probably been treated by their GPs. Clinical outcomes were excellent with 79 patients (92%) reporting complete or almost complete resolution of cough in a mean of two months.

These results suggest that good outcomes can be achieved in most patients without routine investigation. The poor positive predictive value of symptoms quoted by McGarvey et al reflect poor choice of historical features. These authors confirm that any cause of chronic cough increases the sensitivity of the cough reflex, and the finding that cough precipitated by non-specific stimuli is poorly predictive of asthma is unsurprising. Likewise, most patients with reflux associated cough do not have heartburn.

Diagnostic protocols advocated by hospital based researchers may be inappropriate for other settings. Such protocols should be subjected to randomised controlled trial against less interventionist approaches as would be required of a new drug treatment.

GRAHAM SIMPSON
Clinical Associate Professor, University of Queensland, Queensland, Australia

Table 1 Final diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
<th>Mean age (range)</th>
<th>M/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinitis</td>
<td>24</td>
<td>46 (7–75)</td>
<td>8/16</td>
</tr>
<tr>
<td>Reflux</td>
<td>19</td>
<td>53 (40–69)</td>
<td>7/12</td>
</tr>
<tr>
<td>Postural</td>
<td>11</td>
<td>38 (9–67)</td>
<td>4/7</td>
</tr>
<tr>
<td>Reflux + rhinitis</td>
<td>6</td>
<td>58 (44–64)</td>
<td>4/1</td>
</tr>
<tr>
<td>Whooping cough</td>
<td>5</td>
<td>37 (14–64)</td>
<td>4/1</td>
</tr>
<tr>
<td>ACE I inhibitor (ACE I)</td>
<td>4</td>
<td>62 (49–79)</td>
<td>2/8</td>
</tr>
<tr>
<td>ACE I + rhinitis + reflux</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE I + rhinitis</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE I + reflux</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>48</td>
<td>30 (6–68)</td>
<td>4/2</td>
</tr>
<tr>
<td>Asthma + rhinitis</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal lung disease (ILD)</td>
<td>1</td>
<td>78</td>
<td>1/0</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>2</td>
<td>77 (72–81)</td>
<td>0/2</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>2</td>
<td>58 (44–71)</td>
<td>0/2</td>
</tr>
</tbody>
</table>


AUTHORS' REPLY We welcome Dr Simpson's interesting comments. He describes a group of patients which appears to be rather different from the patients reported in our study. Firstly, our patient group had been troubled with cough for a longer period of time (mean cough duration 67 months (range 2–240)
Compared with 18.8 months (range 1–240). Secondly, application to his study of our exclusion criteria—that is, smokers, an abnormal chest radiograph, any preceding viral infections, and patients taking angiotensin converting enzyme inhibitors—would mean that 29 of the 86 patients (33%) he reviewed would not have been included in our study. Dr Simpson relies heavily on patient history in the evaluation of his patients. In our discussion we highlight the limitations of historical features, given the existence of both silent “reflux” and postnasal drip. We do not accept that the poor positive predictive values reflect a bad choice of historical features and believe there are no accurate discriminatory historical features that can be reliably applied to cough patients in general. This is supported by a study which specifically examined features in the clinical history and found that these were unlikely to be useful in diagnosing the cause of cough.6

While we agree that a randomised controlled trial may be one way to address the issue of how best to evaluate patients with cough, we suspect that Dr Simpson is describing a very different patient population from those referred to our cough clinic and that a less interventionist approach may not therefore be appropriate. In the meantime we feel a compromise approach which is consistent with the approach of the recent Consensus Panel Report of the American College of Chest Physicians7 continues to represent the optimum way to evaluate patients referred with chronic cough.


Targeting DNase in cystic fibrosis

Recombinant human DNase is an expensive mucolytic which does not benefit all patients with cystic fibrosis. Company sponsored trials in unselected cystic fibrosis patients have documented wide variability in spirographic responses to the drug, but the data are presented in a way which prevents the clinician from assessing which patients are likely to benefit.

We therefore read with interest the editorial by Dr Innes regarding the assessment of response to DNase in cystic fibrosis. However, whilst we agree that it is necessary to target DNase, we have reservations regarding the use of “n-of-1 trials” for this therapy. Dr Innes states that this approach has been used in Scotland and quotes a study unpublished at the time of writing in support of it. However, this study has already been heavily criticised since many patients refused to take part and others did not complete the trial periods.3 Furthermore, such studies are inherently time consuming and resource intensive.

We have adopted a different approach to ensure that DNase is prescribed in a rational fashion. Before it became available on the NHS we met with local purchasers to define selection criteria and a trial protocol. Following selection, those who have an improvement in forced expiratory volume in one second (FEV1) of >10% after a trial of DNase are defined as “responders” and remain on the drug. A review at two years has shown that, whilst responders maintain their improvement, non-responders are not disadvantaged. Thus, using this protocol we have been able to target DNase to those patients who obtain maximum benefit. This model has now been widely accepted by purchasers for adult and paediatric cystic fibrosis services in North Wales and the Northwest of England and, as such, we have no problems in obtaining funding for this very expensive product.

We suggest that Dr Innes and his colleagues abandon their “n-of-1 trials” and adopt our protocol for the use of DNase.

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TARGETING DNASE IN CYSTIC FIBROSIS


NOTICES

Cochrane Airways Group

An international symposium on “The Basis for Clinical Excellence in the Treatment of Chronic Lung Diseases” organised by the Cochrane Airways Group will be held on 10–11 November 1999 at the Royal Society of Medicine, London. For further information contact Alison Rowley, Symposium Administration Office, Cochrane Airways Group, Battersea Studios, Tackley Road, London SW8 1TW, UK. Telephone +44 (0)1799 542993. Fax +44 (0)1799 541026. Email: greene_room@msn.com

World Association of Sarcoidosis and Other Granulomatous Disorders

The 17th World Congress on Sarcoidosis and Other Granulomatous Disorders (WASOG) will be held in Fumamoto, Japan on 8–13 November 1999. Further details may be obtained from Professor Masayuki Ando, Kumamoto University School of Medicine, 1–1–1 Honjo, Kumamoto 860, Japan. Telephone +81-963-73-5150. Fax +81-963-71-0582.
Health effects of passive smoking

SUSAN CHINN and ROBERTO J RONA

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