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Giant cell myositis associated with metastatic thymoma and granulomatous hypercalcaemia

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SUMMARY

Giant cell myositis (GCM) is a rare inflammatory myopathy associated with myasthenia gravis and thymoma. Here, we report on a woman in her late 50s with a history of myasthenia gravis, systemic lupus erythematosus and stage IV thymoma with pleural metastases, who presented with proximal weakness, neuromuscular respiratory failure and hypercalcaemia. She was diagnosed with GCM via muscle biopsy and screened for myocarditis but showed no evidence of myocardial involvement. Her hypercalcaemia was consistent with a granulomatous process, likely driven by her GCM. Her strength gradually improved, and her hypercalcaemia did not recur after treatment with high dose steroids, intravenous immune globulin and plasma exchange. Her course was complicated by several opportunistic infections in the setting of her immunosuppression. Despite the high morbidity associated with GCM, she demonstrated clinical improvement after initiating immunosuppressive therapy and continues to be managed in the outpatient setting.

BACKGROUND

Giant cell myositis (GCM) is a rare inflammatory myopathy characterised by proximal weakness, and histopathology revealing multinucleated giant cell infiltration of muscle fascicles and associated myofiber necrosis.[1] To date, GCM has been strongly associated with myasthenia gravis (MG) or thymoma,[2 3] and can involve cardiac tissue leading to a rapidly progressive giant cell myocarditis with a high rate of mortality. Here, we present a case of GCM associated with metastatic thymoma and MG, highlighting unique clinical features and their relevance to the existing literature.

CASE PRESENTATION

A woman in her late 50s with a history of MG, systemic lupus erythematosus and stage IV thymoma with pleural metastases, presented with 3 weeks of generalised pain and weakness after receiving the influenza vaccine. At baseline, the patient was active and independent, on a home medication regimen that included prednisone 5 mg, azathioprine 125 mg and hydroxychloroquine 200 mg daily. She was in her usual state of health until she went for her annual influenza vaccine which she received in her left arm. Three days later, she developed left arm swelling and pain, with progressive weakness that involved her bilateral upper and lower extremities, eventually becoming too weak to ambulate. During this time, she also developed dyspnoea on exertion, palpitations, polydipsia, polyuria and non-bilious non-bloody emesis. Review of systems was negative for diplopia, fevers, chest pain, diarrhoea or dysuria. Regarding her thymoma and MG history, the patient was diagnosed with a thymoma 8 years earlier for which she underwent a resection and radiation therapy the following year. Pathological examination revealed a mixed type B2 and B3 thymoma with positive margins, stage IVa, pT4N0, and she was noted to have residual tumour with pleural metastases that were slowly growing and being monitored. She was subsequently diagnosed with MG the year prior to presentation after developing bulbar symptoms and testing positive for acetylcholine binding receptor antibody. She had no history of a myasthenic crisis, and her symptoms were well controlled prior to presentation.

On admission, the patient was tachycardic and hypertensive but did not appear in acute distress. She had proximal greater than distal weakness in her bilateral upper and lower extremities (Medical Research Council Scale for muscle strength: 4/5 in deltoids, biceps brachii and triceps but 4+/5 in finger flexors and extensors; 3/5 in iliopsoas and 4/5 at tibialis anterior), 4/5 strength with neck flexion and maximal inspiratory pressure of −30 cm H_2O. Her left upper extremity was diffusely swollen from the bicep to the dorsum of the hand with non-pitting oedema. Laboratory studies were notable for a mild leucocytosis, severe hypercalcaemia to 14.2 mg/dL, an elevated creatine kinase (CK) to 1541 U/L, as well as elevated C reactive protein, erythrocyte sedimentation rate, transaminases and lactate dehydrogenase (table 1).

Her hypercalcaemia was treated with fluids, calcitonin and zolendronic acid. Her home azathioprine and prednisone were continued. She was admitted to the intensive care unit (ICU) for respiratory monitoring and started on a 5-day course of intravenous immune globulin (IVIG) given concern for a myasthenic crisis. On hospital day 2, she developed a fever without a clear infectious source which was treated empirically with broad spectrum antibiotics and was subsequently intubated for progressive respiratory insufficiency. She required mechanical ventilation in the ICU but did not require sedation for the remainder of her hospital course.

During her fever workup, a CT of the abdomen and pelvis demonstrated abnormal signal of the proximal thighs and pelvic girdle musculature concerning for myositis. She underwent electromyography of the left arm which demonstrated a diffuse myopathic process without membrane

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Table 1 Patient laboratory study results on admission

Laboratory values (units)	Case results	Reference range
Leucocytes (/L)	11.6	3.4–10.0×10^9
Haemoglobin (g/L)	138	120–155
Platelets (/L)	384	140–450×10^9
Erythrocyte sedimentation rate (mm/hour)	19	0–15
C reactive protein (mg/L)	96.7	<5.1
Alanine transaminase (U/L)	306	10–61
Aspartate transaminase (U/L)	184	5–44
Alkaline phosphatase (U/L)	50	38–108
T bili (mg/dL)	0.5	0.2–1.2
Creatine kinase (U/L)	1541	37–241
Lactate dehydrogenase (U/L)	1534	125–243
Troponin (µg/L)	0.04	0.00–0.04
Sodium (mmol/L)	133	135–145
Potassium (mmol/L)	4.1	3.5–5.0
Chloride (mmol/L)	95	101–110
CO_2 (mmol/L)	27	22–29
BUN (mg/dL)	37	7–25
Creatinine (mg/dL)	1.04	0.55–1.02
Glucose (mg/dL)	101	70–199
Anion gap	11	4–14
Calcium (mg/dL)	14.2	8.4–10.5
Parathyroid hormone (ng/L)	22	18–90
Vitamin D, 25-hydroxy (ng/L)	56	20–50
Vitamin D, 1,25-dihydroxy total (ng/L)	>150	20–79
Parathyroid hormone related protein (PMOL/L)	0.9	<4.3

BUN, blood urea nitrogen.

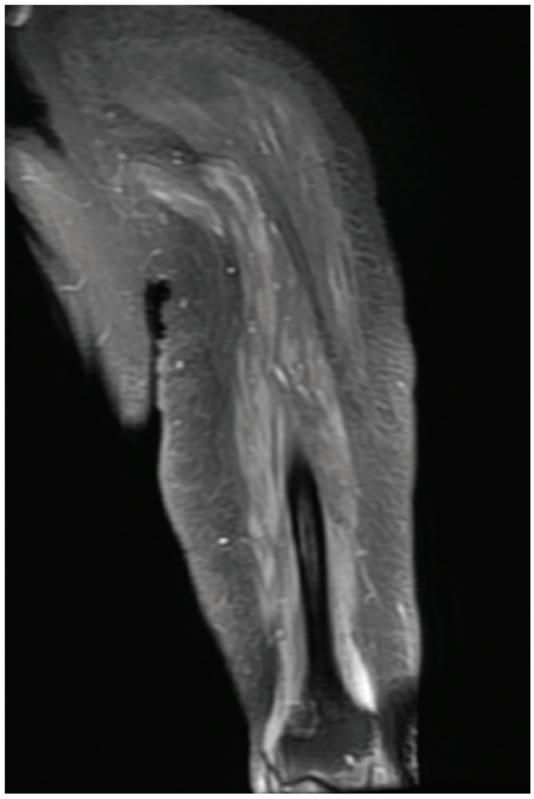

Figure 1 Left humerus gadolinium-enhanced fat-saturated T1-weighted MRI coronal image, showing diffuse enhancement of musculature consistent with myositis.

irritability, most consistent with a critical illness myopathy rather than an inflammatory myopathy. Moreover, myositis autoantibody panel and serology for 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase antibody were negative. Subsequently, MRI of her left upper extremity and right thigh revealed diffuse oedema throughout the musculature compatible with myositis (figure 1).

A muscle biopsy of the right biceps brachii was then performed, which revealed a dense lymphohistiocytic infiltrate with abundant multinucleated giant cells and frequent degenerating/regenerating muscle fibres (figure 2A). Immunohistochemistry revealed abundant CD68-positive macrophages and giant cells (figure 2B), a dense endomysial population of CD3-positive T-lymphocytes and only scattered CD20-positive B-lymphocytes. Immunohistochemistry for Major Histocompatibility Complex I (MHC-I) showed strong and diffuse sarcolemmal staining of the muscle fibres, indicative of upregulation of MHC-I. A stain for acid-fast bacilli did not reveal any acid-fast microorganisms. Notably, this pathology was not characteristic of a hydroxychloroquine myopathy[4] and demonstrated an alternate diagnosis of GCM.

On admission, her troponin level was normal, and ECG demonstrated sinus tachycardia. On diagnosis of GCM, the patient underwent an echocardiogram to assess for potential cardiac involvement which revealed normal biventricular function.

Workup for hypercalcaemia demonstrated a significantly elevated vitamin D 1,25 dihydroxy (table 1), which was consistent with a parathyroid hormone independent, granulomatous aetiology. The patient's home vitamin supplements were reviewed by hospital nutritionists and there was no evidence of a supplement that could account for an elevation in vitamin D 1,25 dihydroxy. CT of the chest and abdomen/pelvis obtained during the hospitalisation did not reveal hilar adenopathy or other lesions concerning for sarcoidosis or lymphoma. Her CT chest showed an interval size increase in multiple left pleural droplet thymoma metastases (figure 3). After initial temporising

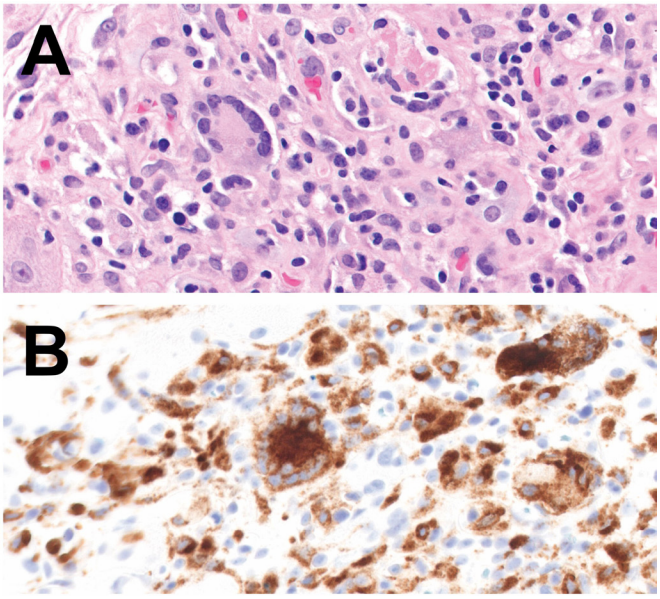

Figure 2 (A) Right biceps brachii muscle biopsy reveals scattered degenerating and regenerating fibres with associated lymphohistiocyte-rich inflammation and multinucleated giant cells (H&E 400×). (B) The giant cells are immunoreactive for CD68 (CD68 immunostain 400×).

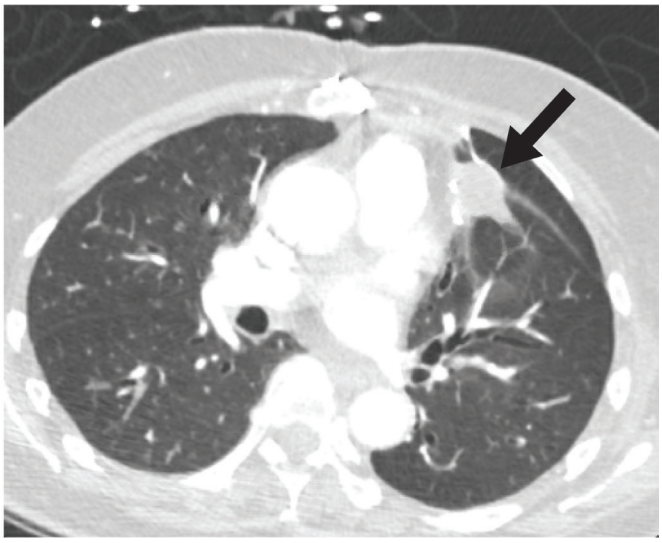

Figure 3 Axial view CT chest with contrast showing thymoma pleural metastases (black arrow).

treatments on admission and with treatment of the patient's GCM as described below, the patient's hypercalcaemia did not recur during the remainder of her hospital course.

TREATMENT

She was treated with a 5-day course of IVIG on admission for a presumed myasthenic crisis, and empiric treatment of myositis was initiated on hospital day 10 with 1 mg/kg/day of IV methylprednisolone after the muscle biopsy was obtained. Her CK levels began to decrease within 48 hours of treatment, but her proximal and respiratory weakness remained unchanged. A tracheostomy was performed on hospital day 13. She was treated with 5 days of plasma exchange (PLEX) starting on hospital day 15 for a presumed component of myasthenic crisis to her respiratory weakness. On hospital day 18, she received 3 days of pulse steroids (1 g/day IV methylprednisolone) after her muscle biopsy pathology provided the diagnosis of GCM, after which she resumed 1 mg/kg/day dosing.

OUTCOME AND FOLLOW-UP

Her course was complicated by cytomegalovirus (CMV) diverticulitis with associated perforation requiring emergent exploratory laparotomy and hemicolectomy with Hartmann's ostomy on hospital day 22. She was treated with a 3-week course of valganciclovir for CMV viremia that was completed as an outpatient.

A gastrostomy tube was placed on hospital day 35 for ongoing dysphagia but she subsequently regained swallowing function and resumed a regular diet while in the hospital. She was discharged home with services after a 6-week hospital course with a tracheostomy and gastrostomy tube still in place, with planned decannulation and closure as an outpatient. At the time of discharge, her proximal strength was slowly improving but the patient was still bed-bound. Her discharge medications included her home azathioprine and prednisone 60 mg daily with plans to complete a slow taper as an outpatient. On returning home, her strength continued to improve, and she was decannulated and took her first steps with a walker approximately 1 month after discharge.

She was readmitted to the hospital 2 months after discharge with acid-fast bacilli bacteraemia and intraabdominal polymicrobial abscesses that required percutaneous drainage by an interventional radiologist, and a prolonged antimicrobial course. She was also treated for an extended spectrum beta-lactamase producing *Escherichia coli* bacterial urinary tract infection during this admission. Her prednisone dose had been decreased to 30 mg daily at time of readmission.

Her outpatient rheumatologist and oncologist opted to avoid further immunosuppressive agents given the patient's numerous infections, thus rituximab treatment was deferred in favour of monthly 2 g/kg IVIG treatments. The patient continues to be followed as an outpatient and is more than 6 months post-biopsy.

DISCUSSION

The above case demonstrates important clinical considerations when managing a patient with GCM. While the patient in this case did not develop giant cell myocarditis, it is critical to assess for cardiac involvement in the acute setting, as GCM has been associated with giant cell myocarditis in over 40% of cases reported to date[2] which can lead to a rapid clinical deterioration with a high mortality rate.[3 5–8] Regarding treatment, this patient responded to a combination of steroids, IVIG and PLEX therapy for treatment of her comorbid MG. This patient's comorbid MG presented a challenge in selecting an appropriate treatment regimen, as throughout her hospital course, it was unclear if her respiratory failure was secondary to a concomitant myasthenic crisis or diaphragmatic involvement of GCM or both, which could not be delineated in the absence of a diaphragm biopsy. Obtaining a biopsy of the diaphragm in living patients is complicated by diaphragmatic movement with respiration, thus diaphragm pathology is usually assessed postmortem. Interestingly, one recent study reported CT-guided needle biopsy of the diaphragm in a patient with respiratory failure and suspected sarcoidosis involving the diaphragm.[3] The procedure was accomplished safely by obtaining the biopsy at the crura of the diaphragm which is fixed, and the biopsy confirmed the diagnosis and was used to guide treatment. Thus, obtaining a diaphragm biopsy may be useful in cases of neuromuscular respiratory failure and GCM, as giant cell inflammation of the diaphragm would considerably affect clinical management. Although the treatment regimen used in this case is in line with therapies used previously,[2] there is no consensus on steroid dosing, maintenance therapy or steroid sparing agents. Furthermore, as demonstrated here, analysis of additional cases will be required to determine whether the benefit of various immunosuppressive therapies outweighs the risk of opportunistic infections.

Regarding the patient's diagnosis of GCM, it is important to consider sarcoid myopathy in this case, which can also present as an acute granulomatous myositis. Histologically, sarcoid myopathy presenting as a granulomatous myositis cannot definitively be differentiated from GCM given significant overlapping morphologic features[9]; however, the diagnosis of sarcoid myopathy requires evidence of sarcoid involvement in at least one additional organ system. In this case, there was no clinical evidence of multisystem sarcoidosis, nor identification of non-myopathic sarcoid lesions from extensive imaging which was obtained throughout her hospital course.

This case also had several unique clinical features that have thus far only rarely been reported. First is the patient's presentation with severe hypercalcaemia, which was consistent with a

granulomatous driven process. Granulomatous hypercalcaemia has been described in cases of sarcoidosis and lymphoma; however, no evidence of these conditions was identified during the patient's workup. Moreover, the patient's hypercalcaemia did not recur after treatment of her GCM. Thus, the aetiology of her granulomatous hypercalcaemia was favoured to be secondary to her GCM, as macrophages and giant cells convert 25-hydroxy vitamin D to 1,25 dihydroxy via increased 1alpha-hydroxylase activity.[10] This is a rare aetiology of granulomatous hypercalcaemia that has only been reported in a handful of case reports to date.[11–14]

Regarding the patient's concomitant metastatic thymoma, although an association between thymoma and GCM has been previously described,[2] few reports have included thymoma staging and pathological subtypes.[3 15–18] Metastatic thymoma is relatively rare, as only approximately 12% of thymic tumours have been found to invade distant structures,[19 20] most commonly pleura or pericardium.[21] Despite the low incidence of metastatic thymoma, 2 out of 5 of the above cited GCM cases describe thymomas with radiographic or autopsy evidence of pleural metastases[3 17] in addition to the case described in the current report. Additional GCM case studies with concomitant thymoma staging and subtype will be required to determine if metastatic thymoma is an independent risk factor for developing GCM. Still, considering the high morbidity and mortality associated with GCM, clinicians should consider this diagnosis when caring for patients with metastatic thymoma who present with weakness and muscular pain.

Finally, it was notable that this patient's symptoms began shortly after receiving the influenza vaccine, suggesting that the effects of the vaccination may have precipitated the onset of GCM in this individual. Previous reports have highlighted an association between vaccine administration and symptom onset of immune-mediated conditions, possibly explained by vaccine adjuvants with inflammatory properties.[22–24] Such conditions are referred to as autoimmune/inflammatory syndrome induced by adjuvants (ASIA).[25] Within this spectrum of conditions, inflammatory myopathies associated with vaccine administration have been described.[26–28] Given the temporal association between the patient's receipt of the influenza vaccine and myopathy symptom onset, a diagnosis of ASIA cannot be excluded in this case. Importantly, ASIA is an extremely uncommon condition, and a review of the literature found no significant increase in the incidence of inflammatory myopathies following previous vaccination campaigns.[27] Thus, the risk of developing a reactive inflammatory myopathy following vaccine administration pales in comparison to the significant benefits of protection against infection conferred by vaccination.

Learning points

- Clinicians should perform an expedited workup for cardiac involvement in all cases of giant cell myositis (GCM) given the rapid progression and mortality associated with giant cell myocarditis.
- Consider myositis in patients with myasthenia gravis (MG) with metastatic thymoma presenting with weakness and muscular pain given the strong association between GCM, MG and thymoma.
- Steroids and intravenous immune globulin may serve as a reasonable treatment regimen for GCM given patient responses in multiple case reports to date.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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