Role of comorbidities in a cohort of patients with COPD undergoing pulmonary rehabilitation

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is often associated with other chronic diseases. These patients are often admitted to hospital based rehabilitation programmes.

Objectives: To determine the prevalence of chronic comorbidities in patients with COPD undergoing pulmonary rehabilitation and to assess their influence on outcome.

Design: Observational retrospective cohort study.

Setting: A single rehabilitation centre.

Patients: 2962 inpatients and outpatients with COPD (73% male, aged 71 (SD 8) years, forced expiratory volume in 1 s (FEV_1) 49.3 (SD 14.8)% of predicted), graded 0, 1 or ⩾2 according to the comorbidity categories and included in a pulmonary rehabilitation programme.

Measurements: The authors analysed the number of self-reported comorbidities and recorded the Charlson Index. They then calculated the percentage of patients with a predefined positive response to pulmonary rehabilitation (minimum clinically important difference (MCID)), as measured by improvement in exercise tolerance (6 min walking distance test (6MWD)), dyspnoea (Medical Research Council scale) and/or health related quality of life (St George's Respiratory Questionnaire (SGRQ)).

Results: 51% of the patients reported at least one chronic comorbidity added to COPD. Metabolic (systemic hypertension, diabetes and/or dyslipidaemia) and heart diseases (chronic heart failure and/or coronary heart disease) were the most frequently reported comorbid combinations (61% and 24%, respectively) among the overall diseases associated with COPD. The prevalence of patients with MCID was different across the comorbidity categories and outcomes. In a multiple categorical logistic regression model, the Charlson Index (OR 0.72 (96% CI 0.54 to 0.98) and 0.51 (96% CI 0.38 to 0.68) vs 6MWD and SGRQ, respectively), metabolic diseases (OR 0.57 (96% CI 0.49 to 0.67) vs 6MWD) and heart diseases (OR 0.67 (96% CI 0.55 to 0.83) vs SGRQ) reduced the probability to improve outcomes of rehabilitation.

Conclusions: Most patients with COPD undergoing pulmonary rehabilitation have one or more comorbidities. Despite the fact that the presence of comorbidities does not preclude access to rehabilitation, the improvement in exercise tolerance and quality of life after rehabilitation may be reduced depending on the comorbidity.

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality.[1 2] Although alarming, this probably underestimates the true burden of this disease on health status, health care costs and overall actual and projected prognoses.[3] COPD is also an important risk factor for other chronic diseases that contribute to morbidity and mortality.[4]

Comorbidities are defined as other chronic medical conditions that accompany a disease process,[5] and they are particularly prevalent in the elderly.[6–8] The most common chronic conditions associated with COPD are hypertension, diabetes, coronary artery disease, heart failure, pulmonary infections, cancer and pulmonary vascular disease.[9–14] Comorbidities are an important determinant of health related quality of life in patients with COPD.[13 15 16]

Pulmonary rehabilitation is a non-pharmacological comprehensive intervention, effective in the long term management of symptomatic COPD of all grades of severity,[17] even in the elderly.[18] Pulmonary rehabilitation improves symptoms, quality of life and exercise performance,[19] and is effective in decreasing consumption of health care resources.[20]

The aim of this study was to determine the frequency and prevalence of chronic comorbidities in patients with COPD and to assess their influence on the effects of pulmonary rehabilitation.

METHODS

Patients

Our study was approved by the our institutional review board.

Of all the patients who were admitted to hospital for rehabilitation purposes from January 2003 to December 2005 (n = 4055), we selected 2962 patients with COPD for retrospective analysis. Patients were selected according to the following criteria: primary diagnosis of (i) COPD (491 codes), as defined and classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[19] and/or (ii) pulmonary emphysema (492 code) and (iii) respiratory failure (518.8× codes). Spirometric severity of COPD was established according to the GOLD guidelines.[21] Therefore, patients with asthma or any other pulmonary diseases (either obstructive or restrictive) were excluded from the study. Discharge diagnosis was made by a physician specialising in pulmonary medicine. The diagnosis of each patient was recorded on an electronic database according to the codes of the International Classification of Diseases, version 9-CM.[22]

Comorbidities

Comorbid conditions were diagnosed according to the International Classification of Health Problems in Primary Care[23] and retrieved from the medical files. All patients were grouped according to the following comorbidity categories: 0 (absence of

Table 1 Anthropometric, demographic and functional characteristics of the study cohort

	All patients	Comorbidity categories			p Value
		0	1	⩾2	
n	2962	1443	1138	381	
Age (y)	71.1 (8.0)	70.9 (8.3)	71.3 (7.6)	71.3 (7.7)	0.429
Sex (M/F) (n (%))	2150/812 (72/28)	1060/383 (73/27)	816/322 (71/29)	274/107 (72/28)	0.188
Charlson Index	1.52 (0.72)	1.25 (0.56)	1.79 (0.78)	2.76 (0.68)	0.001
FEV_1 (% predicted)	49.3 (14.8)	48.8 (14.9)	50.0 (14.5)	49.5 (15.4)	0.128
ATS-ERS* staging (n (%))					
Mild	2 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	
Moderate	1400 (47.2)	648 (44.9)	571 (50.1)	181 (47.5)	
Severe	1251 (42.2)	640 (44.3)	451 (39.6)	160 (41.9)	
Very severe	309 (10.4)	155 (10.7)	114 (10.0)	40 (10.4)	
6MWD (baseline) (m)	335.2 (95.6)	333.5 (96.2)	344.2 (93.1)	313.8 (98.4)	0.001
MRC grade (baseline)	3.7 (0.92)	3.7 (0.91)	3.6 (0.91)	3.9 (0.96)	0.030
SGRQ total score (baseline)	39.5 (16.4)	40.5 (16.8)	39.8 (17.0)	36.3 (12.9)	0.414

Data are mean (SD).
*Mild COPD is defined as FEV_1/FVC ratio ⩽0.7 and $FEV_1\%$⩾80; moderate COPD as FEV_1/FVC ratio ⩽0.7 and $FEV_1\%$ 50–80; severe COPD as FEV_1/FVC ratio ⩽0.7 and $FEV_1\%$ 30–50; and very severe COPD FEV_1/FVC ratio ⩽0.7 and $FEV_1\%$ <30.
6MWD, 6 min walking distance test; FEV_1, forced expiratory volume in 1 s; MRC, Medical Research Council dyspnoea score; SGRQ, St. George's Respiratory Questionnaire total score.

associated chronic conditions), 1 and ⩾2 (depending on the relative number of associated chronic conditions).

The frequency (as a percentage of the total) of each chronic disease and combined diseases—heart disease (chronic heart failure, coronary heart disease), metabolic disease (systemic hypertension, diabetes, dyslipidaemia, namely metabolic syndrome), skeletal disease (osteoporosis, arthrosis) and other disease[1–3]—among the total amount of comorbidities was established. The prevalence of the same single or combined comorbidities was also calculated taking the whole cohort of COPD into account.

Individuals' self-reported comorbidities, as assessed by the Charlson Index,[24] which assigns to each disease a score that is proportional to the disease related risk of death, was also retrieved by these files. The Charlson Index was computed during the hospital stay by the physician in charge of each admitted patient. The computed Charlson Index was not adjusted for age and did not include COPD in the individual's score, as previously suggested.[25]

Pulmonary rehabilitation

Patients were selected for pulmonary rehabilitation according to the British Thoracic Society statement[17] and were treated as inpatients or outpatients, depending on relative indications, preference and the individual's loss of functional limitations other than those related to the lung. Most patients were directly transferred from acute care hospitals. Daily sessions—up to a minimum of 15— including peripheral and/or respiratory muscle training were conducted as previously reported.[26 27]

Pulmonary rehabilitation outcomes

The prevalence of patients with a positive response to pulmonary rehabilitation, corresponding to the minimum clinically important difference (MCID) of each outcome, was calculated in terms of three major measures[28–30]: exercise tolerance (+54 m in the 6 min walking distance test (6MWD)),[31] breathlessness (−1 point on the 1–5 point modified Medical Research Council (MRC) scale)[32] and quality of life (−4 points on the St George's Respiratory Questionnaire (SGRQ)).[33] The percentage of patients who withdrew from pulmonary rehabilitation was also recorded in the study cohort.

Statistics

Analyses were carried out using SPSS software (SPSS 8.0 for Windows; SPSS, Chicago, Illinois, USA). Qualitative variables are expressed as percentages; quantitative variables are expressed as means (SD). Comparison of categorical variables among comorbidity categories was made using the χ^2 test.

Correlations between rehabilitation outcomes (MRC, 6MWD, SGRQ) and categorical variables in the study were first analysed with the univariate method (for details see the online supplement material). The multivariate logistic regression model was then applied to define the predictive role of comorbidities and other potential confounders when related to the outcomes of the rehabilitation program (for details see the online supplement material).

All results were considered to be statistically significant at $p<0.05$.

RESULTS

Patients with COPD treated during the study period and included in this analysis (n = 2962) were 73% of all those respiratory patients who attended the pulmonary rehabilitation programme in our centre between January 2003 and December 2005. The main anthropometric and clinical characteristics of the patients are reported in table 1. Most patients were male (73%) with moderate to severe COPD and a disability grade (mean 6MWD, MRC and SGRQ values) that led to elective indications for rehabilitation. Patients with very severe COPD who were on long term oxygen therapy represented approximately 9% of the total cohort.

Fifty-one per cent (1519 patients) of the cohort reported at least one comorbidity (38%, 11% and 2% for comorbidity categories 1, 2 and >2, respectively). Distribution of staging and functional status was no different across the categories.

Figure 1A shows the frequency distribution (% of total) of the main chronic diseases in those patients with COPD who had at least one comorbidity. The six most frequent diseases represented >85% of the total number of comorbidities. Other, less frequently reported, comorbidities were atherosclerosis (2%), cancer (1%) and dementia (1%), and liver (2%), renal (3%), stomach (1%) and intestinal (1%) diseases. The frequency distribution (% of total) of the comorbidity combinations is

Table 2 Patients with a predefined positive response (MCID) to pulmonary rehabilitation in terms of improvement in exercise tolerance, dyspnoea and quality of life

	All patients (n = 2962)	Comorbidity categories			
		0 (n = 1443)	1 (n = 1136)	⩾2 (n = 383)	χ^2
6MWD +54 m (n (%))	1822 (61.5)	904 (62.6)	680 (59.8)	238 (62.4)	0.298
MRC grade −1 (n (%))	2416 (81.5)	1170 (81.0)	914 (80.3)	332 (87.1)	0.010
SGRQ total −4 (n (%))	1845 (62.2)	962 (66.6)	658 (57.9)	225 (59.0)	0.001
Withdrawal rate (%)	2.82	1.89	3.44	1.26	0.561

Data are presented as mean (SD).
6MWD, 6 min walking distance test; MCID, minimum clinically important difference; MRC, Medical Research Council dyspnoea score; SGRQ, St. George's Respiratory Questionnaire total score.

shown in fig 1B. Heart disease (24%), metabolic disease (62%) and skeletal disease (7%) were the most frequently reported.

Taking the whole cohort of COPD into account, systemic arterial hypertension was the most prevalent comorbidity (27.4%), followed by chronic heart failure (10.5%) and diabetes (10.3%), whereas the prevalence of combined heart disease, metabolic disease and skeletal disease was 16%, 38% and 5%, respectively (figure not displayed).

Mean changes after pulmonary rehabilitation were 67 (SD 47) m in the 6MWD, −1.1 (SD 0.7) for the MRC score and −6.4 (SD 4.5) for the SGRQ score. However, the number and per cent of patients with MCID in the MRC score and SGRQ score (but not in the 6MWD) were different ($p<0.05$) across the comorbidity categories (table 2). Withdrawal rate from pulmonary rehabilitation (3%) was no different across the same categories (table 2).

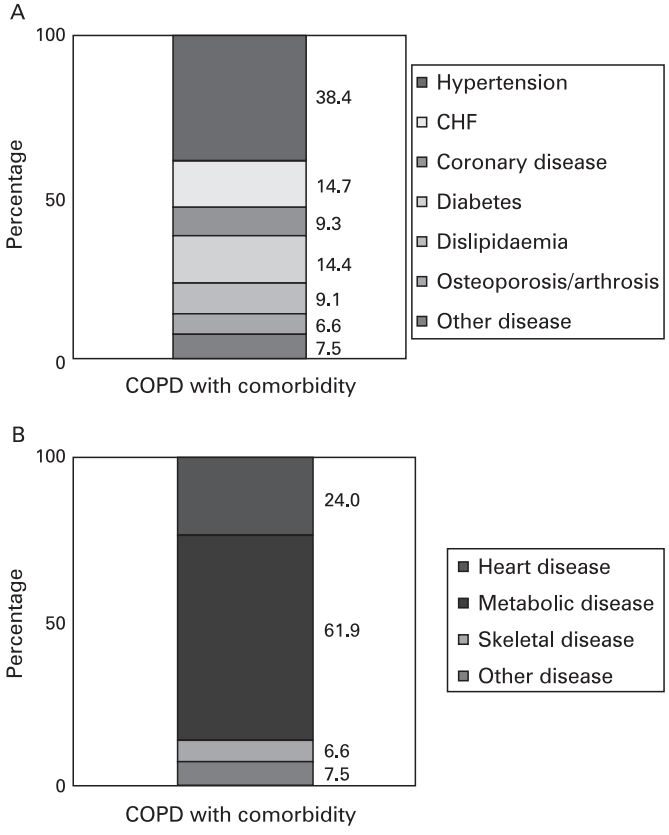

Figure 1 Frequency distribution (% of total) of individual chronic comorbidities (A) and combinations of comorbidities (B) added to chronic obstructive pulmonary disease (COPD) in the population. CHF, chronic heart failure.

Univariate analysis for binary variables showed that age (with SGRQ, $p = 0.001$), Charlson Index (with 6MWD and SGRQ, $p = 0.001$), forced expiratory volume in 1 s (FEV_1) (with MRC, $p = 0.032$), heart disease (with 6MWD and SGRQ, $p = 0.001$), metabolic disease (with 6MWD, $p = 0.001$; MRC, $p = 0.004$; SGRQ, $p = 0.043$) and skeletal disease (with MRC, $p = 0.049$) were significantly related to outcome and were then entered into the multivariate analysis (for detailed statistics, see also the table in the online supplement material).

Table 3 displays the results of the multiple logistic regression analysis. Age, FEV_1, Charlson Index, and heart disease and metabolic disease combinations entered the prediction equation as independent variables. In particular, airway obstruction significantly predicted the improvement in MRC score; Charlson Index and metabolic disease were inversely related to improvement in 6MWD; and heart disease directly and indirectly predicted the improvement in 6MWD and SGRQ, respectively.

The overall results did not change when taking the subgroups of patients with COPD undergoing inpatient and outpatient (13% of total) rehabilitation.

DISCUSSION

Our study showed that most patients with COPD undergoing pulmonary rehabilitation have one or more chronic comorbidities and that the severity of comorbidities, particularly the simultaneous presence of metabolic and/or heart diseases, significantly reduces the beneficial effects of pulmonary rehabilitation on exercise tolerance and perceived quality of life.

Complex chronic comorbidities may significantly affect the clinical severity of COPD,[7 11 18 32] being present in up to 56% of patients with COPD compared with non-COPD subjects of the same age.[32] The prevalence of chronic comorbidities varies among studies.[9 25] Although the methodology was similar, the prevalence of at least one comorbidity in our cohort was lower (approximately 65%) than the prevalence reported in other studies (>70%).[34 35] Indeed, the population we examined was selected because it included only patients referred for pulmonary rehabilitation. The prevalence of comorbidities in patients with COPD referred for pulmonary rehabilitation has not been definitively examined previously,[36 37] probably because of the relatively low number of patients and inclusion/exclusion criteria of pulmonary rehabilitation. Most (>90%) patients included in our study had moderate to severe COPD (stages 2 and 3 according to the GOLD guidelines), suggesting that patients with very severe (stage 4) COPD, possibly with more and more severe chronic comorbidities,[6 38] are less frequently referred for rehabilitation. Interestingly, the reported comorbidity Charlson score[24 39] in our patients was similar (1.26–2.85) to that reported in other studies.[36 40 41]

Table 3 Factors predicting pulmonary rehabilitation outcome in the cohort of patients with COPD

Dependent variable	Variable	β	SE	Exp (β) OR	96% CI	p Value
6MWD improvement	Charlson Index	−0.31	0.14	0.72	0.54 to 0.98	0.024
	Heart disease	0.86	0.11	2.36	1.85 to 3.01	0.001
	Metabolic disease	−0.55	0.07	0.57	0.49 to 0.67	0.001
MRC improvement	FEV_1	0.53	0.13	1.71	1.34 to 2.40	0.001
	Metabolic disease	0.16	0.09	1.17	0.93 to 1.77	0.104
	Skeletal disease	−0.36	0.20	0.69	0.66 to 1.48	0.074
SGRQ Improvement	Age	0.30	0.07	1.35	1.15 to 1.59	0.001
	Charlson Index	−0.66	0.14	0.51	0.38 to 0.68	0.001
	Heart disease	−0.38	0.10	0.67	0.55 to 0.83	0.001
	Metabolic disease	−0.09	0.07	0.91	0.77 to 1.07	0.249

For details of the included variables, see the results section.
6MWD, 6 min walking distance test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; MRC, Medical Research Council dyspnoea score; SGRQ, St George's Respiratory Questionnaire total score.

Systemic hypertension, chronic heart failure, diabetes, coronary heart disease, dyslipidaemia and osteoporosis–arthrosis ranked as the six most frequent among all reported comorbidities; these six represented >85% altogether (fig 1A), and their proportions were similar to those reported in previous studies.[37] The same features were also observed with regard to the prevalence of these diseases within the cohort of studied COPD (see also results).

Metabolic disease and heart disease were the two most frequent disease combinations among all reported comorbidities (fig 1B). It is noteworthy that the term metabolic disease only approximates the internationally shared definition of "metabolic syndrome".[42] Notwithstanding, metabolic alterations together with chronic heart diseases are well known to independently worsen the prognosis of adults.[1–3] In elderly patients with complex comorbidities, obesity and low physical activity are factors that increase the risk of death by 15% and 3%, respectively.[3] Both of these factors are important determinants of survival in patients with COPD[36 43 44] and are likely to be improved with comprehensive rehabilitation.[17] Therefore, it is not surprising to find this frequent pattern of comorbidities in patients with COPD enrolled in pulmonary rehabilitation programmes.

Exercise performance, dyspnoea and quality of life (as assessed by the SGRQ) are widely recognised as important patient centred outcomes of COPD, whose favourable change indicates the clinical effect of treatment,[21] particularly pulmonary rehabilitation.[45] The MCID method adopted here to define the a priori criteria for outcome improvement seems appropriate in this field.[29] The proportion of patients with significant changes in MRC (higher percentage in category ⩾2) and SGRQ (higher percentage in category 0) was different across the comorbidity categories (table 2). However, the magnitude of their change after rehabilitation was similar in these groups, confirming the ability of pulmonary rehabilitation to individually target (whenever possible) the reasonably reachable goals for reducing disability.

The proportion of patients who reported a positive change in all three pulmonary rehabilitation outcomes in our study was >50%. Overall, this percentage was higher than that in a previous study[29] in outpatients with COPD. These differences may be partially explained by the different site (inpatient facility for most of our patients with COPD) and grade of physical disability (mean 285 vs 335 m for the 6MWD in De Torres and colleagues[29] and in our study, respectively) recorded at baseline.

To our knowledge, our study is the first to investigate the predictive role of comorbidities on the effect of pulmonary rehabilitation. To date, this information is still lacking in the field of rehabilitation with regard to patients with COPD. Only one study[38] has considered the independent role of comorbidities on functional outcomes (balance and gait) after physical intervention in over 700 elderly patients who were recovering from stroke or who had Parkinson's disease or osteoarthritis. The investigators observed that the determinants of poor recovery were characterised by the combination of "more disabling diseases" (COPD, heart failure, peripheral artery disease, diabetes and cancer) rather than the effect of each chronic disease, independent of age, cognitive status or functional status at admission.

Our findings are consistent with those of De Fazio and colleagues[38]; indeed, we have shown that the combinations of chronic comorbidities (metabolic and/or heart diseases), but not each chronic disease per se associated with COPD, independently predict improvement after pulmonary rehabilitation (table 3). In addition, the overall impact of comorbidities (here quantified by means of the Charlson Index) inversely predicts the improvement of both exercise tolerance and quality of life after rehabilitation. This suggests that the more complex cases are those less likely to benefit from pulmonary rehabilitation.

The presence of associated metabolic disorders is inversely related to improvement in 6MWD. Indeed, it is likely that the systemic complications associated with hypertension, diabetes, dyslipidaemia and overweight limit the ability to improve physical performance in terms of exercise tolerance, as known in humans.[46]

Interestingly, the presence of combined heart diseases acts as both positive and negative predictors depending on the outcome investigated. In particular, it directly relates to the improvement in 6MWD but inversely relates to the change in quality of life (SGRQ).

Despite the large contribution that cardiac dysfunction may give per se to health status and prognosis in adults,[47] training during rehabilitation in these chronic diseases appears to be recommended.[48] These diseases, even if associated with COPD, are not likely to alter the individual's ability to improve his or her physical performance. On the other hand, the combination with chronic heart diseases (but not of the metabolic disorders) inversely predicts the effect of pulmonary rehabilitation on the quality of life of patients with COPD. We can only speculate that this particular interaction and disease complexity may negatively impact on the potential benefit of rehabilitation on the individual's perceived health status, as reported previously.[49]

Thus on the one hand the presence of more complex comorbidities among patients with COPD undergoing

pulmonary rehabilitation does not necessarily mean that this process is likely to benefit those patients less. On the other hand, however, it probably implies that outcomes should be better targeted and intervention should be better tailored to take account of this factor. Interestingly, despite the fact that rehabilitation in our cohort of COPD was delivered in two different setting (13% as outpatients), the overall results were similar in these subgroups of patients, confirming a quite homogeneous cohort and making the clinical message even stronger.

Despite our new and original findings, our study has limitations which need to be addressed. Firstly, this is a retrospective cohort analysis and hence a further prospective trial is needed to confirm the results. Secondly, the pattern of comorbidities in our single centre COPD cohort, although consistent, should be confirmed in a multicentre study where objective confirmation on the single diagnosis is also considered. Thirdly, diagnosis of the comorbidities was based on a self-reported method; therefore, the predictive role of the metabolic and heart diseases on the effects of pulmonary rehabilitation need to be corroborated by more precise biological or pathogenetic indicators. Fourthly, other potential individual factors such as socioeconomic status, smoking habit and pack years were not retrospectively available nor were they taken into account as potential confounders in the predictive analysis.

Notwithstanding these important factors which limit the generalisability of this study by using a single site, our findings underline the necessity to globally assess patients with COPD for their functions and comorbidities in order to determine the most appropriate approach for treating them.[50]

In conclusion, this study shows that chronic comorbidities are very frequent in patients with COPD undergoing rehabilitation but a positive effect is reached in >50% of patients. Comorbidity risk score and the combinations of both heart and metabolic diseases, in particular, independently predict the effect of pulmonary rehabilitation on exercise capacity and quality of life.

In the context of the current evidence and taking the limitations into account, our findings enable physicians to carefully investigate the impact of comorbidities as potential predictors and confounders in the population of patients with COPD enrolled in rehabilitation programmes.

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Pulmonary puzzle

Progressive dyspnoea, pleural effusions and lytic bone lesions

CLINICAL PRESENTATION

A 72-year-old man was referred following a CT scan which showed lytic and sclerotic lesions in the spine and pelvis with bilateral pleural effusions and thickening. The patient was an ex-smoker with progressive dyspnoea and significant weight loss over 1 year. There was no history of exposure to asbestos. Pleural fluid analysis revealed a transudate with no malignant cells. A repeat CT scan showed small bilateral pleural effusions and rinds of solid tissue within the pleural space extending to surround the descending thoracic aorta and aortic arch. Nodular reticular shadowing was seen in both lungs extending to the periphery, particularly in the upper lobes. Another soft tissue rind surrounded the kidneys with renal sinus fat obliteration. Presumed metastases were seen in both iliac bones with surrounding sclerosis on the left and the T7 vertebral body. An isotope bone scan revealed extensive focal increased tracer activity in lower limb long bones (fig 1). Initial pleural biopsy, performed to investigate the diagnosis of malignancy, showed non-specific fibrosis. Before further investigations could be undertaken, the patient died from aspiration pneumonia following a stroke. Because of the suspicion of mesothelioma, a coronial autopsy was undertaken which confirmed bilateral pleural thickening up to 1 cm with focal calcification but no macroscopic parenchymal infiltration.

QUESTION

What is the diagnosis?

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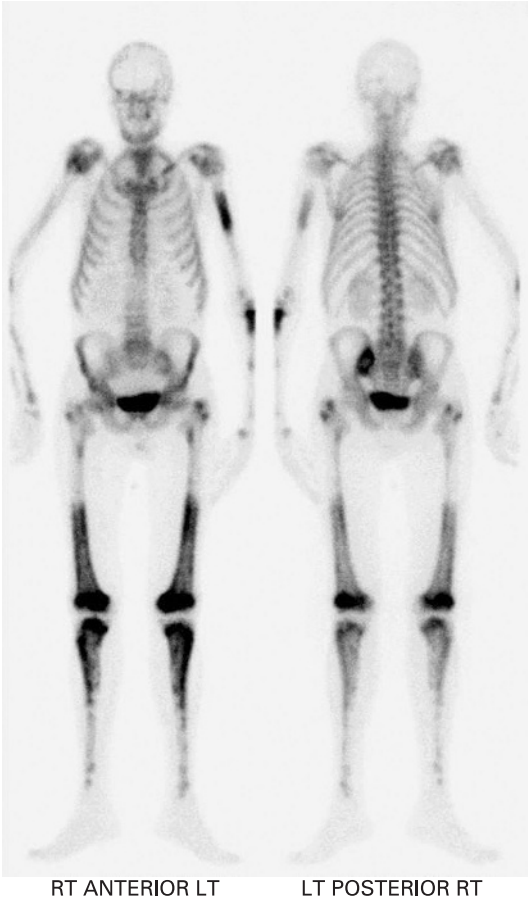

RT ANTERIOR LT LT POSTERIOR RT

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