Arq Neuropsiquiatr 2001;59(2-B):347-352

SYMPTOMATIC MUSCLE INVOLVEMENT IN NEUROSARCOIDOSIS

A clinicopathological study of 5 cases

Rosana Herminia Scola[1], Lineu Cesar Werneck[2], Daniel Monte Serrat Prevedello[3], Priscila Greboge[3], Fábio Massaiti Iwamoto[4]

ABSTRACT - We report on the clinical course and histopathologic muscle alterations of five patients diagnosed with neurosarcoidosis, who underwent biopsy due to their muscle manifestations. The five patients were females and only one was less than 40 years of age. Proximal muscle weakness was presented by all and only two patients complained of myalgia. Only normal values of serum muscle enzymes were detected. Electromyography revealed diverse findings such as normal, myopathic and neuropathic patterns. Granuloma was not present in one muscle biopsy. Two patients thoroughly recovered by taking only prednisone and one patient required a methotrexate addition for 3 months before becoming asymptomatic. The other two patients received azathioprine, one due to steroid side effects but without a satisfactory evolution, and the other to strengthen the prednisone régime, with excellent results.

KEY WORDS: sarcoidosis, myositis, granuloma, central nervous system diseases.

Envolvimento muscular sintomático na neurossarcoidose: estudo clinicopatológico de 5 casos

RESUMO - Relatamos o curso clínico e as alterações histopatológicas musculares de 5 pacientes com diagnóstico clínico de neurossarcoidose, os quais foram submetidos à biópsia por apresentarem sintomatologia muscular. As cinco pacientes eram do sexo feminino e apenas uma com menos de 40 anos. Todas apresentavam fraqueza muscular proximal e apenas duas pacientes se queixaram de mialgia. Valores normais de enzimas musculares foram encontrados em todos os casos. A eletromiografia identificou vários padrões tal como normal, miopático e neuropático. Apenas uma paciente não apresentou granuloma na biópsia muscular. Das cinco pacientes, duas apresentaram melhora completa apenas usando prednisona. Uma paciente necessitou o acréscimo de metotrexato por 3 meses antes de se tornar assintomática. As outras duas pacientes fizeram uso de azatioprina, uma devido a efeitos colaterais do corticóide mas sem evolução satisfatória, e a outra para reforçar a terapia com prednisona com excelente resposta.

PALAVRAS-CHAVE: sarcoidose, miosite, granuloma, doenças do sistema nervoso central.

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology characterized by the accumulation of T lymphocytes and monocytes in the involved organs, noncaseating granulomas and disorganized architecture of the normal tissue. In some cases Schaumann and asteroid bodies are seen as well[1]. Commonly it affects young adults of both sexes and presents bilateral hilar adenopathy, pulmonary infiltration, and ocular, cutaneous and reticuloendothelial system involvement [2]. Nervous system involvement occurs in less than 10% of the patients with sarcoidosis. However, the incidence of subclinical and undiagnosed neurosarcoidosis is much higher[2, 3]. Neurosarcoidosis has a predilection for the base of the brain, but any portion of the central nervous system (CNS) or peripheral nervous system may be affected [2, 4]. The diagnosis of neurosarcoidosis is facilitated in patients with multisystem sarcoidosis who develop neurological features that include cranial nerve palsies, granulomatous meningitis, hypothalamic and pituitary lesions, spinal cord involvement, progressive multifocal leukoencephalopathy, peripheral neuropathy and myopathy[2, 5]. Furthermore, any of the above-mentioned neurological pre-

Neuromuscular Disease Section, Division of Neurology and Department of Internal Medicine, Hospital de Clínicas, Federal University of Paraná, Curitiba PR, Brazil: [1]Associate Professor of Medicine; [2]Tenured Professor of Medicine, [3]Medical Students who are PIBIC/CNPq Research Scholarship Holders, [4]Neurology resident. Partly financed by a grant from CNPq (Brazil)

Received 27 October 2000, received in final form 12 February 2001. Accepted 14 February 2001.

Dra. Rosana Herminia Scola - Serviço de Doenças Neuromusculares, Hospital de Clínicas da UFPR - Rua General Carneiro 181 / 3° andar - 80069-155 Curitiba PR – Brasil. FAX ++55 41 264 3606. E-mail: scola@hc.ufpr.br

sentations can occur without evidence of pulmonary or other systemic features of sarcoidosis hindering the diagnosis [2,6].

Asymptomatic muscle involvement commonly happens in patients with sarcoidosis varying from 50 to 80% of cases and it is evidenced by an inflammatory process including granulomatous formation in muscle biopsy [7]. Muscle involvement with clinical repercussion is a rare condition and it has already been described in less than 0,5% to 2,3% of the patients diagnosed as being afflicted by sarcoidosis [8,9].

We describe the clinical course and the histopathological findings in 5 patients with a clinical diagnosis of neurosarcoidosis, who underwent muscle biopsy due to the presence of muscle weakness during the course of the disease.

METHOD

Records were searched for patients with a previous clinical diagnosis of neurosarcoidosis who were submitted to muscle biopsy due to muscle weakness, from 1976 to 2000. Seven patients presented the criteria, but two of them had been hospitalized before 1980 and the records could not be accessed. The patients were appraised in the Neuromuscular Disorders Service of the "Hospital de Clínicas" of the "Universidade Federal do Paraná" in Curitiba-Brazil. All clinical records bearing these diagnoses were then individually reviewed and the following data were obtained from all patients: (1) demographic: age at diagnosis, sex; (2) dates of disease onset (first symptom); (3) clinical information relevant to sarcoidosis, including data from clinical history focused on chief complaints, and general/neurological physical examination, which analyzed proximal and distal muscle strength, tonus and reflexes in upper and lower limbs; (4) laboratory values of erythrocyte sedimentation rate (ESR) and levels of serum muscle enzymes, creatine kinase (CK), lactate dehydrogenase (LDH), aldolase (ALD), aspartate aminotransferase (AST) and alanine aminotransferase (ALT); (5) chest radiograph; (6) needle electromyographic (EMG) and (7) histopathological findings in fresh-frozen muscle biopsy, which was submitted to the following staining and histochemical reaction: hematoxilin-eosin, modified Gomori trichrome, oil red O, PAS, cresyl violet, sirus red, NADH-tetrazolium reductase, ATPases pH 4.3, 4.6, 9.4, myophosphorylase, non-specific esterase, alkaline phosphatase, acid phosphatase, succinic dehidrogenase and cytochrome c-oxidase [10,11].

A case was included if the diagnosis of neurosarcoidosis with muscle involvement was accepted after the clinical records had been reviewed. Presence of granuloma or a typical chest x-ray with bilateral hilar lymphadenopathy besides signs and symptoms of neural system involvement were enough to consider a case neurosarcoidosis. Any muscle complaint at the time of diagnosis was considered a clinical muscle involvement. On this way, patients presenting muscle weakness during the treatment with steroids or after use it before the diagnosis were not included in the study. Any feature suggesting another disease excluded the case.

RESULTS

All five patients were female. The mean age of the patients at the time the disease was diagnosed was 40 years, varying from 17 to 53. Table 1 shows the signs and symptoms the patients presented in the course of the disease. All patients reported proximal muscle weakness and only one patient failed to report distal weakness. Myalgia was a complaint of three of the five patients. All patients presented normal values of serum muscle enzymes.

Table 2 shows the results of electromyographic-nerve conduction velocity (EMG-NCV), evidencing a heterogeneity of patterns. Electromyography was normal in one patient. A myopathic pattern was shown in two patients and denervation patterns in two other patients.

The histochemical analysis of the muscle biopsies is shown in Table 4. One biopsy was entirely normal. Noncaseating granuloma (Figs 1, 2) was found in four patients and one presented vasculitis in the biopsy. Type 2 fiber atrophy was present in four patients, whereas type 1 fiber atrophy was found in two. Two patients presented endomysial fibrosis in the biopsy.

All patients received prednisone at the beginning of the treatment in initial doses that varied from 40 to 80 mg/day. Aspects of the treatment and of the course of the disease are shown in Table 3. Two patients thoroughly recovered by taking only prednisone. One patient had an azathioprine addition to the prednisone regime, with an excellent result. Another patient started to use azathioprine after interrupting prednisone due to side effects such as osteoporosis; however, the disease continued following a progressive course. One patient had a methotrexate addition to prednisone for 3 months, with a complete remission of the symptoms.

DISCUSSION

Muscle involvement in patients with sarcoidosis is relatively common. Fifty to 80% of patients with sarcoidosis present granulomas in muscle biopsies, despite the absence of signs and symptoms [7,12]. It seems that most patients with sarcoidosis and muscle involvement by granulomatous inflammation have relatively few signs and symptoms related to muscle disease [8].

Table 1. Clinical presentation of 5 patients with chronic sarcoid myopathy.

Case	Age (years) at diagnosis	Sex	Signs and symptoms	
			Neurologic	Others
1	17	F	• Myalgia • Arthralgia • Headache • Proximal and distal MW • Bilateral recurrent facial palsy • Global diminished DTR	• Bilateral hilar lymphadenopathy
2	41	F	• Myalgia • Malaise • Proximal e distal MW • Global diminished DTR • Stocking-glove numbness	• Cutaneous rash • Sinus tachycardia • LV hypertrophy
3	53	F	• Headache • Back pain • Proximal e distal MW • Global muscle wasting • Distal areflexia in UE and LE • Hypotonia • Stocking-glove numbness	• Fever • Weight loss • Bilateral sensorineural hearing loss L>R
4	49	F	• Myalgia • Proximal e distal MW • Left biceps atrophy • Right thenar eminence and bilateral dorsal interosseous atrophy • Global diminished DTR • Vibration sense diminished in LE	• Weight loss • Sleep disorders • Difficulty of personal relationship
5	40	F	• Arthralgia • Back pain • Dysphagia • Proximal MW • Bilateral recurrent facial palsy • Diminished DTR in LE • Paresthesias of EU and LE	• Fever • Edema • Bilateral hilar lymphadenopathy

F, female; L, left; R, right; DTR, deep tendon reflexes; LE, lower extremities; UE, upper extremities; RLE, right lower extremity; MW, muscle weakness; LV, left ventricle.

Table 2. Electrophysiological studies of 5 patients with chronic sarcoid myopathy.

Case	Study/ results
1	EMG: Bordering on denervation NCV: Sensory-motor multiple mononeuropathy
2	EMG: Myopathic NCV: Sensory-motor multiple mononeuropathy
3	EMG: Chronic and active denervation (different muscles) NCV: Sensory-motor multiple mononeuropathy (mainly sensorial)
4	EMG: Myopathic NCV: Sensory-motor mononeuropathy of median nerve bilaterally
5	Normal

EMG, electromyography study; NCV, nerve conduction velocity study.

Table 3. Treatment and clinical course of 5 patients with chronic sarcoid myopathy

Case	Treatment	Course
1	• Prednisone for 2 years • Methotrexate for 3 months	• Initial Symptoms (IS): 11 years ago • Diagnosis (Dx): 7 years ago • Improved, asymptomatic without medication for 5 years.
2	• Prednisone for 1 year (discontinued after complications) • Azathioprine	• IS: 7 years ago (1993) • Dx: 6 years ago • Progressive disease (stopped walking) • Prednisone discontinued for osteoporosis • Azathioprine decreased (lymphopenia)
3	• Prednisone	• IS: 8 years ago • Dx: 7 years ago • Improved, almost asymptomatic in 2 months (did not return to the outpatient clinic)
4	• Prednisone • Azathioprine	• IS: 16 years ago • Dx: 6 years ago • Improved, asymptomatic without prednisone for 1 year and without azathioprine for 3 years
5	• Prednisone	• IS and Dx for 6 years • Improved after 2 months of treatment. • Discontinued prednisone on her own • Symptoms (dysphagia and arthralgia) reappeared 5 months later • Treatment resumed • Improved, asymptomatic without medication for 3 years

Table 4. Histopathological features of 5 patients with chronic sarcoid myopathy.

Case	Histopathological features of 5 patients with chronic sarcoid myopathy								
	Muscle	Noncaseating Granuloma	Vasculitis	Endomysial Infiltration	Perivascular Infiltration	Atrophic Fibers (ATPase)	Angular Atrophic esterase + fibers	Endomysial Fibrosis	AFB Stain
1	Vastus lateralis	-	-	-	-	-	-	-	-
2	Brachial biceps	+	-	-	+	Type 2	-	-	-
3	Vastus lateralis	+	-	+	+	Type 2	-	+	-
4	Brachial biceps	+	+	-	+	Type 1 and 2	+	+	-
5	Brachial biceps	+	-	-	-	Type 1 and 2	-	-	-

AFB, acid fast bacilli.

Significant and symptomatic muscle involvement in sarcoidosis is rare and was noted in 0,5 to 2,3% of patients [1, 8, 9, 13]. Myopathy can be the initial manifestation of sarcoidosis, but when the diagnosis is confirmed, signs and symptoms of other systems are usually present. Three clinical types of sarcoid myopathy have been described: acute myositis, chronic myopathy and palpable nodules [1, 9, 13-15].

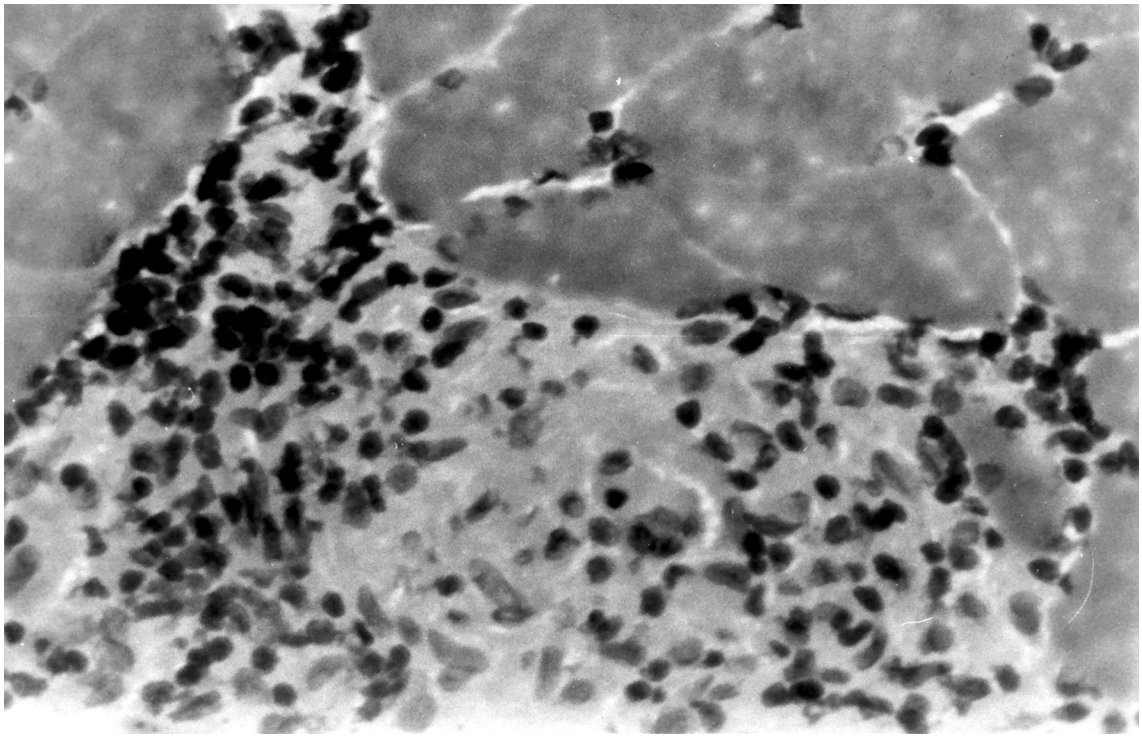

Fig 1. Muscle biopsy specimem from a patient with sarcoidosis presenting a large interstitial granuloma with epithelioid cells. Hematoxilin and Eosin, 400x.

Palpable nodules is the least common type of symptomatic muscle involvement in sarcoidosis and it can cause pain and stiffness with cramps. Weakness is not common during the active phase; however, it may appear later if contractures occur. Acute myositis, another infrequent type of muscle involvement in sarcoidosis, can be clinically indistinguishable from acute polymyositis [8, 15]. Symptoms include proximal muscle weakness, fever and myalgia. Electromyographic studies show unspecific myopathic patterns and creatine kinase values are generally high[14].

Chronic myopathy has been the most frequently reported type of sarcoid myopathy, occurring mainly in older women, and is typically a slow progressive symmetrical weakness involving proximal muscles of the extremities, trunk and neck, that often go on to become muscle atrophy. Distal muscle involvement may be secondary to peripheral neuropathy, which has been well documented in sarcoidosis [13]. Muscle enzymes are usually normal and a myopathic pattern is observed in electromyographic studies. Remissions and exacerbations are noted during the course of the disease[14,15].

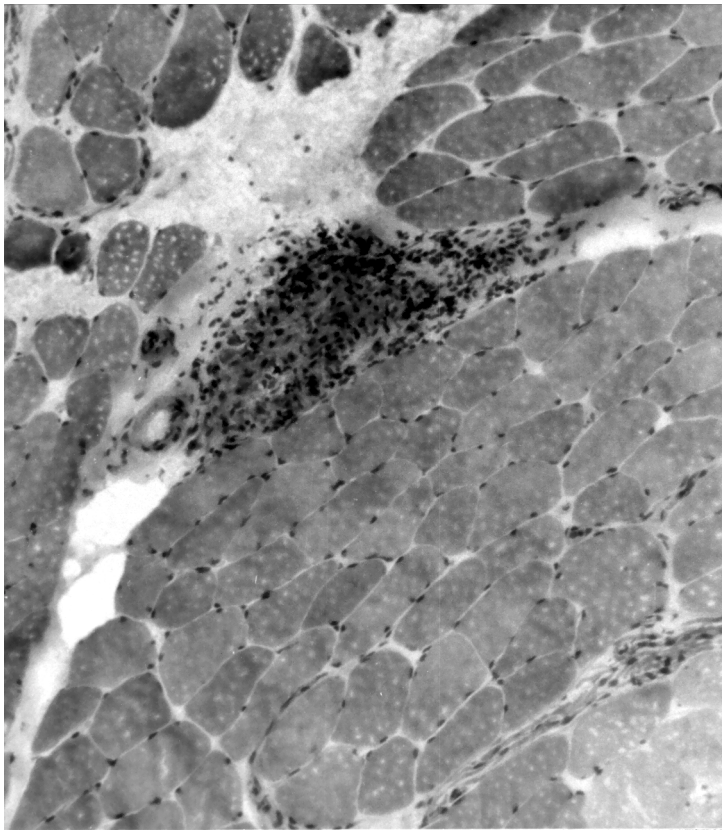

Fig 2. Muscle biopsy specimem from a patient with sarcoidosis presenting granuloma in the perimysium. Hematoxilin and Eosin, 174x.

The five patients presented a diversity of electromyographic findings, such as normal, myopathic

and neuropathic patterns. Most other clinical studies confirm such electromyographic heterogeneity, which is explained by the fact that the EMG had been done during different phases of the disease, including the treatment, when the regeneration of muscle fibers occurs, and by the fact that usually there are mutual muscle and nerve injuries in sarcoidosis[2, 13].

The five reported patients present different clinical manifestations, but they share the same insidious muscle involvement. All cases involve women and four of them are past the age of 40. The only case in which granuloma was not found coincides with the patient less than 40 years old. The fact that granuloma was not found in muscle biopsy does not rule out the clinical diagnosis of sarcoidosis and this situation has been related to the sampling and the time when the patient is submitted to the procedure [13].

Most patients have improved by using prednisone monotherapy with a minimum initial doses that varies from 20 to 80 mg/day in the literature [2, 13]. Prednisone at a dose of 1 mg/Kg is probably a suitable initial dose, since several patients treated with lower doses subsequently suffered relapses [9]. In acute myopathy the response to corticosteroids is good and the course is usually benign. On the other hand, in chronic myopathy the response is unpredictable. Excellent results have been obtained in certain cases, while in others there has been no responses to corticosteroids [13, 15, 17]. In those patients who fail to respond to prednisone therapy and whose conditions continue to deteriorate, other drugs such as cyclophosphamide, cyclosporine, azathioprine and mainly methotrexate should be tried [2, 17].

REFERENCES

1. Jamal MM, Cilursu AM, Hoffman EL. Sarcoidosis presenting as acute myositis. Report and review of the literature. J Rheumathol 1988; 15:1868-1871.
2. Sharma OP. Neurosarcoidosis: a personal perspective based on the study of 37 patients. Chest 1997; 112:220-228.
3. Scott TF. Neurosarcoidosis: progress and clinical aspects. Neurology 1993; 43:8-12.
4. Delaney P. Neurologic manifestations in sarcoidosis: review of the literature, with a report of 23 cases. Ann Intern Med 1977; 87:336-345.
5. Boucher M, Grace J, Java DJ Jr. Sarcoidosis presenting as multiple cranial neuropathies and a parotid mass. Otoryngol Head Neck Surg 1994; 111:652-655.
6. Chapelon C, Ziga JM, Piette JC, et al. Neurosarcoidosis: signs, course and treatment in 35 confirmed cases. Medicine 1990; 69:261-76
7. Silverstein A, Siltzbach LE. Muscle involvement in sarcoidosis. Arch Neurol 1969; 21:235-241.
8. Prayson RA. Granulomatous myositis. Clinicopathologic study of 12 cases. Am J Clin Pathol 1999; 112:63-68.
9. Ost D, Yeldandi A, Cugell D. Acute sarcoid myositis with respiratory muscle involvement. Case report and review of the literature. Chest 1995; 107:879-882.
10. Werneck LC. O valor da biópsia muscular em neurologia. Análise de 290 exames a fresco e pela histoquímica. Rev Bras Clin Terap 1981; 10(supl): 2-22.
11. Werneck LC. Estudo da biópsia muscular e sua relação com enzimas séricas e eletromiografias nas doenças musculares. Tese (Professor Titular) - Setor de Ciências da Saúde, Universidade Federal do Paraná, Curitiba, 1991.
12. Fonseca GA, Baca S, Altman RD. Acute myositis and dermatitis as the initial presentation of sarcoidosis. Clin Exp Rheum 1993; 11:553-556.
13. Wolf SM, Pinals RS, Aelion JA, Goodman RE. Myopathy in sarcoidosis: clinical and pathological study of four cases and review of the literature. Semin Arthritis Rheum 1987; 16:300-306.
14. Matsuo M, Ehara S, Tamakawa Y, Chida E, Nishida J, Sugai T. Muscular sarcoidosis. Skeletal Radiol 1995; 24:535-537.
15. Pettersson T. Rheumatic features of sarcoidosis. Curr Opin Rheumatol 1997; 9:62-67.
16. Hearth-Holmes M, Campbell GD Jr. Muscle weakness, fatigue, and joint pain in a 52-year-old woman. Chest 1995; 108:563-564.
17. Kaye O, Palazzo E, Grossin M, Bourgeois P, Kahan MF, Malaise MG. Low dose metotrexate: an effective corticosteroid-sparing agent in the musculoskeletal manifestations of sarcoidosis. Br J Rheumatol 1995; 34:642-644.