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Symptomatic muscular sarcoidosis

Lessons from a nationwide multicenter study

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Abstract

Objectives

To describe clinicopathologic features of muscular sarcoidosis and the associated sarcoidosis phenotype through a nationwide multicenter study.

Methods

Patients were included if they had histologically proven sarcoidosis and symptomatic muscular involvement confirmed by biological, imaging, or histologic examinations.

Results

Forty-eight patients (20 males) were studied, with a median age at muscular symptoms onset of 45 years (range 18–71). Four patterns were identified: a nodular pattern (27%); smoldering phenotype (29%); acute, subacute, or progressive myopathic type (35%); and combined myopathic and neurogenic pattern (10%). In all patterns, sarcoidosis was multivisceral with a median of 3 extramuscular organs involved (mostly lungs, lymph nodes, eyes, and skin) and a prolonged course with long-term use of corticosteroids and immunosuppressive drugs. Muscular patterns differed according to clinical presentation (myalgia, nodules, or weakness), electromyographic findings, muscular MRI, and response to sarcoidosis treatment. The myopathic and neuromuscular patterns were more severe.

Conclusion

This nationwide study of muscular sarcoidosis allowed the identification of 4 patterns of granulomatous myositis, which differed by phenotypes and the clinical course.

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Glossary

mRS = modified Rankin score.

Sarcoidosis is a multisystemic disease of an unknown cause characterized by the presence of noncaseating granulomas in various organs.[1,2] Clinical muscular involvement is rare, and few series have been described.[3–6] This contrasts with the relatively high frequency of a nonsymptomatic presence of granulomas in muscles from patients with sarcoidosis as revealed by autopsy studies.[7] Three clinical patterns of muscular sarcoidosis have been described[3,8,9]: a nodular form occurring in young adults, an acute myositis presentation, and a pseudomyopathic form seen in older patients. In previous studies, muscular sarcoidosis had poor outcomes, and permanent motor deficit was frequent.[3,10,11] However, data on long-term outcomes of this condition are lacking.

We therefore conducted a nationwide retrospective study to describe clinical, biological, radiologic presentations of muscular sarcoidosis and long-term outcomes.

Methods

We performed a nationwide retrospective multicenter study (2000–2015) including patients with (1) clinical and radiologic presentation consistent with sarcoidosis; (2) histologic presence of noncaseating granulomas; (3) exclusion of other causes of granulomas (all patients underwent an exhaustive search for mycobacterial agents and other causes of infections, hematologic proliferations, and cancers); (4) clinical muscular involvement defined by myalgia and/or a Muscular Research Council score <5 in at least 1 tested muscle without an alternative cause; and (5) at least 1 of the following criteria: creatine kinase enzymes > 2N, myopathic pattern in electrophysiologic studies, muscular inflammation on MRI, multifocal muscular hypermetabolism in ^{18}fluorodeoxyglucose positron emission tomography scan and/or granuloma in muscular biopsy. Exclusion criteria were data insufficiency. The patients in whom inclusion body myositis was finally diagnosed were excluded from this cohort study. The patients were recruited through local databases among the participants of the "Groupe Sarcoïdose Francophone" (a French research network working on sarcoidosis and other granulomatous diseases). Detailed information about screening and excluded patients is provided as supplemental material (links.lww.com/NXI/A42).

The study was conducted in compliance with the Good Clinical Practice protocol and the Declaration of Helsinki Principles. According to the current French Legislation (Loi Jardé 2016 and its subsequent amendments legifrance.gouv.fr/affichTexte.do;jsessionid=D8DE76AD02196EE756E078-C9212A0C6E.tpdila13v_3?cidTexte=JORFTEXT000032719520&categorieLien=id), an observational and retrospective study that does not change the routine management of patients does not need to be declared to the local ethics board.

The Fisher exact test was used to compare qualitative variables, and the Kruskal-Wallis test was used to compare quantitative variables. All tests were 2-sided, and $p < 0.05$ was considered statistically significant. The analyses were conducted with GraphPad Prism Version 6.0 (GraphPad software, La Jolla, CA).

Results

Patients' characteristics

Forty-eight patients, 28 women and 20 men with median age at muscular symptoms onset of 45 years (range 18–75 years), were included in the analysis. Their demographic and clinical characteristics are detailed in table 1. All patients had histologic evidence of noncaseating granulomas and a symptomatic muscular involvement. Forty patients had a muscular biopsy (figure S1, links.lww.com/NXI/A41) and thus had a definite neurosarcoidosis, and 8 a probable neurosarcoidosis according to the Zajicek criteria.[12]

General characteristics of symptomatic muscular sarcoidosis

In patients with symptomatic muscular involvement, sarcoidosis was characterized by a multivisceral involvement with a median of 3 extramuscular localizations per patient. The most frequent localizations concerned the lungs, lymph nodes, skin, and eyes (table 1). Moreover, the heart, CNS, and the skeleton were unexpectedly frequently involved. The outcome was remarkably chronic, and the patients received a protracted treatment (almost all patients were still treated at the end of follow-up, which had a median duration of 6 years).

Patterns of symptomatic muscular sarcoidosis

According to the historical classification of muscular sarcoidosis, 13 patients had a "nodular" presentation, 16 a "myopathic" presentation, 1 an "acute" presentation of muscular sarcoidosis, and 18 patients were not classified. Thus, we identified 4 patterns of muscular sarcoidosis. These patterns included a nodular, a smoldering, a myopathic, and a combined myopathic and neurogenic pattern. The clinical, biological, and imaging data are detailed in tables 1 and 2. The definitions of these patterns are detailed below but briefly, the presence of motor deficit classified the patient as "myopathic," the presence of nodular lesions without motor deficit as "nodular," and the absence of nodular lesions and motor deficit as "smoldering." Moreover, the presence of a neurogenic pattern in electrophysiological studies, in addition to muscular involvement,

Table 1 Demographic and clinical characteristics of the patients

Median (range) or n (%)	All (n = 48)	Nodular form[a] (n = 13)	Smoldering form (n = 14)	Myopathic form[a] (n = 17)	CNM form (n = 5)	*p* Value
Sex (M/F)	20M/28F	8M/5F	7M/7F	6M/11F	0M/5F	—
Afro-American	16 (33%)	7 (54%)	3 (21%)	7 (41%)	0	—
Age at sarcoidosis diagnosis, y	42 (18–77)	34 (22–60)	45.5 (18–65)	38 (19–77)	64 (43–68)	0.02
Age at muscular involvement, y	45 (18–71)	31 (22–60)	49.5 (18–64)	47 (19–68)	64 (53–71)	0.005
Muscular involvement						
At onset	31 (65%)	11 (85%)	7 (50%)	11 (65%)	3 (60%)	—
During follow-up	17 (35%)	2 (15%)	7 (50%)	6 (35%)	2 (40%)	—
Time from sarcoidosis onset to muscular signs, y	4 (0.2–28)	1.6 (0.2–3)	4 (1–9)	9 (3–20)	14.1 (0.2–28)	—
Sarcoidosis involvement						
Lung	38 (79%)	10 (77%)	9 (64%)	16 (94%)	4 (80%)	—
Lymph nodes	37 (77%)	9 (69%)	11 (79%)	15 (88%)	3 (60%)	—
Skin	20 (42%)	7 (54%)	5 (36%)	8 (47%)	1 (20%)	—
Liver/spleen	10 (21%)	1 (8%)	3 (21%)	6 (35%)	0	—
Heart	17/45 (38%)	5/12 (42%)	5/13 (38%)	7/17 (41%)	1/4 (25%)	—
Skeletal	7 (15%)	1 (7%)	5 (36%)	1 (6%)	0	—
Eye	17 (35%)	3 (23%)	7 (50%)	6 (35%)	1 (20%)	—
Kidneys	4 (8%)	1 (8%)	0	3 (17%)	0	—
CNS	4 (8%)	1 (8%)	2 (14%)	0	1 (20%)	—
Clinical symptoms and signs at onset						
Motor deficit (MRC)[b]	21 (44%)	0	0	17 (100%)	4 (80%)	—
Myalgias	36 (75%)	11 (85%)	14 (100%)	10 (59%)	2 (40%)	—
Nodular lesions	13 (27%)	13 (100%)	0	1 (6%)	0	—
Amyotrophy	4 (8%)	0	0	3 (17%)	1 (20%)	—
Modified Rankin score (onset), median (range)	2 (1–4)	2 (1–3)	1 (1–3)	3 (2–4)	3 (1–4)	<0.0001

Abbreviations: CNM = combined neurogenic and myopathic; LL = lower limbs; MRC = muscle research council; UL = upper limbs; y = years.
The modified Rankin score (mRS) (0, no symptoms; 1, no significant disability despite symptoms; 2, slight disability, unable to perform all previous activities but able to look after without assistance; 3, moderate disability, requiring some help but able to walk without assistance; 4, moderately severe disability, unable to walk without assistance; 5, severe disability, incontinent, and requiring constant nursing; and 6, dead) was evaluated at baseline (first evaluation of muscular symptoms) and at the last visit.
[a] One patient appears in these 2 columns because he had a nodular pattern followed 2 years later by a myopathic pattern. To evaluate motor deficit, the MRC scale was used (0, noncontraction; 1, trace of contraction; 2, active movement with gravity eliminated; 3, active movement against gravity; 4, active movement against gravity and resistance; and 5, normal power). Motor deficit was defined by an MRC score <5 in at least 1 upper or lower limb.
[b] When the 2 sides were not similar, the lowest MRC score was taken.

classified the patient in the "combined myopathic and neurogenic" group. Among the myopathic pattern, we observed an acute (when the onset of symptoms was <48 hours), a subacute (48 hours–1 month), and chronic form (if the onset of symptoms was ≥ 1 month).

The nodular pattern was defined by the presence of clinical muscular palpable nodules, myalgias (85%), but no motor deficit. Muscular MRI was almost always abnormal when performed (83%), whereas, conversely, electromyographic studies had a lower tendency to detect myopathic changes in this presentation (normal in 60% of cases). This pattern was frequently seen at the onset of the disease (85%), with the onset of muscular symptoms in young patients (median 31 years), often of Afro-American origin (54%). Cutaneous involvement of sarcoidosis was particularly frequent (54%).

The smoldering pattern referred to patients with constant myalgias but without nodules, motor deficits, or amyotrophy. Muscular MRI was frequently normal (67% of cases). Patients were rarely Afro-American (21%), and relatively old at sarcoidosis diagnosis (median 45.5 years). Muscular

Table 2 Laboratory, imaging, electrophysiologic, and histologic data

	All (n = 48)	Nodular form[a] (n = 13)	Smoldering form (n = 14)	Myopathic form[a] (n = 17)	CNM form (n = 5)
Elevated CK					
n (%)	20/44 (45%)	6/11 (55%)	6/13 (46%)	9/16 (56%)	0/4
Level[b], median (range)	620 (250–7,000)	363 (250–1,300)	1,050 (451–1,500)	1,018 (286–7,000)	
Abnormal muscular MRI	16/19 (84%)	5/6 (83%)	1/3 (33%)	10/10 (100%)	0/0
Hyper T2	6	3	1	2	
Gadolinium enhancement	10	3	0	7	
Other changes	7	3	0	4	
Abnormal electromyogram	29/34 (85%)	3/5 (60%)	8/10 (80%)	14/15 (93%)	5/5 (100%)
Myopathic changes	25	2	7	14	2
Other abnormalities	7	1	1	0	5
^{18}FDG PET scan	6	2	3	1	0
Muscle hypermetabolism	2 (33%)	0	2	0	
Muscle biopsy	40/48	10/13	10/14	16/17	5/5
Granulomas	40	10	10	16	5
Other changes	4	0	0	0	4

Abbreviations: CK = creatine kinase; CNM = combined myopathic and neurogenic; PET = positron emission tomography.
[a] One patient appears in these 2 columns because he had a nodular pattern, followed 2 years later by a myopathic pattern.
[b] Median CK levels of patients with elevated CK levels.

involvement occurred during follow-up of sarcoidosis in 50% of cases, with a median time from sarcoidosis onset to muscular signs of 4 years. Skeletal (36%) and ophthalmic (50%) involvements were remarkably frequent in this presentation.

The myopathic pattern was defined by the presence of motor deficit with myalgias in 60% of cases. Electrophysiologic studies showed myopathic changes in 93% of cases. Motor deficit was usually proximal but 2 patients had a predominant distal pattern and one had a predominant involvement of upper limbs with bicipital deficit. We observed 3 cases (18%) with an acute onset of muscular symptoms (1 at the onset of sarcoidosis and 2 during the follow-up of a previously diagnosed sarcoidosis) and 14 (82%) with a subacute or progressive (or chronic) onset. This pattern occurred sometimes many years after sarcoidosis diagnosis (median 9 years). Thoracic involvement was particularly frequent (94%). Two patients had hypercalcemia.

Finally, the combined myopathic and neurogenic pattern was identified in 5 patients based on the electrophysiologic profile, which showed pure motor (n = 2), sensorimotor (n = 1), sensory (n = 1), or pluriradicular (n = 1) neuropathy, symmetrical (n = 3) or asymmetrical (n = 2), with predominance in the lower limbs (n = 4) or upper limbs (n = 1) without an alternative cause. All these patients had granulomas in muscular biopsy (see below). The electromyogram also displayed myopathic changes in 2 cases and abnormal spontaneous activity in 2 cases. The identification of this pattern was confirmed by muscular biopsy findings. In 2 patients, biopsies showed the presence of granuloma in the nerve and muscle. In 2 patients, it showed perivascular granulomas with lymphocytic infiltration of the vessels, with fibrinoid necrosis in 1 case. In the last case (corresponding to the polyradicular pattern), the nerve was not biopsied. Muscular biopsy showed diffuse granulomas. This patient also had pleocytosis in cerebrospinal fluid.

Follow-up, treatments, and outcomes

The median follow-up duration was 6 years (range 1–27). Therapeutic regimens and clinical course are presented in table 3. Thirty patients were treated with steroids alone as a first-line therapy. All experienced a degree of improvement (partial or complete), except 1 patient who had a worsening of the motor deficit. For this patient, methotrexate was added allowing partial remission.

The nodular pattern of all but 1 patient had a modified Rankin score (mRS) of 0 at the end of follow-up. The nodular pattern was characterized by a high rate of relapsing-remitting course, with 54% having more than 1 flare-up during the follow-up. Likewise, these patients were frequently still undergoing treatment with an immunosuppressive drug at the end of follow-up. The smoldering pattern typically had a monophasic course without relapses (71%). Immunosuppressive

Table 3 Follow-up and treatments

	All (n = 48)	Nodular form[a] (n = 13)	Smoldering form (n = 14)	Myopathic form[a] (n = 17)	CNM form (n = 5)	*p* Value
Follow-up, median (range)	6 yrs (1–27)	9 yrs (1–23)	4 yrs (1–19)	9 yrs (1–27)	4 yrs (2–5)	—
Treatments						
Steroids	46 (96%)	12 (92%)	14 (100%)	17 (100%)	4 (80%)	—
Hydroxychloroquine	14 (29%)	3 (23%)	8 (57%)	3 (17%)	0	—
Immunosuppressive drug[b]	29 (60%)	7 (54%)	9 (64%)	11 (64%)	3 (60%)	—
Methotrexate	27 (56%)	6 (46%)	8 (57%)	11 (64%)	2 (40%)	—
Azathioprine	5 (10%)	2 (15%)	2 (14%)	1 (6%)	0	—
Mycophenolate	7 (15%)	1 (8%)	3 (21%)	2 (12%)	2 (40%)	—
Cyclophosphamide	7 (15%)	1 (8%)	2 (14%)	3 (18%)	2 (40%)	—
TNFα antagonists	3 (6%)	1 (8%)	2 (14%)	0	0	—
Muscular relapses						
1 flare	31 (65%)	6 (46%)	10 (71%)	10 (59%)	5 (100%)	—
>1 flare	14 (29%)	7 (54%)	4 (29%)	4 (24%)	0	—
Progressive disease	3 (6%)	0	0	3 (18%)	0	—
Last visit						
Steroids	39 (81%)	8 (61%)	13 (93%)	17 (100%)	4 (80%)	—
Immunosuppressive drug	18 (38%)	6 (46%)	2 (14%)	6 (35%)	3 (60%)	—
Modified Rankin scale (end of follow-up), median (range)	0 (0–4)	0 (0–2)	0 (0–1)	1 (0–4)	3 (0–3)	<0.0001

Abbreviation: CNM = combined myopathic and neurogenic.
[a] One patient appears in these 2 columns because he had a nodular pattern, followed 2 years later by a myopathic pattern. A flare was defined by an increase of symptoms or worsening of biological or imaging data requiring an increase in steroids above 20 mg/d. A progressive disease was defined by a progressive worsening of symptoms and/or biological and/or imaging data without a remission phase.
[b] At least one among methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, or TNFα antagonists.

drugs were less frequently used (14%). Hydroxychloroquine was used in 8 cases, with efficacy against myalgias in 6 cases (75%). The myopathic presentation was characterized by a progressive pattern in 18% of cases, despite corticosteroid treatment in all patients. Finally, the combined myopathic and neurogenic pattern was characterized by frequent sequelae as demonstrated by a higher mRS at the end of follow-up.[13] Of note, 1 patient had a nodular pattern, followed 2 years later by a myopathic pattern.

Discussion

Symptomatic muscular sarcoidosis is a rare condition observed in association with a multivisceral involvement of sarcoidosis, a protracted course and the need for long-duration treatments. This is in accordance with other localizations of neurosarcoidosis.[14–16] Four muscular patterns were individualized according to clinical manifestations, electromyography, MRI, and pathology: nodular, smoldering, myopathic and combined myopathic, and neurogenic patterns. These patterns differed by age of patients and sarcoidosis presentation and outcomes. The nodular pattern, associated with frequent skin involvement, and the combined myopathic and neurogenic pattern, combining nerve and muscle involvements, may reflect the contiguous spreading of granulomas. The myopathic pattern was associated with intrathoracic involvement. The initial and final mRSs were different between groups. Moreover, the nodular or myopathic patterns were more frequently seen in Afro-American patients.

In the literature, granulomatous myositis, which usually occurs in the setting of sarcoidosis, is reported in a few series of more than 10 patients[3–5] and in other smaller studies.[8–11] Asymptomatic granulomatous involvement is reported to be as frequent as 80% in autopsic studies.[7] In our study, all the patients had a symptomatic and multisystemic disease with at least 2 involved organs. However, some patients did not have the classical intrathoracic localization of sarcoidosis. We identified 5 patients with only muscular and heart disease, corresponding to nodular (n = 2), smoldering (n = 1),

myopathic (n = 1), or combined myopathic and neurogenic (n = 1) patterns.

The classification of granulomatous myositis relied until now on the palpable nodular, acute myositis, and chronic myopathy types. However, this classification does not allow integrating all patients. We suggest that the 4 patterns we described could be used to better classify patients with granulomatous myositis and help to guide treatment.

Some rare phenotypes were also described in our study, such as predominant distal or upper limbs involvement, which were rarely reported previously. Vasculitis presentation of neurosarcoidosis was observed in 2 cases in association with muscular involvement.[13]

The course of muscular sarcoidosis differs depending on muscular patterns: the nodular type is readily relapsing-remitting, although the myopathic one may have a progressive course. Thus, patients having a nodular type are commonly prescribed immunosuppressive drugs. We noted that hydroxychloroquine was a useful treatment for smoldering disease, even if this drug may rarely cause muscular damage. Of note, myalgias often responded to hydroxychloroquine.

This study has several limitations. First, the retrospective design and heterogeneity of patients and treatments do not allow drawing conclusions regarding treatment efficacy. The limited number of patients may have influenced the determination of statistical significance for several comparisons.

This study highlighted 4 patterns of muscular sarcoidosis, which differed according to age of patients, sarcoidosis presentation, and outcomes.

Author contributions

All the authors (F. Cohen Aubart, S. Abbara, T. Maisonobe, V. Cottin, T. Papo, J. Haroche, A. Mathian, M. Pha, L. Gilardin, B. Hervier, M. Soussan, P. Morlat, H. Nunes, O. Benveniste, Z. Amoura, and D. Valeyre) contributed to drafting/revising the manuscript for content and study design, as well as analysis and interpretation of the data. F. Cohen Aubart, S. Abbara, T. Maisonobe, L. Gilardin, and H. Nunes contributed to the acquisition of data. F. Cohen Aubart conducted the statistical analysis. T. Maisonobe centrally reviewed the histologic analyses. F. Cohen Aubart, Z. Amoura, and D. Valeyre coordinated the study.

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