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ScienceDirect

Neuromuscular Disorders 29 (2019) 39–47

www.elsevier.com/locate/nmd

Myopathies featuring non-caseating granulomas: Sarcoidosis, inclusion body myositis and an unfolding overlap

Reem M. Alhammad[a,b], Teerin Liewluck[a,*]

[a] *Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA*
[b] *Section of Neurology, Department of Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia*

Received 22 July 2018; received in revised form 23 October 2018; accepted 31 October 2018

Abstract

Granulomatous myopathies are etiologically heterogeneous myopathies, pathologically characterized by the presence of intramuscular granulomas. Treatment outcomes are variable. We aimed to identify prognostic factors of treatment outcomes in myopathies featuring non-caseating granulomas. Sixteen patients were identified (9 sarcoid myopathy, 6 inclusion body myositis, and 1 granulomatous myopathy of indeterminate cause) over a 21-year period. The median age at diagnosis was 67 years in sarcoid myopathy group, and 64 years in inclusion body myositis group. Three inclusion body myositis patients were initially diagnosed with sarcoid myopathy based on the presence of systemic features of sarcoidosis and findings on muscle biopsies, but subsequent biopsies performed because of treatment refractoriness, showed all canonical pathologic features of inclusion body myositis. We identified sarcoplasmic congophilic inclusions in 6 sarcoid myopathy patients without associated rimmed vacuoles or typical weakness pattern of inclusion body myositis. Four inclusion body myositis and 4 of 5 sarcoid myopathy patients with congophilic inclusions were refractory to immunotherapy. Our study portrays the overlapping clinical and pathological features of sarcoid myopathy and inclusion body myositis. The presence of sarcoplasmic congophilic inclusions in sarcoid myopathy may predict an unfavorable outcome of immunosuppressive therapy, but a larger prospective study is required to further validate this observation.

Keywords: Granulomatous myopathy; Granulomatous myositis; Sarcoid myopathy; Inclusion body myositis; Non-caseating granulomas; Skeletal muscle granulomas.

1. Introduction

Granulomatous myopathy is a clinically and etiologically heterogeneous group of uncommon inflammatory myopathies, pathologically characterized by the presence of granulomas in skeletal muscle. Granulomas may contain necrosis as typically seen in infectious disorders (fungal, tuberculosis, or brucellosis) [1–3] or may occur without necrosis, so-called non-necrotizing or non-caseating granulomas. Various disorders were reported in association with non-caseating granulomatous myopathy, including sarcoidosis and less commonly other autoimmune diseases (Crohn's disease, anti-mitochondrial autoimmunity with or without primary biliary cirrhosis, myasthenia gravis, and programmed cell death-1 inhibitor-associated myopathy) or neoplastic conditions (thymoma and lymphoma) [4–10]. More recently, a few inclusion body myositis (IBM) patients were also reported with intramuscular granulomas, occasionally with coexisting systemic sarcoidosis [11–14]. In two series of granulomatous myopathy patients, sarcoidosis was the most common identified cause, accounting for 40%−60% of patients, and the remaining patients were diagnosed with isolated granulomatous myopathy given the absence of other associated conditions [15,16]. Immunosuppressive therapy in patients with granulomatous myopathy was reported with either favorable or poor outcomes, which at least in part could be due to its etiological heterogeneity [15–17]. The diagnostic approach to granulomatous myopathy presents many challenges with limited studies reporting detailed clinical and myopathologic evaluations that may provide clues in

* Corresponding author.
E-mail address: liewluck.teerin@mayo.edu (T. Liewluck).

https://doi.org/10.1016/j.nmd.2018.10.007
0960-8966/

distinguishing possible underlying etiologies or identifying prognostic features for treatment outcomes.

This study aims to elucidate clinical, laboratory, and myopathologic features of granulomatous myopathy, to identify distinguishing features among diagnostic subgroups, and to determine potential predictors of response to immunosuppressive therapies.

2. Materials and methods

2.1. Patients

We searched the muscle biopsy database to identify biopsies reported to show granulomatous inflammation between September 1996 and April 2017. Only patients clinically evaluated at Mayo Clinic with adequate clinical data were included. Authors reviewed muscle biopsy slides of all included patients blinded to the muscle biopsy reports, the final diagnosis and treatment outcomes. Granulomas were defined as collections of activated macrophages (epithelioid cells) surrounded by lymphocytes [18]. The identification of epithelioid cells was based on the cellular morphology and the increase of acid phosphatase and nonspecific esterase activity. Biopsies that do not fulfill the diagnostic criteria of granulomas upon our review were excluded. Electronic medical records were reviewed to collect demographic data, clinical and laboratory features, electrodiagnostic testing, radiology and histopathology reports for analysis. Follow-up data and treatment responses were obtained when available.

2.2. Diagnostic classification

When various diagnoses were present, the diagnosis on last follow up was considered the final diagnosis. A clinical diagnosis of sarcoid myopathy was established in the presence of compatible clinical or radiologic manifestations in addition to the presence of non-caseating granulomas in skeletal muscle. A diagnosis of probable sarcoidosis was reserved for the patients with one or more of the following features: (1) hilar or mediastinal lymphadenopathy identified on chest computerized tomography (CT), (2) hypercalcemia, (3) elevated angiotensin converting enzyme (ACE) level, (4) uveitis, (5) erythema nodosum, or (6) CSF pleocytosis. Patients with pathologically-proven, extra-muscular granulomas were categorized as definite sarcoid myopathy. Both definite and probable cases of sarcoid myopathy were included in analyses.

In patients with a diagnosis of inclusion body myositis (IBM), the 2011 European Neuromuscular Center (ENMC) IBM research diagnostic criteria were applied to categorize patients as probable, clinically defined, or clinico-pathologically defined IBM [19]. We coined the term pathologically defined IBM for patients whom muscle biopsy findings showed all pathological features of clinico-pathologically define IBM based on the 2011 ENMC IBM research diagnostic criteria (endomysial inflammation, rimmed vacuoles and congophilic inclusions), but lack the characteristic weakness distribution (knee extensor equal to or greater than hip flexor weakness or finger flexor greater than shoulder abductor weakness).

2.3. Grading clinical severity and functional disability

Weakness severity was based on the Medical Research Council (MRC) grade of the weakest muscle group: none (MRC grade 5), mild (MRC grade $\geq$ 4/5), moderate (MRC grade 3/5), severe (MRC grade $<$ 3/5). Disability was graded as requirement of ambulation aids (none, unilateral /bilateral assistance, or wheelchair bound).

2.4. Muscle histopathology

Muscle specimens were frozen in isopentane-cooled in liquid nitrogen. Serial 10-μm-thick sections were cut and stained with hematoxylin and eosin, modified Gomori trichrome, nicotinamide adenine dinucleotide (NADH), succinic dehydrogenase (SDH), cytochrome *c* oxidase, myosin ATPase (pH 4.2, 4.3, and 9.6) acid phosphatase, myophosphorylase, periodic acid-Schiff (PAS), oil red-O, nonspecific esterase, and Congo red. Immunocytochemical studies for p62, SMI-31, TDP-43, ubiquitin and MHC-1 were not performed. Non-caseating granulomas were defined as granulomas without central necrosis [18]. The number of granulomas per low power field was used to reflect granuloma density. Largest granuloma size in each specimen was calculated as the area of an oval where area = a x b x ¶; a = major radius (distance from center of granuloma to farthest edge), b = minor radius (distance from center of granuloma to closest point on edge), and ¶ = 3.14. Congo red stained sections were viewed under rhodamine optics to calculate the number of sarcoplasmic congophilic inclusions per low power field. When patients had more than one muscle biopsy, these were reviewed by the authors if slides were available; only findings from biopsies containing granulomas were included in analyses.

2.5. Grading treatment outcomes

Response to various immunosuppressive therapies on initial or follow up clinical evaluations were documented when available. Response to treatment was graded as: no improvement, mild improvement (1 MRC grade in 1–2 muscle groups), moderate improvement ($>$ 1 MRC grade in multiple muscle groups), marked improvement (symptoms and signs of mild weakness but no functional limitation), or return to baseline (no symptoms or signs of weakness).

2.6. Statistical analyses

Descriptive and statistical analyses were performed when applicable, Wilcoxon rank sum test and Fisher's exact test were used to analyze continuous and categorical data, respectively, all tests were 2-sided with statistical significance defined as $p < 0.05$ [JMP Pro 13.0.0 (2016)].

Table 1
Clinical characteristics and diagnostic features of sarcoidosis of 16 patients with intramuscular granulomas.

Patient number	Characteristics								
	Final diagnosis	Age (years)/ gender	Symptom duration (months)	Presenting symptom(s)	Weakness distribution (last visit)		Other findings	Biopsy-proven extramuscular granuloma	Systemic features of sarcoidosis[e]
					Lower limb	Upper limb			
1	SM-D	67/F	4	Head drop, leg weakness, DOE	P	P	NE, NF	Liver, gall bladder	3,4
2	SM-D	38/F	84	Myalgia, recurrent facial droop	D	D	Myalgia	Lung, lymph node, skin	1,3,5
3	SM-D	69/F	6	Leg weakness	D[b]	D	NE, F	Lymph node	1,2
4	SM-D	76/M	120	Dysphagia	PD	PD	Dysphagia, myalgia, NE, NF	Lung	1,3
5	SM-P	69/M	12	Dysarthria, macroglossia	–	PD[a]	Dysphagia, myalgia, NE, T	–	3,4,6
6	SM-P	66/F	7	Leg weakness, fatigue	PD	PD	Dysphagia, NF	–	1,2,3,4
7	SM-P	69/M	8	Calf pain	D[c]	–	Myalgia	–	2
8	SM-P	67/F	120	Dysphagia, shoulder and hip weakness	P	P	Dysphagia, NE	–	1
9	SM-P	65/M	60	Leg weakness	P[a]	P[a]	Myalgia	–	2
10	IBM-CPD	63/M	36	Leg weakness	D[a]	D[a] (FF)	NF	–	–
11	IBM-CPD	82/F	24	Hand and leg weakness	P	P (FF)	NF	–	–
12	IBM-CPD*	59/F	120	Shoulder and hip weakness	P[a]	P[a] (FF)	Dysphagia, NF	–	4
13	IBM-CPD*	64/F	24	Shoulder and hip weakness	D[a]	D[a] (FF)	NE, NF	–	1
14	IBM-P*	52/M	72	Shoulder and hip weakness	–	–	Dysphagia, myalgia	–	1
15	IBM-P*	70/F	96	Shoulder and hip weakness, myalgia	P	P	Myalgia	Lymph node	1,2
16	GM-NOS	47/F	108	Calf weakness	D[d]	–	Calf and hamstring atrophy	–	–

D, distal weakness; DOE, dyspnea on exertion; F, facial weakness; FF, prominent finger flexor weakness; GM-NOS, granulomatous myopathy of indeterminate etiology; IBM-CPD, clinico-pathologically defined inclusion body myositis; IBM-P, pathologically-defined inclusion body myositis; NE, neck extensor weakness; NF, neck flexor weakness; P, proximal weakness; PD, proximo-distal weakness; SM-D, definite sarcoid myopathy; SM-P, probable sarcoid myopathy; T, tongue weakness; * IBM with coexisting systemic sarcoidosis (SM/IBM); [a] asymmetrical weakness; [b] anterior compartment; [c] Equal anterior and posterior compartments; [d] Posterior compartment; [e] systemic features of sarcoidosis, including (1) hilar or mediastinal lymphadenopathy identified on chest computerized tomography (CT), (2) hypercalcemia, (3) elevated angiotensin converting enzyme (ACE) level, (4) uveitis, (5) erythema nodosum, or (6) CSF pleocytosis.

3. Results

3.1. General clinical characteristics

Among 23,038 muscle biopsies, there were 50 biopsies reported with granulomas but only 20 patients were clinically evaluated at our institution. Four patients were excluded due to insufficient clinical data ($n=1$) or myopathologic features not fulfilling criteria for granulomatous inflammation upon our review ($n=3$). Granulomas observed in all 16 included patients (10 women and 6 men) were non-caseating. Table 1 summarize the clinical characteristics and ancillary tests in all patients (9 sarcoid myopathy, 6 IBM, and 1 granulomatous myopathy of indeterminate etiology), respectively.

In the sarcoid myopathy group, 3 patients had a prior diagnosis of sarcoidosis (patients 2–4), ranging from 2–6 years prior to myopathy onset. The diagnosis of sarcoidosis was definite in 4 patients and probable in 5 patients as shown in Table 1. All 9 patients with sarcoid myopathy had a chronic myopathy type [20,21]. Weakness severity was mild in all patients with no functional limitations in ambulation detected on initial visits.

In the IBM group, 4 patients (patients 10–13) satisfied the 2011 ENMC diagnostic criteria of clinico-pathologically de-

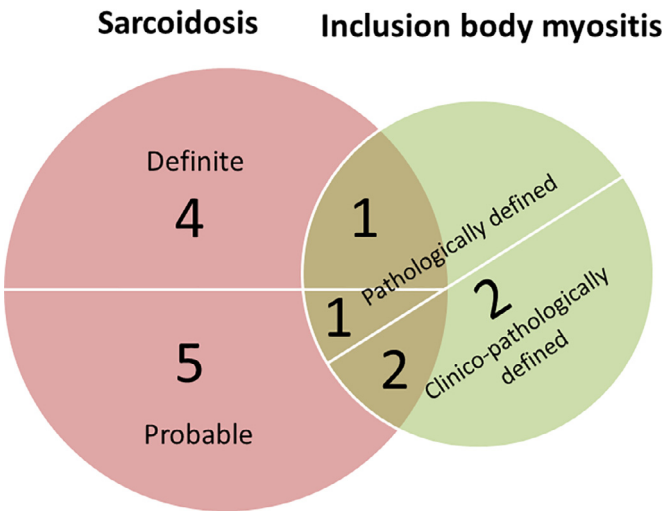

Fig. 1. Overlap in clinical diagnoses of sarcoid myopathy and inclusion body myositis (numbers represent patients in each category).

fined IBM (IBM-CPD). Patients 14 and 15 were classified as pathologically defined IBM based on the modified criteria described earlier (IBM-P). Patients 13, 14 and 15 had a prior diagnosis of sarcoidosis based on systemic features highlighted in Table 1. Granulomas were observed in first muscle biopsies of these three patients, and repeat biopsies were performed due to refractoriness to immunosuppressive therapy. Patient 12 also had a history of anti-mitochondrial antibody-positive primary biliary cirrhosis and uveitis. Uveitis would put her in the category of probable sarcoidosis as well, although the diagnosis of sarcoidosis was not mentioned in her medical records. Her initial muscle biopsy showed inflammatory myopathy with mild perifascicular pathology without granuloma or IBM features, but a subsequent biopsy performed due to refractoriness to immunotherapy showed canonical features of IBM and granulomas. Therefore, patients 12–15 could be further classified as sarcoid myopathy/IBM or SM/IBM (Fig. 1).

Of note, patient 16 presented with a longstanding history of calf weakness with clumsiness starting in the second decade. Her examination showed distal weakness with significant calf atrophy. Muscle dysferlin immunoreactivity was normal. Result of genetic testing for muscular dystrophies was not available for review.

3.2. Ancillary studies

The results of ancillary studies of each patient are summarized in Supplementary Table 1. Table 2 compares clinical and laboratory features between different subgroups of granulomatous myopathies. Finger flexor weakness was observed only in IBM patients ($p < 0.05$). There was no significant different of any laboratory testing between sarcoid myopathy and IBM group despite the ACE level being only elevated in sarcoid myopathy patients. One IBM patient (patient 12) was tested for cytosolic 5′-nucleotidase 1A IgG antibody (anti - cN-1A) and was negative. None of the patients underwent Gallium scan or PET scan.

3.3. Myopathologic findings

Table 3 compares the pathological features between different subgroup of granulomatous myopathies. Epithelioid cells were periodic acid-Schiff-negative in all patients. The only significant difference between sarcoid myopathy and IBM group was the presence of rimmed vacuoles in 4 IBM patients, but in none of sarcoid myopathy patients. Upon review of the biopsy slides, we identified congophilic inclusions in 6 of 9 sarcoid myopathy patients (patients 1, 3, 4, 5, 7, and 9) (Fig. 2).

Patients 13–15, each underwent 2 muscle biopsies. First biopsies were reported as granulomatous myopathy without rimmed vacuoles or congophilic inclusions (patient 14 did not have Congo red stain); therefore, they were initially diagnosed with sarcoid myopathy based on concomitant systemic features of sarcoidosis as shown in Table 1. Upon review of the first biopsy of patient 15 by the authors, congophilic inclusions were detected. These 3 patients underwent second biopsies because of the refractoriness to immunosuppressive therapy and showed endomysial inflammation, rimmed vacuoles, and congophilic inclusions with (patient 14) and without (patients 13 and 15) granulomas, consistent with the canonical pathological features of IBM (Fig. 2). Fig. 3 summarizes the key biopsy findings in all 16 patients, including the evolution of pathological changes of patients 13–15.

3.4. Treatment and outcomes

Immunosuppressive therapies in 13 patients are summarized in Supplementary Table 2. Data on treatment outcomes was available in 11 patients, although only 10 patients returned for follow up. Median follow up was 12 months (range, 7–96) in 7 patients with sarcoid myopathy and 84 months (range, 66–120) in 3 patients with IBM. Three patients were responsive to immunosuppressive therapies with mild improvement of clinical strength grading [all sarcoid myopathy (patients 2, 6, and 9)] and eight were refractory [4 sarcoid myopathy (patients 1, 3, 4 and 7) and 4 IBM (patients 10, 12, 13 and 15)]. Furthermore, patients 10 and 12 developed clinical progression to a severe grade of weakness with impaired ambulation and patient 10 eventually was wheelchair dependent. Supplementary Table 3 compares key clinical and pathological features between treatment responsive and treatment refractory patients. Although finger flexor weakness and rimmed vacuoles were observed only in treatment refractory group and congophilic inclusions were observed in 7 of 8 treatment refractory patients (4 sarcoid myopathy and 3 IBM), the lack of significant differences between both groups could be due to a small sample size. Congophilic inclusions were also observed in one sarcoid myopathy patient who slightly improved with immunotherapy (patient 9). A follow-up EMG at 16 months from initial presentation in patient 9 revealed progression of myopathic changes on needle EMG despite the marginal improvement of muscle strength noted on the exam.

Table 2
Characteristic clinical and laboratory findings in granulomatous myopathy subgroups.

Characteristic	Sarcoid myopathy ($N=9$)	IBM ($N=6$)	P-value [§]	Granulomatous myopathy, indeterminate type ($N=1$)
Clinical				
Median age at diagnosis, years,(range)	67 (38–76)	64 (52–82)	NS	47
Median symptom duration, months (range)	12 (4–120)	54 (24–120)	NS	108
Weakness pattern				
Limb girdle	2	1	NS	–
Proximal predominant	1	2	NS	–
Distal predominant	3	2	NS	1
Proximo-distal	3	0	NS	–
None	0	1	NS	–
Asymmetric weakness	2	3	NS	–
Finger flexor weakness	0	4	0.01	–
Neck weakness	6	4	NS	
Flexor	1	3		–
Extensor	3	0		–
Both flexor and extensor	2	1		–
Myalgia	5	2	NS	–
Focal muscle hypertrophy	2	0	NS	–
Dysphagia	4[a]	2	NS	–
Dyspnea	4	1	NS	–
Peripheral neuropathy	1	2	NS	–
Laboratory				
HyperCKemia	3	3	NS	1
Median CK, times upper limit of normal (range)	4.3 (2–4.5)	3 (2–7)	NS	2.6
Number of patients with elevated ACE level (number of patients tested)	5 (8)	0 (4)	NS	0(1)
Median ACE level, U/L (range)[b]	77.5 (3–282)	18 (1–46)	NS	39

ACE, angiotensin converting enzyme; CK, creatine kinase; IBM, inclusion body myositis; NS, not significant.
[§] Wilcoxon rank sum test for continuous data, Fisher exact test for dichotomous variables.
[a] cricopharyngeus hypertrophy observed on swallow evaluation in patients 5 and 9.
[b] Normal: 7–46 U/L.

4. Discussion

4.1. Clinical features

Our cohort represents one of the largest cohorts of non-caseating granulomatous myopathy reported to date. The most common cause of non-caseating granulomatous myopathy in our patients is sarcoidosis (56%), followed by IBM (38%) and granulomatous myopathy of indeterminate cause (6%). The frequency of intramuscular granulomas in IBM is estimated at 1.09% (6 of 550 patients) in our myopathology database, which is much lower than previously reported (4 of 15 patients with IBM in one series) [11]. Two-thirds of our IBM patients had other diagnostic features of systemic sarcoidosis (3 probable and 1 definite). Coexisting IBM and sarcoidosis has been rarely reported [12,13]. Our findings further emphasize the overlapping features between sarcoid myopathy and IBM.

Skeletal muscle granulomas are common in patients with systemic sarcoidosis, but only a small proportion of patients develop symptomatic sarcoid myopathy [22,23]. Myopathy was the initial manifestation of sarcoidosis in 6 of 9 sarcoid myopathy patients in our cohort, which is in contrast to a prior study showing most sarcoid myopathy patients to have a prior diagnosis of sarcoidosis before myopathy onset [16]. Symmetric proximal lower limb weakness is considered a common presentation of symptomatic sarcoid myopathy, while predominant distal weakness is more common in isolated granulomatous myopathy [15,16]. In contrast to this, 5 of our 9 sarcoid myopathy patients had unusual presentations, including predominant axial, bulbar or distal weakness. Dysphagia was reported to be a common feature (70%) of granulomatous myopathy regardless of the underlying diagnosis in one series [15], but was identified in only rare patients with isolated granulomatous myopathy and in none of the sarcoid myopathy patients in another cohort [16]. In our series, 4 of 9 sarcoid myopathy patients and 2 of 6 IBM patients developed dysphagia.

As shown in Table 2, there are no significant differences in clinical features between patients with sarcoid myopathy and IBM patients featuring skeletal muscle granulomas, except for finger flexor weakness. Although 3 of our 9 sarcoid myopathy

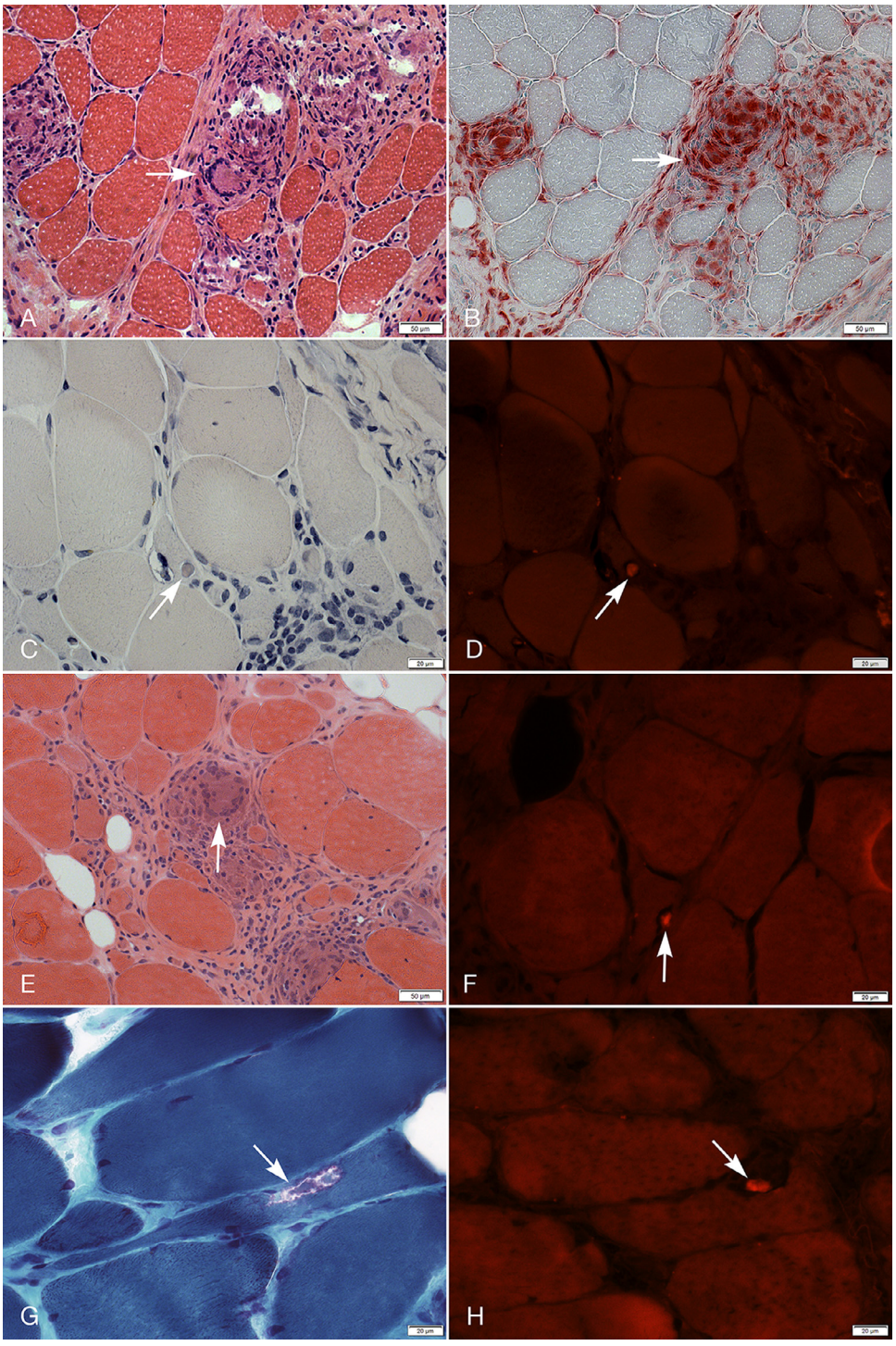

Fig. 2. Histopathologic features of patient 3 (A–D) and patient 15 (E-H). (A–D) Patient 3 (definite sarcoid myopathy) (A) Hematoxylin and eosin (H&E) staining showing granulomas in endomysium with multinucleated giant cells (arrow). (B) Acid phosphatase (AP) staining highlighting epithelioid cells (arrow). (C &D) Muscle fiber featuring a non-rimmed vacuole and a sarcoplasmic congophilic deposit (arrow) in Congo red stain viewed in bright field (C) and under rhodamine optics (D). (E-F) Initial muscle biopsy of patient 15 (pathologically defined IBM). (E) H&E staining showing granulomas in endomysium with multinucleated giant cells (arrow). (F) Sarcoplasmic congophilic deposit in Congo red stain viewed under rhodamine optics (arrow). (G-H) Repeat biopsy of patient 15 (2 years following initial biopsy). (G) Gomori Trichrome stained sections showing a rimmed vacuole (arrow). (H) Sarcoplasmic congophilic deposit in Congo red stain viewed under rhodamine optics (arrow).

Table 3
Myopathologic features of granulomatous myopathy subgroups.

Characteristic	Sarcoid myopathy ($N=9$)	IBM ($N=6$)	$P^{\S}$	Granulomatous myopathy, indeterminate ($N=1$)
Granuloma number per LPF, median (range)	2 (0.4–7)	0.67 (0.4–2.8)	NS	2
Largest granuloma size (mm^2) [a], median (range)	80.95 (19.63–600.53)	102.05 (23.55–251.2)	NS	176.63
Granuloma location				
Perimysium	1	0	NS	
Endomysium	5	5	NS	
Both endomysium and perimysium	3	1	NS	
undetermined	0	0		1
Multinucleated giant cells present	6	3[b]	NS	1
Inflammation outside granuloma	7	6	NS	0
Perimysium	1	1		–
Endomysium	3	3		–
Both endomysium and perimysium	3	2		–
Invasion of non-necrotic fibers (autoaggressive inflammation)	1[c]	3	NS	0
Number of muscle fibers with autoaggressive inflammation per LPF, median (range).	0.44	1.33 (0.25–2.29)	NS	–
Muscle fiber splitting	4	4	NS	1
Muscle fiber necrosis	9	6	NS	0
Rimmed vacuoles	0	4[d]	0.01	0
Non-rimmed vacuoles	1	0	NS	0
Cytochrome c oxidase-negative fibers present	6[e]	5	NS	0
Number of cytochrome c oxidase-negative fibers per LPF, median (range)	4.25 (2–15.5)[f]	2 (1.25–13.3)	NS	–
Congophilic inclusions present	6	5[g]	NS	0
Number of muscle fibers with congophilic inclusions per LPF, median (range)	2.6 (0.5–17.5)	3.75 (1.3–25.6)	NS	–

IBM, inclusion body myositis; LPF, low power field; NS, not significant.

§ Wilcoxon rank sum test for continuous data and Fisher exact test for dichotomous data.

[a] Measured as area of oval where area = a x b x ¶; a = major radius (distance from center to farthest edge), b = minor radius (distance from center to closest point on edge), ¶ = 3.14.

[b] Patients 10, 11, and 13.

[c] Patient 9.

[d] Rimmed vacuoles present in repeat muscle biopsy in patients 13 and 15 on 10 year and 2 year follow up, respectively.

[e] Four patients also had sarcoplasmic congophilic inclusions.

[f] Patients 1, 2, 4, 5, 8, and 9.

[g] Congophilic deposits present in repeat muscle biopsy in patient 13.

patients had distal weakness, none of them had finger flexor involvement. Finger flexor weakness was observed only in IBM patients. This observation highlights the importance of evaluating finger flexor strength in granulomatous myopathy patients to distinguish IBM from sarcoid myopathy, which could potentially spare patients from unnecessary exposure to immunosuppressive therapies.

Of interest, patient 12 had a prior diagnosis of anti-mitochondrial antibody-associated, non-granulomatous, inflammatory myopathy and subsequent biopsy showed all canonical features of IBM plus non-caseating granulomas. Granulomatous myopathy has been described in 6 of 24 patients with anti-mitochondrial antibody-associated inflammatory myopathy but none of them had IBM [8].

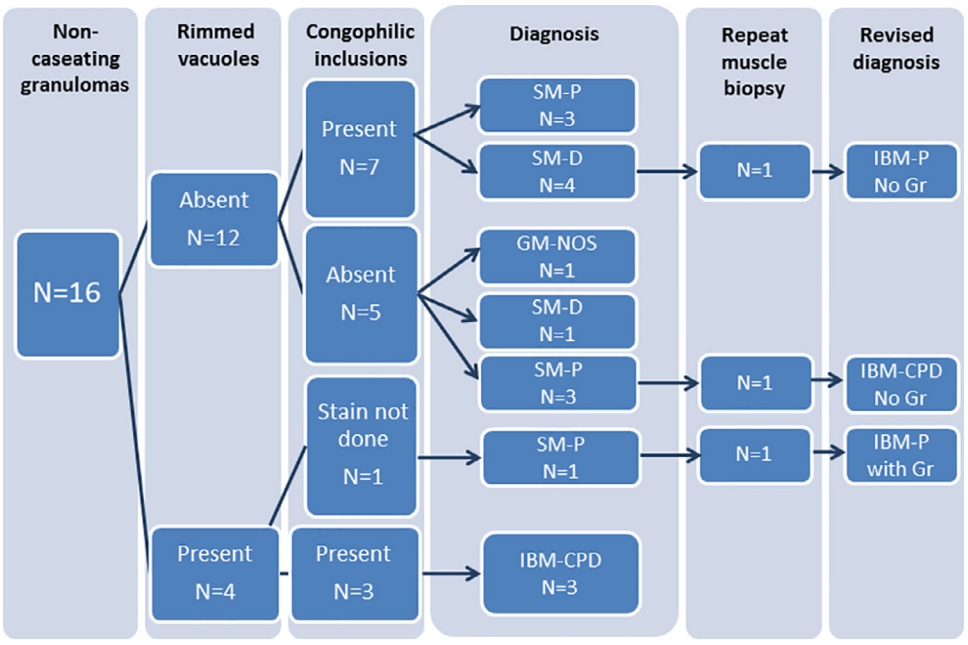

Fig. 3. Myopathologic features in 16 patients with non-caseating granulomas showing evolution of diagnoses from sarcoid myopathy to inclusion body myositis in three patients. GM-NOS, granulomatous myopathy not otherwise specified; Gr, granuloma; IBM-CPD, clinico-pathologically defined inclusion body myositis; IBM-P, pathologically defined-inclusion body myositis; SM-D, definite sarcoid myopathy; SM-P, probable sarcoid myopathy.

4.2. Myopathologic features

An interesting finding was the detection of congophilic inclusions in 6 sarcoid myopathy patients, one of whom also had autoaggressive inflammation. None of these patients had the classic weakness pattern of IBM; therefore, they do not fulfill the ENMC diagnostic criteria of IBM [19]. The evolution of sarcoid myopathy to IBM has been reported in a few cases in the literature, albeit without quantitative descriptions of key pathologic findings [12,24]. Whether our 6 sarcoid myopathy patients featuring congophilic inclusions will eventually develop IBM cannot be determined without longitudinal clinical and detailed myopathologic studies.

All our IBM patients featured the three canonical pathological findings of IBM on initial or repeat muscle biopsies; granulomas coexisted in the same muscle biopsy in all but two patients (patients 13 and 15 described above). Sakai and colleagues described indistinguishable myopathologic features between IBM with and without granulomas (apart from the presence of granulomas) and none of their IBM patients with granulomas had multinucleated giant cells [11]. These findings contrast to the detection of multinucleated giant cells in 3 of our patients with clinico-pathologically defined IBM, 2 of whom had no coexisting sarcoidosis, suggesting that underlying mechanisms regulating giant cell and granuloma formation in IBM could be similar to those described in sarcoid myopathy [25].

4.3. Treatment outcomes

Majority of our patients were refractory to immunosuppressive therapy, which could be in part due to a referral bias. Such patients may constitute a greater diagnostic and therapeutic challenge and hence are more likely referred to a tertiary center for evaluation. In our cohort, there are 3 diagnostic features that may predict poor treatment outcomes in patients with granulomatous myopathies: (1) finger flexor weakness, (2) rimmed vacuoles and (3) sarcoplasmic congophilic deposits.

Finger flexor weakness and rimmed vacuoles were present only in IBM, but not in any of our sarcoid myopathy patients. All 4 IBM patients with intramuscular granulomas, 3 of whom also had coexisting sarcoidosis, did not respond to immunosuppressive therapy. The poor treatment outcome in our IBM patients with intramuscular granulomas is similar to what previously reported [11]. Previous case series showed that distal weakness occurred more frequently in treatment-refractory granulomatous myopathy patients [15,17], although finger flexor involvement was not consistently mentioned in these reported patients with distal weakness. Larue and colleagues described 4 granulomatous myopathy patients with finger flexor weakness partially responded to corticosteroids, but none of their patients had rimmed vacuoles or congophilic inclusions [26]. Among our 7 sarcoid myopathy patients treated with immunosuppressive therapy, 4 were refractory to treatment; all refractory sarcoid myopathy patients had sarcoplasmic congophilic deposits, but no finger flexor weakness. Therefore, sarcoplasmic congophilic inclusions maybe a stronger predicting factor of poor treatment outcome compared to finger flexor weakness or rimmed vacuoles.

Although 1 of our 3 treatment-responsive sarcoid myopathy patients also had sarcoplasmic congophilic inclusions, it is important to note that this particular patient (patient 9) was followed up only for short period of time and his follow-up

EMG showed progression of myopathic changes with clinical improvement being very marginal. A possibility of sarcoid myopathy converting to IBM in this patient cannot be excluded without long-term follow-up given temporary responses to immunosuppressive agents are not uncommon in IBM [27].

4.4. Conclusion

We show that IBM is unexpectedly the second most common cause of myopathies featuring non-caseating granuloma after sarcoidosis, accounting for approximately one-third of patients. IBM with intramuscular granulomas is clinically indistinguishable from IBM without intramuscular granulomas, although some may have coexisting sarcoidosis. Two-thirds of our IBM patients with intramuscular granulomas had coexisting systemic sarcoidosis, and two-thirds of our sarcoid myopathy patients were also found to have sarcoplasmic congophilic inclusions. Our study suggests the intricate link between sarcoidosis and IBM. Patients with congophilic inclusions irrespective to final diagnosis, IBM or sarcoid myopathy, were more likely to be refractory to immunosuppressive therapy. Distal weakness can occur in either sarcoid myopathy or IBM, but finger flexor involvement is more suggestive of IBM. Careful examination of finger flexor strength and search for congophilic inclusions or rimmed vacuoles in patients with granulomatous myopathy could be very helpful in distinguishing IBM from sarcoid myopathy, and also in identifying a subset of patients with granulomatous myopathy that are likely to be unresponsive to immunotherapy when they have not yet fulfilled the diagnostic criteria of clinicopathologically defined IBM. Definite conclusions regarding clinical and myopathologic predictors of treatment outcomes are limited by the small number of patients in this retrospective cohort and only larger prospective, multi-center studies would allow more accurate affirmations in this respect. Such studies should also incorporate histologic markers of protein accumulation (p62, SMI-31, TDP-43, and ubiquitin) and anti-cN-1A antibody as the potential prognostic factors.

Acknowledgements

We thank Dr. Andrew Engel for facilitating the myopathology database search for granulomatous myopathy.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2018.10.007.

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