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Anti-PL12 Anti-Synthetase Syndrome and Amyotrophic Lateral Sclerosis: A Case Report of a Rare Comorbidity

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Patient: Male, 55-year-old
Final Diagnosis: Amyotrophic lateral sclerosis (ALS) • anti-PL12 anti-synthetase syndrome
Symptoms: Dyspnea • joint pain • muscle cramps • muscle weakness • shortness of breath
Clinical Procedure: —
Specialty: Neurology

Objective: Rare coexistence of disease or pathology

Background: Anti-PL-12 syndrome is a rare form of myositis. Amyotrophic lateral sclerosis (ALS) is the commonest of the motor neuron disorders. However, the 2 conditions have not been reported to occur together in a single individual. This case report describes a patient who was diagnosed with anti-PL-12 anti-synthetase syndrome and then subsequently was diagnosed with ALS.

Case Report: A 55-year-old male patient had anti-PL-12 syndrome and ALS occurring together. The patient initially presented with musculoskeletal complaints and was diagnosed with anti-PL-12 syndrome. He later went on to develop shortness of breath. Neurophysiological testing subsequently confirmed ALS as the patient experienced worsening muscle weakness over a 2-year period. A muscle biopsy performed showed neurogenic and myopathic process. The patient eventually lost the ability to ambulate without mobility assistance and suffered cardiac arrest due to complications from ALS, specifically diaphragmatic dysfunction.

Conclusions: This case report represents the first documented case of a patient having both anit-PL-12 syndrome and ALS together. It has been suggested that having an autoimmune disease (AID) may increase the subsequent risk of developing ALS. Previous studies did not conduct evaluation to ascertain serological markers for AS antibodies. Lab tests were rechecked and revalidated multiple times in separate facilities for confirmation of results in case of initial lab error. This may suggest a common etiology for both anti-PL-12 syndrome and ALS.

Keywords: Amyotrophic Lateral Sclerosis • Antisynthetase Syndrome • Case Reports

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Background

There is increasing evidence to suggest autoimmune diseases can precede amyotrophic lateral sclerosis (ALS) [1,2], which is a rapidly progressive neurodegenerative condition. Limited data suggest that ALS and other autoimmune diseases, like polymyositis (PM), can co-exist [1,2]. However, there are no reported cases of anti-synthetase syndrome (AS) and ALS occurring together.

Here, we describe a patient who was diagnosed with anti-PL-12 anti-synthetase syndrome and then subsequently was diagnosed with ALS. To the best of our knowledge these 2 conditions have never been reported to occur together in a single individual.

Case Report

A 55-year-old left-handed man developed multiple joint pains in 2015. Blood test (**Table 1**) revealed elevated anti-citrullinated peptide (anti-CCP) and anti-Sjögren's syndrome A antibodies (anti-SSA). However, he did not have any joint synovitis. In 2017, he developed recurrent muscle cramps and

Table 1. Summary of the clinical serological test results.

Type of testing performed (normal reference)	Results range (N=number of repeat tests)	Results average
Creatine Kinase (39-308 U/L)	298-1292 (N=26)	696.3
Aldolase (≤8.1 U/L)	15.3-22.1 (N =2)	22.1
ESR (0-20 mm/hr)	16-33 (N=4)	27.75
CRP (≤5 mg/L)	1.5-10.9 (N=16)	3.8625
ANA (negative)	Positive, Negative, Negative (N=3)	
RF (<14 IU/mL)	7-8 (N=1)	7.5
CCP (≤4.9 U/mL)	2.9-7.5 (N=3)	5.4
DNA DS AB (≤4 IU/mL)	1 (N=3)	1
Smith antibody (<1.0 IU/mL)	<1.0 (N=3)	<1.0
Smith ab+RNP IGG (<1.0 IU/mL)	<1.0 (N=3)	<1.0
SS-A antibody (≤1.0 IU/mL)	>8 (N=3)	>8
SS-B antibody (≤1.0 IU/mL)	<1.0 (N=3)	<1.0
SCL-70 antibody (<1.0 AI)	<1.0 (N=3)	<1.0
IgG (700-1600 mg/dL)	1106 (N=1)	1106
IgM (40-230 mg/dL)	87 (N=1)	87
IgA (70-400 mg/dL)	148 (N=1)	148
Myositis panel		
* PL-7 Autoantibodies (not detected)	Not detected (N=2)	Not detected
* PL-12 Autoantibodies (not detected)	Detected (N=2)	Detected
* Mi-2 Autoantibodies (not detected)	Not detected (N=2)	Not detected
* Ku Autoantibodies (not detected)	Not detected (N=2)	Not detected
* EJ Autoantibodies (not detected)	Not detected (N=2)	Not detected
* OJ Autoantibodies (not detected)	Not detected (N=2)	Not detected
* SRP Autoantibodies (not detected)	Not detected (N=2)	Not detected
* Jo-1 Antibody (< 1.0 negative)	<1.0 negative (N=2)	<1.0 negative

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Table 2. Neurophysiological testing and muscle biopsy results.

Test performed	Date performed	Conclusions
Electromyography (EMG)	02/01/2017	This is a limited study due to patient being unable to tolerate nerve conductions studies due to discomfort. However, the findings on the EMG are not suggestive of a myopathic disorder, but rather suggestive of a chronic neurogenic disorder with acute on chronic ongoing denervation of several distal and proximal muscles that may be seen in an acute on chronic polyradiculopathy affecting several lumbosacral and cervical nerve roots with the most affected roots being left C6 and left S1. The only muscle that showed some evidence of myopathic changes was left gastrocnemius, which may be considered as a muscle to biopsy, but not on the right side, should there be a high suspicion of myopathy.
	04/10/2017	Left quadriceps needle EMG more consistent with denervation than myositis, but this can sometimes be seen myositis.
	11/20/2017	This study suggests the presence of diffuse lower motor neuron dysfunction including the diaphragm. Motor neuron disease and multilevel radiculopathy are among the differentials in this setting. In addition, there is evidence of sensory and motor neuropathy with mixed features of axonal loss and demyelination as can be typically seen with metabolic diseases such as diabetes. Additional right median neuropathy at the wrist and right ulnar neuropathy at the elbow are also noted.
Right thigh muscle biopsy	05/01/2017	Scattered atrophic and scattered necrotic fibers; Focal chronic inflammation. Addendum: Skeletal muscle, thigh, biopsy: mixed neurogenic and myopathic features. The predominant histopathology is that of neurogenic atrophy. In addition, there is a mild degree of myonecrosis and regeneration along with complement C5b-9 deposition. These myopathic features may correlate with the clinical diagnosis of myositis despite the absence of lymphocytic infiltrates or MCH class I expression. If the patient was treated with corticosteroids prior to the biopsy, the cellular inflammation and MHC class I expression may have been suppressed. CD20, CD3, CD4, CD8 and CD5 immunostaining did not show inflammatory cells. TDP-43 expression was negative.

dyspnea on exertion. Creatine kinase and aldolase were elevated, with normal C-reactive protein. Anti-PL-12 was positive. Pulmonary function testing showed severe restrictive defect with moderate reduction in diffusing capacity. CT scan of the chest showed elevated right hemidiaphragm, but was otherwise negative. EMG showed acute-on-chronic denervation of several distal and proximal muscles. The skeletal muscle histopathology showed mixed, neurogenic, and myopathic features as well as a mild degree of myonecrosis and regeneration along with complement C5b-9 deposition. He received Prednisone, Azathioprine, and intravenous immune globulin (IVIG), but his condition did not improve. He had an allergic reaction to mycophenolate mofetil, manifested by a rash.

By the end of 2017, the muscle weakness worsened, and he was using a walker to ambulate. Muscle atrophy was noted in both shoulders and dorsal webs of the hands. Multiple EMGs and a muscle biopsy were performed (**Table 2**). Because of shortness of breath without evidence of interstitial lung disease and elevated enzymes, a diaphragmatic EMG was performed at a tertiary hospital. It showed abnormal spontaneous activity and neurogenic units in most of the tested muscles of all extremities, trapezius, and right diaphragm, confirming ALS. By late 2018, he had to use a mobility scooter to get around. In 2020, he went into cardiac arrest due to acute respiratory failure due to diaphragmatic dysfunction from ALS.

Discussion

To the best of our knowledge this is the first reported case of Anti-PL-12 anti-synthetase antibody occurring together with ALS. Although it is unclear, some studies suggest that having an autoimmune disease (AID) may increase the subsequent risk of developing ALS. This may suggest a shared etiology [1-3].

A retrospective study using the all-England hospital record-linkage dataset from 1999 to 2011 considered AID preceding ALS. They calculated the rate ratio from the incidence of ALS in each AID cohort and compared it with the incidence of ALS in a cohort of individuals with no prior history of AID. There was a significantly increased incidence of ALS in those who had a previous diagnosis of AID including PM [1].

A study from Taiwan suggests a similar association with AID and ALS. Taiwan's Registry of Catastrophic Illness Database of

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1778 PM patients found 6 patients subsequently developed ALS [3]. Although there is some debate about whether the initial diagnosis of PM was really the onset of ALS [4], the PM patients met the Bohan and Peter criteria, including EMG and muscle biopsy requirements [5,6]. The study concluded that patients with PM had a higher risk of developing ALS [3]. A similar association was noted in 2021 with AID and ALS in a Swedish population-based study [2].

Myositis is a rare systemic condition. The adjusted annual incidence is 5.8-7.9 per 100 000 person-years and the prevalence is 14-17.4 per 100 000 person-years [7]. About 25% of patients with PM or dermatomyositis have AS antibodies [8]. Of the known antibodies, anti-PL-12 accounts for less than 5% [9]. It is possible that other studies had AS antibodies in their PM cohorts and further evaluations to ascertain serological markers were not conducted. There were initially concerns that the anti-PL-12 antibody result was an error. It was rechecked in the same lab, then it was reconfirmed twice at the Oklahoma Medical Research Foundation's Arthritis and Clinical Immunology Research Program.

In daily clinical practice, it is rare that both anti-PL-12 syndrome and ALS would occur concurrently in one individual. Knowing the presence of both would help plan treatment and provide prognostic value. The mainstay of therapies for anti-PL-12 syndrome are corticosteroids and other immunosuppressive agents. The prognosis worsens with the presence of interstitial lung disease (ILD), which is typically present in more than 90% of anti-PL-12 syndrome patients [10]. Although our patient had dyspnea, ILD was not present. While only 14% of patients with AS and ILD die at 5 years [11], mortality is known to be very high with ALS, and life expectancy of 3-5 year is typical [12]. It is important to look for concurrent ALS in patients with AS myositis who appear to be progressing more rapidly. ALS is no longer considered a singular entity but rather a continuum consisting of ALS and other phenotypes, including myopathies. These distinct phenotypes are not attributable solely to motor neuron dysfunction and now are thought to be linked to certain genes: *VCP, MATR3, CHCHD10, HNRNPA2B1,* and *SQTSM1* [13]. While having the *CHCHD10 gene* appears to predispose a person to myopathic conditions (like inclusion body myositis), the presence of the other genetic traits will lead to ALS. The presence of additional genes, like *C9orf72,* can further lead to frontotemporal dementia and other dementing conditions [13]. Other concomitant muscle conditions, like acquired neuromyotonia (Isaac's syndrome), have been reported to occur together [14]. It is postulated that all ALS subtypes (in particular, patients with inclusion body myositis) may have a common pathological feature of accumulation of transactive response DNA binding protein (TDP-43) [15,16]. Our patient did not test positive for TDP-43 (**Table 2**).

While in myositis the presence of antibodies to the protein synthesizing machinery is well established, similarly targeted antibodies are now described in patients with ALS. The myositis specific antibodies are directed towards the tRNA synthetases and have prognostic value. Anti-PL-12 antibodies are directed specifically against alanyl tRNA synthetase. In a small group of patients with ALS, a mutant Cu,Zn-superoxide dismutase (SOD1) leads to misfolding of mitochondrial proteins, leading to cell toxicity [17]. Lysyl-tRNA synthetase appears to be a target propagating mutant SOD1 toxicity [17]. The presence of higher levels of endogenous autoantibodies against the mutant SOD1 are associated with longer survival in ALS patients. Like the anti-PL-12 autoantibodies, the presence of autoantibodies against mutant SOD1 also has prognostic value in ALS patients [18].

Conclusions

This is the first documented case of anti-PL-12 antibody and ALS occurring in the same patient. In our patient, we feel that both conditions existed together, although the anti-PL-12 antibody was identified first. Associations of these diseases occurring together may possibly suggest a common etiology and pathogenesis.

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