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Author contributions

A.G.E. and Ki.O. conceived the project. M.A.R., A.M.,[1] Ke.O. and M.I. designed experiments; M.A.R. performed most of the experiments; Ki.O., D.O.H., Ke.O. contributed to genetic studies, electrophysiological studies, and *in vitro* spliceosome studies, respectively. M.A.R., Ke.O., A.M.,[4] A.G.E. and Ki.O. wrote the paper.

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RESIDENT & FELLOW SECTION

Section Editor
Mitchell S.V. Elkind, MD, MS

Teaching Neuro*Images*: Unilateral arm and contralateral leg amyotrophy in FSHD

Unusual presentation

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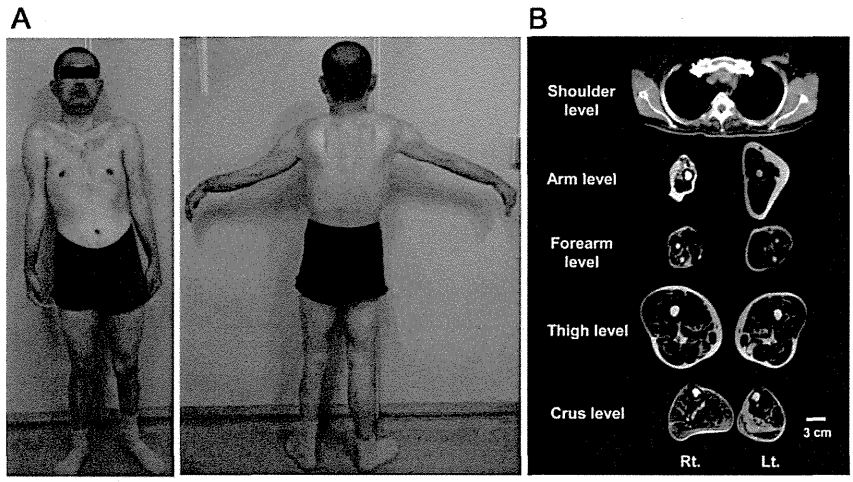
Figure **Photographs and muscle imaging findings of the whole body in a patient with facioscapulohumeral muscular dystrophy (FSHD)**



(A) The patient predominantly shows remarkable atrophy of the right facial, shoulder girdle, and arm muscles and of the left leg muscles. He put his weight on his right leg (with permission). (B) CT of the shoulder and T2-weighted MRI of the 4 limbs. CT shows atrophy of the right shoulder girdle and greater pectoral muscles. Amyotrophy and replacement of muscle tissue by fat is asymmetrically pronounced in the right sides of the biceps and triceps brachii and forearm, and the left sides of the femoral and calf muscles on MRI.

A 43-year-old, right-handed man noticed right arm weakness at age 23, followed by the development of left leg weakness and claudication. Although his deceased mother was considered to have had facioscapulohumeral muscular dystrophy (FSHD), her clinical symptoms were unclear. Neurologic examinations and imaging showed predominant weakness/atrophy in the right arm and left leg (figure). EMG demonstrated predominant myopathic changes in the right arm and left leg. No involvement of the CNS or peripheral nerves was apparent. Southern blotting analysis for FSHD revealed a 20-kb *Eco*RI fragment on 4q35 (normal >35 kb).

Asymmetric muscle involvement is a characteristic feature of FSHD.[1,2] Asymmetry might depend not only on handedness, but also on genetic predisposition.

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suggest a differing pattern of risk factors in CA-MRSA infection in HIV patients in our area resulting from the combination of risk factors. Those patients with poorer control of HIV infection and immigrants, mainly from South America, have the higher risk for such infections, although high-risk sexual behavior seems to be also associated.

Conflicts of interest

All authors declare no conflict of interest.

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Predictors of outcomes in acyclovir-treated limbic encephalitis

Recently published national guidelines for suspected viral encephalitis cover a wide range of encephalitis, including viral infections, especially herpes simplex virus (HSV), and autoimmune inflammatory disorders.[1] Subacute

Table 1 Detailed clinical and neuroradiological and neurophysiological independent variables of 31 patients with subacute limbic encephalitis.

Patient no.	(1) Sex	(2) Age (years)	(3) Detect of viral etiology[a]	(4) Days[g]	(5) GCS score[h]	(6) Maximum monocytes in CSF (/mm^3)	(7) Detection of focal lesion by initial CT[b]	(8) MRI lesions[c]	(9) Detection of PLEDs[d]	(10) Use of steroid treatments[e]	Outcome[f]
1	M	57	0	5	7	128	1	1	1	1	Poor (severe sequela)
2	F	60	0	2	6	28	1	1	1	0	Good (mild sequela)
3	F	30	0	8	7	9	0	1	0	0	Poor (moderate sequela)
4	F	31	0	9	7	296	1	1	1	0	Poor (severe sequela)
5	F	64	0	3	13	49	1	0	0	1	Poor (severe sequela)
6	M	33	0	2	13	54	0	1	1	0	Poor (death)
7	F	51	0	4	13	48	0	0	0	0	Good (mild sequela)
8	M	45	0	4	13	8	1	1	1	0	Good (mild sequela)
9	F	64	0	4	10	257	0	0	1	0	Poor (severe sequela)
10	M	74	0	2	14	426	0	0	1	0	Good (complete recovery)
11	M	29	1	3	13	3	0	0	0	0	Good (complete recovery)
12	M	73	1	3	13	108	1	1	1	0	Poor (severe sequela)
13	M	58	1	10	12	25	1	1	1	0	Poor (moderate sequela)
14	M	62	0	6	10	526	0	0	1	0	Poor (severe sequela)
15	F	34	1	4	11	161	0	1	0	0	Good (mild sequela)
16	F	18	1	2	8	38	0	0	0	1	Good (mild sequela)
17	F	59	0	5	12	50	0	1	0	0	Good (mild sequela)
18	F	59	1	3	11	73	0	0	0	0	Good (mild sequela)
19	F	56	1	12	12	13	0	0	0	1	Poor (moderate sequela)
20	F	28	1	8	11	4	0	0	0	1	Poor (moderate sequela)
21	F	68	1	14	9	6	0	1	1	0	Poor (severe sequela)
22	M	36	1	4	13	16	1	1	0	0	Poor (moderate sequela)
23	F	23	1	5	14	11	0	0	0	0	Good (mild sequela)
24	F	25	1	6	10	56	0	1	0	0	Poor (moderate sequela)
25	M	24	1	2	7	29	0	0	0	0	Poor (moderate sequela)
26	F	23	1	15	14	123	0	1	1	0	Poor (severe sequela)
27	M	29	1	7	14	282	0	0	0	0	Good (mild sequela)
28	F	27	1	3	7	4	0	1	0	0	Poor (severe sequela)
29	M	88	1	26	12	4	0	0	1	0	Poor (death)
30	M	61	1	2	11	98	1	1	1	1	Poor (severe sequela)
31	F	32	1	8	14	98	0	0	0	1	Good (complete recovery)

GCS: Glasgow coma scale CSF: cerebral spinal fluid, CT: computed tomography, MRI: magnetic resonance imaging, PLEDs :periodic lateralized epileptiform discharges.

[a] 0 = absent, 1 = present.

[b] 0 = absent, 1 = present.

[c] Abnormal T2/FLAIR signal hyperintensity on brain MRI restricted to medial temporal areas (=0) or in that plus other areas as shown in Supplemental Table 2 (=1).

[d] 0 = absent, 1 = present.

[e] At acute stage, 0 = given, 1 = not given.

[f] Outcome 3 months after completion of acyclovir treatments.

[g] Duration from neurological onset to acyclovir treatment.

[h] When acyclovir treatment was started.

limbic encephalitis (LE) is a subtype of encephalitis that includes a wide differential diagnosis because of the rapid clinical presentation and lack of specificity. Outcomes of LE have been reported according to the underlying cause. In HSV encephalitis, age, consciousness level, the delay between hospital admission and initiation of acyclovir, and the detection of lesions on computed tomography (CT) are predictors of outcome.[2–4] In encephalitis associated with neuronal antibodies, whether the antibodies are against intraneuronal antigens or neutrophil antibodies[5] and the presence of tumor[6] are important prognostic factors, and antibody suppression and tumor resection are effective treatments. Many patients with LE have initially receive acyclovir with or without steroids if a causal factor is not detected early after disease onset, even in the presence of medial temporal lesions on magnetic resonance imaging (MRI). Since the main predictors of outcome in LE remain unclear, we studied 31 patients with LE who showed medial temporal lesions on MRI to identify potential predictors of outcome.

Subjects and methods

We studied 31 patients with LE (45.8 ± 19 years, range 18–88 years) from among 97 patients with encephalitis between March 1993 and May 2012. Diagnostic criteria for LE and information on detectable viruses and acyclovir treatment are shown in Supplemental material 1.

Statistical analysis

A total of 10 variables divided into the following two sets were evaluated: clinical independent variables and neuroradiological and neurophysiological independent variables (Supplemental material 2).

Variables related to outcomes on univariate logistic regression analysis were entered into multiple logistic regression analysis using forced entry. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Correlations of each variable were also evaluated by Spearman's rank correlation test. Receiver operating characteristic (ROC) analysis was used to determine cutoff values of the significant variables on multiple logistic regression analysis, and the cutoff value derived from the ROC curves at the point of highest accuracy was used to calculate mean sensitivity and specificity. To statistically analyze differences in clinical characteristics between patients with good outcomes and those with poor outcomes, variables were evaluated with Mann–Whitney tests, followed by Fisher's exact probability test. SPSS software (Version 18) was used for statistical analysis.

Results

The clinical and other independent variables of the 31 patients with LE are shown in Table 1. Nineteen patients (61%) had poor outcomes (Table 2). On multiple logistic regression analysis, the Glasgow coma scale (GCS) score at initiation of acyclovir treatment was the best predictor of outcomes (OR = 2.158, p = 0.032, 95% CI = 1.07–4.352) (Table 3). No interactions were found between the GCS score at initiation of acyclovir treatment and the 9 other independent variables. Furthermore, when we additionally entered age, a factor that has been identified as a major determinant of prognosis in encephalitis,[3,4] the results similarly showed that the GCS score was the best predictor of outcomes, with higher odds ratios than the other variables (OR = 1.765, p = 0.029, 95% CI = 1.061–2.936). The GCS score at initiation of acyclovir treatment was higher, and the interval from neurological onset including headache to initiation of acyclovir treatment was shorter in patients with good outcomes than in those with poor outcomes (p = 0.062 and p = 0.072, respectively). No other independent variables differed significantly according to outcome. On ROC analysis, the GCS score cutoff value at initiation of acyclovir treatment was 12.5, with 58.3% sensitivity and 73.7% specificity for outcome; the area under the ROC curve was 0.7 (P = 0.065). Among the 19 patients with a GCS score of <12.5 at the initiation of acyclovir treatment, 14 had poor outcomes.

Table 2 Detailed clinical and neuroradiological and neurophysiological independent variables of 19 patients with subacute limbic encephalitis who had poor outcomes.

Subacute limbic encephalitis with poor outcomes (n = 19)	
Age (years)	Mean 47.7 (SD, 20.1; median, 56)
Sex (Men/Female)	9/10.
No detection of viral etiology (n)	12
Duration from neurological onset to initiation of acyclovir treatment (days)	Mean 7.4 (SD, 6; median, 5)
GCS score at initiation of acyclovir treatment	Mean 10.4 (SD, 2.4; median, 12)
Maximum monocytes in CSF (/mm^3)	Mean 95 (SD, 133.7; median 49)
Presence of focal lesions on initial CT	7
Cranial MRI lesions[a]	12
Presence of PLEDs on electroencephalogram	2
Not given steroid treatments at the acute stage	5

GCS: Glasgow coma scale CSF: cerebrospinal fluid, CT: computed tomography.
MRI: magnetic resonance imaging, PLEDs: periodic lateralized epileptiform discharges, n: number.
[a] Abnormal T2/FLAIR signal hyperintensity on brain MRI restricted to the limbic areas plus other areas.

Discussion

GCS score at admission or treatment initiation was previously reported to be a predictor of outcomes in central infectious diseases such as encephalitis without confirmed viral findings,[7] and HSV encephalitis,[1–3] but not in LE. Since our subjects were evaluated starting in 1993, viral diagnosis might not have been timely. Moreover, our subjects included LE patients with confirmed HSV or varicella

Table 3 Independent variables predictive of outcomes in 31 patients with subacute limbic encephalitis.

	Crude odds ratio (95% CI)	*P*	Adusted odds ratio (95% CI)[a]	*P*
Age (years)	1.066 (0.928–1.225)	0.365		
Sex	0.02 (0–3.236)	0.132	0.075 (0.005–1.097)	0.058
Detection of viral etiology	0.317 (0.01–9.764)	0.511		
Duration from neurological onset to initiation of acyclovir treatment (days)	2.332 (1.043–5.214)	0.039*	0.611 (0.396–0.943)	0.026*
GCS score at initiation of acyclovir treatment	0.311 (0.104–0.934)	0.037*	2.158 (1.07–4.352)	0.032*
Maximum monocytes in CSF (/mm^3)	0.996 (0.997–1.017)	0.717		
Detection of focal lesions on initial CT	1.31 (0.013–128.526)	0.908		
Cranial MRI lesions[b]	4.214 (0.04–440.03)	0.544		
Detection of PLEDs on electroencephalogram	0.001 (0–1.414)	0.063	0.041 (0–3.799)	0.201
Use of steroid treatments at the acute stage	9.75 (0.033–2913.511)	0.434		

GCS: Glasgow coma scale CSF: cerebrospinal fluid, CT: computed tomography, MRI: magnetic resonance imaging.
*$P < 0.05$.
PLEDs: periodic lateralized epileptiform discharges.
[a] Adjusted for the duration from neurological onset to acyclovir treatment, Glasgow coma scale score, sex and the detection of PLEDs.
[b] Abnormal T2/FLAIR signal hyperintensity on brain MRI restricted to the limbic areas or in that plus other areas.

zoster virus who received acyclovir, which is likely to be unsuitable for the evaluation of outcomes. However, all of our patients received acyclovir, and a significant independent variable providing evidence of a viral etiology was not found on single or multiple logistic regression analysis. Because the etiology of LE is unclear in most cases,[6] it is important to identify predictors of outcomes in LE as a whole, including cases in which a cause is not detected. Because the sensitivity was relatively low, whether a cutoff value of 12.5 for the GCS score is useful remains unclear. The initial GCS scores of patients with HSV encephalitis were ≥12 in most cases.[8] The low sensitivity of the GCS score in our study may be attributed to the fact that some patients showed rapid neurological deterioration despite having a high GCS score at admission.[9] The interval from neurological onset to initiation of acyclovir treatment was likely a predictor of outcomes in our study. The delay between hospital admission and the initiation of acyclovir therapy was twice as long for patients with poor outcomes than those with favorable outcomes.[2]

Age was not a significant predictor of outcomes in our study. A possible reason for lack of significance for age may be related to the fact that one-third of the patients were relatively young, between the ages of 18 and 34 years.

When initially treating a patient with LE, the detection of a virus or neuronal antibodies must be the best predictor of outcomes. However, if virus or neuronal antibody is not detected, the identification of early factors that predict outcomes might contribute to better disease management. We hope that our results will enhance the accuracy of predicting outcomes in patients with LE.

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There was no financial disclosure related with our paper.

Disclosure

The authors report no conflicts of interest related with our paper.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jinf.2012.10.007.

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INTERNAL MEDICINE

□ CASE REPORT □

Characterization of Dermatomyositis with Coexistence of Anti-Jo-1 and Anti-SRP Antibodies

Kazuma Sugie, Yasuyo Tonomura and Satoshi Ueno

Abstract

We describe a patient with dermatomyositis who presented with rapidly developing severe muscle weakness complicated by massive pleural effusion with interstitial lung disease. Myopathological analysis was suggestive of dermatomyositis. This patient showed both anti-Jo-1 and anti-SRP antibodies in serum. To our knowledge, the coexistence of these two myositis-specific autoantibodies (MSA) is considered extremely rare and is clearly an exception to the rule of having only one MSA. Our findings provide compelling evidence that the coexistence of these two MSAs may lead to more severe clinical symptoms, interacting in a complex fashion, thus expanding the clinical spectrum of idiopathic inflammatory myopathy.

Key words: idiopathic inflammatory myopathy, dermatomyositis, pleural effusion, myositis-specific autoantibody, anti-Jo-1 antibody, anti-SRP antibody

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Introduction

Idiopathic inflammatory myopathies such as polymyositis (PM) and dermatomyositis (DM) are systemic autoimmune connective tissue diseases characterized by chronic muscle inflammation with involvement of various organs (1). The pathogenesis of PM/DM is unknown, but autoantibodies directed against various cellular constituents have been identified in patients with PM/DM. Some autoantibodies found almost exclusively in PM/DM are known as myositis-specific autoantibodies (MSA), including anti-Jo-1 (histidyl tRNA synthetase) antibody, anti-PL-7 antibody, anti-signal recognition particle (SRP) antibody, anti-Mi-2 antibody, and anti-CADM-140 antibody. Each MSA is associated with a set of unique clinical features (2, 3).

We describe a 61-year-old man with DM who presented with severe muscle involvement characterized by rapidly developing proximal weakness, culminating in severe disability. He also showed massive pleural effusion with interstitial lung disease (ILD). Interestingly, both anti-Jo-1 and anti-SRP antibodies were positive in his serum. To our knowledge, the coexistence of these two types of MSA is considered extremely rare. Only one other case of idiopathic inflammatory myopathy with these two MSAs has been described in a recent report (4). Our findings suggest that coexistence of these two MSAs is associated with specific clinicopathological features.

Case Report

A 61-year-old man was admitted in June because of a 1-month history of rapidly progressive severe weakness of all four extremities. His skin was discolored, and he had dyspnea. The past history was noncontributory to the present illness. On admission, he presented with difficulty in getting up from bed and lifting his arms above his head. Physiological examination showed severe symmetric proximal weakness (less than grade 3 according to the Medical Research Council scale) of all four extremities. There were no other motor deficits. Sensory and stretch reflexes were normal. Erythematous rashes were present on the arms, trunk, legs, and face, including a typical heliotrope rash and Gottron's papules.

Laboratory examinations showed very high levels of creatine kinase (CK) (5,685 IU/L; normal: <160) in serum. The erythrocyte sedimentation rate and C-reactive protein were slightly elevated (80 mm/hr, <10; 2.6 IU/L, <0.1). Serum

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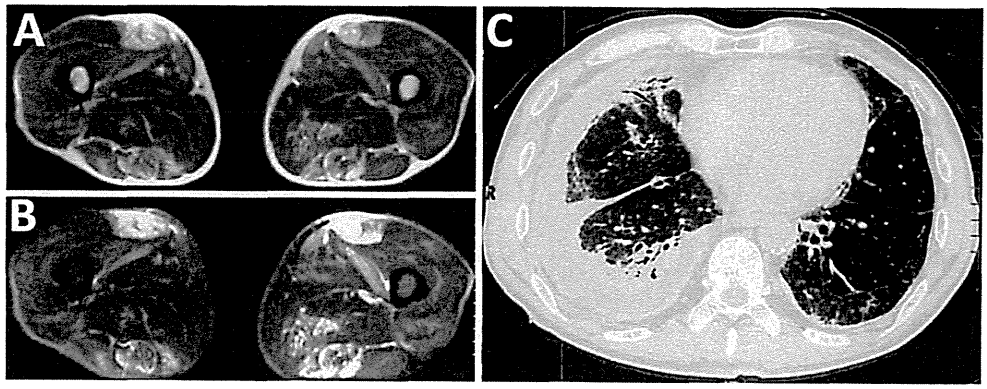

Figure 1. **Magnetic resonance images of the thighs (A, B) and computed tomographic scans of the chest (C). T2-weighted (A) and T2-short-tau inversion recovery (STIR) images (B) showed diffuse high intensity in the frontal and dorsal aspects of both thigh muscles, suggesting intramuscular inflammation and edema. Chest images showed massive pleural effusion with interstitial lung disease (C).**

antinuclear antibody was detected, accompanied by positivity for both anti-Jo-1 and anti-SRP antibodies, but negativity for other MSA, such as anti-PL-7 antibody. Among myositis-associated autoantibodies, anti-SS-A, anti-SS-B, anti-U1-RNP, and anti-Scl-70 antibodies were not detected. Electromyography showed short duration, small amplitude, polyphagic motor unit potentials with fibrillation potentials in the upper and lower limb muscles. Magnetic resonance images of the skeletal muscle showed diffuse inflammation and edema, most prominent in the proximal muscles of all four extremities (Fig. 1A, 1B). Computed tomography of the lung showed severe changes characteristic of ILD, with massive pleural effusion (Fig. 1C). The pleural fluid revealed exudate with no evidence of malignancy. A biopsy of the femoral muscle showed many necrotic and regenerative fibers with marked perimysial cell infiltration (Fig. 2). The infiltrating CD4+/CD8+ T cell ratio at perimysial sites (mean ± SD) was 1.58±0.28. Characteristic perifascicular muscle fiber atrophy was seen. Strong major histocompatibility complex class I (MHC-I) expression, especially in perifascicular atrophic fibers, was positive in cytoplasm. There was no expression of CD8/MHC-I complex, which suggested that CD8+ T cells invaded non-necrotic fibers that express MHC-I antigen. Expression of membrane attack complex (MAC) was present on endomysial capillaries, but not on necrotic fibers. These pathological findings of muscle suggested DM rather than PM.

The patient was given a diagnosis of DM with ILD. He initially received oral prednisone (1 mg/kg/day) for a month, with tapering to 20 mg/day over the course of the next three months. His muscle strength gradually improved, but he was still unable to move independently. Respiratory difficulties and pleural effusion were mildly decreased. The erythematous rashes decreased, but persisted slightly. Four months after the start of treatment, a progressive gastric cancer (papillary adenocarcinoma, stage IIIA) was diagnosed. A gastrectomy was thus performed. Subsequently, the muscle weakness and respiratory difficulties worsened despite an increase in the dose of steroids. One year after gastrectomy, the patient died of progressive ILD with massive pleural effusion and multiple liver metastases from gastric cancer.

Discussion

We described a patient with idiopathic inflammatory myopathy accompanied by ILD with massive pleural effusion, who presented with rapidly developing severe proximal weakness and respiratory difficulty. His skin lesions were suggestive of DM. Histopathological examination of a muscle specimen revealed many necrotic and regenerative fibers with marked perimysial cell infiltration, predominantly involving CD4+ T cells. Strong MHC-I expression by perifascicular atrophic fibers was consistent with DM (5). In addition, expression of MAC on endomysial capillaries, but not on necrotic fibers in our patient distinguished DM from paraneoplastic necrotizing myopathy (6). Collectively, these histopathological findings of muscle, including no expression of CD8/MHC-I complex, suggested DM rather than PM.

Interestingly, the present patient showed both anti-Jo-1 and anti-SRP antibody in his serum. The presence of these two MSAs is considered extremely rare and is clearly an exception to the rule of having only one MSA in association with PM/DM (7). To our knowledge, the coexistence of these MSAs has only been documented one time previously (4). That patient had severe muscle weakness and ILD, characterized by the presence of both anti-Jo-1 and anti-SRP antibody. Although the reason for this association and the pathogenic roles of these two MSAs are unclear, MSA may play a key, yet indirect part in the etiology of PM/DM.

Each MSA is associated with a set of unique clinical features (2, 3). Anti-Jo-1 antibody, one of the aminoacyl tRNA synthetases antibodies, is closely related to PM/DM, which