Coexistence of Familial Amyotrophic Lateral Sclerosis and Sporadic Inclusion Body Myositis – A Case Report

Udaya Bhat[1], Bo Wang[2], Padma Kumar[3*] and Yi He[3*]

[1]Department of Pathology, Central Texas Veteran's Health Care System, USA

[2]Department of Pulmonary Medicine Central Texas Veteran's Health Care System, USA

[3]Central Texas Veterans Health Care Center 1901 Veterans Memorial Drive Temple, USA

***Corresponding author:** Padma Kumar, Central Texas Veterans Health Care Center 1901 Veterans Memorial Drive Temple, USA, Tel: 254-743-0085; Fax: 254-743-2037 76504; E-mail: Padma.Kumar@va.gov

Yi He, Central Texas Veterans Health Care Center 1901 Veterans Memorial Drive Temple, USA, Tel: 254-743-0085; Fax: 254-743-2037; E-mail: Yi.He1@va.gov

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Abstract

Many inclusion body myositis (IBM) patients have been misdiagnosed as amyotrophic lateral sclerosis (ALS). We report a case of IBM coexisting with familial ALS.

Keywords: IBM (Inclusion body myositis), fALS (Famillial amyotrophic lateral sclerosis)

INTRODUCTION

Clinically, Inclusion body myositis (IBM) patients have been misdiagnosed as amyotrophic lateral sclerosis (ALS) [1]. Recent studies have shown that mutations of valosin-containing protein (VCP) are involved in ALS and IBM [2,3]. ALS and IBM may share similar pathogenesis of multisystem proteinopathy [4,5]. We report a case of sporadic IBM coexisting with familial ALS (fALS).

CASE REPORT

A 45 year man was admitted with a 5 months history of progressive weakness mainly of the left lower extremely. He had no pain, paresthesia or incontinence of bowel or bladder. He had no dysphagia, ptosis, diplopia, saddle anesthesia or Lhermitte's symptom. Past medical history was significant for obesity, hyperlipidemia, obstructive sleep apnea and hyperglycemia. Family history is positive for the father dying in his mid-60s and he had become progressively weaker, unable to speak, chew or swallow prior to his death. A paternal aunt had a similar but milder course of weakness. The patient has a healthy sister. His sister has one daughter in her 20's in good health. The patient has no biological children.

On Initial examination, the patient was alert, oriented, and cooperative. He was in mild to moderate respiratory distress and hypophonic. Attention, mood, affect, memory, language and fund of knowledge were normal at baseline. Facial weakness was present left greater than right. Uvula was at midline. No tongue fasciculations were seen. Muscle strength of the neck was normal. Manual muscle strength testing showed 4/5 of major muscles of bilateral upper extremities, 4-/5 to 4/5 of right lower extremity muscles and 0-3/5 of left lower extremity muscles. Reflexes: The right biceps was 1/4 and all other reflexes were absent. Plantar responses were down-going bilaterally. Sensory: Patient had no sensory loss to light touch, pinprick, vibration and proprioception. Fasciculations were not seen.

He had no improvement to treatment courses of prednisone and IVIG as suggested by an outlying institution. Patient developed respiratory failure and pulmonary embolism and had tracheostomy soon after admission. He has been on mechanical ventilation and enteral tube feeding for the last 1 year and has remained quadriplegic.

Laboratory tests revealed increased serum levels of creatine kinase (433 U/L; normal 0-170 U/L). CSF showed mild increase in protein, and was negative for malignant cells. Serum neuronal nuclear (Hu) antibody was negative. MRI of the Brain showed no acute intracranial abnormality, but MRI of the complete spine spondylosis and spinal stenosis at cervical and lumbar regions without myelopathy. Echocardiogram was normal. NCV studies demonstrated non-specific changes, which could be attributed to swollen extremities. Electromyography showed widespread denervation **(Table 1)**.

Muscle biopsy of the left upper and lower extremities showed atrophic myofibers with angular contours in clusters that supported a diagnosis of neurogenic atrophy. However, presence of degenerating myofibers with focal changes reminiscent of rimmed vacuoles and a mild inflammatory infiltration suggested the possibility of an inflammatory myopathy, specifically inclusion body myositis **(Figure 1)**. Electron microscopy findings, additionally confirmed IBM. DNA analysis identified heterozygous exon 1 c.95C>T, p.Ala4Val in the SOD1 gene. VCP gene test showed no sequence variants. There were no GNE gene sequence variants.

Table 1. Needle EMG study showed abnormal spontaneous activities of multiple muscles with some fasciculation.

EMG Studies									
	IA	Fib	PSW	Fasc	H.F	Amp	Duration	PPP	Pattern
L Tib Anterior	N	3+	2+	None	None	N	N	No Vol. units	N
L Gastrocn (Med)	N	2+	2+	1+	None	N	N	No Vol. units	N
L Quadriceps	N	2+	2+	None	None	N	N	No Vol. units	N
L First D Interosis	N	2+	2+	None	None	N	N	N/LDs	RIFP
L Biceps	N	1+	2+	2+	None	N	N	N/LDPs	RIFP
R Tib Anterior	N	3+	2+	None	None	N	N	LD/LDPs	RIFP
R Gastrocn (Med)	N	3+	2+	None	None	N	N	LDs	RIFP
R Quadricceps	N	1+	2+	None	None	Giant	N	LDs	RIFP

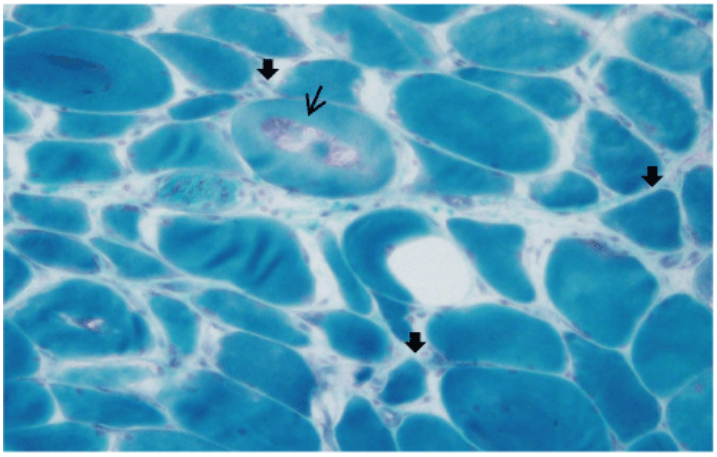

Figure 1. Muscle biopsy shows a rimmed vacuole in the myofiber (thin arrow) and presence of atrophic myofibers with angular contours (wide arrows). Trichrome staining, 40x.

Discussion

Our patient presented with atypical clinical features. Genetic tests were performed based on muscle biopsy results, rapid disease progression and family history of weakness. Hereditary inclusion body myopathy or GNE myopathy were ruled out by negative GNE gene test. However, mutation of SOD1(A4V) was identified, which is the most common gene mutation in familial ALS and this mutation correlates mainly with LMN involvement in familial ALS [6]. A study has shown that 13% of IBM cases were misdiagnosed as motor neuron disease [1].

Our case is the first report of coexistence of sporadic IBM and fALS with SOD1 mutation. Mutations of valosin-containing protein (VCP) gene are responsible for some cases of fALS, [2] IBM with Paget's disease and frontotemporal dementia [3]. VCP mutations promoteTDP-4 [3] protein accumulation and contribute to multisystem proteinopathy which

is a common factor in both ALS and IBM [4,5]. In addition to secondary neurogenic degeneration of myofibers in ALS, recent literature suggests that myofibers might be the direct targets of toxicity of SOD1(G93A) mutations [7]. The gene mutations cause gain of function, resulting in oxidative stress, endoplasmic reticulum stress and related accumulation of unfolded proteins in the cytoplasm primarily in the myofibers, which seem to be the first target. There seems to be an evidence of a muscle to motor neuron dying back process [8].

Novel intracytoplasmic inclusions immunoreactive for phosphorylated transactivation response DNA-binding protein 43 (p-TDP43), cystatin C and transferrin have been found in anterior horn cells in a case of sporadic amyotrophic lateral sclerosis (ALS). They were immunoreactive for ubiquitin, p-TDP43, cystatin C and transferrin. The inclusions ultrastructurally consisted of granule-associated fibrils and, in the central portion, dense aggregates of fibrils were associated with masses of electron-dense, coarsely granular or amorphous material [9]. Although their pathogenesis remains unknown, misfolding of proteins could be the underlying cause in the endoplasmic retinaculum.

It remains unknown if the mutant SOD1(A4V) can be the cause of rimmed inclusion bodies in myofibers, as seen in our case. This could be verified further in a study, where muscle biopsies performed in fALS cases could be additionally studied for rimmed inclusion bodies.

Guided by an integrated conceptual framework of the Australian National Service Improvement Framework for Cancer and Clinical Practice Guidelines for the Psychosocial Care of Adults with Cancer, the purpose of the study reported here is to present findings about whether attendance at MOLW contributed to meeting the needs of cancer survivors. The Australian National Service Improvement Framework for Cancer suggests that “people making that transition reflect on the fact that it is a time of anxiety and uncertainty after a period or relatively intense support” [10]. The framework also states that initiatives must place people affected by cancer at the center of their care. The Clinical Practice Guidelines for the Psychosocial Care of Adults with Cancer suggests that psycho-educational programs should have psychological/supportive and skills/knowledge-building components, provided on a group basis and offer information on cancer and coping strategies, which have been found to decrease anxiety and depression, and increase knowledge [8]. Utilizing the concepts from these frameworks, the MOLW program was designed to increase patient satisfaction and wellbeing, improved patient follow-up and increased efficacy of transition from a hospital to community basis of care.

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