Case report

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.

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 hypventilation with pH 7.39, PaCO2 6.4 kPa, PaO2 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

Table 1 Sequential values for blood tests and pulmonary function tests

<table>
<thead>
<tr>
<th>Immunosuppressive treatment</th>
<th>Prednisone 60 mg/day (+ CSA, MMF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood tests</td>
<td></td>
</tr>
<tr>
<td>CPK (U/l)</td>
<td>946</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>2.06 (41)</td>
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<tr>
<td>FEV₁ (l)</td>
<td>1.40 (35)</td>
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<td>FEV₁/FVC (%)</td>
<td>68</td>
</tr>
<tr>
<td>MIP (cm H₂O)</td>
<td>64.5 (42)</td>
</tr>
<tr>
<td>MEP (cm H₂O)</td>
<td>46.5 (42)</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Pulmonary function tests</td>
<td></td>
</tr>
<tr>
<td>FVC (l)</td>
<td>347</td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>3.04 (60)</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>68</td>
</tr>
<tr>
<td>MIP (cm H₂O)</td>
<td>946</td>
</tr>
<tr>
<td>MEP (cm H₂O)</td>
<td>114 (74)</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td>60</td>
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<tr>
<td></td>
<td>3.42 (68)</td>
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<tr>
<td></td>
<td>2.63 (50)</td>
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<tr>
<td></td>
<td>63</td>
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<tr>
<td></td>
<td>99</td>
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<tr>
<td></td>
<td>145 (94)</td>
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</tbody>
</table>

CPK = creatinine phosphokinase; FVC = forced vital capacity; FEV₁ = forced expiratory volume in one second; MIP = maximum inspiratory and expiratory pressures; CSA = cyclosporin; MMF = mycophenolate mofetil. Values in parentheses are % predicted.

Discussion

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 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 a day. 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 Muscle biopsy specimen of left triceps showing evidence of acute and chronic inflammation associated with muscle necrosis.
involved 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.


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**LETTERS TO THE EDITOR**

**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 obliterated in 24% of patients, a higher proportion of the FOBs were diagnostic, and the test 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) situation of the mass within 4 cm of the origin of the nearest lobar bronchus; and (4) an ill defined edge to the mass. A “gestalt” assessment of the likelihood of positive FOB was slightly more accurate than any individual factor. When two or more predictive factors were present, FOB was positive in >70% of our selected series. Of interest, proximity of the lesion to the hilum per se was a poor predictor of positive FOB.

We agree with Laroche et al that CT scanning should be performed before FOB in most patients with an abnormal chest radiograph and a high clinical suspicion of bronchial carcinoma. Our study clarifies how the CT appearances can be used to select those patients in whom FOB is unlikely to be diagnostic and should probably not be performed.

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**“Opportunist” 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.

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**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 some developed countries like ours, should imitate their methods and their political commitment to a national tuberculosis programme.


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 Italian 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 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 of 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.

While we fully acknowledge the limitation of a relatively small sample, we believe that it is important to report statistically negative findings and to compare them with the previous Asian study. 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.

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Hyperventilation syndrome

The editorial by Dr Gardner1 on controversial aspects of the hyperventilation syndrome (HVS) refers to our study2 in the same issue of Thorax. This study showed that patients with HVS have an accentuated increase in ventilation as a response to change in body position from supine to standing. The editorial was a valuable addition to the difficult subject. We feel, however, that the interpretation of our paper in the editorial did not quite match the purpose or the message of the original study.

We agree with Dr Gardner that the definition of HVS in the literature are unfortunately variable. Dr Gardner suggests that the term HVS should be abandoned and that efforts should be made to find the initiating and sustaining causes of hyperventilation. This is also our view, but we support our strategy, so the subject in our study underwent a comprehensive set of cardiopulmonary examinations. In clinical practice, however, the aetiology of hyperventilation often remains unknown and the only finding may be a disproportionate ventilatory pattern with resulting hypocapnia and alkalosis which may (at least partly) be the sustaining cause of the symptoms. Why would we not call the disorder HVS? An alternative label would be "unknown dyspnoea" which does not carry the patient of the benign nature of the disorder. Dr Gardner suggests that our subjects “fit into a classification of dyspnoea and air hunger with secondary intermittent hyperventilation". This classification may probably include the whole spectrum of differential diagnoses of dyspnoea and it is not justified, when several diagnostic procedures have been performed, to exclude cardiopulmonary diseases. We fully agree with Gardner’s view that the disorder has been objectively documented. The finding of hyperventilation may be of importance when the initiating cause is known, but we think that the last term is difficult to be confused with the process of diagnosis. We consider this to be close to the original definition by Geisser et al. The approach to the definition of HVS was therefore physiological and unambiguous. As this was clearly described in the study, it is difficult to understand the confusion by Dr Gardner when he claims that the diagnosis was made on the presence of normal PaCO2. The measured orthostatic response which was the object of investigation is another matter and should not be confused with the process of diagnosis.

Finally, we would point out that the main purpose of our paper was to describe the accentuated breathing response to orthostatic changes in patients with HVS. We hope that this finding will add to the knowledge of the causes and mechanisms of hyperventilation called for by Dr Gardner. Contrary to the repeated claim in his editorial, our intention was not to present the orthostatic test as a "diagnostic criterion for HVS" but as a basis for its diagnosis—assessment of these patients.
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.

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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 (test 3). I have compared their data on the SWT (mean difference (Borg) in table 1. I have reproduced their data on the SWT (mean difference (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.

Authors’ reply We are grateful for the comments by Dr Ringbaek but, unfortunately, he has confused the data from two separate tables published in our paper. Test 1 concerns baseline data which was performed to minimise practice effects and was not included in the analysis. Test 2 (176.4 and 149.1) concerns the results of the shuttle walking test (SWT) with an oxygen cylinder and air cylinder in the group as a whole and not separate oxygen training (OT) and air training (AT) groups. This was clearly stated in the legend.

The study was concerned with the additional effect of oxygen on a training programme in patients with severe COPD. We take the point that the results depend on the method used to compare the two groups, as is often the case with statistical analysis. However, change was chosen as a more sensitive outcome as it enables one to take account of baseline variables.

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Table 1 | Acute effect of oxygen compared with air and the effect of training with oxygen compared with training with air

<table>
<thead>
<tr>
<th>Test</th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
<th>Test 2—Test 1</th>
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</thead>
<tbody>
<tr>
<td>Oxygen (OT) SWT (m)</td>
<td>160.0</td>
<td>176.4</td>
<td>196.4</td>
<td>16.4</td>
</tr>
<tr>
<td>Borg</td>
<td>3.83</td>
<td>3.52</td>
<td>2.52</td>
<td>0.32</td>
</tr>
<tr>
<td>Air training (AT) SWT (m)</td>
<td>131.0</td>
<td>149.1</td>
<td>192.7</td>
<td>18.1</td>
</tr>
<tr>
<td>Borg</td>
<td>4.53</td>
<td>4.20</td>
<td>4.66</td>
<td>−0.33</td>
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<tr>
<td>Difference (OT—AT) SWT (m)</td>
<td>29.0</td>
<td>27.3</td>
<td>3.7</td>
<td>−1.7</td>
</tr>
<tr>
<td>Borg</td>
<td>−0.70</td>
<td>−0.68</td>
<td>−2.14</td>
<td>0.02</td>
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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 sleeplessness.—JB