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An In-Depth Analysis of Our Myositis Cohort Following the Example of the EuroMyositis Registry

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ABSTRACT

Background
To describe our myositis cohort in-depth.

Methods
From January 2006 to December 2018, all newly diagnosed myositis patients were retrospectively enrolled in the study. We performed a subtype reclassification using the 2017 EULAR/ACR criteria, following the example of the EuroMyositis registry. Disease activity and damage were measured by the newest standardized assessment-tools for clinical studies. Comparisons between myositis subgroups were conducted using Fisher's exact test.

Results
We enrolled 32 patients (25 were female): six patients with dermatomyositis, six with polymyositis, eleven with overlap myositis, six with antisynthetase syndrome, one with autoimmune necrotizing myopathy, one with juvenile antisynthetase syndrome and one with juvenile dermatomyositis. The overall median follow-up period was 23-months (9-44.75). Interstitial lung disease (ILD) was most frequently seen in patients with antisynthetase syndrome. Patients with overlap myositis were more likely to have polyarthritis mimicking rheumatoid arthritis, reduced capillary density in the nail fold capillaroscopy and Raynaud syndrome. Ovarian cancer during the follow-up period occurred in two patients (one with polymyositis and one with dermatomyositis). Myositis-related death was reported in two patients: acute respiratory failure in autoimmune necrotizing myopathy and dysphagia-related complications in polymyositis. Cyclophosphamide, methotrexate and rituximab demonstrated a significant steroid-sparing effect. In 22 of 32 patients, the myositis subgroup classifications made on the basis of our opinion and the new EULAR/ACR classification criteria were different, showing strong disagreement, especially in the subtype polymyositis.

Conclusion
Our analysis highlights the heterogeneity in myositis subgroups and shows the steroid-sparing effect of cyclophosphamide, methotrexate and rituximab.

Keywords
Myositis; Idiopathic inflammatory myopathy; Dermatomyositis; Antisynthetase syndrome; Overlap myositis; Rituximab.

Abbreviations
CCP: Cyclic Citrullinated Peptide; CK: Creatine kinase; CYC: Cyclophosphamide; IIM: Idiopathic Inflammatory Myopathy; ILD: Interstitial lung disease; IMACS: International Myositis Assessment and Clinical Studies Group; MDI: Myositis Damage Index; MMT8: Manual muscle test 8; MTX: Methotrexate; MYOACT: MYOsitis disease ACTivity; RTX: Rituximab; TIF-1γ: Transcriptional factor-1γ.

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BACKGROUND

Myositis is a rare and very heterogeneous autoimmune inflammatory disease, that causes muscle weakness.[1] Because of the disease complexity within individuals and the variety of extra musculoskeletal manifestations, the preferred term is "idiopathic inflammatory myopathy" (IIM) over "myositis".[2] IIM includes dermatomyositis, polymyositis, inclusion body myositis and autoimmune necrotizing myopathy. Overlap myositis is a new form of IIM associated with concomitant features of mixed connective tissue disorders.[3] Antisynthetase syndrome is not universally accepted as a distinct entity, but clearly, the frequency of interstitial lung disease and arthritis differs from that of other IIM forms.[4]

Many publications over the past five to ten years indicate high research activity on IIM, including the new European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria,[5] the first international EuroMyositis registry,[6] standardized tools to measure disease activity and damage by the International Myositis Assessment and Clinical Studies Group (IMACS)[7] and large international genetic epidemiological studies such as the myositis genetics consortium (MYOGEN).[8]

The original Bohan and Peter diagnostic criteria,[9] published in 1975, are still widely used and include characteristic clinical findings of the skin and muscles, elevated muscle enzymes, muscle biopsy, and electromyography (EMG), and most importantly, they provide exclusion criteria to eliminate IIM mimics.[10] At that time, the steroid-resistant form of inclusion body myositis was not known. Little was also known of specific histopathological findings expected to be found in different subsets of myositis[11] or of myositis-specific and myositis-associated antibodies.[12,13] The new 2017 EULAR/ACR classification criteria include most of the new clinical domains in myositis and attempt to categorize IIMs into major subgroups by using 16 weighted variables, with a sensitivity and specificity of 93% and 88%, respectively, when biopsy results are provided.[14]

Managing such heterogeneous and rare diseases will remain challenging. Many treatment approaches are being introduced, including traditional disease-modifying antirheumatic drugs (DMARDS) as well as modern biologic agents.[15] Currently, there is no single regime to cure every possible organ involvement and all underlying overlapping features in all different forms of IIM. In the hope of transitioning to universal treatment standards, further studies are needed.

The objective of this retrospective study was to describe our myositis cohort in depth and to provide real-world data on the efficacy of antirheumatic drugs. The secondary aim was to compare the reclassification in our cohort with the new EULAR/ACR classification criteria.

METHODS

Study Population

From January 2006 to December 2018, thirty-two newly diagnosed myositis patients admitted to HELIOS Vogelsang-Gommern Rheumatology Clinic in Germany were retrospectively enrolled in the study. Patients with inclusion body myositis were excluded because of the absence of follow-up data. The medical records of all patients included were reviewed for demographics; clinical features including muscle strength tests, disease duration, and time between the onset of symptoms and diagnosis; muscle enzymes before, during and after treatment; inflammation markers; and myositis-specific and myositis-associated antibodies. We also reviewed all histopathological findings of the enrolled patients who underwent a muscle biopsy and EMG when available. We performed a retrospective subtype reclassification using all up-to-date research outcomes, following the example of the EuroMyositis registry. Antisynthetase syndrome was considered a separate subtype of myositis.

Disease Activity and Damage

To measure the degree of disease activity of muscle and extramuscular manifestations, we used the MYOsitis disease ACTivity visual analog scales (MYOACT) tool, which is a series of assessments of various organ systems.[16] To assess the extent of damage, we used the myositis damage index (MDI) scoring system.[17] Due to the retrospective collection of data, the global disease activity visual analog scale (VAS) for both physicians and patients was often missing and therefore was not included in the assessment. We are routinely using the hannover functional questionnaire (FFbH) in our clinic to measure functional disability, instead of the health assessment questionnaire (HAQ).

Response to Treatment

The amount of information we collected from the medical records about the manual muscle test 8 (MMT8) and VAS in the follow-up period was very limited. Therefore, we could not calculate the new 2016 IMACS and ACR/EULAR response criteria for myositis.[18] To measure the effectiveness of treatment, we used the daily prednisolone dose and the creatine kinase (CK) serum levels as the best available surrogate tool to estimate the response.

Statistical Analysis

SPSS Statistics, version 25.0, was used for all data analyses. Normally distributed continuous variables were summarized by calculation of means±SDs. Non-normally distributed data were summarized using medians and interquartile range (IQR). Categorical variables were described as counts and frequencies. Comparisons between myositis subgroups were conducted using Kruskal-Wallis test for the non-normally distributed data and one-way Analysis of variance (ANOVA) for normally distributed data. A Bonferroni post hoc test was used to control for type I error. Because of the small sample size of N=32 in our study, Fisher's exact test was used to compare categorical data. To compare creatine kinase (CK) and prednisolone doses before and after treatment, we used wilcoxon test for nonnormally distributed data and Student's *t-test* for normally distributed values. Eta-squared and Pearson's correlation were calculated to assess the correlations (if any) between various parameters, mostly between prednisolone treatment and myositis

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damage. A p value<0.05 was considered significant. Single-subject myositis subgroups with n=1, such as autoimmune necrotizing myositis, juvenile antisynthetase syndrome and juvenile dermatomyositis, were excluded from comparison and correlation tests.

RESULTS

Study Population

Thirty-two patients were enrolled: six patients with dermatomyositis, six with polymyositis, eleven with overlap myositis, six with antisynthetase syndrome, one with autoimmune necrotizing myopathy, one with juvenile antisynthetase syndrome and one with juvenile dermatomyositis. Of those with overlap myosits, systemic sclerosis (SSc) was the most common coexisting connective tissue diseases (CTD), in 7 of 11 patients, followed by Sjögren syndrome in 2 of 11 patients, systemic lupus erythematosus (SLE) in one patient and rheumatoid arthritis (RA) in one patient. Most patients were Caucasian (31/32), and 25 of 32 patients were female. The median age at IIM diagnosis was 49-years (40-67). The overall median interval between onset and IIM diagnosis was 5-months (2-12). The overall median follow-up period was 23-months (9-44.75). Overall, 21 of 32 patients were non-smokers. Three patients had a known malignancy before IIM diagnosis; a 67-year-old female patient had breast cancer six years before being diagnosed with Jo-1-positive antisynthetase syndrome. A 58-year-old female patient had cervical cancer fifteen years before being diagnosed with overlap myositis (Sjögren syndrome). A 62-year-old female patient had ovarian cancer three years before being diagnosed with polymyositis. All three patients were considered to be cancer-free survivors at the time of myositis onset.

Laboratory Data

Supplementary appendix 1 shows the laboratory tests, and Table 1 shows the antibody profiles. CK was elevated at the time of myositis onset in 29 of 32 patients, with a median (IQR) of 25.2 µmol/ls (12.5-61.4), without differences between subgroups. ANAs were more frequently observed in patients with overlap myositis, 1:2560 (1:160-1:2560), n=11, p=0.003. Patients with antisynthetase syndrome had a higher platelet count than other patients, 357 Gpt/l (304-435), n=6, p=0.004. Other laboratory findings, including hemoglobin; leukocytes; alanine aminotransferase (ALT); creatinine; muscle/brain creatine kinase (CK-MB); complement factors C3, C4 and CH50; thyroid stimulating hormone (TSH) and erythrocyte sedimentation rate (ESR), did not show significant differences between the groups.

Disease Activity

Supplementary appendix 2 demonstrates an in depth analysis of all organ manifestations according to MYOACT assessment. Furthermore, it shows results from the MRI, capillaroscopy, EMG, FFbH and MMT8.

The most common organ involvement was skeletal muscles (90%), followed by lung (56%), skeletal (56%), and skin involvement (50%); Raynaud syndrome (46%); esophagus (31%); and cardiac disease (28%). Overall, 25 of 32 patients had myopathic muscle weakness, which was most frequently observed in those with dermatomyositis (p=0.03). Sixteen of 32 patients had cutaneous manifestations; overall, those with dermatomyositis were more likely to have Gottron papules/sign (p=0.04). Polyarthritis mimicking rheumatoid arthritis was significantly more frequent in patients with overlap myositis (p=0.04). Twelve of 32 patients had ILD, which was most common in patients with antisynthetase syndrome (p=0.03). Reduced capillary density in the nailfold capillaroscopy and Raynaud syndrome were most frequently observed in patients with overlap myositis (p=0.03 and 0.001, respectively). Patients with overlap myositis also had a significantly higher functional capacity than patients with antisynthetase syndrome (83.3 *vs.* 59.2%, p=0.02) and dermatomyositis (83.3 *vs.* 62%, p=0.008). In 24 of 32 patients, a muscle biopsy was performed; endomysial infiltration was more common in those with polymyositis (p=0.002), and perifascicular atrophy in dermatomyositis (p=0.002).

Table 1. *Antibody Profiles*

	DM n=6	PM n=6	OM n=11	ASS n=6	ANM n=1	jASS n=1	jDM n=1	Total n=32
Jo-1				5		1		6
PM-Scl			5					5
SRP					1			1
RF			8	1				9
CCP			1	1				2
ANAs	3	2	11	1				17
Sm			3					3
Mi-2	1							1
SS-A/Ro52			3	3				5
MDA-5	1							1
RNP/Sm			2					2
SS-B			1					1
EJ				1				1
ds-DNS			1					1
TIF-1γ	1							1

DM=Dermatomyositis, PM=Polymyositis, OM=Overlap myositis, ASS=Antisynthetase syndrome, ANM=Autoimmune necrotizing myopathy, jASS=Juvenile antisynthetase syndrome, jDM=Juvenile dermatomyositis, ANAs=Antinuclear antibodies, Mi-2=Helicase binding protein, TIF-1γ=Transcriptional factor-1γ, PM-Scl=Polymyositis/Scleroderma exoribonuclease, RF=Rheumatoid factor, CCP=Cyclic citrullinated peptide, Sm=Smith, SS-A=Anti-Ro, SS-B=Anti-La, MDA-5=Melanoma differentiation associated gene 5, RNP/Sm=Ribonucleoprotein complex with Smith polypeptides, ds-DNS=Double stranded DNA, Jo-1, n=Histidyl-tRNA synthetase (Jo is derived from the name of the first patient "John", who was tested positive), EJ=Glycyl-tRNA synthetase, SRP=Signal recognition particle

Disease Damage

Supplementary appendix 3 shows all disease-related complications during the follow-up period (median) of 23-months.

Malignancy occurred in 2 of 32 patients. A 62-year-old female patient was diagnosed with peritoneal carcinomatosis with

Supplementary Appendix 1. Laboratory Data

	DM n=6	PM n=6	OM n=11	ASS n=6	ANM n=1	jASS n=1	jDM n=1	Total n=32
Median CK (IQR) (< 2.3-2.8 µmol/ls)	19.7 (11.7-109.8), n=6	32.8 (17.7-83.8), n=5	25.15 (7.6-42), n=11	15.8 (5.2-91.5), n=5	41.4, n=1	73.8, n=1	38.6, n=1	25.2 (12.5-61.4)
Median myoglobin (IQR) (< 70-100 µg/l)	769 (142-2305), n=5	2391 (560.5-6473.7), n=4	469 (404.6-1212.7), n=8	697.5 (133.7-1496), n=4	NK	NK	NK	606 (361.5-1715.5)
Median aldolase (IQR) (< 7.6 U/l)	28 (13.3-51), n=4	28.5 (19.1-35.7), n=4	29.4 (11.93-45.9), n=9	26.5 (11.6-82.6), n=6	41.82, n=1	NK	NK	29.5 (14.3-43.1)
Median CRP (IQR) (< 5 mg/l)	35.8 (0-37), n=6	5.6 (0-19.2), n=6	0 (0-6.9), n=11	17.8 (0-43.9), n=6	31, n=1	6.9, n=1	5.5, n=1	5.5 (0-19)
NT-pro-BNP positive			n=1	n=1	n=1			
Troponin I positive	n=1	n=1		n=1	n=1			
Mean platelet count (min-max) (176-391 Gpt/l)	256 (182-329), n=6	223 (95-302), n=6	262 (149-340), n=11	357 (304-435), n=6	221, n=1	390, n=1	206, n=1	
Median ANAs (min-max)	1:320 (1:80-1:2560), n=6	1:80 (0-1:640), n=6	1:2560 (1:160-1:2560), n=11	1:160 (1:80-1:640), n=6	1:160, n=1	1:160, n=1	1:160, n=1	

DM=Dermatomyositis, PM=Polymyositis, OM=Overlap myositis, ASS=Antisynthetasesyndrome, ANM=Autoimmune necrotizingmyopathy, jASS=Juvenile antisynthetasesyndrome, jDM=Juvenile dermatomyositis, CK=Creatinekinase, CRP=C reactiveprotein, ESR=Erythrocytesedimentation rate, NT-proBNP=Brainnatriureticpeptide, ANAs=Antinuclearantibodies, NK=Not known

Supplementary Appendix 2. Disease Activity Assessment Using the MYOsitis Disease ACTivity (MYOACT)-tool and Diagnostic Results

	DM n=6	PM n=6	OM n=11	ASS n=6	ANM n=1	jASS n=1	jDM n=1	Total n=32
Muscle disease activity in 29/32 patients (counts)								
Myopathic muscle weakness	6	3	8	5	1	1	1	25/29
Myalgia without weakness	0	3	3	1	0	0	0	7/29
Constitutional disease activity in 27/32 patients (counts)								
Fever	0	0	0	1	0	1	0	2/27
Weight loss	3	3	5	2	1	0	0	14/27
Fatigue	6	5	8	5	1	1	1	27/27
Cutaneous disease activity in 16/32 patients (counts)								
Ulceration	1	0	0	0	0	0	0	1/16
Erythroderma	1	0	3	0	0	0	1	5/16
Erythematosus rashes	0	3	4	0	0	0	0	7/16
Heliotrope rash	1	0	2	0	0	0	0	3/16
Gottron papules/sign	3	0	2	0	0	0	1	6/16
Periungual capillary changes	1	0	3	1	0	0	0	5/16
Alopecia	0	0	0	0	0	0	0	0/16
Mechanic's hands	0	0	1	1	0	0	0	2/16
Calcification	0	0	2	0	0	0	0	2/16
Skeletal disease activity in 18/32 patients (counts)								
Arthralgia	2	0	3	2	0	0	1	8/18
Oligoarthritis	0	1	3	3	0	0	0	7/18
Polyarthritis mimicking a rheumatoid arthritis	0	0	3	5	5	5	5	5
Gastrointestinal disease activity in 10/32 patients (counts)								
Abdominal pain	0	0	0	0	0	0	0	0

Mild dysphagia	2	0	5	1	0	0	0	8
Severe dysphagia	1	1	0	0	0	0	0	2
Pulmonary disease activity in 18/32 patients (counts)								
Dysphonia	3	1	3	0	0	1	0	8/18
Dyspnea without ILD	1	0	1	0	1	0	0	3/18
ILD	2	1	4	5	0	0	0	12/18
Cardiac disease activity in 9/32 patients (counts)								
Myocarditis or pericarditis	0	0	0	0	0	0	0	0
Atrial fibrillation	0	1	0	1	0	0	0	2
Sinus tachycardia	1	1	1	1	0	0	0	4
EMG in 16/32 patients (counts)								
Spontaneous activity	4	2	6	1	NK	NK	0	13/16
Nailfoldcapillaroscopy performed in 19/32 patients (counts)								
Reduced capillary density	0	2	8	3	NK	NK	NK	13/19
Giant capillaries	0	0	4	2	NK	NK	NK	6/19
microhemorrhages	0	1	1	2	NK	NK	NK	4/19
undefined	0	0	1	0	NK	NK	NK	1/19
normal	2	0	0	2	NK	NK	NK	4/19
Raynaud syndrome (counts)	0	2	10	3	0	0	0	15/32
MRI muscle edema (counts) (MRI performed in 10 patients)	3	3	1	0	NK	NK	NK	7/10
FFbH functional ability (counts)								
80-100%	0	3	9	1	0	1	0	14/32
70-80%	1	1	1	0	0	0	0	3/32
60-70%	3	0	0	1	0	0	0	4/32
<60%	2	2	1	4	1	0	1	11/32
Median FFbH score % (IQR)	62 (36-68.9)	80.5 (55.5-92.5)	83..3 (83.3-96.2)	59.2 (54.1-69.4)	42.5	83.3	55.5	71.2 (57.8-86)
Median MMT8 (IQR)	56 (40-58)	69 (55-80)	68 (58-80)	70 (54-80)	43	66	60	60 (55-80)
Mean MYOACT global (0-70) ±SD	16.2 ± 9.84	15 ± 9.2	12 ± 8.4	18.7 ± 3.6	15	10	20	16.2 ± 7.97
Muscle biopsy in 21 patients (counts)								
Endomysial infiltration but not invasion	0	5	3	0	1	1	NK	10/21
Perimysial and/or perivascular infiltration	4	1	3	0	0	0	NK	8/21
Perifascicular atrophy	6	1	1	1	0	0	NK	9/21
Rimmed vacuoles	1	0	0	0	0	0	NK	2/21

DM=Dermatomyositis, PM=Polymyositis, OM=Overlap myositis, ASS=Antisynthetase syndrome, ANM=Autoimmune necrotizing myopathy, jASS=Juvenile antisynthetase syndrome, jDM=Juvenile dermatomyositis, ILD=Interstitial lung disease, EMG=Electromyography, MRI=Magnetic resonance imaging, FFbH=Hannover Functional Questionnaire, NK=Not known

Supplementary Appendix 3. Disease Damage Using the Myositis Damage Index (MDI)

	DM n=6	PM n=6	OM n=11	ASS n=6	ANM n=1	jASS n=1	jDM n=1	Total n=32
Muscle damage in 17/32 patients (counts)								
Muscle atrophy	1	0	1	1	0	0	0	3/17
Muscle weakness without atrophy	0	1	1	1	0	1	0	4/17
Low serum creatinine	2	2	4	4	1	0	0	13/17
Skeletal damage in 7/32 patients (counts)								
Joint contractures	0	0	0	0	0	0	0	0/7
Osteoporosis with fracture	1	0	0	2	0	0	0	3/7
Osteoporosis without fracture	1	2	0	0	0	0	0	3/7
Avascular osteonecrosis	0	0	0	1	0	0	0	1/7
Cutaneous damage in 6/32 patients (counts)								
Calcinosis	1	0	2	0	0	0	0	3/6
Alopecia	0	1	0	1	0	0	0	2/6
Scarring or atrophy	1	0	0	0	0	0	0	1/6
Poikiloderma	0	0	0	0	0	0	0	0/6
Gastrointestinal damage in 5/32 patients (counts)								
Dysphagia	2	1	2	0	0	0	0	5/5
Gastrointestinal dysmotility or abdominal pain	0	0	0	0	0	0	0	0/5
Infarction or resection of bowel	0	0	0	0	0	0	0	0/5
Steatosis	0	0	0	0	0	0	0	0/5
Pulmonary damage in 13/32 patients (counts)								
Fibrosis	1	2	4	5	0	0	0	12/13
Impaired lung function	0	0	1	4	1	0	0	6/13
Dysphonia	0	0	0	0	0	0	0	0/13
Pulmonary hypertension	0	0	0	2	0	0	0	2/13
Cardiovascular damage in 5/32 patients (counts)								
Hypertension requiring treatment	0	1	2	1	0	0	0	4/5
Atrial fibrillation	0	1	0	0	0	0	0	1/5
Peripheral vascular disease in 0/32 patients (counts)								
Venous or arterial thrombosis	0	0	0	0	0	0	0	0/32
Tissue or pulp loss	0	0	0	0	0	0	0	0/32
Endocrine damage in 10/32 patients (counts)0								
Diabetes	0	0	0	0	0	0	0	0/10
Hyperlipidemia	1	2	3	4	0	0	0	10/10
Ocular damage in 0/32 patients (counts)								
Cataract resulting in visual loss	0	0	0	0	0	0	0	0/32
Visual loss	0	0	0	0	0	0	0	0/32
Infection in 4/32 patients (counts)								
Chronic infection	0	0	0	0	0	0	0	0/4
Multiple infections	1	0	2	1	0	0	0	4/4
Malignancy in 2/32 patients (counts)								
Ovarian	1	1	0	0	0	0	0	2/2
Reath in 3/32 patients (counts)								
Ovarian cancer	1	0	0	0	0	0	0	1/4
Acute Respiratory failure	0	0	0	0	1	0	0	1/4
Dysphagia	0	1	0	0	0	0	0	1/4
Median (IQR) Myositis Damage Index (0-110)	8.7 (0-12.5)	10 (5-18.7)	3.7 (1.8-10)	8.3 (4.3-17.1)	NK	NK	NK	7.5 (2.5-10)

DM=Dermatomyositis, PM=Polymyositis, OM=Overlap myositis, ASS=Antisynthetasesyndrome, ANM=Autoimmune necrotizingmyopathy, jASS=Juvenile antisynthetasesyndrome, jDM=Juvenile dermatomyositis, NK=Not known

ascites 10-months after the onset of polymyositis. This patient was diagnosed three years earlier with ovarian cancer, which was considered to be in remission after surgery and chemotherapy. At the time of recurrence, myositis was not active. A 67-year-old female patient was diagnosed with peritoneal carcinomatosis with ascites due to ovarian cancer 10-months after the onset of a TIF-1γ-positive dermatomyositis and died of pulmonary embolism. Myositis-related death was reported in 2 other patients in this study: a 71-year-old female patient with signal recognition particle (SRP)-positive autoimmune necrotizing myopathy died of respiratory failure due to aspiration one month after the onset of disease and a 80-year-old male patient with polymyositis died of complications related to dysphagia (aspiration, an infection of the percutaneous endoscopic gastrostomy tube) one month after the onset of symptoms. Osteoporotic fractures occurred in 3 of 32 patients.

Treatment

The medications used in this study are summarized in Table 2. Thirty of 32 patients were treated with glucocorticoids at the onset of myositis. Overall, 14 of 30 patients were started on a high-dose prednisolone treatment with >1 mg/kg (five patients with dermatomyositis, four with polymyositis, two with overlap myositis, one with antsynthetase syndrome, one with autoimmune necrotizing myopathy and one with juvenile dermatomyositis). Patients with dermatomyositis received a median (IQR) dose of 100 mg prednisolone per day (87.5-137.5), which was significantly higher than that of those with overlap myositis (40 mg, p=0.04) and antisynthetase syndrome (13.5 mg, p=0.01). Tapering prednisolone below 7, 5 mg/d within 6-months after diagnosis was successful in all patients, except for those with dermatomyositis (18-months). A moderate correlation, with r=0.54, between the cumulative glucocorticoid dose and MDI damage score (p=0.002), as well as a moderate correlation, with r=0.51, between the starting prednisolone dose at baseline and MDI, were found. Further correlation tests between laboratory data, MYOACT, MMT8 and MDI did not reach significance.

The most commonly used DMARDs were cyclophosphamid (CYC) (53%), methotrexate (MTX) (34%) and rituximab (RTX) (28%). A total of 15 patients received monotherapy with intravenous CYC as first-line therapy (four patients with antisynthetase syndrome, four with overlap myositis, two with polymyositis, two with dermatomyositis and one with autoimmune necrotizing myopathy) and two as second-line (one patient with antisynthetase syndrome and one with overlap myositis). The median cumulative dose (min-max) was 4000 mg (800-6400). After the initiation of CYC monotherapy, CK was decreased in 14 of 17 patients from a median (IQR) of 24.9 (8.3-58.5) at baseline to 4.1 (1.3-12.5) μmol/ls; p=0.005 after 6-months. Prednisolone daily dose was reduced in 15 of 17 patients from a median (IQR) of 50 (20-100) before CYC to 10 mg (8.75-25) after six-months, p=0.001.

Overall, 11 patients received MTX at a median (min-max) dose of 15 mg (15-20) for a median (min-max) period of 23-months (4-188). MTX was used as a first-line therapy in seven patients (one patient with juvenile dermatomyositis, one with juvenile antisynthetase syndrome, three with overlap myositis, one with polymyositis and one with dermatomyositis), as a second-line therapy three times (in one patient with overlap myositis, one with polymyositis and one with dermatomyositis) and as a third-line therapy in one patient with overlap myositis. After the initiation of MTX, CK was decreased in nine of 11 patients from a median (IQR) of 18.1 (5.6-28.6) at baseline to 2.6 (0.8-6.4) μmol/ls; p=0.009. The prednisolone daily dose was reduced in 10 of 11 patients from a median (IQR) of 27.5 (10-57.5) before MTX to 1.25 mg (0-5.6) after treatment, p=0.005.

Table 2. *Medications Used in this Study (Counts)*

	DM n=6	PM n=6	OM n=11	ASS n=6	ANM n=1	jASS n=1	jDM n=1	Total n=32
Glucocorticoids	6	6	10	5	1	1	1	30
CYC	4	2	5	5	1	0	0	17
MTX	2	2	5	0	0	1	1	11
RTX	2	0	3	1	0	0	0	6
LEF	0	1	1	3	0	0	0	5
MMF	0	0	1	2	0	0	0	3
AZA	0	0	0	1	0	0	0	1
HCQ	0	0	1	0	0	0	0	1
MTX+CicA	1	0	0	0	0	0	0	1
RTX+CYC	0	0	1	0	0	0	0	1
RTX+MMF	0	0	0	1	0	0	0	1
RTX+MMF+CicA	0	0	0	1	0	0	0	1

DM=dermatomyositis, PM=polymyositis, OM=overlap myositis, ASS=antisynthetasesyndrome, ANM=autoimmune necrotizingmyopathy, jASS=juvenile antisynthetasesyndrome, jDM=juvenile dermatomyositis, NK=not known, MTX=methotrexate, CYC=cyclophosphamide, RTX=rituximab, LEF=leflunomide, AZA=azathioprine, MMF=mycophenolatemofetil, HCQ=hydroxychloroquine, CicA=ciclosporine A

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Six patients received RTX monotherapy, while additional DMARDs were continued in three patients. The RA scheme was used (1000 mg IV. on day 1 and 14 every six-months during the first-year, followed by one infusion 1000 mg every six-months later on). RTX monotherapy was used as a first-line treatment in two patients (one with overlap myositis and one with dermatomyositis), as a second-line therapy in two patients (one patient with overlap myositis and one with dermatomyositis), as a third-line in a patient with antisynthetase syndrome and as a fourth-line in a patient with overlap myositis. The median (min-max) duration of RTX treatment was 23-months (3-38). The median (min-max) cumulative dose was 6300 mg (1000-9000). After the initiation of RTX monotherapy, CK was decreased in 5 of 6 patients from a median (IQR) of 8.5 (1.3-37.3) at baseline to 1.4 (1-3.3) μmol/ls; p=0.04. The prednisolone daily dose was reduced in 5 of 6 patients from a median (IQR) of 17.5 (20-100) before RTX to 6.2 mg (1.8-9.3) after treatment, p=0.04. Mild hypogammaglobulinemia of 6.7 g/l (reference range 7-16) occurred in one patient with antisynthetase syndrome after the fifteenth course with RTX.

Reclassification Using the New EULAR/ACR Criteria

Every patient in this study was reclassified and assigned to a single myositis subgroup after collecting all clinical, serological and histological data. The new EULAR/ACR classification criteria were then applied to assess possible discrepancies. In 22 of 32 patients, the myositis-subgroup classifications made on the basis of our opinion and the new classification criteria were different, showing strong disagreement, especially in the subtype polymyositis. All patients with antisynthetase syndrome and the large majority of patients and overlap myositis in this study were then classified as polymyositis.

DISCUSSION

In this observational study, 32 patients were retrospectively enrolled. We analyzed the myositis activity at baseline and the disease damage in the follow-up period by using all current IMACS measurement tools to find useful differences between myositis subtypes. We also present real-life treatment patterns used in our clinic and clinical outcomes to assess treatment responses.

Overall, the lung was the second most commonly affected organ in this study and was more frequently seen in patients with antisynthetase syndrome (n=5; p=0.03). This result is consistent with the data from the EuroMyositis registry showing the presence of ILD in 71% of patients with antisynthetase syndrome.[6] Results from the American and European Network of Antisynthetase Syndrome (AENEAS) indicate the presence of ILD in 82% of all patients.[19] The AENEAS registry also includes 38 patients (11%) with antisynthetase syndrome and coexisting CCP-positive RA, similar to one patient in our cohort. We believe that patients with rheumatoid arthritis and lung involvement should be tested for antisynthetase syndrome antibodies. These findings also disprove previous thoughts about etanercept-induced Jo-1- and PL-12-positive antisynthetase syndrome in patients with RA.[20]

The subgroup with overlap myositis differed from the other IIM types in our study in many ways: muscle weakness was numerically milder, muscle enzymes were numerically lower, and the functional capacity was statistically significantly higher than in antisynthetase syndrome and dermatomyositis patients (83.3 *vs* 59%; p=0.02, 83.3 *vs* 16.1%; p=0.008, respectively). Raynaud phenomenon (p=0.001), reduced capillary density (p=0.03), positive ANAs (p=0.003) and the presence of polyarthritis mimicking RA (p=0.04) were significantly more common than in other subtypes. These features explain why the time interval between the disease onset and diagnosis was larger in the overlap myositis subgroup than in the other subgroups (12 *vs* 5-months), which matches the results found in the EuroMyositis registry (11-months).

Ovarian cancer occurred in two patients, 10-months after myositis onset in both patients. In the first case, the histological findings of muscle biopsy indicated a polymyositis and the 62-year-old patient did not show any dermatomyositis-specific cutaneous exanthems. Unfortunately, she was not tested for TIF-1γ antibodies. This case could easily be reclassified as cancer-associated myositis. On the other hand, in the case of the 67-year-old patient, all known high risk factors for malignancies were fulfilled: older age, subgroup dermatomyositis, and positivity for TIF-1γ antibodies.[21] Interestingly, this patient underwent a thorough screening for ovarian cancer, including computer tomography, MRI and gynecology consultation, immediately after the detection of TIF-1γ antibodies, with negative results. According to published data from 263 patients with dermatomyositis from the UK Myositis Network, anti-TIF-1γ-associated malignancy occurs within a three-year period after myositis onset.[21]

CYC was widely used in 53% of all patients, mostly as a remission-induction therapy in patients with lung involvement. Although our findings demonstrate a very high response rate, this treatment pattern of ours significantly differs from that of the EuroMyositis registry (19% CYC) and from a cohort study in Halle, Germany (11% CYC).[22] Myositis experts like to reserve CYC as a third-line treatment option for refractory patients with life-threatening organ manifestations.[15]

RTX appears to provide another strong treatment option and managed to significantly reduce CK and prednisolone daily dose in five of six patients in our study. These findings support previous research by Unger et al in a cohort study in Dresden, Germany, with 14 of 18 patients responding well to RTX.[23] In the Rituximab in Myositis (RIM) study, however, the largest randomized, double-blind, controlled trial to date with 195 patients, the primary end point was not met.[24]

The discrepancy between our subgroup assignment and the new classification criteria in 22 of 32 patients can be confusing, but was anticipated for two reasons: first, subtypes such as antisynthetase syndrome and overlap myositis are not incorporated into the new classification criteria, and second, clinical rheumatologists can use the full range of additional information, including many different antibodies, EMG, magnetic resonance imaging (MRI) and findings about possible ILD in arriving at a

subtype conclusion. A revision of the EULAR/ACR criteria is planned[10] but will be challenging, since it is difficult to establish criteria that can satisfactorily describe the complexity in IIM.

Aside from the small sample size, the biggest limitation of this study is the retrospective design and therefore the lack of follow-up evaluation of muscle strength *via* MMT8. Our analysis highlights the heterogeneity in IIM subgroups and shows the steroid-sparing effect of certain DMARDs.

CONCLUSION

- Myositis is extremely heterogeneous. Correct classification is here the key for successful treatment.
- Rheumatologists should monitor patients with antisynthetase syndrome very closely for interstitial lung disease.
- Cancer risk factors: subgroup dermatomyositis, older age and positivity for TIF-1γ antibodies.
- Our study shows the steroid-sparing effect of cyclophosphamide, methotrexate and rituximab.
- We used standardized IMACS-tools to measure disease activity and damage.
- Our study is following the example of the EuroMyositis registry (same classification, same measurements-tools) and, therefore, it could be comfortably included in a systematic review for meta-analysis or in a registry-database in the future.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of the Medical Faculty at the University Medical Centre Magdeburg and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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