Why do patients with myositis die? A retrospective analysis of a single-centre cohort

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Abstract

Objective

Causes of death in inflammatory myopathies have rarely been studied. We have assessed a cohort of myositis patients followed in a single centre over a 37-year period, reviewing the mortality rate, causes of death and predictors of poor prognosis.

Methods

We performed a single-centre, retrospective study on patients aged ≥16 years fulfilling 3 or 4 of the Bohan and Peter criteria, noting their demographic data, clinical features, serology, treatment and outcome.

Results

Of 97 patients identified, 74.2% were female. The mean age at diagnosis was 40.5 years (SD 13.2). 38.1% had adult-onset dermatomyositis, 36.1% adult-onset polymyositis and 25.8% overlap myositis. 96.9% had upper and lower limb involvement (UL^+/LL^+) and 62.9% had a highest CK≥10 times the upper limit of normal. 33% had significant infection(s). The disease course was chronic persistent in 29.9%, relapsing and remitting in 34% and monophasic in 36.1%. All received steroids and 92.8% other immunosuppressant(s). The median follow-up was 9 years (IQR 11.5). The estimated cumulative proportion survival at 5, 10, 15 and 20 years were 94.6%, 82.2%, 72,1% and 66.1%, respectively. 24.7% of patients died, mostly due to infection (29.2%). In univariate analysis, lung involvement (HR 1.78, p=0.013), infection (HR 4.18, p=0.003) and UL^+/LL^+ (HR 0.13, p=0.010) were statistically significantly associated with the risk of death. In the multivariate analysis infection (HR 3.68, p=0.009) and UL^+/LL^+ (HR 0.16, p=0.027) were statistically significantly associated with survival.

Conclusion

A good long-term survival is reported. Nevertheless, careful follow-up of myositis patients is important.

Key words

inflammatory myopathies, extramuscular complications, causes of death, long-term survival, predictors of poor prognosis

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Introduction

Idiopathic inflammatory myopathies (IIM) are autoimmune systemic diseases characterised by chronic inflammation with progressive symmetrical mostly proximal muscle weakness, elevated serum muscle enzymes levels, electromyographic abnormalities and inflammatory infiltrates on muscle biopsy (1). The aetiopathogenesis of IIM remains unknown, although environmental factors in genetically susceptible individuals are implicated (2). The classification of IIM can be divided into four main groups: adult onset polymyositis (APM), adult onset dermatomyositis (ADM), juvenile idiopathic inflammatory myopathies (JIIM) and inclusion body myositis (IBM) (3). It may be part of an overlap syndrome (OS), with other autoimmune diseases. The most common are systemic sclerosis, Sjögren's syndrome, systemic lupus erythematosus (SLE), undifferentiated autoimmune rheumatic disease and rheumatoid arthritis. IIM, in particular ADM, can be associated with cancer in a paraneoplastic manner (3-4).

Although muscle biopsy may not show inflammatory cell infiltrates in all cases, it is a valuable diagnostic tool that helps distinguishing different types of IIM and, along with clinical and serological features, may help predicting outcome (5).

Since the 1950s corticosteroids have invariably been used, often with immunosuppressive drugs, notably azathioprine, methotrexate, cyclosporine, cyclophosphamide and mycophenolate mofetil. Intravenous immunoglobulin (IvIg) and rituximab are used in cases of refractory disease and to help minimise the steroid requirements (6). These drugs have clearly been helpful, but do expose these patients to increased risk of infection.

Before corticosteroids and immunosuppressives were introduced, the mortality rate was as high as 50-70% (7-10). Older series reported 5- year survival rates as low as 52% (11) or 65% (12), with survival rates at 7 and 8 years of 53% (12) and 72.8% (13). More recently, earlier diagnosis and more aggressive treatment regimens have improved the survival of these patients (9-10, 14). Malignancy, lung and cardiovascular complications as well as infections are the most common reported causes of death in these patients (3, 7, 8, 10, 14). However, the numbers of patients previously reported have often been quite small and the period of follow-up invariably <15 years.

We have carefully observed a cohort of myositis patients, followed in a single centre for a period of over 30 years. We now review the causes of death, survival and predictors of mortality.

Materials and methods

We performed an observational retrospective study involving patients with IIM followed up between January 1976 and December 2013. 97 patients with myositis, all under the care of one of us (DAI) were identified. Each fulfilled three or four of the Bohan and Peter criteria (1). Those with a final diagnosis of IBM or muscular dystrophy were excluded from this study, as well as those with an age of onset <16 years and patients whose follow-up was less than one year. Patients were divided into three groups: APM, ADM, and OS. From the patient's medical notes we completed a database and analysed the demographic features (gender, ethnicity, age at diagnosis), duration of symptoms before diagnosis, extent of muscle involvement (ascertained by standard clinical assessment noting the presence or absence of upper and lower limb proximity muscles), autoantibody pattern, highest CK level, EMG and biopsy results, treatment, disease course and extramuscular involvement [heart, lung, gastrointestinal (GI) tract, joints, infections, malignancy, skin ulcers and calcinosis], time of follow-up, date and cause of death. The extent of muscle involvement was divided into upper limb (UL) and/or lower limb (LL) involvement. The antinuclear antibody (ANA) was considered positive if the titre was ≥1:80 (by immunofluorescence). The results from a range of other autoantibodies were noted. We have been able to utilise stored serum from patients treated over 20 years ago for the more recently identified auto-antibodies. Serum CK level was considered abnormal when it exceeded the normal limit as

defined by the local reference laboratory. Patients were divided into 5 groups according to levels of CK (Table I). Cardiac involvement was defined by the presence (as a clinical manifestation or as a result of diagnostic tests) of one or more of the following: arrhythmia, conduction abnormalities, congestive heart failure, ischaemic disease and valvulopathy. Pulmonary involvement was defined by persistent respiratory symptoms with abnormal pulmonary function tests, chest computed tomography scan features associated with interstitial lung disease (ILD), or pulmonary hypertension (diagnosed by echocardiography or right heart catheterisation). GI involvement was defined as dysphagia, regurgitation or reflux. Joint involvement was considered to be present in patients with arthralgia or if an inflammatory arthritis was diagnosed (on physical examination or by ultrasound scan). Significant infections were considered in patients with symptoms who needed hospitalisation. Malignancy not linked to the IIM was considered in patients diagnosed more than two years after or before the diagnosis of myositis. Those in whom the malignancy was diagnosed within 2 years were included provided myositis specific autoantibodies were positive. The patients were classified into those who had a monophasic (M) illness (only one episode of active disease), a relapsing-remitting (RR) (disease flares and disease-free periods) and a chronic persistent (CP) disease (evidence of active disease despite treatment) (15). Disease activity was defined as a high serum CK together with symptoms suggestive of myositis or its complications. Duration of symptoms was defined as the number of months since the symptoms started until the diagnosis was established. Duration of follow-up was defined as the number of years from the date of the diagnosis (time 0) to the date of the last visit to our department, to the end of observation period (December 2013) or to the date of death (endpoints). The cause of death was ascertained from a mixture of review of the patient's hospital notes, general practitioner records and death certificates.

Statistical analysis

The IBM® SPSS® Statistics v. 22 was used for statistical analysis. The Kolmogorov-Smirnov test was used as test of normality. Continuous variables with a distribution similar to normal were described by the mean and standard deviation (SD) and the remaining were described by the median and interquartile range (IQR) (P25-P75). Categorical variables were described by percentages. The 1-year survival rate was calculated by the direct method. The 5, 10, 15 and 20 year survival rates were estimated using the Kaplan-Meier analysis. The Log rank test was used to determine the statistical significance of the differences in survival rates between the subgroups of each variable. The Cox proportional hazards regression was used to establish the relationship between the categorical predictor variables and the risk of death. The independent variables shown to be statistically significant in univariate regression were further submitted to multivariate analysis. The missing values were reported and excluded from the analysis. A p-value <0.05 was considered statistically significant.

Results

Ninety-seven patients were assessed (Table I). Most (74.2%) were females, with a female to male ratio of 2.9, and most (63.9%) were Caucasian. The mean age at diagnosis was 40.5 years (SD 13.2). 44 (45.4%) patients were diagnosed between the ages of 20 and 39 years old. The diagnosis was ADM in 37 (38.1%) patients, APM in 35 (36.1%), and OS in 25 (25.8%). For the 81 patients whose notes provided reliable information, the median duration of symptoms before the diagnosis was made was 6 months (IQR 9). In 26 (26.8%) patients the symptoms were present for less than 3 months before the diagnosis was made; 9 (9.3%) patients reported symptoms for at least 18 months before the diagnosis.

In terms of clinical presentation, most patients (96.9%) had upper and lower limb involvement (UL^+/LL^+) while 1 had proximal weakness affecting only lower limbs (UL^-/LL^+) and 2 had no evidence of proximal weakness (UL^-/LL^-). Among the patients whose results were available, 47 (49%) were ANA positive, 22 (23.2%) had positive anti-synthethase antibodies (20 with anti-Jo1, 1 with PL7 and 1 with PL12), SRP and Mi2 antibodies were positive in 3 (3.2%) and 5 (5.3%), respectively, and RNP was positive in 13 (13.7%). Most patients (62.9%) had a highest CK more than 10 times the upper limit of normal. Among those whose EMG and muscle biopsy reports were available (85 and 82 patients, respectively), these were compatible with an inflammatory myopathy in 89.4% and 85.4% of cases, respectively. The biopsy was normal in 11% and inconclusive in 3.6% of cases. In terms of extramuscular features, significant infection was reported in 32 (33%) patients, lung and GI complications were each reported in 31 (32%) patients, cardiac complications in 24 (24.7%), and malignancy in 12 (12.4%) (the prevalence of cancer was 15.6% in ADM patients and 9.6% in APM patients). Furthermore, 45 (46.4%) patients had joint involvement, 8 (8.2%) had skin ulcers and 7 (7.2%) had calcinosis. Among the patients with malignancies, 4 were diagnosed within 2 years of the myositis diagnosis (all were female; 1 with ADM, positive ANA and Mi 2, who was diagnosed with Hodgkin Lymphoma (HL); 1 with ADM, Jo1 positive, diagnosed with an endocrine carcinoma of the pancreas; 1 with OS, ANA and RNP positive, diagnosed with a HL; 1 with ADM, Jo1 positive, who had an endometrial carcinoma). The course of the disease was RR in 33 (34%), M in 35 (36.1%) and CP in 29 (29.9%). Therapeutically, all patients received steroids and most (92.8%) also received one or more immunosuppressive drugs. The ones more frequently used were azathioprine, methotrexate, cyclosporine, cyclophosphamide and IvIg.

The median duration of follow-up was 9 years (IQR of 11.5 years). 20 (20.6%) patients were followed up for at least 20 years. The observed survival at 1 year was 100% and the estimated cumulative proportion survival at 5, 10, 15 and 20 years were 94.6%, 82.2%, 72,1% and 66.1%, respectively (Fig. 1). During follow-up, 24 patients (24.7%) died, af-

Table I. Descriptive analysis of the study population.

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		97 patients	24 patients who died
Diagnostic category, n (%)	ADM	37 (38.1)	9 (37.5)
	APM	35 (36.1)	8 (33.3)
	OS	25 (25.8)	7 (29.2)
Sex, n (%)	Female	72 (74.2)	14 (58.3)
	Male	25 (25.8)	10 (41.7)
Ethnicity, n (%)	Caucasian	62 (63.9)	16 (66.7)
	Afro-Caribbean	21 (21.7)	5 (20.8)
	South Asian	10 (10.3)	2 (8.3)
	Asian	3 (3.1)	0 (0)
	Other	1 (1)	1 (4.2)
Age at diagnosis, mean (SD)		40.5 (13.2)	41.6 (14.6)
Age groups (years), n (%)	<20	6 (6.2)	1 (4.2)
	20 – 39	44 (45.4)	11 (45.8)
	40 – 59	37 (38.1)	8 (33.3)
	≥60	10 (10.3)	4 (16.7)
Duration of symptoms (months), median (IQR)		6 (9) (16 missing values)	6 (5.5) (3 missing values)
Duration of symptoms (months), groups n (%)	<3	26 (26.8)	4 (16.7)
	3 – <9	28 (28.9)	12 (50)
	9 – <18	18 (18.5)	5 (20.8)
	≥18	9 (9.3)	0 (0)
		(16 missing values)	(3 missing values)
Upper/Lower limb involvement, n (%)	UL^+/LL^+	94 (96.9)	22 (91.6)
	UL^-/LL^+	1 (1)	1 (4.2)
	UL^-/LL^-	2 (2.1)	1 (4.2)
Highest CK, n (%)	N	8 (8.2)	3 (12.5)
	N – <2x upper limit	3 (3.1)	0 (0)
	2 – <5x upper limit	10 (10.3)	2 (8.3)
	5 – <10x upper limit	12 (12.4)	3 (12.5)
	≥10x upper limit	61 (62.9)	16 (66.7)
		(3 missing values)	
ANA +, n (%)		47 (48.5) (1 missing value)	14 (58.3) (1 missing value)
Other autoantibodies, n (%)	Antisynthetase +	22 (22.7)	8 (33.3)
	SRP +	3 (3.1)	0 (0)
	Mi 2 +	5 (5.2)	1 (4.2)
	RNP +	13 (13.4)	5 (20.8)
		(2 missing values for each antibody)	(1 missing value for each antibody)
Extramuscular complications, n (%)	Cardiac involvement	24 (24.7)	12 (50)
	Lung involvement	31 (32)	11 (45.8)
	Malignancy	12 (12.4)	6 (25)
	Infection	32 (33)	14 (58.3)
	GI involvement	31 (32)	8 (33.3)
	Skin ulcers	8 (8.2)	3 (12.5)
	Calcinosis	7 (7.2)	3 (12.5)
	Joint involvement	45 (46.4)	8 (33.3)
		*	*
Treatment, n (%)	S	7 (7.2)	3 (12.5)
	S + 1 IS	26 (26.8)	4 (16.7)
	S + 2 IS	25 (25.8)	8 (33.3)
	S + 3 IS	11 (11.3)	4 (16.7)
	S + ≥4 IS	28 (28.9)	5 (20.8)
Disease course, n (%)	M	35 (36.1)	6 (25)
	RR	33 (34)	8 (33.3)
	CP	29 (29.9)	10 (41.7)
Duration of follow-up (years), median (IQR)		9 (11.5)	10 (8.75)

SD: standard deviation; IQR: interquartile range; ADM: adult onset dermatomyositis; APM: adult onset polymyositis; OS: overlap syndrome; UL^+/LL^+: upper and lower limb involvement; UL^-/LL^+: only lower limb involvement; UL^-/LL^-: no evidence of proximal weakness; N: normal CK; N – <2x upper limit - CK level between the upper limit of normal and two times the upper limit of normal; 2 – <5x upper limit - CK level between two and five times the upper limit of normal; 5 – <10x upper limit - CK level between five and ten times the upper limit of normal; ≥10x upper limit - CK level of at least ten times the upper limit of normal; GI: gastrointestinal; S: steroids; IS: immunosuppressants; M: monophasic; RR: relapsing and remitting; CP: chronic persistent.
*Data were missing in 3 patients in each category, except for malignancy where we lacked information on 2 patients.

ter a median follow up of 10 years (IQR of 8.75 years). The mortality rate was 24.3% in ADM patients, 22.9% in APM and 28% in OS. Infection was the most common cause of death [n=7 (29.2%)]. Pneumonia was the most frequent specific cause of death, being responsible for 20.8% of deaths in our cohort. Six patients (25%) died as a consequence of a malignancy, 4 (16.7%) died because of a cardiac complication and 2 (8.3%) because of a lung complication (Table II). Among patients who died, most were females and Caucasian (58.3% and 66.7%, respectively). The mean age at diagnosis was 41.6 years (SD 14.6). Nine (37.5%) had ADM, 8 (33.3%) had APM and 7 (29.2%) had OS. The median duration of symptoms before diagnosis among these patients was 6 months (IQR 5.5). Most (91.6%) had involvement of upper and lower limb. Among the 23 patients whose results were available, ANA was positive in 14 (60.9%) and 8 (34.8%) had positive anti-synthetase antibodies. In 66.7% of patients who died, the highest CK was ≥10 times the upper limit of normal. A CP course was reported in 41.7% of these patients and the treatment included steroids+2 immunosuppressants in 33.3% (Table I).

There was no significant statistical difference in the risk of death between APM, ADM and OS patients, which led to their combination for survival analyses. Age, sex, ethnicity, disease course, CK level, ANA, antisynthetase antibodies, SRP, Mi2 and RNP antibodies, treatment, delay in diagnosis, malignancy, cardiac, GI and joint involvement, skin ulcers and calcinosis were not statistically significantly related to the risk of death. In the univariate analysis, lung involvement [hazards ratio (HR) 1.78; 95% confidence interval (CI):1.13-2.82; p=0.013], infection (HR 4.18; 95% CI:1.61-10.91; p=0.003) and UL+/LL+ (HR 0.13; 95% CI:0.03-0.62; p=0.010) were statistically significantly associated with the risk of death. In the multivariate analysis, infection (HR 3.68; 95% CI:1.38-9.82; p=0.009) and UL^+/LL^+ (HR 0.16; 95% CI:0.03-0.81; p=0.027) were the only factors statistically significantly associated with survival.

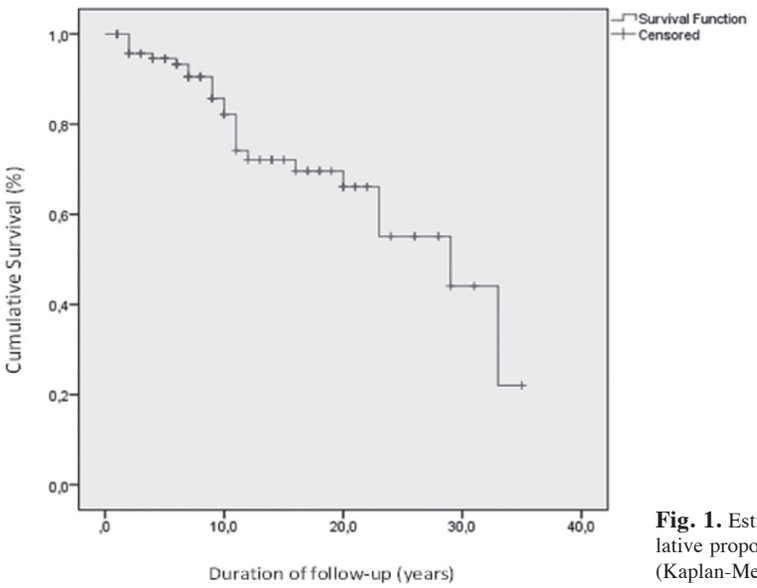

Fig. 1. Estimated cumulative proportion survival (Kaplan-Meier curve).

Discussion

This study reports the longest follow up period of myositis patients that we are aware of (9, 12, 16-19). We have focused on the number and causes of mortality in this group.

Our study population had a female preponderance (F:M ratio of 2.9), as previously reported in other series (9, 13, 16-18, 20-21). The mean age at onset was similar to that reported by Danko *et al*. (17) (40.5 and 39.2 years, respectively). In other reports, the mean age at onset was higher, varying between 45 and 52 years (13, 18, 20-21) or 56 years for polymyositis (PM) and 53 for dermatomyositis (DM) in another study (16). In terms of clinical presentation, most patients (97.9%) had evidence of proximal muscle weakness, with involvement of upper and lower limb in 96.9%. Previous series (13, 17, 22) have reported evidence of proximal weakness in 80, 93 and 100% of patients. Like in other studies (9, 13, 20, 22), all of our patients received steroids. 93.3% also received other immunosuppressives, which is a higher percentage compared to that in other reports (13, 20, 22). While the early use of appropriate and aggressive immunosuppressive therapy is one of the factors contributing to an improved survival in IIM patients (17), it has been observed that steroid therapy predicts infection onset in APM/ADM, while other cytotoxic drugs amplify their immunosuppressive effects (23). Additionally, the incidence of malignant diseases may be increased by the long-term use of cytostatic drugs (16). Therefore, these patients must be closely monitored for extramuscular complications resulting from the disease and its treatment.

In a small series of PM/DM patients (24), severe infections occurred in 26.1% of patients. Another study assessed the frequency of severe pyogenic and non-pyogenic/opportunistic infections, requiring hospitalisation, in a large cohort (279 PM/DM patients) (23). Severe infections were reported in 37.3% of patients, most of them (68.3%) pyogenic (the majority aspiration pneumonia), but 35.7% were nonpyogenic/opportunistic infections, including infection by *Mycobacterium tuberculosis* and *Candida albicans*. In our study, significant infection(s) occurred in 32 (33%) patients and lower respiratory tract infections (pneumonia, tracheobronchitis) were the most frequent. They were reported in 30 patients, 19 (63.3%) of whom had ILD. It is possible that pre-existent changes in the lung as well as the immunosuppressive treatment required for ILD creates a favourable environment for the development of pyogenic infections. Two patients had septicaemia, one of them of pulmonary origin and the other due to multiple infections (respiratory, urinary tract, pancreatic abscess). They were both on steroids and azathioprine and the second one had been treated with cyclophosphamide in the past. Two patients had articular tuberculosis.

ILD was present in 32% of our cohort, a higher prevalence than that seen in previous reports (22.2%–23.1%) (17, 25). In another study (26), the prevalence of ILD in PM and DM was 32%. These authors considered the possibility of selection bias caused by the severity of the disease in patients referred to specialised centres (like our own) and that patients with both clinical and subclinical disease were detected. This might also explain the high percentage of ILD in our cohort.

In a systematic review (14), the incidence of cardiac involvement was 9 to 72% and heart failure was the most frequently reported symptom (32 to 77%). Cardiac involvement is also one

Table II. Causes of death.

Causes of Death	Lung	Cardiac	Malignancy	Infection	Other / uncertain	Total
n (%)	2 (8.3)	4 (16.7)	6 (25)	7 (29.2)	5 (20.8)	24 (100)
Specific causes, n	ILD – 2	Myocardial infarction – 3 Cardiac involvement*- 1	Lung cancer – 1 Haematological (HL) – 2 Gynecological – 2 (1 ovarian, 1 endometrial) Uncertain - 1	Pneumonia – 5 Sepsis – 2	Trauma – 1 GI bleeding – 1 Uncertain - 3	

ILD: interstitial lung disease; HL: Hodgkin lymphoma; GI: gastrointestinal. *this patient had heart failure, mitral valvulopathy and a conduction defect.

of the most important causes of mortality in patients with DM, mainly due to congestive heart failure which is related to old age, metabolic syndrome and hypertension (5). In our study, 24 (24.7%) patients had cardiac involvement and, among these, 7 had heart failure and 11 had ischaemic changes. It has been established that autoimmune disorders increase the risk of cardiovascular disease, which is not fully explained by traditional risk factors (27). It is possible that the chronic inflammation that occurs in inflammatory myopathies plays a role in the progression of coronary atherosclerosis (28). Nevertheless, among the patients with heart failure and/or ischaemic changes, 12 had a diagnosis of hypertension, diabetes and/or dyslipidaemia.

The risk of cancer is increased in patients with DM or PM (29-30), and the risk is higher in DM patients (25). The cancers most frequently reported in western countries are lung, breast, ovarian, pancreatic, colorectal and stomach (31-32). In our study, 12 (12.4%) patients were diagnosed with a malignancy and the prevalence was higher in ADM patients. The types of cancer were consistent with those previously reported. In 66.7% of patients with cancer, the malignancy was diagnosed more than two years apart from the myositis. This is in agreement with the previous observation that, although the risk of cancer is higher in the first year after the diagnosis of the IIM, it is still higher than in the general population for more than five years (31).

Our frequencies of GI involvement, calcinosis and skin ulcers are similar to what has been previously reported (9, 17).

Except for the study by Airio *et al*. (16), in which the median follow up was 11 years, our median time of follow up (9 years) is longer than that reported in most studies. (10, 17-18, 20-22). Furthermore, a fifth (20.6%) of our cohort was followed up for at least 20 years.

Similar to other reports (9, 13), we did not find statistically significant difference in survival between APM, ADM and OS groups. Our survival rate for the whole group was 100% at 1 year and estimated cumulative survivals at 5, 10 and 15 years were 94.6%, 82.2% and 72.1%, respectively. Furthermore, we report an estimated survival rate at 20 years of 66.1%. Danko *et al*. (17) reported similar survival rates (95% at 1 year, 92% at 5 years and 89% at 10 years). These survival rates are higher than those reported in older series (11-13, 19), reflecting the improvement in diagnostic and therapeutic management of myositis patients. In other recent series involving cancer associated myositis (9, 18, 21), survival rates were also lower than in our report. In the study by Airio *et al*. (16), the lower survival rates reported (75% and 55% for PM at 5 and 10 years, respectively; 63% and 53% for DM at 5 and 10 years, respectively) may be explained by a selection bias towards the severe end of the spectrum of myositis.

Our mortality rate (24.7%) was similar to previous reports (9, 33). Other studies also reported infections as the main (7, 13) or as the second cause of death (10). In a study that analysed death certificates of DM/PM patients (8), infections were the fourth cause of death. Nevertheless, like in our study, pneumonia was the commonest specific cause of death, but it was included in the group of diseases of the respiratory system. Malignancies have been the main or one of the most frequent causes of death in some studies, particularly those including malignancy associated myositis (7, 9, 20, 22). Cardiac and lung involvement have also been described as common causes of death in other studies (9-10, 13, 17, 21-22).

Among the patients who died of pneumonia, one had a previous diagnosis of ILD, one (who died of aspiration pneumonia) had dysphagia, and another one had ILD and dysphagia. The extramuscular complications may have directly contributed to the cause of death of these patients.

A number of unfavourable prognostic factors have been described in myositis: older age, male sex, longstandig symptoms before diagnosis, cardiac and lung involvement, presence of cancer, dysphagia, anti-synthetase and anti-SRP antibodies (9, 13, 16, 19-20, 24, 34-37). In our series, in univariate analysis, infection (HR 4.18; 95% CI:1.61–10.91; p=0.003) and lung involvement (HR 1.78; 95% CI:1.13-2.82; p=0.013) were statistically significantly associated with an increased risk of death. Previous studies (38-39) have noted a decreased survival in patients with ILD compared with those without ILD, which makes early detection of ILD a priority in these patients. In the multivariate analysis, patients with infections had a 3.68 greater probability of dying compared to those without infections (HR 3.68; 95% CI:1.38–9.82; p=0.009). We would emphasise the need for close monitoring of myositis patients in order to promptly diagnose and treat infections. Patients with both upper and lower limb involvement had a 84% lower probability of dying compared to other patients (HR 0.16; 95% CI:0.03–0.81; p=0.027). However, most patients [n=94 (96.9%)] had upper and lower limb involvement (23.4% of whom died) and, among the remaining 3 patients, 2 (66.7%) died. This may represent a statistical bias that has contributed for this result.

Of note, the discrepancies regarding study designs, inclusion criteria and subgroups of IIM considered, make it difficult to compare results between different series.

Our study is retrospective, observational and single-centre which may, nevertheless, have the advantage of a careful consistent approach to follow-up. Given the very long duration of follow-up we were not able in the study to utilise some of the more sophisticated methods of muscle weakness assessment. But all of these patients were examined repeatedly by the same observer (DAI) over many years. The present study is one of the first to detail causes of death in patients with inflammatory muscle diseases followed for very long periods of time. Our observation period is longer than previously reported and our median follow up was higher than that reported in most studies. Although the numbers are relatively small, our cohort has demonstrated multiple ethnicities. We report a good survival rate compared to other studies, over a follow up of ≥20 years in many cases. Nevertheless, 24.7% of the patients died, the main cause being infection. Infection, malignancy, cardiac and lung

involvement were, not only important causes of death, but also common extramuscular features of these patients, leading to a significant morbidity. This highlights the importance of a regular and careful follow up in these patients in order to promptly diagnose and treat or, whenever possible, prevent these complications.

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