Myositis associated graft-versus-host-disease presenting as respiratory muscle weakness

A L Stephenson, I R A Mackenzie, R D Levy, J Road

Abstract
Myositis associated with graft-versus-host-disease (GVHD) typically presents with proximal muscle weakness, myalgias, and a raised creatinine phosphokinase (CPK) level. We report a case of a 51 year old man who developed respiratory muscle weakness five years after an allogeneic bone marrow transplant for multiple myeloma. His symptoms included tachypnoea, abdominal paradox, and orthopnoea. Pulmonary function tests revealed diminished vital capacity and maximal inspiratory and expiratory pressures. Serum CPK levels were raised and a peripheral muscle biopsy specimen was consistent with GVHD. He improved with immunosuppressive therapy.

(Thorax 2001;56:82–84)

Keywords: graft-versus-host-disease; myositis; respiratory muscle weakness

Case report
A 51 year old man who was a non-smoker was admitted to the hospital with a three month history of progressive orthopnoea and cough. He had undergone an allogeneic BMT from a matched sibling donor for multiple myeloma in 1993. His course was complicated by GVHD involving the skin, bronchiolitis obliterans of the lungs, pulmonary embolism, and central nervous system toxoplasmosis. On admission his medications included prednisone 20 mg alternating with 15 mg daily, trimethoprim-sulphamethoxazole 20 ml twice daily Saturday and Sunday, clindamycin 300 mg three times daily three times per week, pyrimethamine 25 mg three times per week, leucovorin 5 mg daily, fluticasone 250 µg twice daily, and salbutamol four times daily. Clinically he was tachypnoeic, using accessory muscles of respiration as well as having abdominal paradox, particularly in the supine position. He was noted to have slightly decreased peripheral muscle strength in the upper extremities. The deltoid, triceps, and biceps muscles were graded 4/5 while the muscle groups in the lower limbs were normal strength. A chest radiograph did not show evidence of active pulmonary disease. Arterial blood gas tensions showed evidence of hypoventilation with pH 7.39, Paco₂ 6.4 kPa, PacO₂ 10.5 kPa, and HCO₃⁻ 29 mmol/l on room air. Nocturnal nasal BIPAP was initiated in hospital with symptomatic improvement of his orthopnoea.

Blood tests showed markedly raised CPK levels and pulmonary function tests revealed significantly decreased vital capacity and severely reduced maximum inspiratory and expiratory pressures (table 1) consistent with respiratory muscle weakness. The vital capacity was performed in the upright position and hence probably overestimated the supine vital capacity by at least 30%. Chest fluoroscopy showed severely diminished (virtually absent) bilateral diaphragm motion. No increase in diaphragmatic excursion was seen during the sniff test. A computed tomographic scan of the neck and mediastinum did not show any lesion along the expected course of the phrenic nerve to explain his diaphragmatic weakness. Electromyography (EMG) showed positive sharp waves and fibrillation in the left biceps, triceps, infraspinatus, right biceps, diaphragm, and the paraspinal muscles consistent with either
Myositis associated GVHD presenting as respiratory muscle weakness

Inflammatory myopathy has been seen with chronic GVHD, although involvement of the respiratory muscles is rare with only one case report found in the literature. Five years after BMT our patient developed orthopnoea, general muscle weakness, and increased CPK levels with evidence on clinical examination, pulmonary function testing, and EMG studies of respiratory muscle weakness, particularly of the diaphragm. Although the EMG results are non-specific, they can be seen in inflammatory myopathies caused by GVHD. He responded dramatically to prednisone, cyclosporin, and MMF with resolution of his symptoms, normalisation of his CPK, and improvement of his vital capacity and respiratory muscle strength to the normal range. Interestingly, the spirometric parameters, as well as the inspiratory and expiratory pressures, improved between 22 July and 11 August before his immunosuppression was increased. His corticosteroid inhaler dose was increased during that period as well as his use of β agonists, which may have contributed to an improvement in his forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC). Respiratory muscle strength may have improved following the institution of nocturnal BIPAP which began on 24 July. BIPAP is known to decrease the work of breathing which may have allowed the respiratory muscles to recover partially and hence improve their function.

The muscle biopsy specimen showed evidence of muscle necrosis and an inflammatory infiltrate. The inflammatory cells seen were both neutrophils and monocytes which is somewhat atypical of GVHD myositis. Reported cases have documented a lymphocytic/monocytic predominant infiltrate on the muscle biopsy specimen. The presence of neutrophils in this case raised the possibility of an infectious process although no organism was cultured. Toxoplasma infection is a recognised risk in the immunocompromised host. Increased toxoplasma IgM levels suggestive of an active infection have been reported in idiopathic polymyositis but not in GVHD myositis. Our patient had a history of CNS toxoplasmosis and was on suppressive therapy with clindamycin, pyrimethamine, and leucovorin. No toxoplasma organism was cultured in blood, cerebrospinal fluid, or muscle biopsy, making active infection very unlikely in this patient. In addition, increasing the steroid dose would have worsened infection if present, but instead his clinical picture improved. Other possible causes for his weakness include steroid myopathy, but this seems unlikely given his clinical response to augmented steroids.

In conclusion, myositis associated with GVHD typically affects the proximal muscles, but it can also affect the respiratory muscles and cause significant morbidity in this population. The one published case report of GVHD involving the respiratory muscles resulted in respiratory failure and death soon after a donor leucocyte transfusion. It is possible that the donor T cells were responsible for causing severe GVHD. Our case illustrates that BMT patients are at risk for respiratory muscle

### Table 1  Sequential values for blood tests and pulmonary function tests

<table>
<thead>
<tr>
<th></th>
<th>July 22</th>
<th>Aug 11</th>
<th>Aug 20</th>
<th>Aug 27</th>
<th>Oct 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPK (U/l)</td>
<td>946</td>
<td>347</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary function tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC (l)</td>
<td>2.06 (41)</td>
<td>2.39 (47)</td>
<td>3.04 (60)</td>
<td>3.42 (68)</td>
<td></td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>1.40 (35)</td>
<td>1.81 (45)</td>
<td>1.92 (48)</td>
<td>2.03 (50)</td>
<td></td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>68 76 93 97</td>
<td>68 76 93 97</td>
<td>68 76 93 97</td>
<td>68 76 93 97</td>
<td></td>
</tr>
<tr>
<td>MIP (cm H₂O)</td>
<td>32 (31)</td>
<td>49 (48)</td>
<td>59 (58)</td>
<td>99 (99)</td>
<td></td>
</tr>
<tr>
<td>MEP (cm H₂O)</td>
<td>64.5 (42)</td>
<td>81 (52)</td>
<td>114 (74)</td>
<td>145 (94)</td>
<td></td>
</tr>
</tbody>
</table>

CPK = creatinine phosphokinase; FVC = forced vital capacity; FEV₁ = forced expiratory volume in one second; MIP, MEP = maximum inspiratory and expiratory pressures; CSA = cyclosporin; CPK = creatinine phosphokinase; FVC = forced vital capacity; FEV₁ = forced expiratory volume in one second; MMF = mycophenolate mofetil.

Values in parentheses are % predicted.

myositis, axonal degeneration, or neuromuscular junction dysfunction. A muscle biopsy of the left triceps showed evidence of acute and chronic inflammation with associated muscle fibre necrosis (fig 1) The actively necrotic areas were infiltrated by both polymorphic leucocytes and mononuclear cells. Gram stain and culture of the tissue failed to reveal any infectious aetiology.

The results of the investigations were interpreted as indicating an inflammatory myositis involving not only the proximal muscles, but both the inspiratory and expiratory respiratory muscles, particularly the diaphragm. His prednisone was increased to 60 mg daily and one day later he was started on cyclosporin 50 mg twice daily and mycophenolate mofetil (MMF) 1 g twice daily. His symptoms improved dramatically over the following week and his CPK level normalised. Repeat pulmonary function testing showed improved muscle strength with increased vital capacity and normal inspiratory and expiratory pressures. Lung volumes measured on 27 August (table 1) revealed total lung capacity of 5.51 l (77% predicted), residual volume of 2.47 l (117% predicted), and normal transfer factor. One month after starting treatment he no longer needed nocturnal BIPAP and his orthopnoea had completely resolved.

![Figure 1](https://example.com/muscle-biopsy-specimen-left-triceps-showing-evidence-of-acute-and-chronic-inflammation-associated-with-muscle-necrosis)
involvement with GVHD and that this can be an insidious process occurring many years after the BMT. Furthermore, once muscle atrophy occurs, it has been suggested that the muscle may not recover despite increased immunosuppression and control of the inflammatory process. For this reason, a high clinical index of suspicion is needed for accurate diagnosis so that appropriate treatment can be instituted promptly.


CT scanning in lung cancer

We read with interest the article by Laroche et al on the cost effectiveness of performing computed tomographic (CT) scanning before fiberoptic bronchoscopy (FOB) in patients with suspected endobronchial carcinoma. Compared with the group in which FOB was performed blind to the result of the CT scan, in the group in which the CT result was available before FOB was performed the FOB was obviated in 24% of patients, a higher proportion of the FOBs were diagnostic, and the initial invasive investigation was more frequently diagnostic. The authors do not specify which CT appearances determined that FOB should not be undertaken.

We have recently performed a complementary study evaluating the ability of CT scanning to predict in which patients with an abnormal chest radiograph and high clinical suspicion of bronchial carcinoma FOB is likely to provide a positive histological diagnosis. In distinction to Laroche et al, we excluded patients with pulmonary collapse but included patients with peripheral lesions.

We identified four CT features which predict a positive FOB. In descending order of accuracy these were: (1) a segmental or larger airway leading to the mass; (2) an endobronchial component; (3) the situation of the mass within 4 cm of the origin of the nearest lobar bronchus; and (4) an ill defined edge to the mass. We excluded patients with peripheral lesions.

We identified four CT features which predict a positive FOB. In descending order of accuracy these were: (1) a segmental or larger airway leading to the mass; (2) an endobronchial component; (3) the situation of the mass within 4 cm of the origin of the nearest lobar bronchus; and (4) an ill defined edge to the mass. We excluded patients with peripheral lesions.

We identified four CT features which predict a positive FOB. In descending order of accuracy these were: (1) a segmental or larger airway leading to the mass; (2) an endobronchial component; (3) the situation of the mass within 4 cm of the origin of the nearest lobar bronchus; and (4) an ill defined edge to the mass. We excluded patients with peripheral lesions.

With reference to the letter by Drs Davies and Grange in the August edition of Thorax and the response to this by Drs Campbell and Ormerod representing the committee that prepared the guidelines to which this letter refers, and despite the hope of Drs Campbell and Ormerod that arguments about the nomenclature of mycobacterial grouping would have been laid to rest by now, I believe I can see why this issue remains topical.

Drs Davies and Grange argue that the term "environmental mycobacteria" is the preferred term and should be universally adopted. However, as recently as 1994 Dr Davies suggested that, in recognising it is time the world agreed on what to call these mycobacteria, the term "non-tuberculous mycobacteria" should be used and not "environmental mycobacteria" as he now suggests in his letter. With high profile, expert clinicians changing their minds and advice, it is hardly surprising that guidance is somewhat unreliable and continuously being sought, especially by more junior members of staff. I suspect that, in view of this, it will be some time before this issue is finally laid to rest.

GARY PORTER-JONES
Respiratory Specialist Nurse, Department of Respiratory Medicine, North West Wales NHS Trust, Wrexham, Denbigh, and Glyndwr GR7 LL13 2RF, UK.
gary.porter-jones@nuhs.wales.nhs.uk

CT scanning in lung cancer

The CT appearances can be used to select those patients in whom FOB is unlikely to be diagnostic and should probably not be performed.

H K BUNGAY
R J O DAVIES
F V GLEESON
Department of Radiology, Churchill Hospital, Headington, Oxford OX3 7JF, UK

Correspondence to: Dr F V Gleeson.

LETTERS TO THE EDITOR

“Opportunistic” mycobacterial infection

With reference to the letter by Drs Davies and Grange in the August edition of Thorax and the response to this by Drs Campbell and Ormerod representing the committee that prepared the guidelines to which this letter refers, and despite the hope of Drs Campbell and Ormerod that arguments about the nomenclature of mycobacterial grouping would have been laid to rest by now, I believe I can see why this issue remains topical.

Drs Davies and Grange argue that the term "environmental mycobacteria" is the preferred term and should be universally adopted. However, as recently as 1994 Dr Davies suggested that, in recognising it is time the world agreed on what to call these mycobacteria, the term “non-tuberculous mycobacteria” should be used and not “environmental mycobacteria” as he now suggests in his letter. With high profile, expert clinicians changing their minds and advice, it is hardly surprising that guidance is somewhat unreliable and continuously being sought, especially by more junior members of staff. I suspect that, in view of this, it will be some time before this issue is finally laid to rest.

GARY PORTER-JONES
Respiratory Specialist Nurse, Department of Respiratory Medicine, North West Wales NHS Trust, Wrexham, Denbigh, and Glyndwr GR7 LL13 2RF, UK.
gary.porter-jones@nuhs.wales.nhs.uk

Tuberculosis in Cuba

I congratulate Dr Marrero and colleagues on the excellent paper published recently in Thorax about their experience with tuberculosis in Cuba from 1962 to 1997 and consider that many developing countries, together with some developed countries like ours, should imitate their methods and their political commitment to a national tuberculosis programme. However, I wish to raise some questions and to comment on some points.

I was pleasantly surprised at the considerable improvement in the case finding from 1993 onwards. From 1983 to 1993 the number of new cases of tuberculosis per year ranged from 514 to 789 with 85.5%–91% smear positive patients (similar to the period since 1962). In 1994 there was a sudden increase to 1617 cases (from 789 cases in 1993) with a significant decrease in the percentage of smear positive patients to 56% (from 91% in 1993). This sharp fall was maintained up to 1997. The authors consider that this expansion of the case definition by the World Health Organization in 1994 to include “clinical symptoms and radiological features suggestive of tuberculosis but with negative sputum smears and negative culture” may have been a significant factor, but in my opinion this is already included in the

www.thoraxjnl.com
Birth weight and adult lung function in China

In a study published in Thorax in 1997 Stein and colleagues' showed that birth weight was associated with adult lung function in an Indian population. We have carried out a similar analysis in a Chinese cohort of 59 men and 61 women born in Hong Kong in 1967 and followed up in 1997. This Hong Kong study has been described recently and has shown a significant inverse association between size at birth and adult blood pressure.' Spirometric tests were performed according to the American Thoracic Society's criteria to assure the quality. The same equipment (Sensor Medics 2200) was used in all subjects. Data were analysed by multiple linear regressions; adult height, smoking status, and sex were included as covariates.

The mean birth weight was 3.1 kg (range 2.3–4.1). Table 1 shows that babies of low birth weight (<2.5 kg) had lower mean values of forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio at the age of 30 years, adjusted for sex, adult height, and smoking. However, there was no significant trend (each p>0.1). It can be seen from the findings presented by the Indian study that the previously reported associations between birth weight and FEV1, in men and between birth weight and FVC in both sexes were largely attributable to a lower lung function in subjects with birth weight of less than 5 lb (2.27 kg; table 2 in Stein et al?). In that study there was no obvious trend among the other subjects.

Table 1  Mean (SD) FEV1, FVC, and FEV1/FVC ratio at 30 years of age, adjusted for sex, height, and smoking (ex-smoking) according to birth weight (n=120)

<table>
<thead>
<tr>
<th>Birth weight (kg)</th>
<th>n</th>
<th>FEV1 (l)</th>
<th>FVC (l)</th>
<th>FEV1/FVC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.50</td>
<td>4</td>
<td>3.09 (0.20)</td>
<td>3.64 (0.33)</td>
<td>84.7 (6.2)</td>
</tr>
<tr>
<td>2.50–2.74</td>
<td>18</td>
<td>3.23 (0.46)</td>
<td>3.69 (0.47)</td>
<td>87.9 (8.9)</td>
</tr>
<tr>
<td>2.75–2.99</td>
<td>26</td>
<td>3.38 (0.32)</td>
<td>3.85 (0.50)</td>
<td>89.1 (5.6)</td>
</tr>
<tr>
<td>3.00–3.24</td>
<td>33</td>
<td>3.79 (0.44)</td>
<td>3.79 (0.51)</td>
<td>88.6 (5.4)</td>
</tr>
<tr>
<td>3.25–3.49</td>
<td>19</td>
<td>3.34 (0.41)</td>
<td>3.81 (0.54)</td>
<td>88.4 (6.0)</td>
</tr>
<tr>
<td>3.50–3.74</td>
<td>11</td>
<td>3.32 (0.28)</td>
<td>3.76 (0.36)</td>
<td>88.5 (4.7)</td>
</tr>
<tr>
<td>&gt;3.75</td>
<td>6</td>
<td>3.36 (0.37)</td>
<td>3.68 (0.47)</td>
<td>91.0 (4.1)</td>
</tr>
</tbody>
</table>

p for trend * 0.36 0.87 0.30

* Using birth weight as a continuous variable.

Hyperventilation syndrome

The editorial by Dr Gardner1 on controversial aspects of the hyperventilation syndrome (HVS) refers to our study1 in the same issue of Thorax. That our study has shown a statistically significant relation between size at birth and adult blood pressure also suggests that the numbers were sufficiently large to reveal a clinically important association. Having considered findings from our study and the previous one we suggest that, while low birth weight may be associated with a reduced lung function in adults, variation in birth weight among subjects with a normal birth weight did not appear to be relevant.

Y B CHEUNG
J P E KARLBERG
L LOW
Department of Paediatrics
Department of Medicine,
University of Hong Kong,
Hong Kong
(jpkarl@hkucc.hku.hk)

Correspondence to: Professor J P E Karlberg

is much more complicated. Instead, we stated that measurements of pulmonary gas exchange during the orthostatic test “are/may be useful in the clinical evaluation of patients with hyperventilation disorders”. However, based on our results and clinical experience over 15 years, we believe that this test is, indeed, helpful as part of the diagnostic evaluation of HVS.

Correspondence to: Professor A Sovijarvi
anssi.sovijarvi@hus.fi
Laboratory of Clinical Physiology, Helsinki University Central Hospital, Haartmaninkatu 2, FIN 00290 Helsinki, Finland

Supplemental oxygen in COPD

I read with interest the study by Garrod et al on the use of supplemental oxygen during pulmonary rehabilitation in patients with COPD with exercise hypoxaemia.1 Most studies on supplemental oxygen are difficult to interpret because they are either not randomised or placebo controlled. It is therefore important that they have dealt with these problems. Nevertheless, I have some difficulty in interpreting their results. The patients were randomised to either training with air (AT) or oxygen (OT). These two groups were tested without additional gas (test 1), with gas (air or oxygen) before training (test 2), and with gas after six weeks of training (test 3). I have reproduced their data on the shuttle walk test (SWT) and post SWT Borg score (Borg) in table 1.

When they compared AT and OT at test 2 they found that oxygen had a significant effect on the SWT (mean difference 27.3 m) and on the Borg score (mean difference −0.68). Surprisingly, although the difference between OT and AT at test 1 was larger, this difference was reported as insignificant.

If changes in the mean outcome measures (test 2 minus test 1) are compared (as they did after six weeks of training), the differences between OT and AT are −1.7 m for SWT and 0.02 for the Borg score. The results therefore depend on the methods used to compare the two groups. The authors need to explain why they compared absolute values when they evaluated the acute effect of oxygen and differences when they evaluated the effect of oxygen during training.

BOOK REVIEW


This excellent book, written by one of the pioneers of sleep disordered breathing in the UK, provides a broad coverage of disorders of sleep that is especially relevant for respiratory physicians. The particular strength of this book is that it provides fascinating background information on the physiology and pathophysiology of sleep which ideally complements the chapters on more specific respiratory problems such as obstructive sleep apnoea syndrome and disorders of respiratory drive and mechanics. Respiratory physicians who see patients with obstructive sleep apnoea syndrome will invariably get involved in trying to assist those with clear evidence of a sleep disorder but without any apparent common respiratory problems. This book will provide such physicians with a background working knowledge of the differential diagnosis in these circumstances, together with some especially helpful summaries and breakdowns of the investigation and management of abnormal sleep cycles.

The book is also well laid out. I found the layout of the book in twin columns to be physically very accessible, and my only criticism is the frequent use of abbreviations in tables and text which, for the unfamiliar reader, is the only interruption to the flow of ideas in the book. Overall, however, I think this is a highly informative text which I imagine will provide a valuable resource to anyone seeing patients who complain of sleepiness.—JB