



Giant cell myositis associated with concurrent myasthenia gravis: a case-based review of the literature

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Abstract

The term “giant cell myositis” has been used to refer to muscle diseases characterized histologically by multinucleated giant cells. Myasthenia gravis is an autoimmune neuromuscular junction disorder. The rare concurrence of giant cell myositis with myasthenia gravis has been reported; however, the clinical and histological features have varied widely. Here, we present such a case and a review of the literature. An 82-year-old woman admitted for subacute, progressive, proximal muscle weakness developed acute-onset dysphagia, dysphonia, and respiratory distress 5 days after admission. Laboratory findings were positive for acetylcholine receptor binding antibodies and striational muscle antibodies against titin. Muscle biopsy demonstrated widespread muscle fiber necrosis with multinucleated giant cells, consistent with giant cell myositis. She died despite treatment with pulse methylprednisolone and plasma exchange. A literature review of the PubMed and Scopus databases from 1944 to 2020 identified 15 additional cases of these co-existing diagnoses. We found that giant cell myositis with myasthenia gravis primarily affects female patients, is typically diagnosed in the 6–7th decades, and is characterized by the presence of thymoma. Muscle histology predominantly shows giant cell infiltrate *without* granulomas. The onset of myasthenia gravis symptoms may precede, follow, or coincide with symptoms of myositis. Treatment with thymectomy, anticholinesterase inhibitors, or immunosuppressive therapy may lead to favorable clinical outcomes.

Keywords Giant cell · Giant cell myositis · Granuloma · Granulomatous myositis · Myasthenia gravis · Myositis

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Introduction

The idiopathic inflammatory myopathies (IIM) consist of a group of acquired muscle diseases characterized typically by proximal weakness, elevated creatine kinase, extramuscular manifestations, and associated myositis-specific antibodies (MSAs), and are confirmed histologically by the presence of inflammatory infiltrates on muscle biopsy among other findings. There are five major categories which are clinically and histologically distinct: dermatomyositis, immune-mediated necrotizing myopathy (IMNM), inclusion body myositis (IBM), overlap myositis, and polymyositis [1–4].

Giant cell myositis (GCM) is another idiopathic inflammatory myopathy outside of the typical classification of IIM characterized by the presence of abundant multinucleated giant cells within muscle tissue that may or may not also feature noncaseating epithelioid granulomas [5]. GCM on histology has notoriously aggressive inflammation with muscle fiber necrosis. The terms “giant cell myositis” and “granulomatous myositis” are often used to describe the same disease process

in the literature [6–10]; as such, the specific terminology of this disease class remains unclear, with observations primarily documented in isolated case reports. As a descriptor of muscle disease involving multinucleated giant cells, we prefer and will hereupon use the term “giant cell myositis.”

Myasthenia gravis (MG) is an autoimmune, T-cell-dependent disease with various autoantibodies targeting the post-synaptic membrane causing a defect in neuromuscular transmission that has been associated with GCM [6, 7]. The clinical hallmark of MG is that of fluctuating, fatigable weakness of the extremity, extraocular, and/or bulbar muscles. Thymomas are present in approximately 10–15% of MG patients [11, 12]. Acetylcholine receptor (AChR) antibodies are found in approximately 80% of patients, and in the remaining 20%, antibodies targeting muscle-specific tyrosine kinase (Musk) can be seen in approximately 30–40% [13]. Other antibodies have also been identified in MG, including Low-Density Lipoprotein Receptor-Related Protein 4 (LRP4), agrin, rapsyn, and striational antibodies [14]. Striational muscle autoantibodies bind to skeletal and heart muscle antigens, and most commonly target the proteins titin, ryanodine receptor (RyR) [11], and the voltage-gated potassium channel, Kv1.4 [15]. These antibodies can be found in 30% of patients with MG and in 80% of patients with thymoma without MG [12]. In a study of 924 patients with MG by Suzuki et al., 0.9% (8 patients) were found to have inflammatory myopathies, and 7 out of those 8 patients also had striational muscle antibodies, suggesting an association of these antibodies with myasthenia gravis and inflammatory myositis [16].

Given the field’s limited understanding of the disease association between GCM and myasthenia gravis, we provide a case report and a review of the literature. Our case is that of an 82-year-old woman who was admitted to our hospital with symptoms suggestive of an inflammatory myopathic process, who shortly after developed severe, acute-onset bulbar weakness and respiratory distress after admission. We then provide a systematic review of the literature to identify all published cases of concurrent giant cell myositis with myasthenia gravis. In reviewing these studies, we characterize the clinical, laboratory, and histological features of this rare disease association.

Case report

An 82-year-old Caucasian woman with a history of coronary artery disease, remote myocardial infarction, hypertension, hyperlipidemia, and gastroesophageal reflux disease was admitted with 2 weeks of progressive proximal muscle weakness. Prior to the onset of weakness, she was active and independent in all of her activities of daily living. She reported difficulty walking, standing from a seated position, and combing her hair. Four months prior to presentation, she was started on 40 mg of simvastatin daily after reestablishing care with a

new cardiologist. She had no family history of autoimmune disease.

On presentation, her physical exam was notable for 3/5 muscle strength in the proximal lower extremities and 4/5 strength in the proximal upper extremities. There was no rash and the rest of her physical examination was within normal limits. Initial blood tests showed normal leukocytes, hemoglobin, platelets, erythrocyte sedimentation rate (ESR), and thyroid-stimulating hormone (TSH). Creatine kinase, aldolase, C-reactive protein, lactate dehydrogenase, and troponin were all elevated (Table 1). The patient denied chest pain, and an electrocardiogram (ECG) did not show any new ischemic changes compared to a prior ECG.

A panel of autoantibodies, including anti-nuclear antibodies (ANA), anti-double stranded DNA (dsDNA) antibodies, anti-SSA antibodies, anti-SSB antibodies, cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA), and perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), were non-reactive. A serum angiotensin-converting enzyme (ACE) test was in the normal range. An infectious panel, including West Nile Virus, *Toxoplasma*, *Bartonella Henselae*, *Bartonella Quintana*, *Mycoplasma*, interferon- γ release assay, and *Histoplasma*, was also negative.

An electromyography (EMG) study was performed, which showed short duration and low amplitude motor unit potentials, without the muscle membrane irritability typically seen in IIM (Table 2). As she showed some clinical improvement with intravenous (IV) hydration and discontinuation of her statin, drug-induced myotoxicity was suspected, and the initial plan involved outpatient rheumatology follow-up with a short, low-dose (20 mg) course of prednisone to cover for any inflammatory component of her clinical presentation pending further workup. However, as she was awaiting placement to a rehabilitation facility, on day 5 of hospitalization, she developed acute onset dysphonia and dysphagia. Given the acuity of these new symptoms, a magnetic resonance imaging (MRI)

Table 1 Relevant patient laboratory values

Laboratory values (units)	Results	Reference range
Leukocytes (\times mm ³)	9.7	4.0–11.0
Hemoglobin (g/L)	13.4	11.0–15.0
Platelets (\times mm ³)	242	150–400
Erythrocyte sedimentation rate (mm/h)	26	0–33
C-reactive protein (mg/dL)	82.18	0.0–7.48
Creatine kinase (IU/L)	2368	20–165
Aldolase (IU/L)	84.9	<8.1
Lactate dehydrogenase (IU/L)	305	120–220
Angiotensin-converting enzyme (U/L)	11	9–67
Troponin (ng/mL)	0.30	0.00–0.03

Table 2 Progression of patient's symptoms, creatine kinase, and electrodiagnostic studies

Hospital day	Predominant clinical presentation	Creatine kinase (IU/L)	Nerve conduction study (NCS)	Electromyography (EMG)
Day 1	Proximal muscle weakness	2368	---	---
Day 3	Continued proximal muscle weakness	1613	Normal right median, ulnar, superficial peroneal, and sural SNAPs Normal right median, ulnar, peroneal, and tibial CMAPs	Left iliopsoas—short duration MUAPs Left deltoid, FDI, TFL, and triceps—many polyphasic MUAPs
Day 8	Acute onset bulbar muscle weakness + Increased oxygen requirement	537	NCS - not performed Normal 3-Hz RNS of the right nasalis, trapezius, and ADM	R trapezius—low amplitude and polyphasic MUAPs
Day 14	ICU and intubated for respiratory failure	Not tested	Normal right radial, superficial peroneal, and sural SNAPs Reduced amplitudes of the right median and ulnar CMAPs	+1 fibs and PSWs in the bilateral FDI, left trapezius, and left biceps Myotonia in the left deltoid No recruitable MUAPs in the left VL, TA, deltoid, trapezius, biceps, and bilateral FDI
Day 21	ICU and intubated for respiratory failure	432	Normal left sural SNAP	+3 fibs/PSWs in the right deltoid, trapezius, FDI, VL, and TA with no recruitable MUAPs in these muscles
Day 23	Patient expired	---	---	---

ICU, intensive care unit; RNS, repetitive nerve stimulation; Hz, Hertz; CMAP, compound muscle action potential; SNAP, sensory nerve action potential; MUAP, motor unit action potentials; FDI, first dorsal interosseous; ADM, abductor digiti minimi; TFL, tensor fascia lata; VL, vastus lateralis; TA, tibialis anterior; fibs & PSWs, fibrillation potentials and positive sharp waves (range from mild +1 to severe +4)

was performed to evaluate for a brainstem stroke which was negative.

Her dysphagia progressed and a nasogastric tube was placed, and she soon developed dyspnea with an increasing oxygen requirement on nasal cannula. A barium swallow was performed and was consistent with pooling of food and microaspiration into the lungs. A transthoracic echocardiogram (TTE) showed a normal left ventricular ejection fraction (LVEF) of 55%. By day 6 of hospitalization, her dysphagia and dyspnea continued to progress, and she was started on bi-level positive airway pressure (BiPAP). A 3-Hz repetitive nerve stimulation study was unremarkable, showing no amplitude decrement at baseline or after exercise (Table 2). She continued to deteriorate, and on day 10, she was transferred to the intensive care unit due to hypercapnic hypoxic respiratory failure requiring intubation. She was started on a regimen of high-dose (1 g) IV methylprednisolone for 5 days, as the differential now included IIM and myasthenia gravis given the new bulbar symptoms.

Computerized tomography (CT) scans of the chest, abdomen, and pelvis were negative for mass to suggest malignancy. Given concerns for Guillain-Barre syndrome, a lumbar puncture was performed which showed normal cerebrospinal fluid (CSF) cell counts and protein levels. Antibody panels for neuropathies and paraneoplastic syndromes were also negative. On day 14, a repeat EMG was performed, now noted for abnormal spontaneous activity and small motor unit

potentials, consistent with a myopathic process with muscle membrane irritability (Table 2). Muscle biopsy of the right deltoid muscle demonstrated widespread muscle fiber necrosis with sheets of infiltrating histiocytes, lymphocytes, and numerous multinucleated giant cells (Fig. 1). These giant cells and histiocytes stained positively with immunohistochemistry for CD68 and CD74.

Myositis antibody studies were negative, including anti-Jo-1 (histidyl-tRNA synthetase); anti-PL-7 (threonyl-tRNA synthetase); anti-PL-12 (alanyl-tRNA synthetase); anti-EJ (glycyl-tRNA synthetase); anti-OJ (isoleucyl-tRNA synthetase); anti-SRP (signal recognition particle); anti-Mi-2/NuRD (Nucleosome Remodeling Deacetylase); anti-MDA5 (melanoma differentiation-associated protein 5); anti-TIF-1 γ (transcription intermediary factor 1-gamma); and anti-HMGCR (3-hydroxy-e-methylglutaryl coenzyme A reductase). In contrast, a myasthenia gravis antibody panel (Table 3) demonstrated elevated titers of AChR binding antibodies (13.3 nmol/L) and striational muscle antibodies (1:3840). Further characterization of these myasthenia gravis antibodies revealed that the striated muscle antibodies were reactive to the titin peptide, MGT-30. A diagnosis of giant cell myositis with concurrent myasthenia gravis was made.

Plasma exchange (PLEX) and high-dose steroids were administered for 5 days given her rapidly progressive symptoms without clinical response. Intravenous immunoglobulin (IVIg) therapy was considered; however, the patient quickly

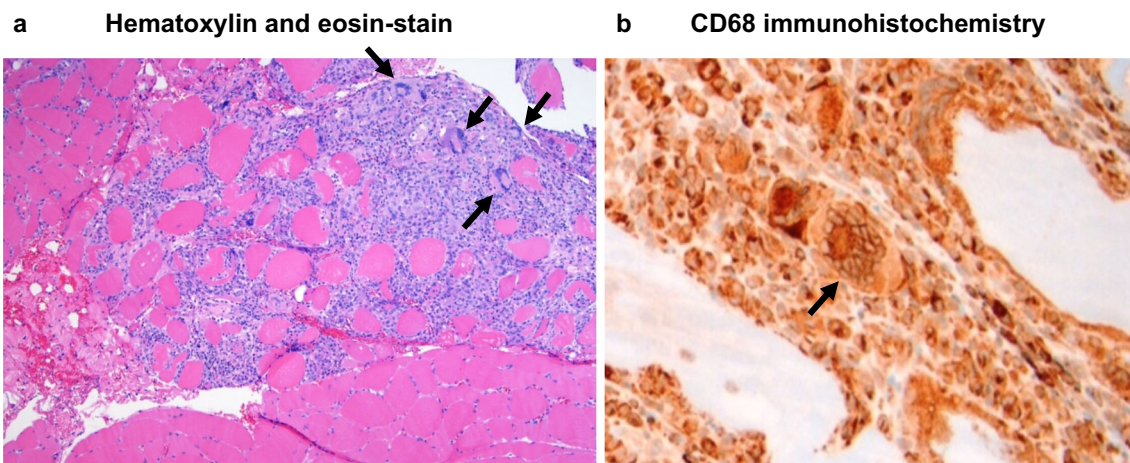


Fig. 1 Right deltoid muscle biopsy histology. **a** Hematoxylin and eosin stain shows endomyrial infiltrate with mononuclear cells with numerous giant cells (arrows), scattered eosinophils, and muscle fiber necrosis. $\times 40$

magnification. **b** CD68 immunohistochemistry shows giant cells (arrow) and macrophage predominance. $\times 200$ magnification

developed septic shock secondary to ventilator-acquired pneumonia. Her sepsis was treated with IV vancomycin and cefepime. Given her multiple comorbidities and need for a tracheostomy, she was transitioned to comfort measures only in accordance with her goals of care. She died shortly after; the family elected not to perform an autopsy. Post-mortem analysis of her chest CT did show a possible thymic lesion in the anterior mediastinum (Fig. 2).

Methods

Our literature review involved the PubMed and Scopus databases using guidelines published from Gasparyan et al. [17]. The Medical Subject Headings (MeSH)-based search terms utilized were (“myasthenia gravis” [All fields] AND “granuloma” [All fields]) and (“myasthenia gravis” [All fields] AND “giant cell” [All fields]). The time period of the search started from May 1944, when Giordano and Haymond described the first case of myasthenia gravis with giant cell myositis [18], through May 2020 (Fig. 3). We ultimately included 15 studies in the English, Spanish, French, and German languages for the literature review [5–9, 18–27]. Five Japanese studies [28–32] and 1 Czech study [33] were excluded based on translational barriers. Three articles were excluded based on confounding etiologies [34–36].

Results

A summary of the clinical information and relevant characteristics from the literature review is provided below (Tables 4 and 5, Fig. 4). Sixteen individual case reports were identified. Patients affected with concurrent giant cell myositis and myasthenia gravis ranged from 40 to 82 years (average age 65 with a standard deviation of 11 years). Women were predominantly affected (11/16, 68.8%). 43.8% (7/16) were initially diagnosed with myasthenia gravis, while another 43.8% (7/16) were initially diagnosed with both MG and myositis concurrently. The remaining 2/16 (12.5%) were initially diagnosed with myositis. Previous statin use was not mentioned in any case except for our patient. Eighty percent had thymomas (12/15) with our case not included because her thymoma CT findings were equivocal. Five studies recorded World Health Organization (WHO) thymoma classifications, which included 2 mixed (AB) thymomas, 2 bioactive lymphocyte rich (B1) thymomas, and 1 bioactive epithelial (B3) thymoma. 43.8% (7/16) had myocarditis confirmed on biopsy of which 5 had giant cell myocarditis. Myocarditis was not investigated in 6/16 cases (37.5%). 43.8% (7/16) either expired or required intubation due to respiratory failure.

When CKs were reported, 90.9% (10/11) were found to be elevated. When reported, 3/6 had an elevated ESR and 3/3 had an elevated CRP [6, 7, 20, 22, 23, 26]. The serum ACE levels

Table 3 Relevant neuromuscular autoimmune antibody serologies

Laboratory values (units)	Results	Reference range
Acetylcholine receptor binding antibody (nmol/L)	13.3	≤ 0.02
Striated muscle antibody (titers)	1:3840	$< 1:20$
Neuronal voltage gated K ⁺ channel antibody (nmol/L)	0.00	< 0.02
Titin reactive IgG antibodies	Positive	Negative

K, potassium; IgG, immunoglobulin G

Fig. 2 Chest CT scan showing a possible anterior mediastinal mass in the thymic region (red circle)



were measured in 6 studies and none had elevated levels [8, 9, 23, 25, 26]. AChR antibodies were measured in 10 cases, all of which had elevated levels (100%) [6–9, 23–27]. The striated muscle antibody was assayed in 8 cases, and 87.5% (7/8) had positive findings [5, 7–9, 20, 22, 23]. Antinuclear antibodies were reported in three cases, while anti-thyroid antibodies and p-ANCA were found in one case each. Myositis specific antibodies (MSAs) were measured in four cases, and none had positive results [6, 8, 9].

Results of the skeletal muscle biopsies revealed giant cells *without granulomas* in 81.3% (13/16). Two patients had both giant cells and granulomas on skeletal muscle histology (2/16, 12.5%), and one patient had granulomas without giant cells in the skeletal muscle (1/16, 6.25%). This one patient without skeletal muscle giant cells had giant cells present in the myocardium.

The nerve conduction studies were mentioned in 12 cases and of those, 9/12 had findings consistent with a post-synaptic neuromuscular junction disorder. The needle EMG results were described in 7 studies. The most frequent findings were that of abnormal spontaneous activity at rest (5/7, 71.4%), followed by small motor unit potentials of short duration and low amplitude (3/7, 42.9%) and an increased insertional activity (2/7, 28.6%). Only 3 studies reported muscle imaging. Lin et al. reported multifocal high intensity signals on short T1-weighted inversion recovery images in multiple groups of extremity muscles [6]. Two studies performed muscle ultrasonography. Shah et al. showed multiple hypoechoic lesions as well as a large focal mass in the brachialis muscle with peripheral vascularity [7]. Stefanou et al. had ultrasound findings with increased muscle echogenicity and prominent vascularization [9].

Fig. 3 Flow chart of study selection from PubMed and Scopus databases using Medical Subject Headings search criteria

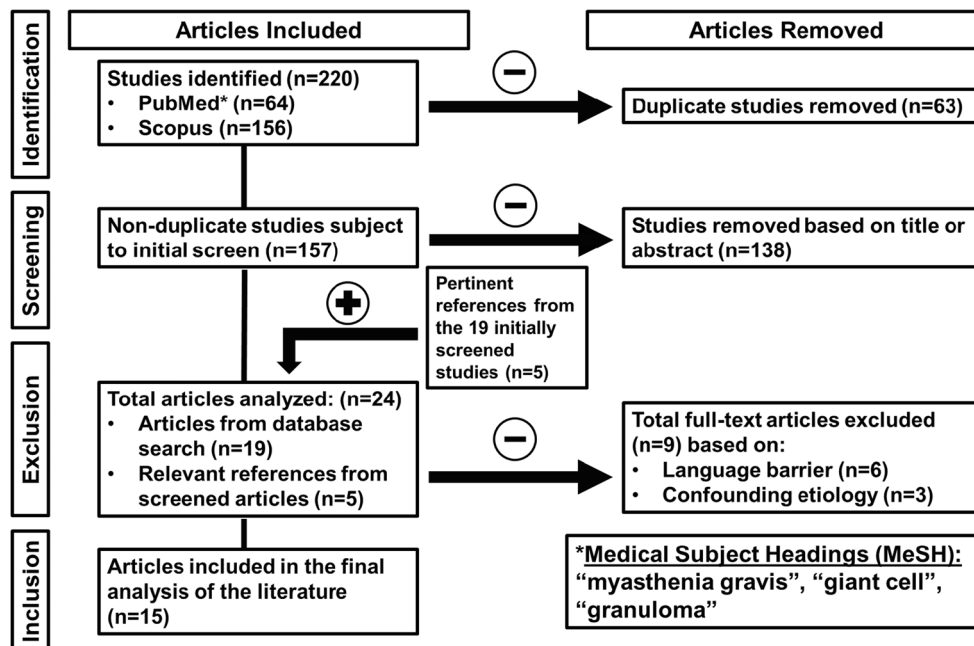


Table 4 The demographic characteristics, initial diagnoses, associated medial comorbidities, laboratory findings, and histology findings in 16 patients with concurrent giant cell myositis and myasthenia gravis

No.	First author (year) [Ref.]	Age	Sex	Initial diagnosis	Thymoma	Myocarditis	Respiratory failure	Creatine kinase	Positive autoantibodies	Skeletal muscle histology
1	Giordano (1944) [18]	57	M	Myositis	Present (unclassified)	Present	Yes	N.E.	N.E.	Giant cells
2	Klein (1966) [19]	69	F	MG	Present (unclassified)	Present (giant cell)	No	N.E.	N.E.	Granulomas
3	Burke (1969) [20]	47	F	MG	Present (unclassified)	Present (giant cell)	Yes	N.E.	Indirect striational muscle IF	Giant cells
4	Reznik (1974) [21]	66	M	MG	Present (unclassified)	Present (giant cell)	No	N.E.	Anti-thyroid	Giant cells
5	Namba (1974) [5]	57	F	Both	Present (unclassified)	Present	Yes	Elevated	Striational muscle binding globulin	Giant cells
6	Bourgeois-Droin (1981) [22]	76	F	MG	Present (unclassified)	Present (giant cell)	Yes	N.E.	ANA, striational muscle	Giant cells
7	Pascuzzi (1986) [23]	76	F	MG	Absent	Absent	No	Elevated	AChR	Both
8	Kon (2013) [24]	64	F	MG	Present (WHO B1)	Present (giant cell)	Yes	Elevated	AChR	Giant cells
9	Illiac (2013) [25]	63	F	MG	Absent	Unknown	No	Elevated	AChR, ANA	Giant cells
10	Jasim (2013) [26]	59	M	Both	Present (unclassified)	Unknown	No	Elevated	AChR	Both
11	Lin (2014) [6]	40	F	Both	Present (WHO B3)	Unknown	No	Elevated	AChR, ANA, p-ANCA	Giant cells
12	Shah (2015) [7]	70	M	Both	Present (WHO AB)	Absent	Yes	Elevated	AChR, anti-skeletal muscle	Giant cells
13	Stefanou (2016) [9]	72	F	Both	Present (WHO AB)	Unknown	No	Normal	AChR, striated muscle (titin, RyR)	Giant cells
14	Rodriguez (2018) [27]	63	F	Both	Present (WHO B1)	Absent	No	Elevated	AChR	Giant cells
15	Iqbal (2019) [8]	77	M	Both	Absent	Unknown	No	Elevated	AChR, striational muscle	Giant cells
16	Current case (2020)	82	F	Myositis	Equivocal	Unknown	Yes	Elevated	AChR, striated muscle (titin)	Giant cells

[ref], reference; M, male; F, female; MG, myasthenia gravis; WHO, World Health Organization Thymoma Classification (A—atrophic, B—bioactive, AB—mixed, B1—bioactive lymphocyte rich, B2—bioactive cortical, B3—bioactive epithelial, C—carcinoma); N.E., not examined; IF, immunofluorescence; ANA, anti-nuclear antibodies; AChR, acetylcholine receptor; RyR, ryanodine receptor; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies

Table 5 The electromyography findings, treatments, and clinical outcomes in 16 patients with concurrent giant cell myositis and myasthenia gravis

No.	First author (year) [Ref.]	Electromyography findings	Treatments	Outcome
1	Giordano (1944) [18]	N.E.	Supportive care only, no immunotherapy	Unfavorable (expired)
2	Klein (1966) [19]	Diagnostic of myasthenia gravis	Not mentioned	Unfavorable (expired)
3	Burke (1969) [20]	N.E.	Thymectomy and radiotherapy	Unfavorable (expired)
4	Reznik (1974) [21]	Suggest the possibility of a myasthenic syndrome	Not mentioned	Unfavorable (expired)
5	Namba (1974) [5]	20% decrease in amplitude on RNS and small, polyphasic motor units.	Steroids, pyridostigmine, then steroids were changed to azathioprine	Unfavorable (expired)
6	Bourgeois-Droin (1981) [22]	EMG normal	PLEX	Unfavorable (expired)
7	Pascuzzi (1986) [23]	Amplitude decrement on RNS, spontaneous activity (fibrillation), and small polyphasic motor units.	Steroids	Favorable
8	Kon (2013) [24]	Waning decrement pattern on RNS	Nitrates, diuretics, catecholamines	Unfavorable (expired)
9	Illac (2013) [25]	Muscle damage with spontaneous activity.	Steroids, IVIg, cyclophosphamide	Unfavorable (no clinical response)
10	Jasim (2013) [26]	20% decrement on post-exercise repair, increased insertional activity, spontaneous activity (fibrillation) with short duration motor units.	Thymectomy, steroids, pyridostigmine, azathioprine	Favorable
11	Lin (2014) [6]	26–36% decrease in amplitude on RNS and myopathic units.	Neostigmine, steroids, thymectomy, radiotherapy	Favorable
12	Shah (2015) [7]	Could not assess for NMJ disorder.	IVIg, steroids, thymectomy	Favorable
13	Stefanou (2016) [9]	Spontaneous activity (fibrillation and positive sharp wave)	Pyridostigmine, steroids, azathioprine	Favorable
14	Rodriguez (2018) [27]	Postsynaptic NMJ involvement	Steroids, pyridostigmine, IVIg, thymectomy, azathioprine (which was changed to MTX)	Favorable
15	Iqbal (2019) [8]	13% decrease in amplitude on RNS	Steroids, mycophenolate mofetil	Favorable
16	Current case (2020)	No amplitude decrement on RNS. Increased insertional activity, spontaneous activity (fibrillation), and small polyphasic potentials with short duration motor units.	Steroids, PLEX	Unfavorable (expired)

[ref], reference; *N. E.*, not examined; *RNS*, repetitive nerve stimulation; *EMG*, electromyography; *NMJ*, neuromuscular junction; *PLEX*, plasma exchange; *IVIg*, intravenous immunoglobulin; *MTX*, methotrexate

For treatments of concurrent giant cell myositis and myasthenia gravis, most patients received corticosteroids (10/16, 62.5%). Other treatments included anticholinesterase inhibitors (5/16, 31.3%), thymectomy (5/16, 31.3%), azathioprine (4/16, 25%), IVIg (3/16, 18.8%), and PLEX (2/16, 12.5%). Cyclophosphamide, methotrexate, and mycophenolate mofetil were given to one patient each. Eight patients died, and one patient survived but had no clinical improvement after therapy. These patients were defined as having an “unfavorable” clinical outcome (Table 5), while a “favorable” clinical outcome designation was given to those who had symptomatic relief or complete remission after hospitalization with continued outpatient immune suppression.

Of the 7 studies with favorable outcomes, most of them (4/7, 57.1%) employed a combination therapy of thymectomy, anticholinesterase inhibitors, and immunosuppression, usually by steroids. 28.6% of studies (2/7) with favorable clinical outcomes achieved these effects with either steroids alone [23] or with steroids and mycophenolate mofetil [8]. Finally, Shah et al. successfully managed the patient’s symptoms with a combination of thymectomy, steroids, and IVIg (1/7, 14.3%) [7].

Discussion

We present a case of an 82-year-old woman who developed concomitant giant cell myositis and myasthenia gravis. From

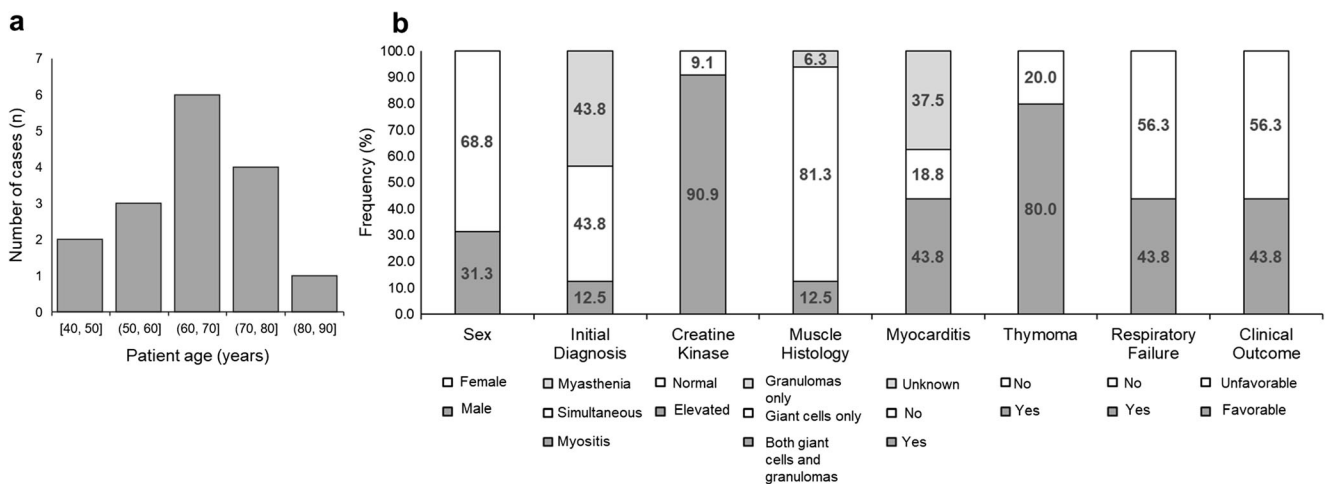


Fig. 4 Clinical characteristics of patients with concurrent giant cell myositis and myasthenia gravis. **a** Age histogram of all patients from the literature review. **b** Frequencies of various demographic, clinical, laboratory, histological, and prognosis characteristics among this patient cohort

our review of 16 cases in the literature, we found that this rare disease association most commonly affects women, usually in the 6–7th decades, and is often rapidly progressive with a high mortality. Autoantibodies targeting the AChR were the most commonly positive serological test (positive in 10 out of 10 of the examined studies), followed closely by antibodies against striational muscle (positive in 7 out of 8 of the examined studies). In contrast, none of the patients had positive myositis-specific antibodies, although the number of studies measuring MSAs was modest. Furthermore, aside from our case report, previous statin use was not mentioned in any of the other studies analyzed in this review. Since these data are unavailable, it is currently unclear if statin toxicity plays a role in the pathogenesis of concurrent myasthenia gravis and giant cell myositis. However, the existence of this disease association prior to the development of statin drugs in the 1980s, as well as the lack of typical pathologic findings of statin toxicity argue against a significant role of statins in these cases [37].

Our patient’s EMGs rapidly progressed over a period of 18 days. The initial EMG revealed subtle changes, including normal motor nerve conduction studies with few small motor unit action potentials (MUAPs) without spontaneous activity which is consistent with a myopathic process without muscle membrane irritability. In contrast, the last EMG revealed marked reduction in CMAP amplitudes in proximal and distal muscles with diffuse and florid spontaneous activity and no recruitable motor units; we interpreted this finding as a loss of continuity between the motor axon and muscle fibers. Despite this electrical progression, the CKs trended downward, which we suspect was due to severe failure of neuromuscular transmission (i.e., between the motor axon and muscle endplate) causing a “functionally myopathic” picture rather than that of a rampant myositis, in which elevated and/or uprending CKs would have been expected [38]. Despite

our proposed mechanism of failure of neuromuscular transmission, her repetitive nerve stimulation test was normal; however, this has been reported in cases of acute-onset MG [39].

In our review of the literature, we encountered the term “granulomatous myositis” in addition to and sometimes instead of the term “giant cell myositis” in the description and labeling of the cases being reported. Notably, however, the histologic findings in each of the 16 cases were characterized by the presence of giant cells with 11 of 16 being reported in skeletal muscle, 4 of 16 in skeletal muscle and myocardium together, and 1 of 16 in the myocardium alone. In contrast, only 3 of 16 cases reported granulomas. We therefore propose using the term “giant cell myositis” when referring to the disease association with myasthenia gravis; unless, the histological results for the patient specifically show granulomas without giant cells (a finding that was not common in our systematic review).

The co-occurrence of myasthenia gravis with other forms of IIM, particularly polymyositis, is well supported in the literature. Suzuki et al. demonstrated that the prevalence of inflammatory myopathies in a cohort of 924 MG patients was 0.9% (8/924) [16]. Similar co-existing diagnoses were reported in an analysis of 970 confirmed IIM patients, where Uchio and colleagues found that the prevalence of concomitant MG was 1.03% (10/970) [40]. The clinicopathologic features of these 10 patients were comparable to those in our literature review. Similar features included the age distribution (47–78 years), female predominance (60%), thymoma association (70%), association with respiratory failure (50%), and elevation of AChR autoantibodies (90%). Importantly, as the total incidence of respiratory failure for all myasthenia patients ranges from 15 to 20%, these data (along with our results) suggest that any concurrent inflammatory myopathy is a poor prognostic factor when present along with myasthenia gravis [41].

A plausible pathophysiologic mechanism for concurrent giant cell myositis in myasthenia gravis relates to the presence of thymomas. Our patient's CT scan did have a suspicious nodule concerning for thymic hyperplasia and possible thymoma (Fig. 2). Thymomas typically lack myoid self-antigens and can have defective expression of the autoimmune regulator (AIRE) which may cause preferential autoimmune responses to muscle antigens [42]. Additionally, based on the histological classifications in our review, bioactive B thymomas may be the most important subtype involved for this disease pathogenesis. Of the 5 studies with WHO classifications, all 5 have some aspect of bioactive thymoma histology, whether it be the mixed AB thymomas (2/5), the lymphocyte rich bioactive B1 thymomas (2/5), or the epithelial bioactive B3 thymomas (1/5). These bioactive B thymomas typically have large dendritic-shaped epithelial cellular networks which support the growth of local lymphocytic cell populations, highlighting the importance of immune dysfunction in promoting myasthenia gravis and giant cell myositis [43].

On the level of T lymphocytes, new data on cancer immunotherapies may reveal some of the underlying pathogenesis behind these diseases, as patients treated with antibody blockade of T cell inhibitory receptors, such as Programmed cell death protein-1 (PD-1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), may likewise develop symptoms of combined myasthenia gravis and inflammatory myopathic disease [44]. Additionally, giant cell myositis can also be induced with anti-PD-1 antibodies, suggesting that T cell hyperactivation may be a common critical factor in driving these phenotypes [34, 45]. Future studies investigating the expression of inhibitory and costimulatory immunoreceptors in muscle infiltrates of myositis with myasthenia gravis may help to clarify some of these questions.

Giant cell myocarditis is likewise reported in association with myasthenia gravis and can cause rapidly progressive disease with cardiac failure and sudden death from arrhythmia [7, 46]. Giant cell myocarditis is often associated with other autoimmune diseases and can even recur in allografts from a previously affected host, after heart transplant [47]. Although we never performed an autopsy to confirm whether our patient had giant cell myocarditis, her troponin levels were elevated on admission which may have been an indication of cardiac involvement.

Our review has several limitations. First, because of the patient's family's wishes, we did not have access to an autopsy to histologically confirm the presence of a thymoma or myocarditis. Second, the diagnostic studies reported in our review differed at least partly because of the wide variability in the time periods of the publications analyzed. Third, as this was a literature review of previous publications, we were limited to reporting the clinical histories and laboratory tests

provided in the texts. Finally, conclusions on the relative efficacy of treatment options are difficult to achieve with a retrospective study based on a modest number of patients.

In summary, we provide a retrospective, case-based review of concomitant giant cell myositis and myasthenia gravis. We conclude that this rare disease association commonly affects women, peaks in the 6–7th decade, is associated with the presence of bioactive thymomas and elevated AChR binding antibodies in the absence of MSAs, and frequently has a rapidly progressive course featuring respiratory failure and a high mortality. The typical histological findings consist of multinucleated giant cells within muscle with only a minority exhibiting granuloma formation. Patients typically present initially with MG features alone or with myositis; less commonly myositis presents first as was the case in our patient, and later develop features of MG. Awareness not only of the disease association but of the fact that they may not present simultaneously is important, as to not exclude either potential co-existing diagnoses even in the setting of normal repetitive nerve stimulation studies. In conclusion, this work provides the first systematic review of concurrent giant cell myositis and myasthenia gravis and lays the foundation to support future studies of this rare disease association.

Code availability Not applicable.

Author contribution The case was diagnosed and followed up by LAB, MLO, AG, KA, OS, and MV. FAS, LAB, MLO, AG, and RK conceived and planned the case report. Literature review and article collection were performed by FAS. Data collection was performed by FAS, LAB, and MLO. Data analysis and literature review figure preparation were performed by FAS. FAS, LAB, and MLO wrote the initial manuscript with help from AG, KA, OS, MV, and RK all revised and edited the manuscript. The final version was read, corrected, and approved by all the authors.

Data availability Not applicable.

Compliance with ethical standards

Ethics approval This manuscript does not contain clinical studies or identifiable patient data.

Disclosures None.

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