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ORIGINAL ARTICLES

Predictors of myositis in mixed connective tissue disease: A multicentre retrospective study

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ABSTRACT

Objectives: We aimed to identify clinical and serological predictors of myositis in mixed connective tissue disease (MCTD).

Methods: We performed a nationwide, retrospective, multicentre study including adult-onset MCTD patients fulfilling at least one of the following diagnostic criteria: Sharp's, Kasukawa, Alarcón-Segovia, or Kahn's. Univariable analysis was performed using Chi-square, Fisher exact, Student's t or Mann-Whitney U tests, as appropriate. Multivariable analysis was performed using binary logistic regression.

Results: Ninety-eight patients were included. Myositis was observed in 43.9% of patients, of whom 60.5% had myositis at disease onset.

Proximal muscle weakness was described in 30 patients with muscle involvement (70%). Gastrointestinal involvement was identified in 28% and respiratory involvement in 29% of myositis patients. In the same subgroup of patients, 41.7% had a myopathic pattern on electromyography, and 47.1% had histological myositis features in the muscle biopsy.

Fever (OR=6.96, p=0.022) was an independent predictor of myositis, regardless of sex, age at diagnosis, ancestry, and respiratory involvement. African ancestry (OR=8.39, p=0.019), leukopenia at the disease onset (OR 6.24, p=0.021), and younger age at diagnosis (OR=1.07/year, p=0.035) were identified as independent predictors of myositis at disease onset, regardless of sex and scleroderma pattern in capillaroscopy.

Conclusions: Myositis is a common manifestation of MCTD, even at the disease onset. African ancestry, leukopenia at the disease onset, younger age at diagnosis, and fever should prompt a thorough evaluation for myositis.

Keywords: Mixed connective tissue disease; Myositis; Predictors.

INTRODUCTION

Mixed connective tissue disease (MCTD) is a rare connective tissue disease (CTD) characterised by overlapping features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and polymyositis, associated with the presence of high titres of anti-U1-ribonucleoprotein complex (U1-RNP) autoantibodies[1,2]. Common clinical features include Raynaud's phenomenon, puffy hands, arthralgia, arthritis, myalgia, and myositis[2]. The previous notion of MCTD as a benign condition has been abandoned, with some patients having an unfa-

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vourable course with pulmonary hypertension being the leading cause of death[3,4]. Myositis may be present in up to 79% of MCTD patients[5,6], and it is included in all diagnostic criteria[6]. MCTD patients with myositis may present with muscle weakness, and involvement of the pelvic girdle musculature is frequent[7]. Although similar to other inflammatory myopathies, the severity of MCTD-myositis is variable and may be milder and more responsive to treatment[6]. However, this muscle involvement can also cause severe symptoms, namely dysphagia; respiratory symptoms and, rarely, myocarditis[7,8]. Thus, muscle involvement may have prognostic relevance, and has an important impact on therapeutic decisions. Literature on myositis in MCTD is scarce, specifically on disease severity and potential organ involvement, and, to the best of our knowledge, no independent predictors of MCTD-related myositis have been described. In this study, the primary aim was to identify predictors for muscle involvement in a nationwide MCTD cohort. As secondary aims, we intended to characterise the myositis-MCTD group of patients and identify possible clinical associations.

MATERIALS AND METHODS

Study population

This is a nationwide multicentre study involving sixteen Portuguese Rheumatology departments. The inclusion criteria were (i) a clinical diagnosis of MCTD, (ii) ≥18 years of age, (iii) fulfilment of at least one of the four diagnostic criteria sets for MCTD (Sharp's, Kasukawa, Alarcón-Segovia, or Kahn's criteria) (Figure 1).[6]

Data collection

Portuguese Rheumatology physicians were invited by e-mail to collaborate in this multicentric project. From each centre, a more experienced physician (locally responsible for the patient) and one resident (responsible for inserting the centre's data) reviewed and validated the database.

Data were collected through a retrospective review of clinical files. Demographic data, age of first symptoms, age of diagnosis, clinical manifestations at presentation and during follow up, immunological features and years of disease duration were registered.

Clinical features were recorded according to the time of onset. Those present at the time of diagnosis were coded as "onset-<manifestation>" (e.g., onset-arthritis), and those starting at any time throughout the disease course were coded as "<manifestation>" (e.g., arthritis).

For each patient, muscle involvement was defined according to the attending physician and, whenever available, information was collected on criteria met: proximal muscle weakness, creatine kinase elevation not justified by another more plausible cause, electromyography compatible with myopathic changes (describing fibrillation potentials, positive sharp waves, myotonic discharges, motor unit action potentials that are small, short and polyphasic) or myositis evidence in histopathological samples retrieved through muscle biopsy (mononuclear cell infiltrates, muscle fibre necrosis, regeneration, atrophy). Dysphagia or oesophageal dysmotility were also considered to support muscular involvement[9].

Respiratory involvement was evaluated through pulmonary function tests (restrictive/obstructive pattern, lung volume, capacity, rates of flow and gas exchange) and high-resolution chest CT (nonspecific interstitial pneumonia, usual interstitial pneumonia, lymphoid interstitial pneumonia patterns were registered). Myocarditis and serositis (including pleuritis and pericarditis) were confirmed with imaging. Gastroesophageal involvement encompassed dysphagia, gastroesophageal reflux, or dysmotility confirmed through manometry. Lymphadenopathy was considered if detected during physical examination or through imaging findings, after exclusion of alternative diagnoses. Renal involvement was identified by urinary sediment alterations, or the identification of glomerulonephritis retrieved through kidney biopsy.

Each centre had one month to complete the data. After the fulfilment of data by each centre, the inclusion criteria were further reviewed by coauthors of the centre responsible for the study.

Statistical analysis

Continuous data are presented as mean (standard deviation) or median (interquartile range), whereas categorical variables are presented as absolute frequencies (percentages). The Shapiro-Wilk test was used to test normal distribution for continuous data. Univariable analysis was performed using Chi-square or Fisher exact tests for comparisons between categorical variables and Student's t-test or Mann-Whitney U test for comparisons between categorical and continuous variables with and without normal distribution, respectively. Predictors of muscle involvement were identified through binary logistic regression modelling. The linearity of the continuous variables was assessed via the Box-Tidwell procedure. Some of the variables chosen are demographic data, relevant in the phenotyping of patients with connective tissue diseases, such as MCTD, and were predetermined to enter the model (race, age, sex). Cases with missing information and outliers were excluded from the multivariable analysis to fulfil all assumptions necessary to assure the validity of the regression. SPSSV25 was used for statistical analysis, and the significance level was defined as 2-sided $p<0.05$.

Ethical Approval

This study was approved by the Ethics Committee of all participant centres and conducted by the principles of the Declaration of Helsinki. Written informed consent was waived by the Ethics Committee, considering the retrospective nature of the study and the appropriate measures that were taken to ensure compliance with the General Data Protection Regulation (GDPR) (EU) 2016/679. Patient confidentiality was maintained through the pseudonymization of data, and the access to the full clinical files was limited to the patient's attending physician, minimizing any risk of breaching confidentiality or impacting the rights of the patients following GDPR guidelines.

RESULTS

Demographic data

Ninety-eight patients were included. Myositis was reported in 43 patients (43.9%), of whom 26 (60.5%) had myositis at disease onset. The median age at diagnosis (34.8 vs 41.6 years, *p*=0.018) and disease duration (4.1 vs 7.0 years, *p*=0.023) in patients with myositis were lower than those without myositis. There were no differences in sex or ancestry between the two groups (Table I).

Clinical features of MCTD patients with muscle involvement

Proximal muscle weakness was described in 30 patients with muscle involvement (70%). Of those patients, gastrointestinal involvement was identified in 12 patients (28%) [dysphagia reported in 7 patients (16%), gastroesophageal reflux reported in 1 (2%), dysmotility in 4 (9%)]. In the same group of patients, renal involvement was identified in 7 patients (16%) [6 patients (14%) had proteinuria and/or hematuria and 1 (2%) had membranous glomerulonephritis]. Twelve patients with myositis (29%) also had respiratory involvement confirmed.
Among all MCTD patients, myocarditis was reported only in 1 patient who had also myositis.
Of the five patients with malignancy in the MCTD cohort only one had myositis.

Complementary diagnostic exams

Creatine kinase elevation was identified in 33 patients (77%); electromyography was performed in 24 patients, of whom 10 (42%) had a myopathic pattern; muscle biopsy was performed on 17 patients, of whom eight (47%) had histological myositis features; nailfold capillaroscopy was performed on 24 patients, of whom 12 (50%) had a scleroderma pattern.

Predictors of myositis in MCTD

African ancestry (42.3% vs 16.9%, p=0.011) and leukopenia at the onset of the disease (50.0% vs 17.1%, p=0.001) were positively associated with myositis at onset of MCTD (Table II).
The multivariable analyses predicting myositis at onset included 54 patients. This model explained 37.8% (Nagelkerke R^2) of the variance in myositis and correctly classified 79.6% of all cases.
African ancestry (OR 8.39, 95% CI: 1.43-49.37), leukopenia at onset of MCTD (OR 6.24, 95% CI: 1.32-29.48), and younger age at diagnosis (OR 1.07/year, 95% CI: 1.01-1.14) were identified as independent predictors of myositis at onset of disease, regardless of sex and scleroderma pattern (Table III). Fever at disease onset (27.9% vs 3.8%, p=0.001) or fever over the course of the disease (30.2% vs 7.4%, p=0.003) were positively associated with myositis (Table II).
The multivariable analyses predicting myositis at any time of the disease included 90 patients, explained 26.9% of the variance and correctly classified 73.3% of all cases. Fever (OR 6.96, 95% CI: 1.32-36.53) was an independent predictor of myositis, irrespective of sex, age at diagnosis, ancestry, and respiratory involvement (Table III).

DISCUSSION

In this cohort of 98 patients with MCTD, myositis was reported in 43 patients (43.9%).

In our study, fever was a predictor of MCTD-myositis, while African ancestry, leukopenia at the disease onset, and younger age at diagnosis were independent predictors of myositis at disease onset.

Myositis was identified in almost half the patients of our cohort, which is aligned with previous literature[5,6].

There was no association between myositis and malignancy in our MCTD cohort, as opposed to what is usually found in idiopathic inflammatory myopathies (IIM)[10]. This result follows the literature that reveals that U1-RNP antibodies are not associated with an increased risk of malignancy[10].

Although it did not reach statistical significance, there was a tendency for a more frequent respiratory involvement at onset of the disease in patients with myositis (21.4% vs 7.5%, p=0.051). This result is in line with that reported by Szodoray P et al., in which patients with MCTD could be classified into different clusters according to clinical phenotypes and one of those clusters was patients with myositis and interstitial lung disease[11]. No other association between myositis and severe organ involvement was found.

TABLE I. Characteristics of the MCTD patients according to the occurrence of myositis at any time of the disease

	Without myositis (n=55)	With myositis (n=43)	p-value
Sociodemographic characteristics			
African ancestry, n/N (%)	9/50 (18.0%)	14/42 (33.3%)	0.091
Age at diagnosis, median (IQR), years	41.6 (19.0)	34.8 (13.9)	**0.018**
Disease duration[a], median (IQR), years	7.0 (7.8)	4.1 (5.8)	**0.023**
Female sex, n/N (%)	46/54 (85.2%)	39/43 (90.7%)	0.413
Clinical manifestations, n/N (%)			
Arthralgia			
Onset	47/53 (88.7%)	33/43 (76.7%)	0.119
Ever	51/54 (94.4%)	41/43 (95.3%)	1.000
Arthritis			
Onset	32/52 (61.5%)	23/43 (53.5%)	0.429
Ever	42/54 (77.8%)	30/43 (69.8%)	0.370
Chronic disease anaemia[b]			
Onset	14/52 (26.4%)	11/43 (25.6%)	0.882
Ever	21/53 (39.6%)	16/43 (37.2%)	0.809
Cutaneous thickening			
Onset	13/51 (25.5%)	7/42 (16.7%)	0.303
Ever	17/52 (32.7%)	12/43 (27.9%)	0.614
Digital ulcers			
Onset	9/53 (17.0%)	6/43 (14.0%)	0.685
Ever	17/54 (31.5%)	10/43 (23.3%)	0.369
Erosions			
Onset	2/45 (4.4%)	0/37 (0%)	0.499
Ever	3/47 (6.4%)	0/38 (0%)	0.250
Fever[c]			
Onset	2/53 (3.8%)	12/43 (27.9%)	**0.001**
Ever	4/54 (7.4%)	13/43 (30.2%)	**0.003**
Gastroesophageal involvement[d]			
Onset	7/53 (13.2)	4/43 (9.3%)	0.749
Ever	17/54 (31.5%)	12/43 (27.9%)	0.702
Leukopenia[e]			
Onset	11/53 (20.8%)	14/43 (32.6%)	0.190
Ever	20/54 (37.0%)	19/43 (44.2%)	0.476
Lymphadenopathy[f]			
Onset	2/53 (3.8%)	6/43 (14.0%)	0.134
Ever	8/54 (14.8%)	9/43 (20.9%)	0.431
Myocarditis			
Onset	0/54 (0%)	1/43 (2.3%)	0.443
Ever	0/54 (0%)	1/43 (2.3%)	0.443
Neuropathy			
Onset	1/53 (1.9%)	2/43 (4.7%)	0.585
Ever	1/54 (1.9%)	4/43 (9.3%)	0.167
Puffy fingers			
Onset	27/53 (50.9%)	21/43 (48.9%)	0.837
Ever	33/54 (61.1%)	25/43 (58.1%)	0.767
Pulmonary hypertension[g]			
Onset	1/53 (1.9%)	1/43 (2.3%)	1.000
Ever	9/54 (16.7%)	6/40 (15.0%)	0.827
Raynaud phenomenon			
Onset	48/53 (90.6%)	36/43 (83.7%)	0.313
Ever	53/54 (98.1%)	41/43 (95.3%)	0.583
Renal involvement[h]			
Onset	1/53 (1.9%)	1/43 (2.3%)	1.000
Ever	3/54 (5.6%)	7/43 (16.3%)	0.103

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TABLE I. Continuation

	Without myositis (n=55)	With myositis (n=43)	p-value
Respiratory involvement			
Onset	4/53 (7.5%)	9/42 (21.4%)	0.051
Ever	20/54 (37.0%)	12/42 (28.6%)	0.383
Sclerodactyly			
Onset	21/53 (39.6%)	14/42 (33.3%)	0.528
Ever	29/54 (53.7%)	17/43 (39.5%)	0.165
Serositis			
Onset	2/54 (3.7%)	0/43 (0%)	0.501
Ever	4/54 (7.4%)	0/43 (0%)	0.127
Sicca syndrome			
Onset	9/53 (17.0%)	7/43 (16.3%)	0.927
Ever	13/54 (24.1%)	10/43 (23.3%)	0.925
Thrombocytopenia[i]			
Onset	4/52 (7.7%)	3/43 (7.0%)	1.000
Ever	8/54 (14.8%)	6/43 (14.0%)	0.905
Weight loss[j]			
Onset	7/51 (13.7%)	13/43 (30.2%)	0.051
Ever	9/52 (17.3%)	14/43 (32.6%)	0.084
Serological characteristics, n/N (%)			
Anti-beta-2 glycoprotein 1	1/50 (2.0%)	5/39 (12.8%)	0.082
Anti-cardiolipin	1/50 (2.0%)	5/39 (12.8%)	0.082
Anti-citrullinated protein antibodies	5/47 (10.6%)	1/35 (2.9%)	0.232
Anti-dsDNA	11/54 (20.4%)	10/43 (23.3%)	0.732
Anti-La	14/54 (25.9%)	17/43 (39.5%)	0.153
Anti-Ro	2/54 (3.7%)	5/43 (11.6%)	0.236
Anti-Sm	10/52 (19.2%)	11/43 (25.6%)	0.458
Lupic anticoagulant	5/46 (10.9%)	2/37 (5.4%)	0.453
Rheumatoid factor	25/53 (47.2%)	13/40 (32.5%)	0.154
Onset erythrocyte sedimentation rate[l], median (IQR), mm/hr	63 (66)	51 (91)	0.579
Onset gamma globuline[l], median (IQR), g/dL	1.8 (1.1)	1.8 (1.0)	0.843
Capillaroscopic pattern, n/N (%)			
Scleroderma pattern	11/34 (32.4%)	12/24 (50.0%)	0.176

[a]Disease duration up to the point of data collection; [b]Chronic disease anaemia if hemoglobin <12 mg/dL, after exclusion of alternative diagnoses; [c]Fever if axillary temperature >38ºC or tympanic temperature >38.3ºC; [d]Gastroesophageal involvement included dysphagia, gastroesophageal reflux, or dysmotility confirmed by manometry; [e]Leukopenia if leukocyte count <4000/uL; [f]Lymphadenopathy at any site detected on physical examination or imaging finding, after exclusion of alternative diagnoses. [g]All patients with reported intermediate to high ecocardiographic probability for pulmonary hypertension. [h]Renal involvement included urinary sediment alterations, membranous glomerulonephritis, proliferative glomerulonephritis, or tubulointerstitial nephritis; [i]Thrombocytopenia if platelet count <150000/uL; [j]Unintentional weight loss of at least 5% within the preceding 6 months. [l]Data regarding onset erytrocyte sedimetation rate and gamma globulin levels reported in 11/54 patients without myositis and 11/43 patients with myositis, respectively. IQR: interquartile range

The multivariable analysis showed that fever was an independent predictor of MCTD-myositis and that African ancestry, leukopenia at the disease onset, and younger age at diagnosis were independent predictors of myositis at disease onset. Although the relation between African ancestry and myopathy may be biased by ethnic differences [serum creatine kinase is higher in black people[12]], it has been previously associated with myositis in SSc[13] and SLE[14] patients. Also, younger age at diagnosis and leukopenia were previously associated with SSc-myositis[15] and SLE-myositis[16], respectively. These associations suggest that younger patients with African ancestry may have more haematologic abnormalities and fever, reflecting higher disease activity. These MCTD patients have a higher risk of having myositis, such as in other CTD[13–16]. Thus, when these risk factors are present, especially at the time of diagnosis, a more proactive screening for muscle involvement

TABLE II. Characteristics of the MCTD patients according to the occurrence of myositis at disease onset

	Without myositis (n=72)	With myositis (n=26)	p-value
Sociodemographic characteristics			
African ancestry, n/N (%)	11/65 (16.9%)	11/26 (42.3%)	**0.011**
Age at diagnosis, median (IQR), years	40.0 (19.1)	39.5 (11.6)	0.843
Disease duration, median (IQR), years	5.4 (8.6)	4.0 (2.8)	0.064
Female sex, n/N (%)	60/70 (85.7%)	24/26 (92.3%)	0.503
Clinical manifestations at disease onset, n/N (%)			
Arthralgia	60/70 (85.7%)	20/26 (76.9%)	0.359
Arthritis	41/69 (59.4%)	14/26 (53.8%)	0.624
Chronic disease anaemia	17/69 (24.6%)	8/26 (30.8%)	0.545
Cutaneous thickening	15/68 (22.1%)	5/25 (20.0%)	0.830
Digital ulcers	11/70 (15.7%)	4/26 (15.4%)	1.000
Erosions	2/58 (3.4%)	0/24 (0%)	1.000
Fever	9/70 (12.9%)	5/26 (19.2%)	0.517
Gastroesophageal involvement	9/70 (12.9%)	2/26 (7.7%)	0.722
Leukopenia	12/70 (17.1%)	13/26 (50.0%)	**0.001**
Lymphadenopathy	4/70 (5.7%)	4/26 (15.4%)	0.206
Myocarditis	0/70 (0%)	1/26 (3.8%)	0.271
Neuropathy	1/70 (1.4%)	2/26 (7.7%)	0.177
Puffy fingers	34/70 (48.6%)	14/26 (53.8%)	0.646
Pulmonary hypertension	1/70 (1.4%)	1/26 (3.8%)	0.470
Raynaud phenomenon	61/70 (87.1%)	23/26 (88.5%)	1.000
Renal involvement	1/70 (1.4%)	1/26 (3.8%)	0.470
Respiratory involvement	7/69 (10.1%)	6/26 (23.1%)	0.176
Sclerodactyly	24/70 (34.3%)	11/25 (44.0%)	0.387
Serositis	2/70 (2.9%)	0/26 (0%)	1.000
Sicca syndrome	10/70 (14.3%)	6/26 (23.1%)	0.359
Thrombocytopenia	5/69 (7.2%)	2/26 (7.7%)	1.000
Weight loss	14/68 (20.6%)	6/26 (23.1%)	0.792
Serological characteristics, n/N (%)			
Anti-beta-2 glycoprotein 1	3/65 (4.6%)	3/24 (12.5%)	0.337
Anti-cardiolipin	3/65 (4.6%)	3/24 (12.5%)	0.337
Anti-citrullinated protein antibodies	5/62 (8.1%)	1/20 (5.0%)	1.000
Anti-dsDNA	14/70 (20.0%)	7/26 (26.9%)	0.466
Anti-La	4/70 (5.7%)	3/26 (11.5%)	0.384
Anti-Ro	20/70 (28.6%)	11/26 (42.3%)	0.201
Anti-Sm	14/68 (20.6%)	7/26 (26.9%)	0.510
Lupic anticoagulant	7/61 (11.5%)	0/22 (0%)	0.181
Rheumatoid factor	30/69 (43.5%)	8/24 (33.3%)	0.384
Onset erythrocyte sedimentation rate[2], median (IQR), mm/hr	70 (66)	41 (95)	0.420
Onset gamma globuline[2], median (IQR), g/dL	2.1 (1.1)	1.8 (1.1)	0.765
Capillaroscopic pattern, n/N (%)			
Scleroderma pattern	13/41 (31.7%)	10/17 (58.9%)	0.055

[2] Data regarding onset erytrocyte sedimetation rate and gamma globulin levels reported in 12/70 patients without myositis and 10/26 patients with onset-myositis, respectively. IQR: interquartile range

Table III. Multivariable analysis according to myositis

Multivariable analysis	OR (95% CI)	p-value
Independent predictors of myositis (ever)		
African ancestry	1.70 (0.54-5.43)	0.368
Age at diagnosis	0.98 (0.94-1.02)	0.313
Fever	6.96 (1.32-36.53)	**0.022**
Male sex	0.39 (0.08-1.97)	0.254
Respiratory involvement	4.49 (0.78-25.70)	0.092
Independent predictors of onset-myositis		
African ancestry	8.39 (1.43-49.37)	**0.019**
Age at diagnosis	1.07/year (1.01-1.14)	**0.035**
Onset-leukopenia	6.24 (1.32-29.48)	**0.021**
Male sex	0.25 (0.02-3.11)	0.280
Scleroderma pattern	3.88 (0.87-17.31)	0.076

OR: Odds ratio; CI: Confidence interval

should be performed.

While our study presents valuable findings, it is important to acknowledge certain limitations.

This disease is considered by many to be an overlap of several diseases and for this reason, there would always be an asymmetry in the population. However, despite the various diagnostic criteria applied, 92% of patients (n=90) fulfilled Kasukawa's criteria.

Unfortunately, it was not possible to perform electromyography or muscle biopsy at an early stage of the disease in all the included patients. This may explain the absence of typical alterations in a significant percentage of patients with proximal muscle weakness or creatine kinase elevation, once some of them were already under treatment. Additionally, the muscle biopsy was often not image-guided, so non-affected areas of muscle may have been biopsied. The variability of the criteria employed to categorize patients with myositis and the potential underpowering of our analysis ow-

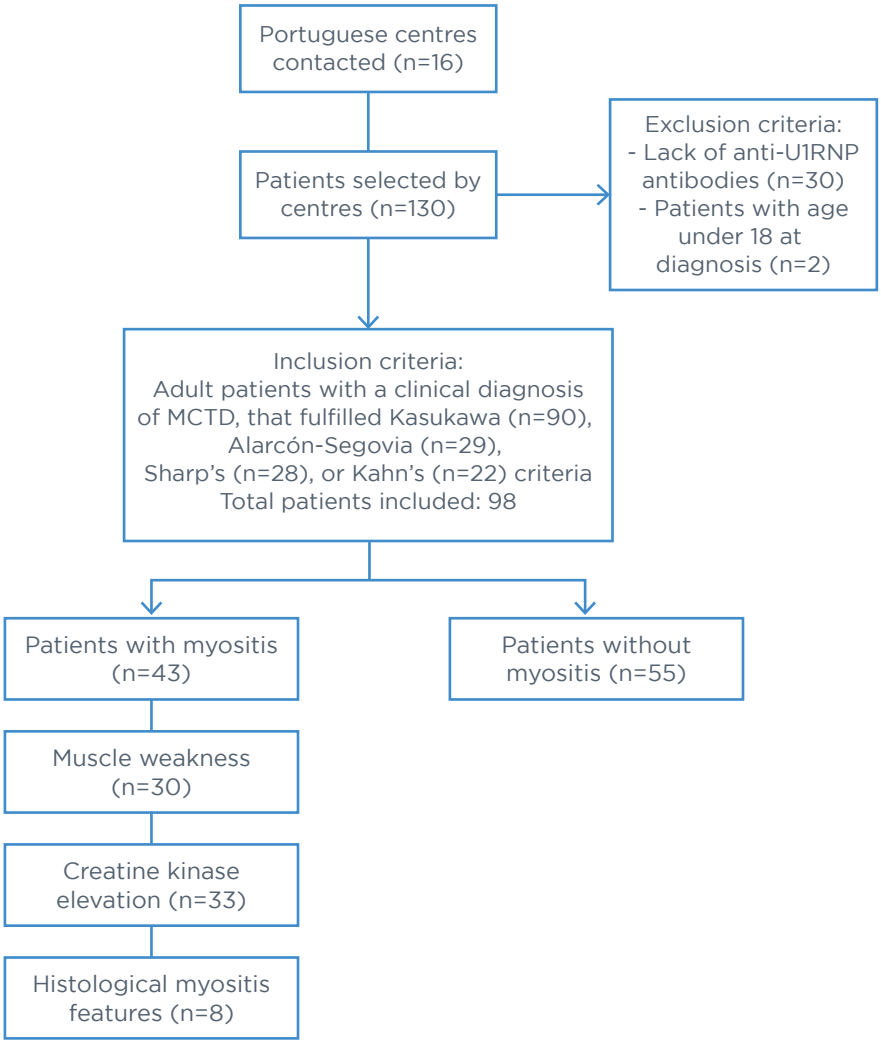

Figure 1. Workflow chart of selection of patients

ing to the relatively small sample size and retrospective study design are noteworthy. MCTD has overlapping features with other CTD. Our results provide new data suggesting predictors of muscle involvement, a common manifestation in these patients. Early myositis identification could have implications for the treatment and prognosis of this group of patients.

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