



# Clinical and histopathological features of myositis in systemic lupus erythematosus

Eleni Tiniakou <sup>1</sup>, Daniel Goldman,<sup>1</sup> Andrea Corse,<sup>2</sup> Andrew Mammen,<sup>2,3</sup> Michelle A Petri <sup>4</sup>

**To cite:** Tiniakou E, Goldman D, Corse A, *et al.* Clinical and histopathological features of myositis in systemic lupus erythematosus. *Lupus Science & Medicine* 2022;**9**:e000635. doi:10.1136/lupus-2021-000635

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/lupus-2021-000635>).

AM and MAP contributed equally.

Received 2 December 2021  
Accepted 14 March 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

<sup>1</sup>Rheumatology, Johns Hopkins University, Baltimore, Maryland, USA

<sup>2</sup>Neurology, Johns Hopkins University, Baltimore, Maryland, USA

<sup>3</sup>Muscle Disease Unit, NIAMS, Bethesda, Maryland, USA

<sup>4</sup>Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

## Correspondence to

Dr Eleni Tiniakou; [etiniak1@jhmi.edu](mailto:etiniak1@jhmi.edu)

## ABSTRACT

**Objective** The objectives of this study were to compare the clinical features of patients with SLE with and without myopathy and to describe the muscle biopsy features of patients with SLE myopathy.

**Methods** This nested case–control study included all subjects enrolled in the Hopkins Lupus Cohort database from May 1987 to June 2016. Subjects with elevated creatine kinase along with evidence of muscle oedema on MRI, myopathic electromyography and/or myopathic muscle biopsy features were defined as having SLE myopathy. Demographic, serological and clinical features were compared between patients with SLE with and without myopathy. Muscle biopsies were histologically classified as polymyositis, dermatomyositis, necrotising myopathy or non-specific myositis.

**Results** From among 2437 patients with SLE, 179 (7.3%) had myopathy. African American patients were more likely to develop myositis than Caucasian patients ( $p<0.0001$ ). Compared with those without myopathy, patients with SLE myopathy were more likely to have malar rash (OR 1.67, 1.22–2.29), photosensitivity (OR 1.43, 1.04–1.96), arthritis (OR 1.81, 1.21–2.69), pleurisy (OR 1.77, 1.3–2.42), pericarditis (OR 1.49, 1.06–2.08), acute confusional state (OR 2.07, 1.09–3.94), lymphopaenia (OR 1.64, 1.2–2.24), anti-double-stranded DNA antibodies (OR 1.52, 1.09–2.13), lupus anticoagulant (OR 1.42, 1–2), cognitive impairment (OR 1.87, 1.12–3.13), cataract (OR 1.5, 1.04–2.18), pulmonary hypertension (OR 1.98, 1.13–3.47), pleural fibrosis (OR 2.01, 1.27–3.18), premature gonadal failure (OR 1.9, 1.05–3.43), diabetes (OR 1.92, 1.22–3.02) or hypertension (OR 1.45, 1.06–2). Among 16 muscle biopsies available for review, the most common histological classifications were necrotising myositis (50%) and dermatomyositis (38%).

**Conclusions** Patients with SLE myopathy have a higher prevalence of numerous SLE disease manifestations. Necrotising myopathy and dermatomyositis are the most prevalent histopathological features in SLE myopathy.

## INTRODUCTION

SLE is a chronic systemic autoimmune disease that may target a wide variety of tissues including the skin, lungs, kidneys, joints, blood, as well as peripheral and central nervous systems.<sup>1</sup> While skeletal

## Key messages

### What is already known about this subject?

- Skeletal muscle involvement has been described in 4%–16% of patients with SLE.
- The clinical features and muscle biopsy characteristics of patients with SLE myopathy have been poorly described.

### What does this study add?

- SLE myopathy, strictly defined as elevated creatine kinase along with evidence of muscle oedema on MRI, myopathic electromyography and/or myopathic muscle biopsy features, was present in 7.3%.
- The most prevalent histological features in SLE myopathy were necrotising myositis (50%) and dermatomyositis (38%).
- African American patients were more likely to develop SLE myopathy.

### How might this impact on clinical practice or future developments?

- This study can inform about screening of patients with lupus for muscle involvement.
- Further studies are necessary to investigate the response to treatment of necrotising myopathy in the setting of lupus.

muscle involvement has been described in 4%–16% of patients with SLE,<sup>2–6</sup> the clinical features and muscle biopsy characteristics of patients with SLE myopathy have been poorly described.

In the current study, we compare the demographic, clinical and serological features of patients with SLE with and without myopathy in a large and well-characterised cohort of patients with SLE. In addition, we describe the muscle biopsy features of patients with SLE myopathy. Our results demonstrate that patients with SLE myopathy have a markedly higher prevalence of certain SLE clinical features, including arthritis, pericarditis, cognitive impairment and pulmonary hypertension. In addition, we show for the first time that most muscle biopsies in SLE myopathy

are consistent with a histological diagnosis of either a necrotising myositis or dermatomyositis.

## PATIENTS AND METHODS

### Patient characterisation

This is a nested case-control study of all subjects enrolled in the Hopkins Lupus Cohort database from May 1987 to June 2016. This database included 2437 subjects who met the revised 1982 American College of Rheumatology criteria for SLE<sup>7,8</sup> or the Systemic Lupus Collaborating Clinics (SLICC) criteria for the classification of SLE.<sup>1</sup> All patients have given informed consent before participating in the study. The patients were seen at least every 3 months, and at each visit all relevant clinical information was collected. Patients were diagnosed with SLE myopathy if they had muscle weakness/myalgias along with one or more of the following: (1) elevated creatine kinase (CK) levels, (2) muscle oedema on MRI, (3) myopathic electromyography (EMG) findings or (4) a muscle biopsy demonstrating a myopathic process.

### Clinical data

Demographic data including age, gender and race were obtained from the database. Clinical data analysed included SLE manifestations, serological markers and SLE-associated damage. If missing, additional clinical information was obtained from a comprehensive medical chart review.

### Muscle histology

For patients who had muscle biopsies obtained at Johns Hopkins, frozen sections were stained using H&E, modified Gomori trichrome, myosin adenosine triphosphatase

(pH 4.3, 4.6 and 9.4), nicotinamide adenine dinucleotide (NADH)-tetrazolium reductase, acid phosphatase, succinate dehydrogenase stain (SDH), cytochrome esterase, alkaline phosphatase, Periodic Acid-Schiff stain (PAS), PAS-diastrase control and Congo red. All available muscle biopsies were reviewed by the same pathologist (AC) and assessed for myofibre necrosis, perifascicular atrophy, perivascular inflammation, lymphocytic invasion of non-necrotic muscle fibres (ie, primary inflammation), and endomysial or perimysial inflammation. Based on their individual features, these were categorised as polymyositis, dermatomyositis, necrotising myopathy or non-specific myositis; these categories were adapted from the European NeuroMuscular Centre histopathological criteria as previously described.<sup>9</sup>

### Statistical analyses

Patients with myositis versus those without myositis were compared with respect to patient characteristics and clinical features. OR, p values and 95% CIs were determined using Fisher's exact test for categorical variables. ORs were adjusted for gender and race. For continuous variables, p values were determined using a t-test. All statistical calculations were performed using JMP V.14.0 (SAS, Cary, North Carolina).

## RESULTS

### Demographics

From among 2437 patients included in the Hopkins Lupus Cohort, 179 (7.3%) were diagnosed with SLE myopathy. Among these patients, 47 had an EMG performed, 17 had a muscle MRI and 39 had a muscle biopsy. African

**Table 1** Demographic features of patients with SLE and history of myositis versus no myositis

Demographics	With myositis (n=179)	Without myositis (n=2258)	P value
Gender, n (%)			NS
Female	171 (95.5)	2083 (92.3)	
Male	8 (4.5)	175 (7.8)	
Race, n (%)			<0.0001
African American	112 (62.6)	837 (37.2)	
Caucasian	57 (31.8)	1249 (55.4)	
Other	10 (5.6)	170 (7.5)	
Years of education	13.7±2.9	14.4±3.1	0.0029
Private insurance, n (%)			<0.0001
Yes	116 (65.5)	1718 (79.3)	
No	61 (34.5)	448 (20.7)	
Family history of SLE, n (%)			
Yes	52 (29.2)	599 (26.6)	NS
No	126 (70.8)	1651 (73.4)	
History of smoking, n (%)			NS
Yes	61 (34.1)	824 (36.6)	
No	118 (65.9)	1428 (63.4)	

**Table 2** Association of SLE manifestations with SLE myopathy

SLE manifestation	Myositis, n (%)	No myositis, n (%)	OR	P value	Adjusted OR	Adjusted p value	
Malar rash	103 (57.5)	1095 (48.6)	1.44 (1.06–1.95)	0.0212	1.67 (1.22–2.29)	<b>0.0014</b>	
Photosensitivity	100 (55.9)	1172 (52)	1.17 (0.86–1.59)	0.3217	1.43 (1.04–1.96)	<b>0.0273</b>	
Arthritis	147 (82.1)	1594 (70.8)	1.9 (1.28–2.81)	0.0014	1.81 (1.21–2.69)	<b>0.0035</b>	
Serositis	Pleurisy	102 (57)	951 (42.2)	1.82 (1.34–2.47)	0.0001	1.77 (1.3–2.42)	<b>0.0003</b>
	Pericarditis	56 (31.3)	479 (21.3)	1.68 (1.21–2.35)	0.0021	1.49 (1.06–2.08)	<b>0.0214</b>
Renal disorder	11 (6.1)	182 (8.1)	0.74 (0.4–1.39)	0.3556	0.62 (0.33–1.18)	0.1474	
Neurological	Seizures	21 (11.7)	210 (9.3)	1.3 (0.8–2.09)	0.2872	1.3 (0.8–2.1)	0.2898
	Acute confusional state	12 (6.7)	69 (3.1)	2.28 (1.21–4.29)	0.0107	2.07 (1.09–3.94)	<b>0.0269</b>
Haematological	Haemolytic anaemia	23 (13.9)	213 (9.7)	1.5 (0.94–2.38)	0.0863	1.39 (0.87–2.22)	0.1699
	Leucopenia	99 (55.3)	1019 (45.2)	1.5 (1.1–2.04)	0.0096	1.31 (0.96–1.78)	0.0925
	Lymphopaenia	94 (52.8)	900 (40.2)	1.66 (1.22–2.26)	0.0011	1.64 (1.2–2.24)	<b>0.0017</b>
	Thrombocytopenia	39 (21.9)	454 (20.2)	1.11 (0.77–1.61)	0.5783	1.09 (0.75–1.58)	0.6589
Immunological	Anti-dsDNA	127 (70.9)	1376 (61.1)	1.55 (1.11–2.17)	0.0095	1.52 (1.09–2.13)	<b>0.0149</b>
	Anti-Smith	41 (23.3)	443 (20.2)	1.2 (0.83–1.73)	0.3308	0.95 (0.65–1.38)	0.7791
Antiphospholipid	Anticardiolipin	90 (52.3)	1047 (47.8)	1.2 (0.88–1.63)	0.2541	1.24 (0.91–1.7)	0.173
	Anti-beta-2 glycoprotein	33 (30.3)	398 (29)	1.06 (0.69–1.62)	0.783	1.13 (0.73–1.73)	0.5854
	LAC	53 (30.8)	569 (26)	1.27 (0.91–1.78)	0.1645	1.42 (1–2)	0.0478

P values <0.05 were considered statistically significant.

Anti-dsDNA, anti-double-stranded DNA; LAC, lupus anticoagulant.

American patients were more likely than Caucasians to develop myositis (table 1). There were no differences in gender, family history of SLE or smoking history among those with and without myositis.

### Clinical features

Myositis occurred at a median of 1.54 years (range –17 to 35 years) after the diagnosis of SLE, and 16% (28 out of 176 patients) carried a diagnosis of myositis prior to the diagnosis of SLE. Documented muscular atrophy and/or muscle weakness were present in 10.7% of patients with SLE myopathy compared with 2% of patients without myopathy (OR 5.43, 3.05–9.66). Patients with SLE myopathy were more likely to have malar rash (OR 1.67, 1.22–2.29) and photosensitivity (OR 1.43, 1.04–1.96) (tables 2 and 3). The vast majority of patients with myositis had a history of arthritis (OR 1.81, 1.21–2.69), and there was a trend of increased incidence of deformities or erosions, although it did not reach statistical significance (OR 1.66, 0.99–2.78). Serositis was also more common, in the form of either pleurisy (OR 1.77, 1.3–2.42) or pericarditis (OR 1.49, 1.06–2.08), and they were also more likely to have pulmonary hypertension (1.98, 1.13–3.47) and pulmonary fibrosis (2.01, 1.27–3.18). There was no change in the prevalence of seizures (OR 1.3, 0.8–2.1) or neuropathy (OR 1.42, 0.88–2.31), but they were more likely to develop acute confusional state (OR 2.07, 1.09–3.94) and some type of cognitive impairment (OR 1.87, 1.12–3.13). There was no significant difference found in

the incidence of renal involvement (OR 0.62, 0.33–1.18), proteinuria (OR 0.93, 0.54–1.6) or decreased glomerular filtration rate (GFR) (OR 0.75, 0.38–1.46). For a detailed analysis, please refer to online supplemental tables 1 and 2. There was no significant difference in other clinical characteristics (table 1).

### Detailed clinical features of patients with SLE myopathy who underwent muscle biopsy

Nineteen muscle biopsies were available for review, majority of which were from women (89.5%) and 14 from African Americans (73.7%). Of these, two had normal creatine phosphokinase (CPK) and no evidence of myopathy on muscle biopsy and therefore did not meet the criteria for lupus myopathy. Additionally, a third biopsy from a 42-year-old African American woman on hydroxychloroquine with history of fatigue, myalgias and subjective muscle weakness showed an accumulation of small acid phosphatase positive vacuoles in otherwise normal myofibres, consistent with hydroxychloroquine myopathy. Therefore, we included only 16 muscle biopsies in our analysis.

The mean maximum CK of the remaining 16 patients undergoing biopsy was elevated at 6240 (SD 6441), and 11 (68.75%) had documented proximal muscle weakness. Twelve patients had an electromyogram and four (33.33%) of these were consistent with non-irritable myopathy, seven (58.33%) had irritable myopathy and one of them was normal. One had electrophysiological

**Table 3** Association of SLE damage with SLE myopathy

Damage component	Myositis, n (%)	No myositis, n (%)	OR	P value	Adjusted OR	Adjusted p value
Cataract	41 (23.2)	374 (16.8)	1.5 (1.04–2.16)	0.0307	1.5 (1.04–2.18)	<b>0.0318</b>
Cognitive impairment	19 (10.8)	150 (6.7)	1.69 (1.02–2.79)	0.0422	1.87 (1.12–3.13)	<b>0.0166</b>
Seizure	9 (5.1)	102 (4.6)	1.13 (0.56–2.27)	0.7337	1.23 (0.61–2.5)	0.5674
Cranial or peripheral neuropathy	21 (11.9)	199 (8.9)	1.39 (0.86–2.24)	0.1784	1.42 (0.88–2.31)	0.1527
Transverse myelitis	1 (0.6)	17 (0.8)	0.75 (0.1–5.64)	0.7773	0.6 (0.08–4.59)	0.6234
Proteinuria	16 (9.1)	184 (8.2)	1.11 (0.65–1.9)	0.6912	0.93 (0.54–1.6)	0.786
Pulmonary hypertension	16 (9.1)	97 (4.3)	2.21 (1.27–3.84)	0.005	1.98 (1.13–3.47)	<b>0.0171</b>
Pulmonary fibrosis	25 (14.2)	154 (6.9)	2.24 (1.42–3.53)	0.0005	2.01 (1.27–3.18)	<b>0.003</b>
Cardiomyopathy	9 (5.1)	79 (3.5)	1.47 (0.73–2.99)	0.2827	1.24 (0.6–2.54)	0.5613
Muscular atrophy/weakness	19 (10.7)	45 (2)	5.89 (3.37–10.32)	<0.0001	5.43 (3.05–9.66)	<0.0001
Arthritis	19 (10.7)	130 (5.9)	1.93 (1.16–3.2)	0.0112	1.66 (0.99–2.78)	0.0546
Premature gonadal failure	14 (8)	100 (4.5)	1.85 (1.03–3.3)	0.039	1.9 (1.05–3.43)	<b>0.0346</b>
Diabetes	26 (14.8)	168 (7.5)	2.13 (1.37–3.33)	0.0009	1.92 (1.22–3.02)	<b>0.0048</b>
Hypertension	79 (44.9)	720 (32.4)	1.7 (1.24–2.31)	0.0008	1.45 (1.06–2)	<b>0.0212</b>

P values <0.05 were considered statistically significant.

findings consistent with a neurogenic process. Eight (50%) of the muscle biopsies were histologically classified as necrotising myopathy and six (38%) were histologically classified as dermatomyositis based on the presence of perifascicular atrophy, the hallmark feature of dermatomyositis (table 4). Regarding individual histological features, 25% had primary inflammation, 87.5% had necrosis and/or regeneration, 25% had perimysial inflammation and 37.5% had endomysial inflammation (table 5). A single biopsy did not reveal any pathological findings, although the EMG demonstrated irritable myopathy and there was elevation of CPK.

The vast majority of the patients responded to immunosuppressive treatment and had normal muscle strength at their last visit (73.3%), and only four patients continued to have muscle weakness. Interestingly, a 42-year-old African American woman presented with only weakness of the finger flexors and positive anti-NT5c1A antibodies, which would fit a clinical diagnosis of inclusion body myositis. However, her muscle biopsy was consistent with dermatomyositis and her strength actually improved with immunosuppression.

### Laboratory markers

There was an increased incidence of lymphopaenia (OR 1.64, 1.2–2.24) in patients with lupus myopathy, but no difference in haemolytic anaemia, leucopenia or thrombocytopenia (table 2). The presence of anti-double-stranded DNA (anti-dsDNA) antibodies (OR 1.52, 1.09–2.13) or lupus anticoagulant (OR 1.42, 1–2) was more common as well. However, there was no change in anti-Smith antibodies (OR 0.95, 0.65–1.38), false-positive

rapid plasma reagin (OR 1.39, 0.9–2.14) or other antiphospholipid-associated antibodies (table 2).

Patients with necrotising myopathy and dermatomyositis features on muscle biopsy had similar clinical features (online supplemental table 3). Regarding the autoantibody profile, of those with muscle biopsy consistent with dermatomyositis, two patients were positive for anti-ribonucleoprotein (anti-RNP) antibodies and one for anti-melanoma differentiation-associated protein 5 (MDA5). Anti-RNP antibodies were present in seven patients (43.75%), and 57% of them had muscle biopsy consistent with necrotising myopathy. Anti-Ro antibodies were present in 12 patients (75%) (table 4).

### DISCUSSION

In this study we identified patients with SLE myopathy in a large cohort of patients with SLE based on the presence of CK elevation along with imaging, electrophysiological features and/or histological features consistent with an active myopathic process. We then compared the clinical features of patients with SLE with and without myopathy. Additionally, we investigated the characteristics of the available muscle biopsies and the associated clinical findings of those patients with a biopsy.

Tsokos *et al*<sup>10</sup> reported an 8% (18 patients) incidence of myositis in patients with SLE hospitalised in a span of 6.5 years, but the definition of myositis was broad and included any patient with muscle complaint. Foote *et al*<sup>4</sup> studied 11 patients who met the criteria for both lupus and myositis, as outlined by Bohan and Peter.<sup>11 12</sup> They were not able to describe any clinical features that were

**Table 4** Demographic features of patients with SLE myopathy and available muscle biopsy (n=16)

ID	Sex	Race	Maximum CK	Strength	EMG	ENMC		Medications	Improvement
						diagnosis	Antibodies		
1	F	AA	Normal	Proximal muscle weakness	Normal	DM	ANA, dsDNA, Ro	Steroids, HCQ	-
2	F	C	12 740	Proximal muscle weakness	Non-irritable myopathy	DM	ANA, RNP, Ro, ACA, b2GP	Steroids, HCQ, CYC, MTX, IVIG	Normal strength
3	F	C	918	Proximal muscle weakness	None	DM	ANA, dsDNA, LAC, ACA, b2GP, Ro	Steroids, AZA	Proximal muscle weakness
4	F	C	6900	Proximal muscle weakness	Irritable myopathy	DM	ANA	Steroids, HCQ	Normal strength
5	F	H	93	Distal muscle weakness	Non-irritable myopathy	DM	ANA, MDA5, Ro	Steroids, IVIG	Normal strength
6	F	AA	6511	Proximal and distal muscle weakness	Irritable myopathy	DM	ANA, RNP, Ro, La, NT5c1A	Steroids, HCQ, AZA, MMF, MTX, rituximab	Proximal and distal muscle weakness
7	F	AA	18 455	Proximal muscle weakness	None	PM	ANA, SRP, Ro, ACA, b2GP, Sm	Steroids, HCQ, MTX, MMF, leflunomide	Normal strength
8	F	AA	1212	Proximal muscle weakness	Irritable myopathy	NM	ANA, RNP, dsDNA, Sm, ACA, Ro, La	Steroids, HCQ, AZA	Normal strength
9	F	AA	5744	Normal	Irritable myopathy	NM	ANA, RNP, ACA	Steroids, HCQ	Normal strength
10	F	AA	1908	Proximal muscle weakness	None	NM	ANA, dsDNA, b2GP	Steroids, HCQ, AZA, MTX, MMF	Proximal muscle weakness
11	F	AA	1828	Proximal muscle weakness	Irritable myopathy	NM	ANA, dsDNA, Ro, La, ACA	Steroids, HCQ, MTX, MMF	Proximal muscle weakness
12	F	AA	1810	Proximal muscle weakness	Irritable myopathy	NM	ANA, RNP, dsDNA, Sm, Ro	Steroids, HCQ, MMF, IVIG	Normal strength
13	M	AA	2640	Normal	Chronic neurogenic changes	NM	ANA, dsDNA, ACA, b2GP	Steroids, HCQ, CYC	Normal strength
14	F	C	4000	Normal	Non-irritable myopathy	NM	ANA, Ro	Steroids, HCQ	Normal strength
15	F	AA	6388	Normal	Non-irritable myopathy	NM	ANA, RNP, Ro, Sm, dsDNA, LAC, ACA	Steroids, HCQ, AZA, Benlysta	Normal strength
16	M	AA	22 450	Proximal muscle weakness	Irritable myopathy	Normal	ANA, RNP, dsDNA, Sm, Ro, LAC	Steroids, CYC	Normal strength

AA, African American; ACA, anticardiolipin antibodies; AZA, azathioprine; b2GP, anti-beta-2 glycoprotein antibodies; C, Caucasian; CK, creatine kinase; CYC, cyclophosphamide; DM, dermatomyositis; dsDNA, anti-double-stranded DNA antibodies; EMG, electromyography; ENMC, European NeuroMuscular Centre; F, female; H, Hispanic; HCQ, hydroxychloroquine; ID, identification; IVIG, intravenous immunoglobulin; LAC, lupus anticoagulant; M, male; MDA5, Melanoma Differentiation-Associated protein 5; MMF, mycophenolate mofetil; MTX, methotrexate; NM, necrotising myopathy; PM, polymyositis; RNP, anti-ribonucleoprotein antibodies; Sm, anti-Smith antibodies; SRP, Signal Recognition Particle.

**Table 5** Histological features of SLE myopathy muscle biopsies (n=16)

ID	ENMC diagnosis	Necrosis/regeneration	Perifascicular atrophy	Primary inflammation	Endomysial inflammation	Perimysial inflammation
1	DM	+	+	+	-	-
2	DM	+	+	+	+	+
3	DM	+	+	-	+	-
4	DM	+	+	-	+	+
5	DM	-	+	-	+	+
6	DM	+	+	+	+	-
7	PM	+	-	+	+	+
8	NM	+	-	-	-	-
9	NM	+	-	-	-	-
10	NM	+	-	-	-	-
11	NM	+	-	-	-	-
12	NM	+	-	-	-	-
13	NM	+	-	-	-	-
14	NM	+	-	-	-	-
15	NM	+	-	-	-	-
16	Normal	-	-	-	-	-

DM, dermatomyositis; ENMC, European NeuroMuscular Centre; ID, identification; NM, necrotising myopathy; PM, polymyositis.

associated with muscle involvement. Of note, these two studies were performed in 1981 and 1982, respectively. There have been changes in the accepted criteria for diagnosis of SLE and pathological classification of muscle biopsies, making their results difficult to interpret and apply to our current cohorts. There have been three recent investigations on lupus myositis. Jakati and colleagues<sup>6</sup> described 15 patients with lupus and muscle complaints undergoing muscle biopsy. Approximately half of these patients had histological evidence of myositis, but they failed to find any other common characteristics. Liang *et al*<sup>3</sup> defined myositis as reported muscle weakness, with elevated CK and abnormal EMG findings. They reported a prevalence of 2.6% of myositis within their cohort of hospitalised patients with SLE in the Anhui province in China. Cotton *et al*<sup>13</sup> described an incidence of 1.05 cases per 1000 person-years in a North American cohort. Non-Caucasian patients with a history of arthritis, Raynaud's phenomenon and anti-Smith antibodies were found to have a higher risk of developing myositis.

In the current study, we found a 7.3% prevalence of myopathy in patients with SLE, which is in accordance with all previous reports. CK is one of the serologies obtained regularly at the Johns Hopkins Lupus Cohort, and a consistent increase of its value initiates further work-up even in the absence of muscular symptoms. Given that patients with lupus tend to have lower CK values,<sup>14 15</sup> an increase over normal values can be significant. These patients tended to have concomitant malar rash, photosensitivity, arthritis and serositis, indicative of a diffuse SLE involvement. However, there was no association with lupus nephritis. In the central nervous system (CNS) realm, it is interesting that these patients were more

likely to have cognitive impairment and an association with acute confusional states. These patients exhibited a borderline association with erosive arthritis ( $p=0.0546$ ), resembling previous findings of a British cohort.<sup>16</sup>

Pulmonary hypertension is an uncommon but partially lethal complication of lupus, with a prevalence estimated at 3%–5%.<sup>3 17</sup> While the prevalence of pulmonary hypertension was 4.3% in patients without myopathy, patients with overlap myopathy were twice more likely to have lung involvement as well as lung fibrosis. This suggests that patients who exhibit objective evidence of muscle disease should also be screened with an echocardiogram and lung functional and imaging studies.

Of the serological markers, patients with lupus myositis overlap were more likely to have leucopenia/lymphopaenia and anti-dsDNA, as has been reported in the Chinese lupus cohort as well,<sup>3</sup> but additionally we found that lupus anticoagulant was an independent marker associated with lupus myopathy in our cohort. Contrary to the study by Cotton *et al*,<sup>13</sup> we did not find an association with anti-Smith antibodies.

Dissimilar to previous cohorts,<sup>3</sup> the patients of our cohort with muscle disease were more likely to have hypertension and diabetes, as well as premature gonadal failure, likely as a result of previous treatments. These conditions though should be screened and considered especially on decision for treatment.

For our current study, we included all muscle biopsies of our cohort that were performed at the Johns Hopkins Hospital. Remarkably, we were able to identify only 19 of 179 (10.6%) patients with documented myopathy who had a muscle biopsy performed from our chart review. This most likely reflects our ability to diagnose myopathy

using imaging studies (such as MRI), the low prevalence of significant muscle weakness that would prompt an invasive procedure to accurately diagnose the nature of muscle involvement, and/or quick resolution of muscular symptoms with treatment that would deter from further work-up. On the same note, only one biopsy revealed normal muscle tissue, which again mirrors perhaps the practice of our institution to reserve invasive methods cautiously. Of the available muscle biopsies 40% were consistent with dermatomyositis and half of them demonstrated elements of necrotising myopathy. These results come in contrast to previous studies, where the majority showed polymyositis.<sup>4 6 18</sup> While necrotising myopathy is associated with a rapidly progressive and severe prognosis requiring multiple therapeutic agents,<sup>19</sup> the majority of patients with SLE regained full muscle strength with the use of steroids and one immunosuppressive agent. We did not find any association of the type of muscle biopsy with any clinical characteristic, considering though the small numbers of samples.

Of the 15 patients with available muscle biopsy, 7 were positive for anti-RNP antibodies, and in the majority of these muscle biopsy was consistent with necrotising myopathy. This is similar to a different study from the Johns Hopkins Myositis Center when examining patients who were referred for anti-U1-RNP-positive myositis.<sup>20</sup>

There are several limitations to the present study. This study is nested case-control in nature and we cannot conclude the temporal and pathogenetic nature of the above associations. Additionally, we do not have information on the exact degree of muscle weakness. The study population is based in the Baltimore community.

This is the largest analysis of clinical characteristics associated with myopathy in patients with lupus, as defined by objective measures of muscle disease. This study reveals that lupus myopathy is associated with a higher prevalence of lung involvement (pulmonary hypertension, lung fibrosis), and clinicians need to be aware to proceed with appropriate screening tests for these patients. Moreover, the most likely histological phenotype of muscle disease is necrotising myopathy, which seems to be responsive to first-line immunosuppressive treatment, although further studies are necessary to determine if treatment should be adjusted similarly.

**Contributors** ET, ALM and MAP contributed to study conception and design. MAP managed the recruitment of patients with SLE. MAP and ET contributed to acquisition of data. DG performed the statistical analyses. All authors contributed to the analysis and interpretation of data. ET and AM drafted the manuscript. All authors reviewed and edited the final manuscript. All authors have read and agreed to the published version of the manuscript. ET and MAP accept full responsibility for the work and/or conduct of the study, had access to the data, and controlled the decision to publish.

**Funding** This work was supported by grant number RO-1 AR 069572 from the National Institutes of Health (NIH) and by the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

**Ethics approval** This study involves human participants and was approved by IRB NA\_00039294. The centre is approved on an annual basis by the Johns Hopkins Institutional Review Board. Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iDs

Eleni Tiniakou <http://orcid.org/0000-0003-4749-870X>

Michelle A Petri <http://orcid.org/0000-0003-1441-5373>

#### REFERENCES

- Petri M, Orbai A-M, Alarcón GS, *et al*. Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012;64:2677–86.
- Isenber DA, Snaith ML. Muscle disease in systemic lupus erythematosus: a study of its nature, frequency and cause. *J Rheumatol* 1981;8:917–24.
- Liang Y, Leng R-X, Pan H-F, *et al*. Associated variables of myositis in systemic lupus erythematosus: a cross-sectional study. *Med Sci Monit* 2017;23:2543–9.
- Foote RA, Kimbrough SM, Stevens JC. Lupus myositis. *Muscle Nerve* 1982;5:65–8.
- Garton MJ, Isenberg DA. Clinical features of lupus myositis versus idiopathic myositis: a review of 30 cases. *Br J Rheumatol* 1997;36:1067–74.
- Jakati S, Rajasekhar L, Uppin M, *et al*. Sle myopathy: a clinicopathological study. *Int J Rheum Dis* 2015;18:886–91.
- Tan EM, Cohen AS, Fries JF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–7.
- Hochberg MC. Updating the American College of rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:40.
- Paik JJ, Wigley FM, Lloyd TE, *et al*. Spectrum of muscle histopathologic findings in forty-two scleroderma patients with weakness. *Arthritis Care Res* 2015;67:1416–25.
- Tsokos GC, Moutsopoulos HM, Steinberg AD. Muscle involvement in systemic lupus erythematosus. *JAMA* 1981;246:766–8.
- Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975;292:344–51.
- Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). *N Engl J Med* 1975;292:403–10.
- Cotton T, Niaki OZ, Zheng B, *et al*. Myositis in systemic lupus erythematosus. *Lupus* 2021;30:615–9.
- Wei N, Pavlidis N, Tsokos G, *et al*. Clinical significance of low creatine phosphokinase values in patients with connective tissue diseases. *JAMA* 1981;246:1921–3.
- Font J, Ramos-Casals M, Vilas AP, *et al*. Low values of creatine kinase in systemic lupus erythematosus. clinical significance in 300 patients. *Clin Exp Rheumatol* 2002;20:837–40.
- Dayal NA, Isenberg DA. SLE/myositis overlap: are the manifestations of SLE different in overlap disease? *Lupus* 2002;11:293–8.
- Lian F, Chen D, Wang Y, *et al*. Clinical features and independent predictors of pulmonary arterial hypertension in systemic lupus erythematosus. *Rheumatol Int* 2012;32:1727–31.

- 18 Lim KL, Abdul-Wahab R, Lowe J, *et al.* Muscle biopsy abnormalities in systemic lupus erythematosus: correlation with clinical and laboratory parameters. *Ann Rheum Dis* 1994;53:178–82.
- 19 Allenbach Y, Benveniste O, Stenzel W, *et al.* Immune-Mediated necrotizing myopathy: clinical features and pathogenesis. *Nat Rev Rheumatol* 2020;16:689–701.
- 20 Casal-Dominguez M, Pinal-Fernandez I, Corse AM, *et al.* Muscular and extramuscular features of myositis patients with anti-U1-RNP autoantibodies. *Neurology* 2019;92:e1416–26.