Published in final edited form as:

Muscle Nerve. 2009 February ; 39(2): 234–238. doi:10.1002/mus.21159.

AMYOTROPHIC LATERAL SCLEROSIS AND NEUROSARCOIDOSIS: A CASE REPORT

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Abstract

Amyotrophic lateral sclerosis (ALS) remains a clinical diagnosis without definable biomarkers. The pathomechanism of motor neuron degeneration in ALS has yet to be elucidated. Here we present a case of limb-onset ALS, with autopsy findings of Bunina bodies and skein-like inclusions, as well as sarcoid granulomas predominating among motor neurons. The targeting of the motor neurons by the sarcoid inflammation raises questions regarding the role of cellular immunity in the pathomechanisms for ALS.

Keywords

amyotrophic lateral sclerosis; sarcoidosis; autopsy; ubiquitin; TDP-43

To our knowledge, there have been four case reports of clinical amyotrophic lateral sclerosis (ALS) and sarcoidosis.^{2,7,9,11} Only one of them included an autopsy study that confirmed the coexistence of both diseases, although the sarcoidosis did not have pathological involvement of the nervous system.¹¹ Here we present a case of a 61-year-old woman with autopsy-proven ALS who had a striking sarcoid-granulomatous reaction chiefly at sites of motor neurons in the brain and spinal cord.

CASE REPORT

A 61-year-old woman was evaluated in our center for progressive extremity weakness and gait difficulty. She had a 5-year history of urinary urgency with intermittent incontinence, and a few-month history of paresthesia in her arms. The incontinence worsened in the months prior to our evaluation, possibly due to gait difficulty. Her paresthesia resolved spontaneously. She denied any other central nervous system symptoms. Examination revealed normal mental status, cranial nerves, sensory systems, and coordination. Motor system examination revealed no fasciculations, but muscle tone was increased. Muscle atrophy was present in both the deltoid and intrinsic hand muscles. Formal power testing showed diffuse weakness in the distal arm muscles with strength less than anti-gravity, and moderate weakness in the proximal arm muscles with strength against resistance. Strength in the legs was full except for hip and knee

flexion, which were against resistance. There was pathological hyperreflexia, including a brisk jaw jerk, bilateral Hoffman signs, and ankle clonus. The plantar responses are flexor.

Routine laboratory tests were normal, including complete blood cell counts, routine chemistry, sedimentation rate, rheumatoid factor, and anti-SSA/ SSB (extractable nuclear antigens) antibodies. The antinuclear antibodies (ANA) titer was 1:80 (reference <01:40), speckled pattern. Angiotensin-converting enzyme (ACE) was 69 (reference 8 -52). Chest x-ray from 3 months earlier was normal without hilar lymphadenopathy (LAD). Magnetic resonance imaging (MRI) of the brain and cervical spine was unre-markable. Electromyogram (EMG) and nerve conduction studies obtained 8 months prior to our evaluation showed acute and chronic denervation in left arm myotomes and absent F waves in the ulnar nerve, which was initially thought to suggest left brachial plexopathy. A second EMG obtained 1 month prior to our evaluation showed diffuse fibrillation and fasciculation potentials and chronic motor unit potential reinnervation with reduced motor unit recruitment in four extremities and fasciculation potentials in the thoracic paraspinal muscles. The progression of EMG findings along with the clinical examination suggested that she had probable ALS by El Escorial criteria.³

Because of some atypical features for ALS in her presentation, including transient paresthesia and urinary urgency and incontinence, we obtained visual-and somatosensory-evoked potentials and they were normal. Magnetic resonance spectroscopy showed reduced N-acetylaspartate to creatine (NAA/Cr) ratio in bilateral motor strips in the cortex (right motor strip NAA/Cr = 1.52, left motor strip NAA/Cr = 1.93; lower limit normal = 2.5).⁸ Transcranial magnetic stimulation showed prolonged central conduction times of both arms and legs, as well as prolonged peripheral conduction times in the left arm and both legs. Repeat EMG showed active and chronic denervation in three limbs and thoracic paraspinals, sparing the tongue. Cerebrospinal fluid (CSF) analysis showed 3 white blood cells and 0 red blood cells with normal glucose and protein. The CSF was not tested for IgG index and oligoclonal bands. The patient was started on Riluzole and Baclofen. In subsequent months, she developed increasing spasticity, limb dysfunction, and bulbar palsy along with pseudobulbar affect. Due to her progressive diaphragm insufficiency, the forced vital capacity dropped from 100% at initial evaluation to 76% of predicted value 2 months later and to 49% at 5-month follow-up. She was transferred to hospice care and died 19 months from the onset of limb weakness.

Autopsy determined that the patient most likely died from aspiration pneumonia with mixed flora found in the left lung and a few Klebsiella pneumoniae in the right lung cultures. Sarcoid-type noncaseating granulomas were present in both lungs and hilar lymph nodes. Neuropathology of the brain and spinal cord confirmed the clinical diagnosis of ALS. The nervous system demonstrated degeneration of the pyramidal tracts (Fig. 1A) with more severe abnormality in the spinal cord than in the brainstem and internal capsule, as highlighted by CD68-stained microglia and macrophages. There was also loss of motor neurons and astrocytosis in the motor nuclei of cranial nerves VII and XII with sparing of the oculomotor nucleus. Neuronal loss was present in the ventral horns and was most severe at cervical levels. Sparse surviving motor neurons contained intracytoplasmic Bunina bodies and skein-like inclusions which expressed ubiquitin (Fig. 1B) and TDP-43, strongly supporting the diagnosis of ALS. However, to our surprise, small granulomas were found chiefly at sites of motor neurons, including the precentral gyrus, motor nuclei of cranial nerves (V, VII. and XII), and ventral horns (Fig. 1C). Most granulomas in the precentral gyrus were located around or adjacent to venules, but these lesions were not clearly related to blood vessels in brainstem, spinal cord, or elsewhere. A few granulomas were also found in the putamen and red nucleus, and they were seen rarely in the caudate nucleus, globus pallidus, thalamus, substantia nigra, and medullary tegmentum. Uncharacteristically, the granulomatous lesions were observed rarely in their typical location for neurosarcoidosis, such as the leptomeninges and base of the

telencephalon. Skeletal muscle was severely involved and included large tumor-like granulomas (Fig. 1D).

DISCUSSION

To date, ALS remains a clinical diagnosis of exclusion because it has no identifiable biomarkers. Our patient presented with weakness that appeared to spread from upper to lower extremities, and then involved her oropharyngeal muscles. The disease eventually affected the diaphragm, with evidence for both upper and lower motor neuron dysfunction. Her presentation and clinical course was rather characteristic of ALS, and the diagnosis was confirmed by the neuropathological findings with pyramidal tract degeneration and characteristic motor neuron involvement including Bunina bodies and skein-like inclusions. However, the autopsy finding of sarcoid granulomas in the lungs, lymph nodes, skeletal muscle, and the nervous system was not anticipated. Clinically, the patient did not have the typical features of systemic sarcoidosis, such as skin plaques, facial lupus pernio, anterior uveitis, or hilar lymphadenopathy. Although prior evaluation revealed a slight elevation of ACE levels, this is neither specific nor diagnostic of sarcoidosis.^{5,6} Interestingly, neurosarcoidosis represents about 5%-15% of all sarcoidosis cases, and the diagnosis is made antemortem only 50% of the time.¹⁰ Given the clinical and electrodiagnostic evidence for motor neuron dysfunction in our patient, we did not further investigate the possibility of neurosarcoidosis, as that is also a diagnosis of exclusion.

There have been two case reports of clinical “bulbar ALS,” in whom subsequent studies suggested the patients had sarcoidosis.^{2,9} One of the patients had improved bulbar and limb function in response to prednisone treatment after a lymph node biopsy indicated sarcoidosis.⁹ The “bulbar ALS” patient was later diagnosed as “sarcoid brainstem encephalitis” after autopsy.² Pathologically, this case differs from ours, as the brain and spinal cord did not have histopathological evidence of ALS, such as motor neuron loss, intracytoplasmic Bunina bodies, or ubiquitinated inclusions (pathologist Martin Lammens, personal communication) (Table 1). Both cases highlight the significant overlap in the clinical presentation of neurosarcoidosis and bulbar ALS, and they remind clinicians of the need to maintain a high clinical suspicion for this form of brainstem encephalitis when evaluating patients for bulbar ALS.

There have been two reported cases of ALS and sarcoidosis that coexist in the same patient.^{7,11} One patient with autopsy-proven ALS exhibited sarcoid granulomas in the lungs and muscles with sparing of the meninges, brain, and spinal cord. The other patient had clinical resolution of hilar LAD in response to prednisone treatment, but the motor disorder progressed to a state of severe, diffuse weakness in the subsequent 10 months. No autopsy was performed to determine whether sarcoidosis involved the central nervous system (Table 1). Our patient appears to be the first case of ALS that shows coexisting neurosarcoidosis. Moreover, sarcoid granulomas targeted chiefly the anterior horns, brainstem motor nuclei, and motor cortex.

The etiology of sarcoidosis is not known, but the disorder is thought to result from an immunological response to poorly soluble or insoluble antigen. Epidemiological studies suggest that the disease is likely a consequence of a genetic susceptibility of patients in combination with exposure to an environmental agent.⁵ Although the disorder shows a predilection for lymph nodes, lungs, skin, eyes, and skeletal muscle, it only rarely exhibits tissue specificity as exemplified in the nervous system in this ALS case. Rarely, sarcoid granulomatous lesions appear in skin tattoos or scars of systemic sarcoidosis,^{1,4,12} and they sometimes demonstrate exquisite specificity of the inflammatory response to one pigment of a multicolor tattoo. This rare granulomatous manifestation of sarcoidosis in tattoos suggests possible shared pathomechanisms with this ALS patient. It is possible that the motor neuron degeneration in this case resembled tattoos or scars and triggered a local granulomatous inflammatory reaction to an insoluble material in the setting of sarcoidosis. In addition,

cytokines or other factors arising in the inflammatory cells may have contributed to the degeneration of motor neurons. Clearly, the molecular basis of this interesting phenomenon requires a better understanding of the pathomechanisms of both ALS and sarcoidosis.

Our experience suggests that ALS is a clinical syndrome and that autopsy study is still of paramount importance for confirmation of the diagnosis and furthering understanding of the disease pathology. The rate of autopsy has gradually declined in recent years. However, clinicians must confirm their diagnosis with autopsy even when we are quite confident about the clinical diagnosis.

Acknowledgments

This study was supported by MDA Wings Over Wall Street (HM). The authors thank Dr. Alexander G. Khandji for reviewing the neuroimages and the patients and family for their support of autopsy-based research in amyotrophic lateral sclerosis. We express special gratitude to the patient's three daughters, Dominique Mahal, Angelique Mahal, and Dr. Jacqueline Mahal, MD, for arranging and providing support for this autopsy study since it fulfills the mother's final desire as a way to contribute to science. They also have given permission for the publication of this report.

Abbreviations

ACE	angiotensin-converting enzyme
ALS	amyotrophic lateral sclerosis
ANA	anti-nuclear antibodies
CD	cluster of differentiation
CSF	cerebrospinal fluid
EMG	electromyogram
LAD	lymphadenopathy
NAA/Cr	N-acetylaspartate/creatine
SSA/SSB	extractable nuclear antigens

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FIGURE 1.

Spinal cord and skeletal muscle in autopsy of a patient with ALS and sarcoidosis. **(A)** The cervical level of the spinal cord shows prominent infiltration of the region of the crossed and uncrossed pyramidal tracts (arrows) by microglia and macrophages. Immunoperoxidase stain of CD68; scale bar = 1.0 mm. **(B)** A ventral horn motor neuron contains ubiquitinated fibrils that form skein-like inclusions within the cytoplasm (arrow). Immunoperoxidase stain of ubiquitin; scale bar = 50 μ . **(C)** A ventral horn displays two small granulomas (arrows) near surviving motor neurons. Hematoxylin and eosin; scale bar = 100 μ . **(D)** Two large granulomas (arrows) are found within skeletal muscle. Hematoxylin and eosin; scale bar = 200 μ .

Table 1
Data from four patients with sarcoidosis and ALS or bulbar ALS-like syndrome

	Age, gender	Clinical ALS features	Atypical ALS features/ comments	Response to steroids	Diagnosis/autopsy findings
Koide et al., 2005 ⁹	50, F	- weight loss - dysphagia - dysphonia - absent gag reflex - hyperreflexia - muscle atrophy - proximal limb weakness	- MRI with signal abnormalities in bilateral Meckle's cave - Chest X-ray with hilar LAD - anterior scalene muscle lymph nodes biopsy revealed sarcoidosis	Yes: - bulbar function improved - motor strength improved after 6 months	Sarcoid brainstem encephalitis/no autopsy performed
Bos et al., 2006 ²	63, F	- dysarthria - dysphagia - respiratory symptoms - tongue atrophy with fasciculations - hyperreflexia	- EMG with only neurogenic changes in the left first dorsal interosseous muscle - Muscle biopsy showed nemaline rods	N/A	Sarcoid brainstem encephalitis/at 3 years of symptom onset, autopsy: - nemaline rods in several muscles - lymphocytes in two muscles - sarcoidosis of medulla, without involvement of cranial or spinal nerves/meninges/anterior horn cells - hyperreflexia - no pathological evidence of ALS
Saiki et al. 2001 ¹	63, F	after 11 months of previously diagnosed uveitis and hilar LAD: - left leg weakness with left calf mass	- uveitis and hilar LAD at 11 months prior to motor deficits - calf biopsy revealed sarcoidosis	No	ALS & sarcoidosis: at 14 months of motor symptom onset, autopsy showed: A. sarcoidosis in lungs only (no mononuclear cell infiltration or granulomatous lesion in SC or nerve roots)

Age, gender	Clinical ALS features	Atypical ALS features/ comments	Response to steroids	Diagnosis/autopsy findings
	- progressive leg weakness in spite of immunotherapy			B. ALS features included
	- contralateral leg and arm weakness			1. loss of anterior horn cells
				2. axonal spheroids
	- bulbar palsy			3. Bunina bodies
	- mildly brisk reflexes in arms, hyporeflexia in legs			4. Myelin pallor & vacuolar degeneration in corticospinal tract
Karacostas et al., 2007 ⁷	56, F - 1 year of left foot drop	- (concurrently) elevated serum ACE, normal CSF-ACE	- Partial response to steroid with resolution of hilar LAD	ALS/no autopsy performed
	- progressive gait difficulty	- hilar LAD; biopsy revealed granulomas	- no improvement of motor function	
	- distal to proximal gradient weakness			
	- fasciculations in all extremities and tongue			
	- hyperreflexia			

ACE, angiotensin-converting enzyme; CSF, cerebrospinal fluid; EMG, electromyogram; F, female; LAD, lymphadenopathy; MRI, magnetic resonance imaging; N/A, not available.