Intrathoracic extramedullary haematopoiesis complicated by massive haemothorax in alpha-thalassaemia

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Abstract

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 αCS/αCS. 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 αCS/αCS (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, haematocrit value of 27.1%, mean corpuscular volume (MCV) of 71.9 fl, mean corpuscular haemoglobin concentration (MCHC) of 25.1 g/dl, red blood cell count of 3.7 × 10^12/mm^3, white blood cell count of 14 × 10^9/mm^3, and platelet count of 2.7 × 10^11/mm^3. Serum biochemical analysis gave the following values: iron 140 µg/dl, ferritin 374 ng/ml, total iron binding capacity (TIBC) 187 µg/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 × 10^12/mm^3, white blood cell count 2 × 10^9/mm^3, and negative cytological results. Video-assisted
Intrathoracic extramedullary haematopoiesis with massive haemothorax in α-thalassaemia

Discussion

Alpha-thalassaemia is caused by deletion or mutation of α-globin genes. In order of increasing severity they are α-thalassaemia-2 trait (α/αo), α-thalassaemia-1 trait (α/αα), Hb H disease (α/–α), and Hb Barts (–/–). Haemoglobin constant spring (HbCS) is a common non-deletional α-thalassaemia mutation and is an important cause of HgH-like disease in south-east Asia. The genotype αα/αα established in our patient by polymerase chain reaction is an uncommon genotype of Hg H disease. Extramedullary haematopoiesis usually develops as a compensatory response in various anaemias including thalassaemia, sickle cell anaemia, and myelofi-

Figure 2  Computed tomographic scan of the chest showing (A) massive left sided pleural effusion and multiple lobulated paravertebral masses with well enhanced contrast (arrowheads) and (B) one year later only multiple lobulated paravertebral masses (arrowhead) were found.

thoracoscopy disclosed several lobulated reddish tumour masses over the lower paravertebral region and a large amount of bloody effusion. The pathological findings of a biopsy specimen of the tumour obtained by thoracoscopic revealed normal haematopoietic tissue with normal maturation process of three lineage cells.

The patient was discharged in fair condition three weeks later without additional preventive sclerosing therapy or low dose radiation therapy. Follow up chest radiography revealed almost complete reabsorption of the left sided haemothorax and there has been no recurrence of bleeding to date.

As far as we are aware, only four patients with intrathoracic EMH complicated with haemothorax have been previously reported in the English literature. Smith et al. reported a case of thalassaemia intermedia who developed intrathoracic EMH and haemothorax which was treated with local radiation therapy to prevent recurrent bleeding. Muthuswamy and colleagues described a patient with hereditary spherocytosis who presented with post-traumatic intrathoracic haemorrhage due to intrathoracic EMH. Kupferschmid and colleagues reported a case of myelofibrosis with intrathoracic EMH. The complicated massive haemothorax did not respond to tetracycline pleurodesis and was ultimately controlled with low dose radiation therapy. Bartlett et al. described a case of agnogenic myeloid metaplasia with haemothorax. The intrathoracic EMH, confirmed by a technetium-99 bone marrow scan, was treated successfully with low dose irradiation to prevent recurrent haemothorax. In the case presented here, thoracoscopic biopsy and decortication were performed not only for tissue diagnosis of the posterior mediastinal mass but also for better lung expansion.

Various non-invasive diagnostic procedures are advocated to establish the diagnosis of EMH. These include contrast enhanced computed tomography, magnetic resonance imaging of the thorax, technetium-99 sulphur colloid radionuclide bone marrow scanning, cytological study of the pleural fluid, and fine needle aspiration examination which may carry a risk of haemorrhagic complications. Computed tomographic scanning of intrathoracic EMH typically reveals smoothly margined mass(es) with homogenous soft tissue over the lower paravertebral regions without bony erosion. A radionuclide bone marrow scan may demonstrate activity in the mass.

Treatment of intrathoracic EMH is usually unnecessary except in the presence of complications. Because the haematopoietic tissue is highly radiosensitive, low dose radiation has been suggested as an effective method for controlling symptomatic spinal cord compression and haemothorax. 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 stages.

In general practice, especially in the early stages of COPD, it is common practice to use peak expiratory flow to determine whether or not to purchase a spirometer, and exploring their use 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. Even in the infancy of FEV1 and long before COPD, Lung function measurements were 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 and exploring their use 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 in healthy subjects and none with COPD. The 1962 Lancer article by Ritchie dates from the infancy of FEV1, and long before COPD was defined as a discrete entity.

The most important and fundamental point is that PEF cannot differentiate between obstructive and restrictive patterns of abnormal function. If the diagnosis is not made correctly then the GP cannot hope to manage the patient correctly. The implications of a restrictive defect will often necessitate referral to secondary care to assess the cause, whereas most cases of obstructive COPD are manageable within primary care.

The FEV1 is a more reproducible measurement so that measurements on a single occasion can be of value whereas, to obtain similar accuracy with PEF, serial measurements are required. By inspecting the FEV1, traces it is possible to know whether a patient has performed the manoeuvre correctly, whereas no such confirmation exists for PEF. Even in asthma, studies of repeated measurements of serial PEF using computerised measurements confirm that up to 50% of readings may be non-valid.

To understand the relationship between the level of PEF and the level of FEV1, it is necessary to go—not to epidemiology—but to the physiology underlying the shape of the flow-volume loop in COPD. In the first draft of the guidelines we included a figure illustrating how the FEV1 could be reduced to 33% of predicted at a time when the PEF remains relatively preserved at 60% of predicted. The discrepancy arises because of the airway collapsibility present in COPD secondary to the loss of elastic tissue. The PEF is generated by the instantaneous flow of air leaving the trachea in the first 0.1 seconds of expiration, while the FEV1 includes air leaving the airways through airways that have collapsed after about 0.2 seconds of expiration.

Despite the fact that COPD is a chronic obstructive pulmonary disease, the patient’s FEV1 is markedly reduced to 0.25 l/s. Thus, for the remaining 0.75 s the subject with COPD reaches the point of expiratory collapse (point "d") and obstructive airway collapsibility present in COPD secondarily to the loss of elastic tissue. The PEF is generated by the instantaneous flow of air leaving the trachea in the first 0.1 seconds of expiration, while the FEV1 includes air leaving the airways through airways that have collapsed after about 0.2 seconds of expiration.
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 19 out of 42 studies that met their primary criteria that they “provide some data, but insufficient to be included in the quantitative overview”. In the case of our own study they concluded that they were unable to transform our results to the desired effect measure. They used the “difference in outcome measure between the exposed and non-exposed children expressed as a percentage of the level in the non-exposed group” and reported that they were unable to do this with our results as we “reported differences in standard deviation scores with no baseline data.”

The standard deviation scores were calculated using the mean and standard deviation of the ratio of actual to lung function predicted for height, age and sex. Hence, the approximate percentage difference can be calculated by multiplying by the appropriate published standard deviation. Using an estimate of 15.6 cigarettes per day for the average amount smoked by parents at home, calculated from the same data for white English children in 1988, the effect of parental smoking on forced expiratory volume in one second (FEV1) was -0.37% (SE 0.51%) for boys and -0.18% (SE 0.5%) for girls. The wide confidence intervals on our estimates encompass the greater negative estimates of Cook et al, but inclusion of our results would have decreased our negative estimates for all four lung function parameters.

The approximation in assuming FEV1, percent predicted to be 100 for the unexposed group is no greater an assumption than combining studies using different definitions of parental smoking and different measures of mid expiratory flow. We invite Cook et al to update their estimates accordingly.

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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) 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 and all reported complete resolution of their symptoms. Clinical diagnoses in the 14 others were similar and they probably defaulted because of improvement, but none were excluded 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 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 high 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 control trial against less interventionist approaches as would be required of a new drug treatment.

GRAHAM SIMPSON
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Investigation and management of persistent dry cough

McGarvey et al suggest that full investigation of patients with persistent cough improves treatment.

I reviewed 100 such patients seen consecutively. All had normal chest radiographs, two were current smokers, and their mean cough

Table 1 Final diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mean age (range)</th>
<th>M/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinitis</td>
<td>24 (7-75)</td>
<td>8/16</td>
</tr>
<tr>
<td>Reflux</td>
<td>19 (50-69)</td>
<td>7/12</td>
</tr>
<tr>
<td>Postural</td>
<td>11 (9-67)</td>
<td>4/7</td>
</tr>
<tr>
<td>Reflux + rhinitis</td>
<td>6 (58-64)</td>
<td>4/1</td>
</tr>
<tr>
<td>Whooping cough</td>
<td>5 (37-64)</td>
<td>4/1</td>
</tr>
<tr>
<td>ACEI inhibitor (ACEI)</td>
<td>4 (62-79)</td>
<td>2/8</td>
</tr>
<tr>
<td>ACEI + rhinitis + reflux</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ACEI + rhinitis</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>ACEI + reflux</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>5 (48-60)</td>
<td>4/2</td>
</tr>
<tr>
<td>Asthma + rhinitis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Intestinal lung disease (ILD)</td>
<td>1</td>
<td>7/0</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>2 (77-82)</td>
<td>0/2</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>2 (58-74)</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.
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 56 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. 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 comprehensive protocol which is consistent with the approach of the recent Consensus Panel Report of the American College of Chest Physicians continues to represent the optimum way to evaluate patients referred with chronic cough.

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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 spirometric 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. 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. Follow-up 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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AUTHOR’S REPLY

We would urge Drs Ledson and Walshaw, before suggesting we abandon the Scottish n-of-1 DNase assessment protocol, to read it! The protocol has not been “heavily criticised” as they claim since the article they quote was also written without knowledge of the results (only recently published). In our experience it is very unusual for patients to refuse to undergo our assessment process.

Where we do agree is in the need to test the DNase response in individual patients. However, we disagree on how this should be done. Ledson and Walshaw advocate an unblinded, open label, two week trial of DNase using an increase in FEV1, of >10% as the only end point. We contend that this is less than ideal because (a) double blinding and placebo control periods are needed to obviate bias, given the high expectations generated in patients and carers by new treatments for cystic fibrosis; (b) using the single end point of increased FEV1, may be less reliable than combining this with other measures including exercise capacity, oxygen saturation and symptom scores; (c) a criterion of a >10% increase in FEV1 is inherently unreliable since day-to-day variability in FEV1, is around 160 ml (95% CI) regardless of the magnitude of the FEV1, so it is easier for patients with a low FEV1, to achieve an increase of >10% by chance. Indeed, Ledson et al in the description of their own protocol quote the day-to-day variability of FEV1, in cystic fibrosis as “up to 13%”, so clearly some 10% increases will be spurious. We agree that DNase can and should be targeted to maximise benefit, but feel that this targeting should be made as objective as possible. This may be laborious for doctors, but it is not nearly as laborious for patients as consigning a non-responder to long term daily nebulised therapy on unreliable evidence.

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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 information contact Alison Rowley, Symposium Administration Office, Cochrane Airways Group, Battersea Studios, Thackeray Road, London SW8 1TW, UK. Telephone +44 (0)1799 542993. Fax +44 (0)1799 541026. email: greene_room@msn.com

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, Thackeray Road, London SW8 1TW, UK. Telephone +44 (0)1799 542993. Fax +44 (0)1799 541026. email: greene_room@msn.com

CORRECTION

In the “Smoking Cessation Guidelines and their Cost Effectiveness” which was published as a supplement to the December issue of Thorax (December 1998; 54 (Suppl 5)), the name of one reviewer was inadvertently omitted from the list of reviewers on page S1 of Part 1:

Gay Sutherland, Clinical Psychologist, National Addiction Centre, Institute of Psychiatry, University of London, London, UK.