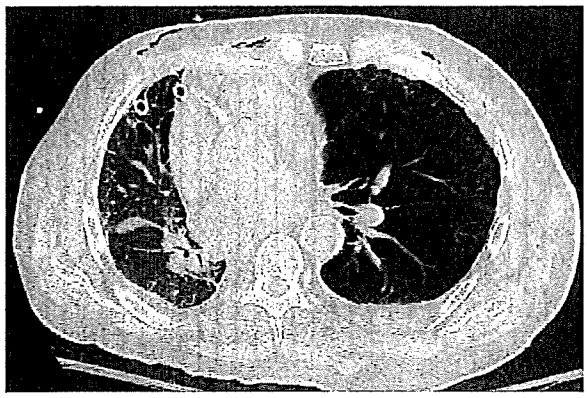

*Fig 2. Computed tomographic scan depicting shift of heart after single right lung transplant.*

shift was a result of the hyperinflated, native left lung further expanding while unopposed by the normal, transplanted right lung (Fig 2). Although the proximal RCA kringle appeared obstructive, the artery had adequate measured flow, so no intervention was performed at the time. However, during the next 24 hours the patient demonstrated episodes of positional cardiac ischemia. If the patient was positioned with his right side up, he remained hemodynamically stable. However, if he was placed supine or with his right side down, evidence of ischemia was noted on telemetry with corresponding hypotension. Such positional episodes of ischemia were presumed to result from intermittent proximal RCA occlusion due to extreme angulation of the heart into the right chest. Serial troponins were monitored and peaked at 4.3 ng/mL on postoperative day 2.

Given his positional hemodynamic instability, we concluded that the right coronary artery required revascularization. Once the decision was made to proceed with percutaneous treatment, the patient was returned to the interventional cardiology suite and underwent placement of two Promus drug-eluting stents (4.0 × 15 mm and 4.0 × 8 mm) in the kinked segment of the right coronary artery, with no residual stenosis (Fig 1C). After intervention, the patient had no further episodes of positional instability. Inotropic and intra-aortic balloon pump support were successfully weaned, and the patient was transferred out of the intensive care unit and subsequently discharged home. One month post discharge the patient represented to our institution with a right sided empyema and sepsis. Despite surgical debridement the patient expired from systemic sepsis. We believe that this complication to be unrelated to his perioperative coronary artery management.

## Comment

Lung transplantation for end-stage chronic obstructive lung disease is now considered the standard of care in most institutions. Although we, and others, too, have previously shown that bilateral lung transplant recipients have better long-term outcomes [2, 3], some have argued that the potential for transplanting two recipients may make single lung transplantation advantageous for patients who older than 60 years of age [4]. Although complications specifically related to single lung transplantation have been previously described [5], we believe that this is the first report of coronary artery obstruction due to mediastinal shift in a single lung transplant recipient. Although there is a paucity of data on myocardial ischemia due to mediastinal repositioning after thoracic surgery, a similar complication has been described in the cardiology literature due to diaphragmatic paralysis [6]. Therefore, anatomic distortion should be considered in the differential diagnosis for cardiac ischemia after single lung transplantation for emphysema.

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FEATURE ARTICLES

# Thymoma With Lambert-Eaton Myasthenic Syndrome

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**We describe a rare case of thymoma with Lambert-Eaton myasthenic syndrome. A 62-year-old woman reporting weakness in her legs and arms was found to have an anterior mediastinal mass on computed tomography. Electromyography showed incremental response to repeated stimulations, and thymoma with Lambert-Eaton myasthenic syndrome was diagnosed. The patient was**

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**successfully treated with video-assisted thoracoscopic extended thymectomy.**

**(Ann Thorac Surg 2010;89:2001–3)**


Lambert-Eaton myasthenic syndrome (LEMS) is a disorder distinguished from myasthenia gravis (MG) by the clinical symptoms and a characteristic electrophysiological picture [1]. LEMS is usually associated with small cell lung carcinoma. We describe here the extremely rare case of the concurrence of the LEMS and thymoma.

A 62-year-old woman who 1 year earlier had been diagnosed with Sjögren's syndrome, and 2 years earlier had been diagnosed with thoracic aorta aneurysm, was found to have a well circumscribed, solid anterior mediastinal mass by enhanced thoracic computed tomographic scan (Fig 1).

The mediastinal mass had subsequently increased in size from 12 mm to 16 mm. One year earlier she became aware of weakness in her legs and arms and these symptoms had subsequently worsened. Prior to surgery, the patient was referred to the neurologic department with suspected MG associated with thymoma.

Neurologic examination showed weakness of the truncal and proximal limb muscles. There was transient improvement in muscle strength after brief rest. Muscle powers were intact in the distal arms and legs. Tendon reflexes in her extremities were absent. Dry mouth, diplopia, ptosis, and dysphagia were not seen. The patient had negative results for acetylcholine receptor-binding antibodies and antibodies to P/Q-type voltage-gated calcium channels. A tensilon test was positive. Electromyography was performed on the abductor hallucis muscle and a repetitive nerve stimulation test showed reduced compound muscle action potential amplitude (0.8 mV), a decremental response (10%) when stimulated at 3 Hz, and a marked incremental pattern (284%) at 30 Hz (Fig 2). A positron emission tomographic scan showed no significant accumulation and no other malignant lesions were found. Lambert-Eaton myasthenic syndrome without small cell lung carcinoma was diagnosed and anti-cholinesterase was prescribed. This treatment was effective for the muscle weakness and the patient was admitted to our department for surgery.

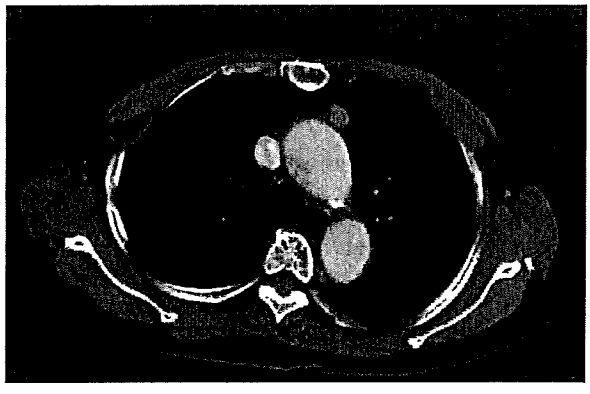

*Fig 1. Enhanced abdominal computed tomographic scan showed a well-circumscribed, solid anterior mediastinal mass with heterogeneous contrast enhancement.*

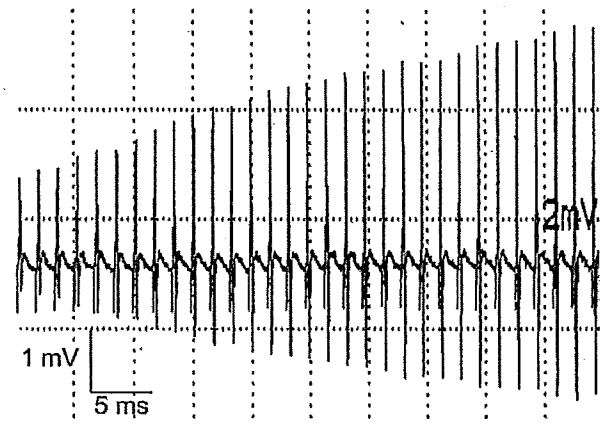


*Fig 2. Electromyography showed incremental response (> 200%) at 30 Hz of stimulation in the abductor hallucis muscle.*

A video-assisted thoracoscopic extended thymectomy was carried out. All the surgically available thymus and surrounding adipose tissue in the neck and mediastinum were removed by a combination of bilateral intercostal incisions, three thoracoscopic port incisions, and a 5-cm right anterolateral incision in the second intercostal space.

Gross examination revealed that the tumor had not invaded the attached surrounding tissue and was limited to the mediastinal adipose tissue. The excised specimen (diameter, 16 × 12 mm) contained a well-demarcated, solid tumor. Microscopic examination revealed nodules of tumor cells separated by fibrous septae with minimal invasion of the capsule (Fig 3A). The nodules were composed of a mixture of epithelial and polymorphic cells surrounded by lymphocytes (Fig 3B). This finding is consistent with a diagnosis of cortical thymoma (type B2 thymoma, minimally invasive, and Masaoka stage II). Neither postoperative radiation nor chemotherapy was carried out.

The patient suffered acute hyponatremia and delirium in the postoperative course. These symptoms gradually improved after administration of sodium replacement and sedatives. The muscle weakness improved mildly after the operation and anti-cholinesterase administration was no longer necessary. The patient was given ambulatory discharge on postoperative day 18.

## Comment

Lambert-Eaton myasthenic syndrome is characterized by progressive muscle weakness that usually starts in the proximal lower limb muscles and is occasionally associated with autonomic dysfunction [1]. Lambert-Eaton myasthenic syndrome is believed to be caused by antibodies

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CASE REPORT

# A case of primary Sjögren's syndrome complicated with inflammatory myopathy and interstitial lung disease

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Received: 1 February 2010 / Accepted: 27 April 2010


**Abstract** We experienced a case of a 63-year-old woman with primary Sjögren's syndrome (pSS) complicated with inflammatory myopathy and interstitial lung disease (ILD). She had suffered from morning stiffness and dry mouth for 1 year without being medically examined. A chest CT scan demonstrated ground glass opacity and a reticular shadow in the lower lung field. A diagnosis of SS was made based on positive findings from Schirmer's test, sialography of the parotid gland, a labial salivary gland biopsy and the presence of anti-SS-A antibody. Musculoskeletal symptoms were absent; however, the elevation of creatine kinase (CK) as well as magnetic resonance imaging (MRI)-proven inflammatory change of bilateral muscles of the thigh was evident. Histological examination of the thigh revealed diameter variation, degeneration of muscle fibers and inflammatory cell infiltration in the perivascular area, corresponding to the inflammatory myopathy of pSS. Oral prednisolone 30 mg/day was introduced, and serum CK rapidly decreased within 2 weeks. ILD also responded well to prednisolone without relapse. These clinical outcomes are consistent with extraglandular organ involvement of pSS.

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**Keywords** Sjögren's syndrome · Inflammatory myopathy · Magnetic resonance imaging · Interstitial lung disease

## Introduction

Sjögren's syndrome (SS) is a chronic inflammatory disorder, which primarily involves the lacrimal and salivary glands. Skeletal muscle involvement in primary SS (pSS) is a relatively rare complication, and its precise clinical and pathological spectrum remains obscure.

Secondary Sjögren's syndrome (sSS) refers to those cases that occur in association with another connective tissue disease, most commonly as a complication of rheumatoid arthritis [1]. With regard to pulmonary complications, interstitial lung disease (ILD) in sSS is clinically more severe than ILD of pSS; however, its prevalence is higher in pSS than sSS [2].

We present a case of pSS complicated with inflammatory myopathy and ILD, with clinical features resembling those of dermatomyositis (DM)/polymyositis (PM), though the case did not fulfill Bohan and Peter's criteria for DM/PM [3]. Both the inflammatory myopathy and the ILD responded well to a moderate dosage of prednisolone, which is consistent with pSS-related extraglandular organ involvement.

## Case report

A 63-year-old Japanese female, who had been diagnosed with diabetes 2 years earlier, complained of dry mouth without muscle weakness or myalgia. Laboratory tests showed positive antinuclear antibody (ANA) and elevation

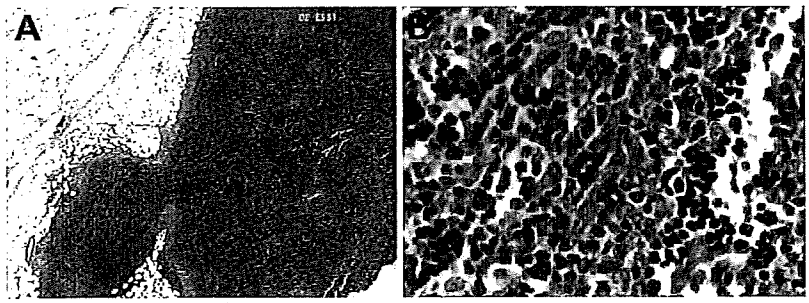


*Fig 3. (A) Microscopic examination revealed nodule of tumor cells separated by fibrous septa with minimal invasion. (Hematoxylin and eosin, ×40 original magnification.) (B) The nodule was composed of a mixture of epithelial and polymorphic cells surrounded by lymphocytes. This finding is consistent with the diagnosis of cortical thymoma. (Hematoxylin and eosin, ×400 original magnification.)*

against the P/Q-type voltage-gated calcium channels located at the pre-synaptic side of the neuromuscular junction, and these antibodies are present in the serum of at least 85% of patients [2]. The antibodies inhibit acetylcholine release and cause neuromuscular transmission failure and muscle weakness [3]. Lambert-Eaton myasthenic syndrome is diagnosed if the patient has muscle weakness and either anti- P/Q-type voltage-gated calcium channels serum antibodies or abnormal electromyography in which reduced resting compound muscle action potential amplitude is increased by > 100% after high-frequency repetitive nerve stimulation [4]. Incremental response to high-frequency repetitive nerve stimulation may also be observed in some cases of MG. Thus, it could be argued that our patient might have had MG instead of LEMS, because she had thymoma and responded favorably to anti-cholinesterase treatment. However, the clinical images and electromyography results that showed a low resting compound muscle action potential amplitude and an incremental response exceeding 200% led us to diagnose LEMS rather than MG.

Thymomas are found in 15% of patients with MG [5]. The incidence of MG among a reported series of patients with thymoma ranged from 7% to 54%, with an overall average of 35% [5]. Myasthenia gravis is an autoimmune disease caused by anti-acetylcholine receptor antibodies, and its association with thymoma and treatment by thymectomy seems to be related to the role of the thymus in the creation of these antibodies [6]. On the other hand, approximately 60% of LEMS cases are associated with small cell lung carcinoma. We believe there are only a few reports of thymoma associated with LEMS [7]. Approximately 15% of LEMS patients lack anti-P/Q-type voltage-gated calcium channel antibodies, especially in cases without small cell lung carcinoma. This indicates there are some unknown antibodies that target molecules other than P/Q-type voltage-gated calcium channels. Treatment of an underlying neoplasm associated with LEMS is necessary, and may also result in improvement in the neurologic symptoms, presumably because of the reduction or removal of the antigen stimulus [8]. Although there is no known relationship between thymoma autoimmune factors and LEMS, thymectomy may have a significant effect on LEMS associated with thymoma.

This case is of special interest because it suggests the existence of an unidentified LEMS-specific antibody associated with thymoma.

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FEATURE ARTICLES

# Inflammatory Malignant Fibrous Histiocytoma of Thymus Origin

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**A 46-year-old man was referred to our department complaining of anterior chest pain. A chest computed tomographic scan revealed an anterior mediastinal tumor measuring 38 × 35 × 50 mm. Suspecting a thymoma, we performed extended thymectomy through a median sternotomy under general anesthesia. Pathologically, the tumor was composed of pleomorphic spindle-shaped cells arranged in a storiform pattern, with marked inflammatory**

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of creatine kinase (CK), while mild intestinal pneumonia was shown by chest computed tomography (CT), and high signal intensity in the bilateral muscles of the thigh was shown by femoral magnetic resonance imaging (MRI). She was admitted to our hospital for further evaluation.

Physical examination revealed that she had no skin lesions or neurological abnormalities. There was no peripheral lymphadenopathy in the cervical, axillary or inguinal regions. Laboratory investigations revealed the following: hemoglobin 13.2 g/dl, white blood cell count 5.4 × $10^3$/μl (neutrophils 59%, lymphocytes 31%, monocytes 9% and eosinophils 1%), platelet count 313 × $10^3$/μl, erythrocyte sedimentation rate 20 mm/hour, C-reactive protein 0.10 mg/dl, total protein 7.6 g/dl, albumin 4.1 g/dl, total bilirubin 0.5 mg/dl, creatine kinase 1,254 IU/l, aldolase 17.9 IU/l, lactate dehydrogenase 462 IU/l, alkaline phosphatase 232 U/l, aspirate aminotransferase 51 IU/l, alanine aminotransferase 40 IU/l, γGTP 84 IU/l, blood urea nitrogen 14.0 mg/dl, creatinine 0.55 mg/dl, hemoglobin A1c 5.9% and KL-6 782 U/ml. Immunological studies showed the following: antinuclear antibody 1:2,560 (speckled pattern), anti-dsDNA antibody 1.8 IU/ml, anti-Sm antibody 3.3 U/ml, anti-SS-A antibody 86.2 U/ml, anti-SS-B antibody 3.0 U/ml, IgG 1,700 mg/dl and IgA 426 mg/dl. Anti Jo-1 antibody was negative.

There was no evidence of keratoconjunctivitis sicca; however, an apple tree-like pattern was observed by sialography, and lymphocytic infiltration was found in minor salivary glands. These findings were consistent with SS (Fig. 1a). SS was diagnosed in accordance with the American-European Consensus Group criteria [4].

A chest CT scan demonstrated ground glass opacity and a reticular shadow in the lower lung field (Fig. 2a). Radiographic images of femoral MRI (Fig. 2b) showed high intensity in the bilateral quadriceps of the thigh. Electromyography (EMG) revealed no evidence of obvious myogenic change. A biopsy of the left quadriceps muscle revealed fiber diameter variation, degeneration and inflammatory cell infiltration of perivascular tissue (Fig. 1b). Since she did not fulfill the criteria of DM or PM proposed by Bohan and Peter [3], we diagnosed her condition as inflammatory myopathy and ILD complicated with pSS. Oral prednisolone of 30 mg/day was introduced, and serum CK rapidly decreased to almost normal range within 2 weeks. ILD also improved.

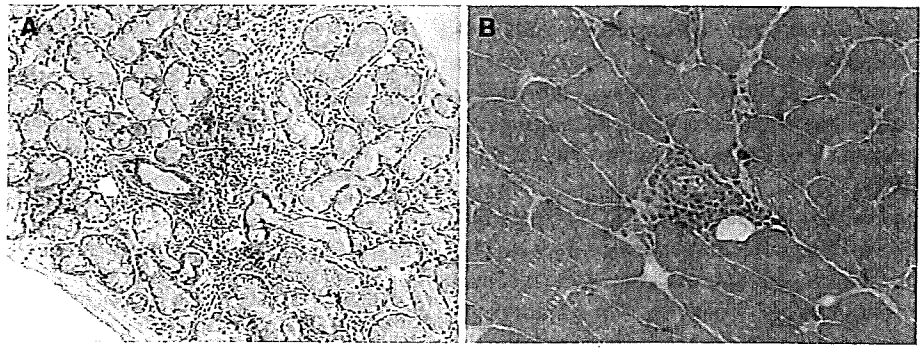


**Fig. 1** **a** Histological examination of a minor salivary gland in the lower lip. Focal lymphocytic sialadenitis, which is compatible with the histology of Sjögren's syndrome was found (hematoxylin and eosin staining, original magnification ×100). **b** Histology of left quadriceps muscle. Fiber diameter variation, degeneration and inflammatory cell infiltration of the perivascular region are evident. (hematoxylin and eosin staining, original magnification ×400)

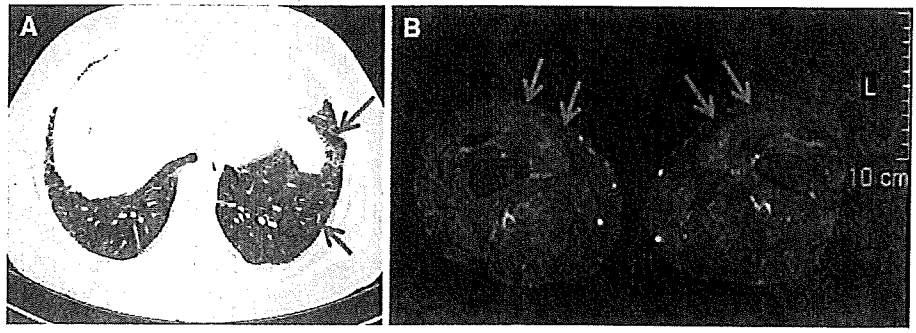


**Fig. 2** **a** Chest CT scan showing ground glass opacity and a reticular shadow in the lower lung field (*arrows*). **b** STIR axial magnetic resonance imaging demonstrating a high-intensity signal in the bilateral quadriceps (*arrows*)

## Discussion

Extraglandular organ involvement occurs at varying frequency in pSS [5]. It is important to distinguish extraglandular organ involvement of pSS from that in sSS with overlap syndrome, since pSS-related extraglandular organ involvement in general shows favorable outcome in response to glucocorticoids [2].

A mild inflammatory myopathy characterized by the insidious onset of proximal muscle weakness occurs in SS. The frequency of skeletal muscle involvement ranges from 2.5 to 47% [6]. The inflammatory cell infiltration can be found in muscle biopsy even in asymptomatic patients [7]; however, only scattered reports involving muscle biopsies in SS have been found [8, 9]. A study involving muscle biopsies in SS [7] showed histological muscle inflammation in 26 out of 36 muscle biopsies (72%), and the inflammation was always perivascularly localized. Our present case is consistent with inflammatory myopathy in pSS since MNC infiltration was found in the perivascular area. Thus, we suggest that histological study of muscle biopsy of SS patients complicated with inflammatory myopathy is meaningful to guide an accurate clinical diagnosis. Our case did not show skeletal muscle symptoms clinically or EMG abnormality. Kraus et al. have reported two pSS patients who developed myopathy and were treated with moderate doses of PSL [9, 10]. Our case also responded well to 30 mg/day of PSL. Accordingly, inflammatory myopathy complicated with pSS may be less severe in comparison with that in dermatomyositis (DM) or polymyositis (PM) [11].

Our present case also demonstrated ILD. ILD complicated in DM/PM is often refractory to glucocorticoids [12]; however, ILD of the present case showed favorable response to prednisolone of 30 mg/day. This clinical outcome also agrees with the report that the prognosis of ILD is less severe in pSS than in overlap syndrome [2].

In summary, we present a case of pSS complicated with inflammatory myopathy and ILD. The clinical manifestations of the present case resembled those of DM/PM, but did not meet Bohan and Peter's criteria. Furthermore, inflammatory myopathy as well as ILD responded quickly and well to a moderate dose of prednisolone, which is quite different from the outcome of DM/PM.

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DOI 10.1007/s00296-009-1015-3

CASE REPORT

# Macrophagic myofascitis associated with rheumatoid arthritis

**Kiyoshi Migita · Ruka Ueda-Nakata · Tomoko Masuda · Taichiro Miyashita · Tomohiro Koga · Yasumori Izumi · Katsuhiro Ichinose · Hironori Ezaki · Masahiro Ito · Masakatsu Motomura · Katsumi Eguchi**

Received: 10 March 2009 / Accepted: 2 June 2009 / Published online: 19 June 2009


**Abstract** Macrophagic myofascitis (MMF) is an unusual inflammatory myopathy characterized by muscle infiltration by macrophages and lymphocytes. Here, we describe a case of MMF which is associated with rheumatoid arthritis. A 53-year-old Japanese rheumatoid arthritis (RA) patient presented with focal tenderness of lower extremities. Magnetic resonance imaging showed evidence of myofascitis involving fascias of anterior tibialis muscle. Muscle biopsy showed a unique pathological pattern of MMF. MMF is known to be associated with vaccination containing aluminum. However, our case was not related to aluminum containing vaccinations and etiologies are unknown. The possible link needs to be discussed.

**Keywords** Macrophage · Myofascitis · Rheumatoid arthritis · Tacrolimus

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## Introduction

Macrophagic myofascitis (MMF) is known to be associated with vaccinations containing aluminum as an adjuvant [1]. Herein, we describe a case of MMF unrelated to vaccination that presented as focal muscle tenderness in a Japanese patient with rheumatoid arthritis (RA). Magnetic resonance imaging showed evidence of unilateral myofascitis involving the anterior tibialis muscles. Muscle biopsy showed a pathological pattern typical of MMF. This observation suggests that the appearance of focal myalgia during the course of rheumatic diseases must arouse the suspicion of an association of macrophagic myofascitis, independent of the history of vaccination.

## Case report

A 53-year-old Japanese woman was admitted to our hospital due to stiffness and myalgia of the lower extremities on 28 January 2008. She had been diagnosed with rheumatoid arthritis and had been treated with methotrexate for 2 years. Three months prior to admission, she had complained of myalgia of the both lower extremities (lt-dominant)) and gait disturbance as a consequence of the pain of these lesions. She had no history of immunization containing aluminum during the past 20 years.

On physical examination, her blood pressure was 120/72 mm Hg, pulse 82/min, and body temperature 36.6°C. Focal tenderness in the left lower limbs was noted with mild muscle weakness. Laboratory examination, including blood counts, biochemistry, thyroid function and angiotensin-converting enzyme (ACE) were normal. Mild elevations of CK (278 IU/ml) and aldolase (9.1 IU/ml) were noted. Serological tests for anti-neutrophil cytoplasmic

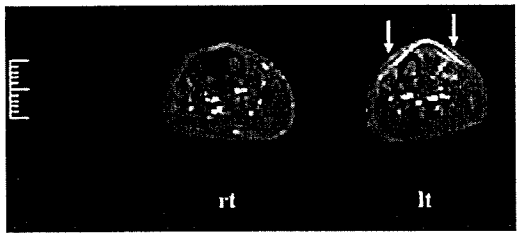


**Fig. 1** STIR axial magnetic resonance imaging demonstrating a high intensity signal in the fascia of the left anterior tibialis muscle

autoantibodies (ANCA), cryoglobulin, Epstein–Barr virus, Parvovirus, hepatitis B and C viruses were all negative. Cytomegalovirus antigen was not detected. Both the sedimentation rate (ESR) and the serum C-reactive protein (CRP) were slightly elevated (ESR 27mm/h, CRP 1.11 mg/dl). Anti-nuclear antibodies (ANA) were positive with low titers (×40, speckled pattern) and anti-cyclic citrullinated peptide antibodies were also detected (54.1 IU/ml; normal range <4.5 IU/ml). Magnetic resonance imaging (MRI) of the left lower limbs showed hyper intense signals in the fascia of the left anterior tibialis muscle suggesting fascial inflammation (Fig. 1). Muscle biopsy obtained from the anterior tibialis muscles revealed the massive infiltration of macrophages in the perifascial regions (Fig. 2a). There was neither granuloma nor vasculitis. The macrophages were CD68-positive (Fig. 2b) and some macrophages exhibited cytoplasm filled with periodic acid Schiff (PAS)-positive material (Fig. 2c). The findings typical of cytophagic histiocytic panniculitis were not observed. Muscle necrosis in association with lymphocytic infiltration, typical finding for myositis was also not observed. The patient was diagnosed as having MMF.

The elevated levels of CK and aldolase were normalized by a moderate dose of corticosteroid (prednisolone 20 mg/day); however, her symptoms were not improved. Therefore, we added tacrolimus in addition to the corticosteroid treatments. Treatment with tacrolimus (2.0 mg/day) led to the disappearance of myalgia and stabilization of the muscle weakness.

## Discussion

Macrophagic myofascitis is an unusual inflammatory myopathy, which has almost exclusively been reported in French adults with diffuse arthromyalgia [1]. Diagnosis is based on muscle biopsy that usually shows specific histological abnormalities characterized by dense infiltration of $CD68^+$ macrophages with basophilic PAS-positive content [1]. We report a Japanese patient with MMF that was accompanied by RA, independent of vaccination. The

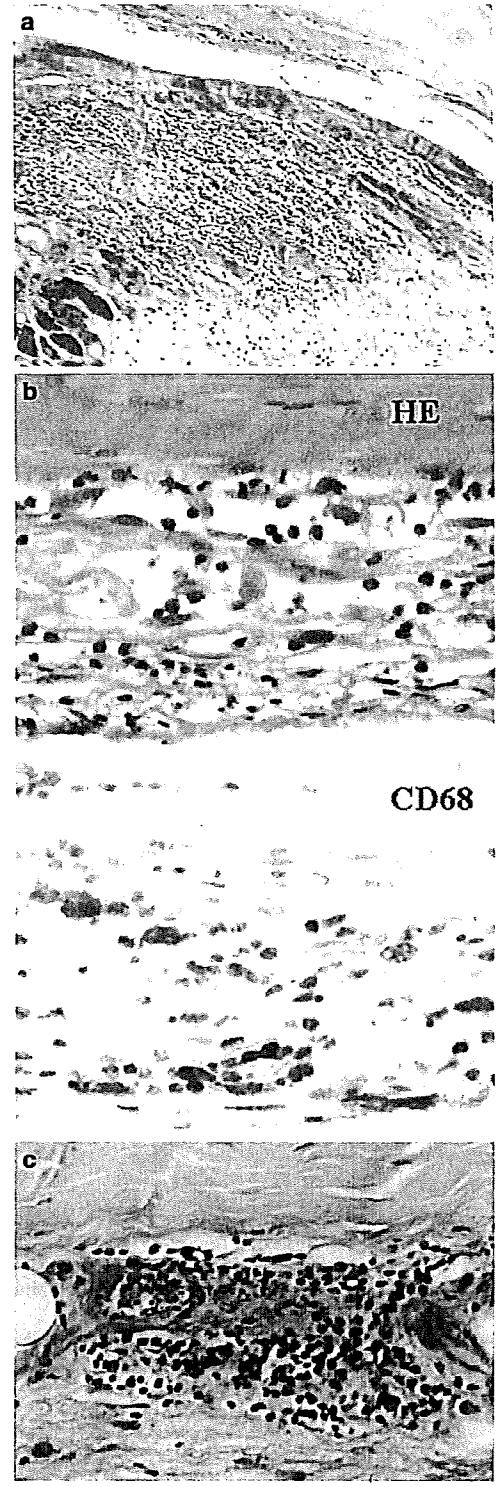


**Fig. 2** Findings of lt anterior tibialis muscle biopsy. **a** Massive perifascicular infiltration of large macrophages (hematoxylin–eosin; ×100). **b** $CD68^+$ immunoreactivity showing a large predominance of macrophages. (immunoperoxidase procedure; ×400). **c** Focal perifascicular accumulation of macrophages filled with PAS-positive materials. (periodic acid Schiff; ×400)

clinical symptoms, affecting the lower limbs, and pathological findings were quite typical of MMF in the presence of remarkable myofascial involvement. Laboratory tests only showed slight elevations of muscle enzyme levels.

The role of vaccines containing aluminum hydroxide in the pathogenesis of MMF has been suggested [2]. However, there is a discrepancy between the wide usage of aluminum hydroxide-containing vaccines and the very limited numbers of reported cases of MMF. Furthermore, systemic symptoms are observed despite the fact that histological abnormalities are present only at the site of vaccination. This case report suggests that additional factors, other than vaccination, may influence the occurrence of MMF. Many patients with MMF exhibit preexisting autoimmune diseases, including thyroiditis, systemic lupus erythematosus, Sjögren's syndrome and RA [3]. The association of MMF with autoimmune diseases suggests that autoimmune mechanisms might play a critical role in its pathogenesis. Chronic immune stimulation, which results from persistence of aluminum hydroxide, has been proposed as a possible cause of MMF [4]. While a chance association between MMF and RA cannot be ruled out, RA-related altered immunity, such as inflammatory cytokine regulation, may contribute to the occurrence of MMF. The direct connection between MMF and RA remains unclear. However, one interpretation of the occurrence of both MMF and RA in our patient suggests that immune activation contributed to the macrophage perifascicular infiltration and subsequent fascicular inflammation.

Some efficacies have been reported for a variety of treatments against MMF, including antibiotics, glucocorticoids and immunosuppressants [1, 5, 6]. Tacrolimus is an immunosuppressant that is widely used in transplantation and rheumatoid arthritis [7]. The primary immunosuppressive effect of tacrolimus is suppression of activated T cells via calcineurin inhibition; however, actions against monocytes have also been demonstrated [8]. Interestingly, Ida et al. [9] reported the impressive effect of tacrolimus in TNF receptor-associated periodic syndrome (TRAPs), which is characterized by monocytic fasciitis due to the uncontrolled macrophage activation. Further clinical studies are required to evaluate the efficacy of newer immunosuppressive agents, including tacrolimus, for the treatment of resistant cases of MMF.

In summary, the findings of the present case suggest that MMF is rarely observed in the Japanese population, independent of vaccination. It is likely that MMF remains under-diagnosed and clinicians should consider MMF in focal myalgia with elevated CK during the course of rheumatic diseases, independent of the history of vaccination.

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SHORT REPORT

ABSTRACT: A 67-year-old man was admitted with a 2-year history of dropped head. Neurological examination revealed ptosis, dysarthria, neck weakness, hyporeflexia of all limbs, and autonomic failure. Electrophysiologic study showed a 400% increment response to high-rate repetitive nerve stimulation. Serum anti-P/Q-voltage-gated calcium channel antibody was positive, confirming the diagnosis of Lambert–Eaton myasthenic syndrome (LEMS). His symptoms and electrophysiological abnormalities improved with oral prednisolone following plasmapheresis. This is the first report of LEMS as a cause of dropped head syndrome.

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# "DROPPED HEAD SYNDROME" CAUSED BY LAMBERT–EATON MYASTHENIC SYNDROME

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"Dropped head syndrome" has been reported as a symptom of various diseases. We report a patient with Lambert–Eaton myasthenic syndrome (LEMS) with dropped head who improved dramatically after treatment.

## CASE REPORT

A 67-year-old man with dropped head and generalized weakness was referred to our hospital for further examination and treatment. He had noted weakness of all extremities for 2 years. He visited a local clinic and was diagnosed with cervical spondylotic myelopathy. His muscle weakness gradually worsened, and it had become impossible for him to go up or down stairs 1.5 years before admission. He required rest even after walking only about 50 m on a flat surface. One year before his visit to our clinic he became unable to keep his head up during sitting and standing. He also noted dysphagia in response to solid foods. His past history and family history were noncontributory. He smoked 20 cigarettes per day for 45 years.

He had lost about 10 kg in weight within 2 years. Fine crackles were detected in both lungs, but no heart murmur was heard. Neurological examination revealed bilateral moderate eyelid ptosis, anisocoria, mild dysarthria and dysphagia, weakness of the neck and upper limbs bilaterally with mild muscular atrophy, attenuation or disappearance of deep tendon reflexes in all extremities, and hypoalgesia of both hands. Babinski's sign was positive bilaterally. He also complained of constipation, thirst, and impotence.

On laboratory examination the anti-P/Q type voltage-gated calcium channel antibody titer was extraordinarily high, at 450.0 pmol/l (normal less than 20.0 pmol/l). Respiratory function testing revealed a restrictive ventilatory defect (%VC was 64.8% and 1.0% of forced expiratory volume was 78.8%). Chest x-ray and computed tomography demonstrated chronic diffuse interstitial fibrosis. Evaluation for an occult malignancy was negative including fluoro-deoxyglucose/positron emission tomography. Cervical magnetic resonance imaging demonstrated advanced cervical spondylotic change that appeared to be the cause of the hypoalgesia in his hands and extensor toe responses. The amplitude of the compound muscle action potential (CMAP) in the abductor pollicis brevis

**Abbreviations:** APB, abductor pollicis brevis; CMAP, compound muscle action potential; LEMS, Lambert–Eaton myasthenic syndrome; PSL, prednisolone

**Key words:** dropped head syndrome; Lambert-Eaton myasthenic syndrome; compound muscle action potential

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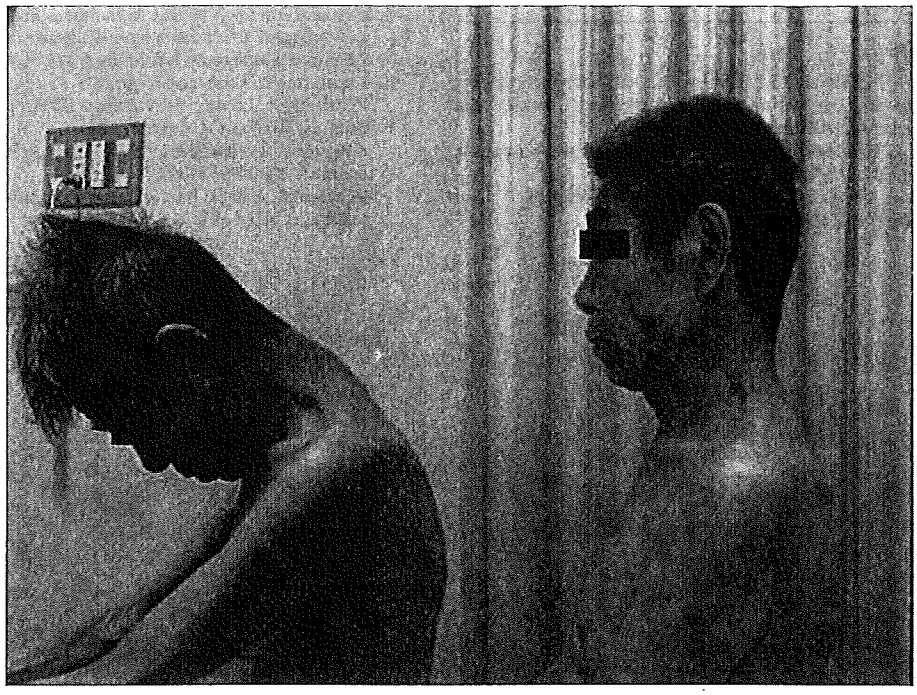

**FIGURE 1.** Left: on admission. Right: at discharge. His dropped head dramatically improved after treatment.

(APB) muscle was 0.62 mV after median nerve stimulation. Repetitive stimulation revealed a 62% decrement of the CMAP in the APB in response to 3 Hz stimulation and facilitation of 400% after high-frequency (50 Hz) stimulation. Concentric needle electromyography showed instability of motor unit potentials in the muscles triceps brachii and musculus tibialis anterior.

His clinical and laboratory findings confirmed the diagnosis of LEMS. Pyridostigmine bromide did not improve his symptoms. Prednisolone (PSL) 40 mg/day (1 mg/kg/day) was therefore started. In addition, he underwent three treatments with double-film filtration plasmapheresis, which markedly improved his clinical symptoms and increased the CMAP amplitude on electrophysiological study. His respiratory function improved as well. His dropped head also improved dramatically (Fig. 1).

## DISCUSSION

The causes of dropped head are various and can be divided into two types: weakness of the posterior cervical muscles and involuntary contraction of the cervical muscles, i.e., dystonia. In 1992, Suarez and Kelly[7] reported four cases and reviewed dropped head syndrome, but they did not mention diagnoses of underlying diseases responsible for this condition. There have since been a number of reports that deal with the diseases underlying dropped head syndrome. In 2003, Gourie-Devi et al.[4] reviewed the literature and classified dropped head syndrome based on its cause as follows: myogenic, neurogenic, miscellaneous, and those with local causes. Recently, several cases of dropped head caused by dystonia have been reported in relation to Parkinson disease/syndrome or the use of dopamine agonists.[3,5]

Katz et al.[6] described four cases of dropped head syndrome due to "isolated neck extensor myopathy." Dropped head syndrome due to cervical muscle weakness has been reported in neurogenic disorders such as amyotrophic lateral sclerosis,[6] neuromuscular junction disorders such as anti-acetylcholine antibody- or anti-MuSK antibody-positive myasthenia gravis,[1] myogenic disorders such as polymyositis or mitochondrial myopathy,[2] and others. However, to our knowledge no report of dropped head syndrome caused by LEMS has been reported previously. In patients with dropped head syndrome it is important to search carefully for causes that are treatable.

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LETTER TO THE EDITORS

# Efficacy of tacrolimus in Sjögren's syndrome-associated CNS disease with aquaporin-4 autoantibodies

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Sirs,

We present two patients with central nervous system (CNS) disease associated with Sjögren's syndrome (SjS) and positive for antiaquaporin-4 water channel autoantibodies (AQP4-Ab) who were treated successfully with tacrolimus. Tacrolimus is an immunosuppressant that acts as a calcineurin inhibitor and suppresses T helper 2 (Th2) cells [1]. Tacrolimus may also act as a neuroprotectant by reducing axonal and myelin damage, as shown in a mouse model of experimental autoimmune encephalomyelitis [2]. SjS is a chronic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands. SjS-associated inflammation sometimes spreads into the CNS (CNS–SjS), occasionally mimics relapsing-remitting multiple sclerosis (MS), and inflammation often involves the brain, spinal cord, and optic nerve [3]. Neuromyelitis optica (NMO) is also a relapsing inflammatory disease of the CNS, characterized by severe attacks of optic nerve neuritis and longitudinally extensive transverse myelitis [4]. NMO is distinguished from MS by the presence of AQP4-Ab and differences in the distribution of inflammatory lesions and pathological findings. Combination therapy with a corticosteroid and azathioprine is the current standard treatment for preventing NMO relapse [5]; however, some patients are refractory to this therapy. Approximately 3% of patients with NMO have coexisting systemic lupus erythematosus (SLE) or SjS, and CNS–SjS patients with optic nerve neuritis or longitudinal myelitis (conditions called "NMO spectrum disorder") often present with positive findings for AQP4-Ab [4, 6, 7]. To our knowledge, this is the first reported assessment of tacrolimus in patients with CNS–SjS with AQP4-Ab. This treatment was approved by the ethical committee of our university, and the patients provided written informed consent.

A 48-year-old female (Patient 1, Fig. 1) was admitted to the hospital with rapidly progressive nausea, hiccups, dysphagia, and drowsiness. Magnetic resonance imaging (MRI) revealed T2 hyperintensities of the hypothalamus bilaterally and the dorsal medulla oblongata. After three courses of intravenous high-dose methylprednisolone (IHMP, 1 g/day for 3 days in one course), the patient recovered completely, except for mild dysphagia. One year after the first attack, she developed limb weakness. Laboratory test results revealed high levels of anti-Ro (SSA) antibodies and positive antinuclear antibody. The Schirmer test and the Saxon test revealed decreased salivary secretion (Table 1). She was diagnosed with CNS–SjS [8]. She experienced nine attacks during the entire disease course, and we started treatment with oral tacrolimus during her ninth admission. No recurrent attacks have been observed for 49 months since the start of this treatment.

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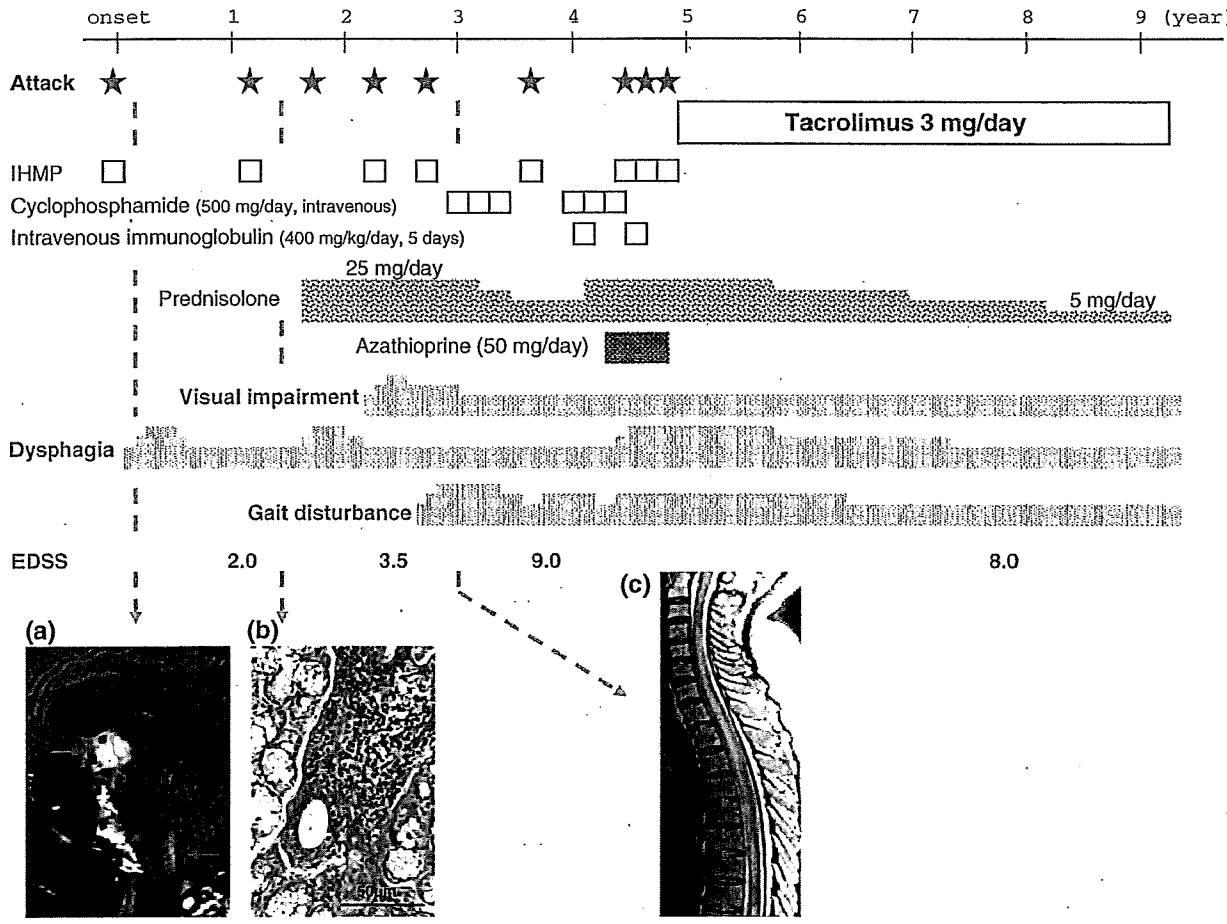


**Fig. 1** Time course of relapse, therapies, symptoms, and images of Patient 1. *Stars* indicate attacks. The *thickness of each line* represents the severity of any symptom or the dose of drug. Nine attacks had occurred in spite of therapeutic approaches, and no attacks were observed after starting tacrolimus. **a** A sagittal fluid-attenuated inversion recovery (FLAIR)-weighted image at onset shows hyperintense lesions in the thalamus, the mammillary bodies, and the dorsal portion of the medulla oblongata (*arrows*). **b** A photomicrograph of a labial salivary gland biopsy at the second admission. An aggregate of lymphocytes surrounding a salivary gland. Size bar is 50 μm. **c** A sagittal T2-weighted image at the fifth admission shows hyperintense lesions throughout the spinal cord (*arrowheads*). *IHMP* Intravenous high-dose methylprednisolone (1 g/day for 3 days in one course), *EDSS* expanded disability status scale

A 50-year-old female (Patient 2) visited our hospital with acute left visual loss and depression. She was diagnosed with retrobulbar optic nerve neuritis, but she rejected steroid therapy and was not admitted to our hospital. One year later, she was sent to our hospital by ambulance due to weakness. Physical examination revealed dysphagia, dysarthria, incomplete tetraplegia, urinary retention, and depression. MRI revealed T2 hyperintensities in the corpus callosum, thalamus, midbrain, and pons. She was diagnosed with CNS–SjS based on SjS criteria (Table 1), and she was treated with IHMP. Because high doses of oral steroids may exacerbate depression, we started therapy with tacrolimus (3 mg/day) to prevent relapse. No recurrence was observed for nine months, but she could not continue the therapy due to exacerbation of depression. Two years after withdrawal, she suffered right hemiplegia, and MRI revealed a relapse lesion in the left posterior limb of the internal capsule.

The serum of both patients was positive for AQP4-Ab after the initiation of tacrolimus. Because no recurrences were observed for at least 9 months for one patient (Patient 2) and 49 months for the other (Patient 1), we concluded that tacrolimus is effective in CNS–SjS with AQP4-Ab. Considering the pathological observations that indicate loss of AQP4 with deposition of antibody and compliment in CNS lesions in NMO [9, 10], we speculate that tacrolimus may act by suppressing the humoral immunity against AQP4 through Th2 inhibition.

**Table 1** Clinical features of two patients

| | Patient 1 | Patient 2 |
|---|---|---|
| Age at onset (years), sex | 48, female | 50, female |
| Ethnicity | Japanese | Japanese |
| Dry mouth | + | + |
| Number of relapses[a] | 9 | 2 |
| MRI findings | | |
| Optic lesion | + | + |
| Cerebral lesion | + | + |
| Pontine lesion | − | + |
| Medullary lesion | + | − |
| Longitudinal cord lesion | + | − |
| Autoantibodies | | |
| ANA | + | + |
| SS-A | + | + |
| SS-B | − | + |
| Aquaporin-4 | + | + |
| Diagnostic tests for SjS | | |
| Schirmer test | + | + |
| Saxon test | + | + |
| Salivary gland biopsy | Compatible for SjS | Not done |
| Sialography | Not done | Compatible for SjS |
| CSF findings | | |
| Cells/μl | 26 | 37 |
| MBP (mg/dl, <4.0) | 6.2 | 56.3 |
| Oligoclonal IgG bands | − | − |
| Diagnosis | | |
| Criteria of SjS | Fulfilled | Fulfilled |
| Criteria of NMO | Fulfilled | Not fulfilled |

*ANA* antinuclear antibody, CSF cerebrospinal fluid, IgG immunoglobulin G, *MBP* myelin basic protein, MRI magnetic resonance imaging, *NMO* neuromyelitis optica, *SjS* Sjögren's syndrome

[a] Including first attack

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特集：傍腫瘍性神経筋疾患 update

# 重症筋無力症
## ――病原性のある自己抗体は何か

本 村 政 勝

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特 集 ◻ 傍腫瘍性神経疾患 update

# 重症筋無力症——病原性のある自己抗体は何か

## Pathogenic Antibodies in Myasthenia Gravis

本 村 政 勝*

Masakatsu Motomura*

**Abstract**

Myasthenia gravis (MG) is the most common autoimmune disorder of the neuromuscular junction and is clinically characterized by weakness and muscle fatigue. We have classified MG into 3 types on the basis of the antibody pattern. The first type associated with acetylcholine receptor (AChR) autoantibodies, which predominantly belong to IgG1 subclass and are measured by a conventional radioimmunoprecipitation assay with $^{125}$I-alpha-bungarotoxin. This subtype occurs in approximately 80% of patients with MG and leads to the loss of AChR number and function, mainly by complement-mediated destruction of the neuromuscular junction. Approximately 40% of patients with MG who have AChR antibodes have a thymoma as a paraneoplastic neurological syndrome. However, the role of antigen expression by thymomas is unclear. The second type of MG occurs in a proportion of "seronegative" patients who did not have AChR autoantibodies. These patients process IgG autoantibodies to muscle-specific tyrosine kinase (MuSK); these antibodies are predominantly of the IgG4 subclass but are not associated with complement-mediated damage to the neuromuscular junction or with the presence of thymomas. In most patients with MuSK antibodies, the symptoms of MG improve after plasma exchange; these patients show a good response to steroid and immunosuppressive drugs but a poor response to thymectomy. MG not associated with the presence of the 2 abovementioned pathogenic autoantibodies is classified as heterogeneous "double seronegative" MG. Our classification is superior to the present classifications with regard to the mechanism, treatment, and prognosis of the disease.

Key words：myasthenia gravis, acetylcholine receptor antibodies, muscle-specific tyrosine kinase antibodies, double seronegative, neuromuscular junction

## はじめに

重症筋無力症（myasthenia gravis：MG）は，神経筋接合部に対する自己免疫疾患の代表である。一方，傍腫瘍性神経疾患の立場からは，20～30%に胸腺腫を合併する。本特集は，傍腫瘍性神経症候群であるが，MGにおいてその機序は本流ではないと思われる。その理由としては，胸腺組織においてアセチルコリン受容体（acetylcholine receptor：AChR）抗原の供給源は，胸腺腫ではなく，筋様細胞と考えられているからである。その根拠であるが，オックスフォード大学のグループが，若年発症MGにおいて胸腺過形成の筋様細胞で，神経筋接合部で証明される補体介在性の変化を証明した[1]。さらに彼らは，血清AChR抗体が検出できない症例で筋様細胞の所見がみられた場合には，実際にはAChR抗体があることを示し，*in vitro* のアッセイ系でも，血清AChR抗体が検出できない症例のIgGがclustered AChRに結合し補体介在性変化を起こすことを証明した[2]。このような胸腺組織を摘除するとMG症状が改善することは容易に想像される。しかしながら，筋様細胞は正常胸腺にも存在し，MG患者の胸腺過形成組織において，なぜ筋様

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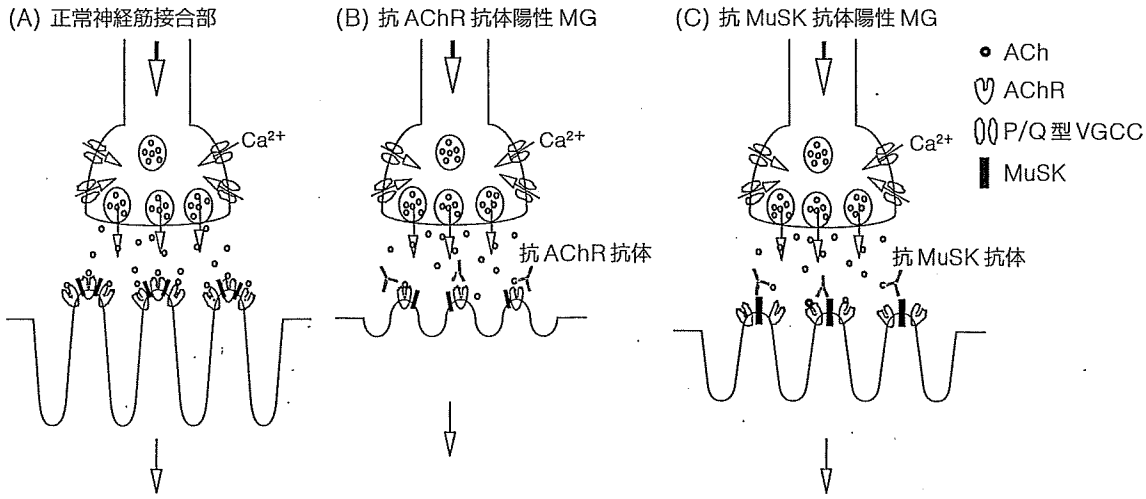


Fig. 1　重症筋無力症と自己抗体

A：正常の運動終板の刺激伝達は，$Ca^{2+}$ が P/Q 型電位依存性カルシウムチャネルより神経終末部へ流入することによって起こる。アセチルコリン（ACh）がシナプス間隙へ放出され，後シナプス膜にあるアセチルコリン受容体（AChR）と結合し，イオンチャネルが開口する。B：抗 AChR 抗体陽性 MG では抗 AChR 抗体が主に補体介在性に後シナプス膜を破壊し，AChR 量を減少させるために刺激伝達が障害される。C：抗 MuSK 抗体陽性筋無力症（MG）では，抗 MuSK 抗体が補体介在性に後シナプス膜を破壊することはなく，運動終板に及ぼす機序は不明である。

細胞が抗原呈示細胞と作用し胚中心が形成されることにより AChR 抗体が産生されるかはいまだ不明のままである。いずれにせよ，胸腺腫が AChR 抗原の供給源になる可能性は低く，傍腫瘍性機序は考えにくい。本稿では，当初の目的とは外れるが，MG の主役である自己抗体に焦点をあて，その病態と臨床を中心に解説する。

## Ⅰ．病原性のある自己抗体

自己抗体の立場から，MG 全体の約 80％の患者ではシナプス後膜に存在する AChR に対する自己抗体が検出され，残りの一部に筋特異的チロシンキナーゼ（muscle-specific tyrosine kinase：MuSK）陽性患者が含まれる。その病態機序を Fig. 1 に示した。そして，前記の抗体が検出されない double seronegative MG に分類される。1970 年代に始まる AChR 抗体測定の開発[3]と実験的 MG 動物モデルを惹起するモノクローナル抗体の開発[4]により，MG の原因物質は抗 AChR 抗体であると結論された。その後，AChR$\alpha$ サブユニットの細胞外領域 67～76 部位が病原性を有するエピトープ，main immunogenic region（MIR）と想定され，MG 惹起性を有するモノクローナル抗体の結合部位であると結論された[5,6]（Fig. 2, 3）。その際，動物モデルとヒト MG の MIR が同じかどうか論争されたが[7]，その結論は出ないまま現在に至っている。一方，2001 年，Hoch ら[8]が最初の抗 MuSK 抗体 MG の報告を行った後，世界中で多くの臨床研究が行われ，その臨床像はほぼ確立した[9-13]。ところが，抗 MuSK 抗体が MG 症状を引き起こす機序のエビデンスレベルは，抗 AChR 抗体と比べると非常に低く，その詳細な病態はいまだに不明である。ただし，基礎科学の分野では，神経筋接合部の AChR に関連する重要な蛋白，Dok-7[14]や LDL-receptor-related protein 4（Lrp4）[15]などが次々に発見され，AChR の局在化の機序が詳細に解明されつつある（Fig. 4）。

## Ⅱ．神経筋接合部の病態

抗 AChR 抗体の作用機序としては，①アセチルコリン（acetylcholine：ACh）と AChR の結合阻害（阻害型抗体），②AChR 崩壊促進，③補体介在性運動終板破壊，などの機序が考察されてきたが，特に，補体介在性運動終板破壊に伴って AChR の数が減少することが病態の本質であると考察されている。実際に，抗 AChR 抗体陽性 MG 患者の運動終板を生検して観察すると，AChR 量は減少し，免疫グロブリン・補体などの免疫複合体の沈着を認める（Fig. 5 A）。また，電子顕微鏡でその微細構造を観察すると，正常運動終板にみられる襞状の構造は破壊され，後シナプス膜の平坦化，シナプス間隙の拡大などの所見が観察される（Fig. 6 B）。これらの病理より，抗 AChR 抗体による補体介在性運動終板破壊が本病態の

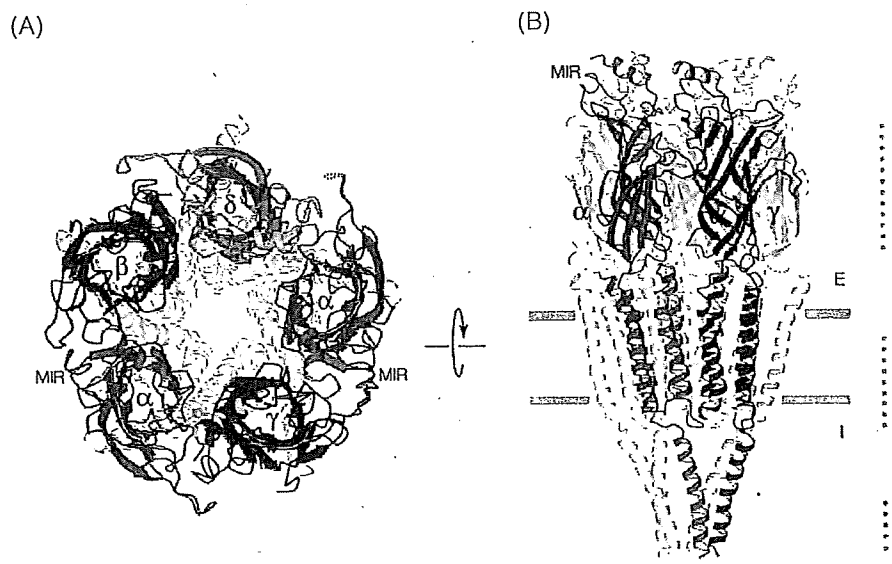


Fig. 2　アセチルコリン受容体の3次元微細構造（Unwin N, 2005[5]より引用）
アセチルコリン受容体（AChR）の構造は，シビレエイの発電器官から精製したニコチン性AChRを用いて，ケンブリッジ大学のNigel Unwin博士によって，その3次元微細構造が明らかにされた[5]。その模式図を示す。A：神経終末側から観察した。AChRは，5つのサブユニット，2つのα（赤），β（緑），δ（青），γ（水色）からなる5量体で，それらが環状に配置してイオンチャネルを形成している。B：側面図で，細胞外領域（E），膜貫通領域，そして，細胞内領域（I）からなる。細胞外領域には，2つのαサブユニットとそれぞれ隣接するγまたはδサブユニットとの間にリガンド結合部位が形成されており（黄色），この部位にアセチルコリン（ACh）やヘビ毒のα-bungarotoxinが結合する。また，2つのαサブユニットの最外側に位置するα67-76は，MG病原性を有するエピトープ，Main immunogenic region（MIR）と想定され，MG惹起性を有するモノクローナル抗体，mAb35の結合部位である。

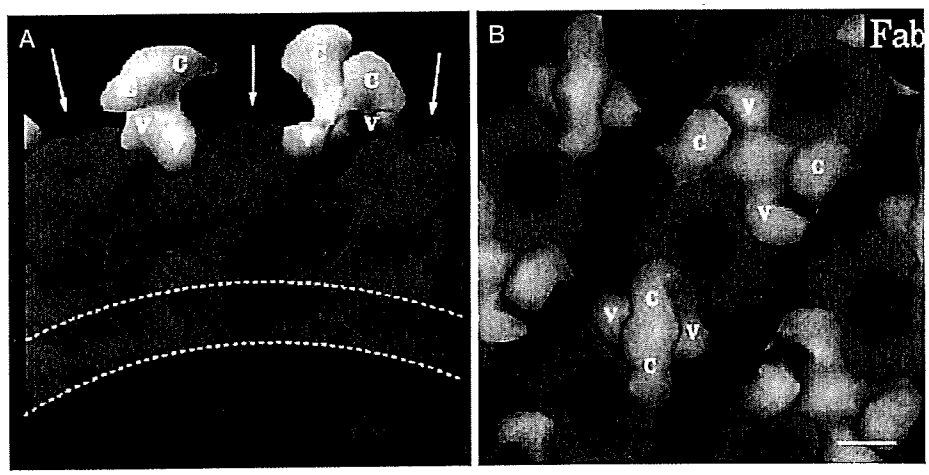


Fig. 3　アセチルコリン受容体Main immunogenic regionの3次元構造（Beroukhim & Unwin, 1995[6]より引用）
Beroukhimらは，シビレエイ発電器官のAChRにmAb35を結合させて，極低温電子顕微鏡を用いた構造解析を行い，その結合部位を解析した[6]。A：AChR（青）を側面から観察すると，mAb35の可変領域（V）が，αサブユニットの最外側，α67-76，MIRに結合していることを示した。（C）はmAb35の定常領域で，矢印はイオンチャネルを示す。B：神経終末側から観察すると，mAb35のFabは，2つのAChRをcross-linkして結合していることを示した（Bar＝50Å）。このmAb35は，MG動物モデルで補体介在性に運動終板の膜破壊を引き起こし，そして，細胞培養系でAChRにcross link結合をしてAChRのターンオーバーを高めて，AChR数を減少させることが証明されている。

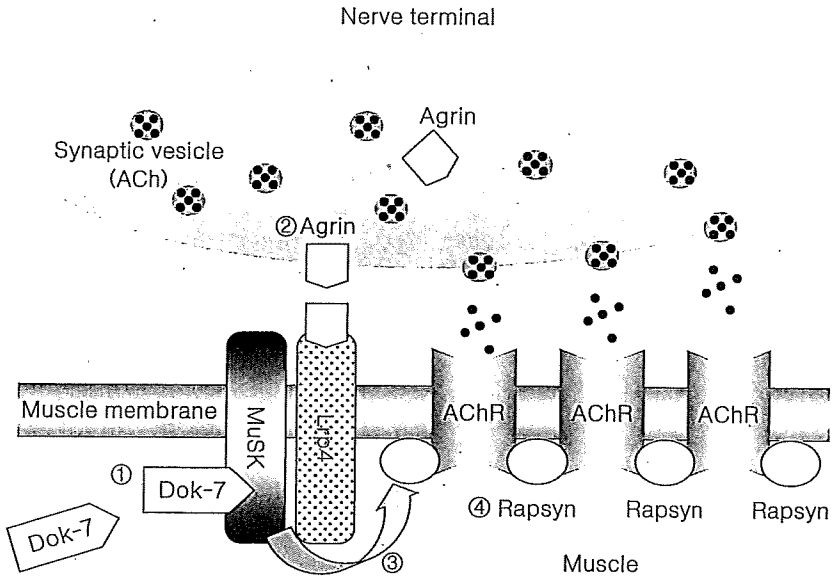


**Fig. 4 アセチルコリン受容体の集中的な発現（clustering）に関わる蛋白群**

現在，以下のような仮説のもといくつかの蛋白が関わり，神経筋接合部のアセチルコリン受容体（AChR）が集中的に局在し，その機能を果たしていると考えられている。①Dok-7は筋細胞内面よりMuSK蛋白に結合し，MuSKをリン酸化し，活性化させる。②Agrinは神経終末から分泌され，筋細胞膜のLrp4蛋白に結合し，その結果，MuSK蛋白を活性化させる。③Dok-7およびAgrinによって活性化したMuSKは，矢印で示した部分で連鎖的にいくつかの蛋白を介したシグナル伝達がなされ，rapsynの活性化が起こる。④Rapsynの活性化によりAChRは群化し，神経筋接合部に高密度に集積する。その結果，運動終板が形成される。

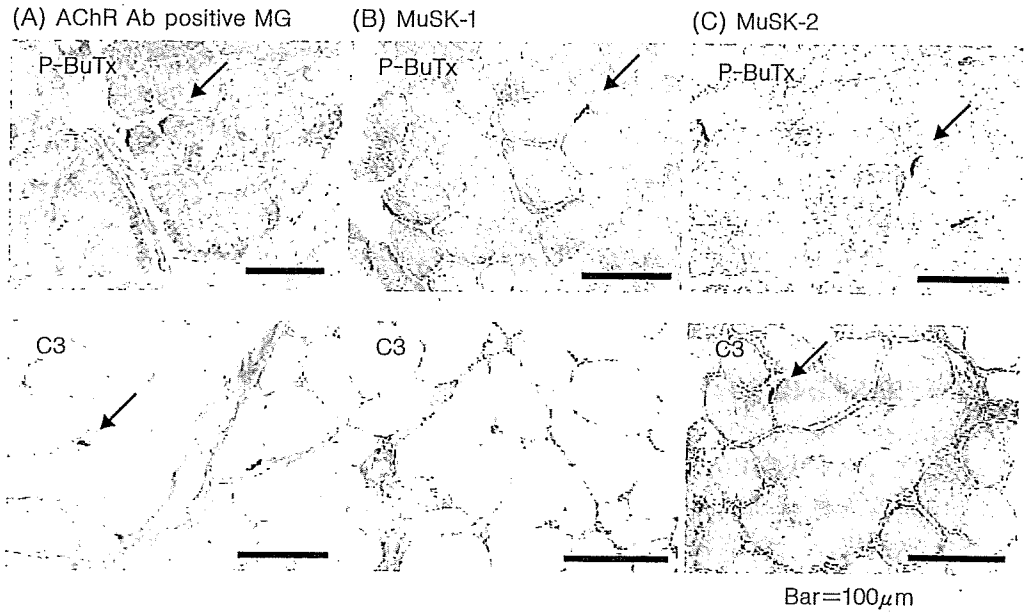


**Fig. 5 抗MuSK抗体陽性MG患者の神経筋接合部におけるアセチルコリン受容体と自己抗体**（Shiraishi et al, 2005[16]より引用）

ペルオキシダーゼ標識α-バンガロトキシン（上段），および補体C3染色像（下段）を示す。抗AChR抗体陽性MG患者の運動終板のAChR量は著減し，補体などの免疫複合体の沈着を認める（A）。一方，抗MuSK陽性MGでは運動終板のAChR量は減少していない。抗MuSK陽性MG 8例中6例では運動終板に免疫複合体の沈着は認められず（B：MuSK-1），2例のみに認められた（C：MuSK-2）。以上より，抗MuSK陽性MG患者の病態機序は抗AChR抗体陽性MGとは異なり，補体介在性後シナプス膜破壊の関与は少ないことが推測されている。

重要な作用機序と考えられている。一方，抗MuSK抗体陽性MG病態機序を解明するために，Shiraishiら[16]は，8例の抗MuSK抗体陽性MG患者の上腕二頭筋より神経筋接合部生検を行い，運動終板の免疫学的・形態学的検討を行った。その結果，抗AChR抗体MGの病態とは異なり，抗MuSK抗体陽性MG患者の運動終板AChR量は減少しておらず，8例中6例では免疫複合体の沈着を認めなかった（Fig. 5 B）。さらに電子顕微鏡での観察では，後シナプス膜の形態学的変化は非常に軽微であった（Fig. 6 C, D）[7]。さらには，McConvilleら[17]は，抗