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CASE REPORT
Heart failure

Successful bridge to recovery in a patient with fulminant giant cell myocarditis that developed from multiple autoimmune disorders including myasthenia gravis: a case report

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Background A recently indicated immunotherapy strategy, combined with mechanical circulatory support (MCS), seems to improve outcomes in patients with fulminant giant cell myocarditis (GCM). However, characterizing a definitive clinical outcome of this strategy remains challenging, and the autoimmunity associated with the onset of GCM remains controversial.

Case summary A 26-year-old man with poor control of atopic dermatitis and ulcerative colitis presented with cardiogenic shock requiring MCS. He was diagnosed with fulminant GCM; hence, immunotherapy (including steroids and intravenous immunoglobulin) was administered and an extracorporeal left ventricular assist device (LVAD) was needed. As the patient complained of prominent fatigue and double vision before myocarditis onset, and acetylcholine receptor-binding antibody titres were elevated, he was diagnosed with myasthenia gravis (MG). No anti-striational antibodies known to be associated with GCM in patients with MG were found in the patient's serum. Cyclosporin-based immunosuppression under LVAD therapy led to an almost complete resolution of his muscle weakness, intermittent ptosis, and cardiac dysfunction along with the histopathological remission of GCM resulting in LVAD removal. He remained at home without recurrence of GCM and worsening symptoms of MG over the 6-month period following discharge.

Discussion We describe a case of GCM with multiple autoimmune disorders, which recovered by treatment with early cyclosporin-based immunosuppressive therapy under LVAD therapy. The present case suggests the involvement of unknown anti-striational antibodies in the development of GCM in patients with MG and may provide information to guide a novel therapeutic regimen for patients with fulminant GCM requiring mechanical circulatory support.

Keywords Giant cell myocarditis • Bridge to recovery • Ventricular assist device • Autoimmune disorder • Myasthenia gravis • Case report

ESC Curriculum 6.4 Acute heart failure • 6.2 Heart failure with reduced ejection fraction

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Learning points

- A modified immunotherapy regimen including aggressive cyclosporin-based immunosuppression combined with ventricular assist device could achieve successful bridge to recovery in patients with fulminant giant cell myocarditis (GCM) accompanied by myasthenia gravis (MG).
- Unknown anti-striational antibodies may affect the development of GCM in patients with MG.
- The activation of the autoimmune system in patients with multiple autoimmune disorders may be associated with the development of giant cell cardiomyopathy.

Introduction

Giant cell myocarditis (GCM) is associated with various non-cardiac autoimmune disorders and has been suggested to be associated with some anti-striational antibodies that bind to the heart muscle.[1,2] Giant cell myocarditis is a fatal inflammatory heart disease that has historically led to very high death rates or cardiac transplantation.[1,3] Although recent immunotherapy strategies combined with mechanical circulatory support (MCS) improve patient outcomes,[4] the clinical course of this disease is still challenging, particularly in patients with ventricular assist device.[5] Concomitant autoimmunity conditions may correlate with patient prognosis and therapeutic strategy selections.[2] Herein, we describe a case that had successful bridge to recovery in a patient with fulminant GCM presenting multiple non-cardiac autoimmune disorders and unique autoimmunity status.

Timeline

7 years prior	Patient was diagnosed with ulcerative colitis.
2 years prior	He was diagnosed with atopic dermatitis.
Admission	He presented to our hospital with fever and chest. His haemodynamic status was an unstable. Veno-arterial extracorporeal membrane oxygenation and intra-aortic balloon pumping (IABP) were initiated. Steroid pulse therapy and intravenous immunoglobulin were administered. He was diagnosed with giant cell myocarditis (GCM).
Day 2	Veno-arterial extracorporeal membrane oxygenation and IABP were switched to an extracorporeal biventricular assist device system.
Day 5	Right ventricular support was removed.
Day 18	He complained of fatigue and double vision during rehabilitation. Acetylcholine receptor-binding antibody titres were elevated at 6.3 nmol/L. He was diagnosed with myasthenia gravis (MG).
Day 33	Combined immunosuppressive therapy with cyclosporine and steroid was started.
Day 41	We performed left ventricular assist device removal and concomitant extended thymectomy for thymoma.
Day 91	He was discharged with an almost complete solution of GCM and MG.
6-month follow-up	He remained at home without recurrence of GCM and did not have worsening symptoms of MG.

Case presentation

A 26-year-old man with a 7-year history of ulcerative colitis (UC) and a 2-year history of atopic dermatitis (AD) presented to our hospital with fever and chest pain. He had been treated for UC with 5-aminosalicylic acid (mesalamine, 4000 mg/day), but this regimen was erroneously disregarded based on his self-judgement 6 months before admission. He had also refused topical steroid treatment and had only been using a moisturizer to treat AD skin lesions; hence, his AD was poorly controlled. On admission, he appeared visibly unwell and presented with an unstable haemodynamic status. Laboratory results suggested multiple organ failure (MOF), with aspartate aminotransferase level of 1299 U/l, alanine aminotransferase level of 1142 U/l, creatinine level of 1.44 mg/dL, creatine kinase level of 3029 IU/L, and creatine-MB isoenzyme level of 136 IU/L. Echocardiography revealed a severely reduced left ventricular ejection fraction (LVEF) of 16% (*Figure 1A* and *B*). After tracheal intubation, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) and intra-aortic balloon pumping (IABP) were initiated. He was presumptively diagnosed with fulminant myocarditis with cardiogenic shock. On Day 2, VA-ECMO and IABP were switched to an extracorporeal biventricular assist device (BiVAD) system under median sternotomy. Histopathological examination of the endomyocardial biopsy on admission led to a diagnosis of GCM (*Figure 2A* and *B*).

Steroid pulse therapy (intravenous methylprednisolone, with a dose of 1000 mg/day for 3 days) and intravenous immunoglobulin (IVIG, 5 g/day for 3 days) were administered. Following this, the patient was administered steroid therapy via oral prednisolone (60 mg daily), which was subsequently reduced (see *Figure 3*). The patient's MOF gradually improved with the support of BiVAD; hence, on Day 5, right ventricular support was removed after extubation, and rehabilitation was started with the remaining left ventricular assist device (LVAD) support. The patient complained of fatigue and double vision during rehabilitation. Three months before the present

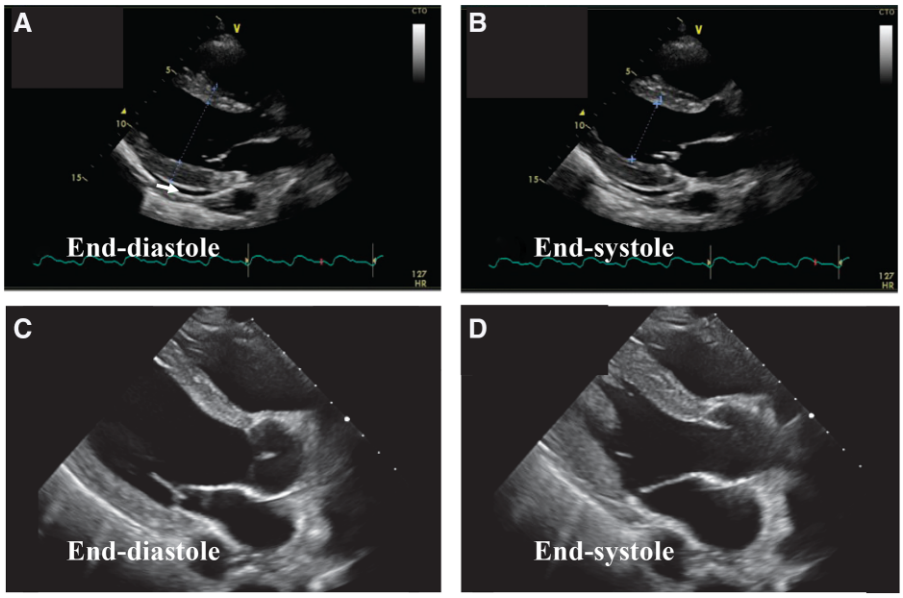

Figure 1 Echocardiographic and electrocardiographic findings. (*A*) On the day of admission, an end-diastolic image and (*B*) an end-systolic image on the parasternal long-axis view . Pericardial effusion was detected (indicated with a white arrow), and a thickened ventricular wall and severe bi-ventricular dysfunction were observed. We observed a hypertrophied interventricular septum thickness and posterior left ventricular wall thickness of 11 and 15 mm, respectively, as well as a left ventricular ejection fraction of 16%. Left ventricular diameter was not enlarged; the left ventricular diastolic diameter and left ventricular systolic diameter were 46 and 43 mm. (*C*) On postoperative Day 36 after left ventricular assist device removal, the end-diastolic image and (*D*) the end-systolic image on the parasternal long-axis view are shown. Cardiac function and wall thickening improved to the normal range: left ventricular ejection fraction = 56%, interventricular septum thickness/posterior left ventricular wall thickness = 8/8 mm. The left ventricular diastolic diameter and left ventricular systolic diameter were 51 and 33 mm. (*E*) At admission, electrocardiography is shown.

hospital admission, he was aware of intermittent ptosis. Physical examination revealed weakness in all skeletal muscles and orbicularis oculi muscles. Acetylcholine receptor (AchR)-binding antibody titres were elevated at 6.3 nmol/L (*Table 1*). Computed tomography of the chest did not reveal an apparent thymoma. Based on these findings, the patient was diagnosed with myasthenia gravis (MG) without thymoma. Oral prednisolone was tapered to 20 mg, and subsequently, cyclosporine (CYA) was started with a target trough level of 100–150 ng/mL. These treatments led to an almost complete resolution of muscle weakness, intermittent ptosis, and improved cardiac function with no infiltration of eosinophils or giant multinucleated cells.

On Day 41, we performed LVAD explantation and concomitant extended thymectomy as a treatment for MG. In addition, high-dose IVIG (25 g/day) was administered to prevent postoperative myasthenic crisis on Days 1–2 after LVAD explantation. Thymus hyperplasia was not anatomically observed, and histopathological findings did not show a thymoma (*Figure 2C–E*). Postoperatively, the patient recovered uneventfully with normal neurologic and end-organ function, and follow-up biopsy on Day 80 showed improvement of the inflammatory component of his disease presentation, with no giant multinucleated cells or injury (i.e. findings of resolving myocarditis) (*Figure 2F* and *G*). His LVEF improved to 56% on Day 36 after the LVAD explantation (*Figure 1C* and *D*). Regarding MG, he achieved minimal manifestation status, and the AchR-binding antibody titres gradually decreased. The patient was discharged on Day 91. During his hospital stay, he achieved maintenance of remission in UC and improved control in AD. He remained at home without recurrence of GCM and did not have worsening symptoms of MG over the 6-month follow-up period following discharge.

Discussion

Combined double- or triple-drug CYA-based immunosuppressive regimens have been used with evidence of improvement in terms of clinical remission and heart transplantation-free survival rates in patients with GCM.[6–8] However, since the early administration of immunosuppressants may lead to MCS-related infections, which is one of the critical complications occurring during MCS, they may need to be cautiously prescribed in patients with fulminant GCM requiring MCS. Our previous study reported poor clinical outcomes in patients with fulminant GCM requiring LVAD. Specifically, all three patients with fulminant GCM requiring extracorporeal LVAD treated with single steroid therapy during LVAD support died; one of these patients was prescribed CYA after LVAD explantation.[3] The present patient was successfully rescued from fulminant GCM by introducing CYA after reducing his oral prednisolone dose to 20 mg/day while wearing an extracorporeal LVAD. Thus, this case may provide valuable information regarding another option for immunotherapy regimens in patients with GCM requiring LVAD.

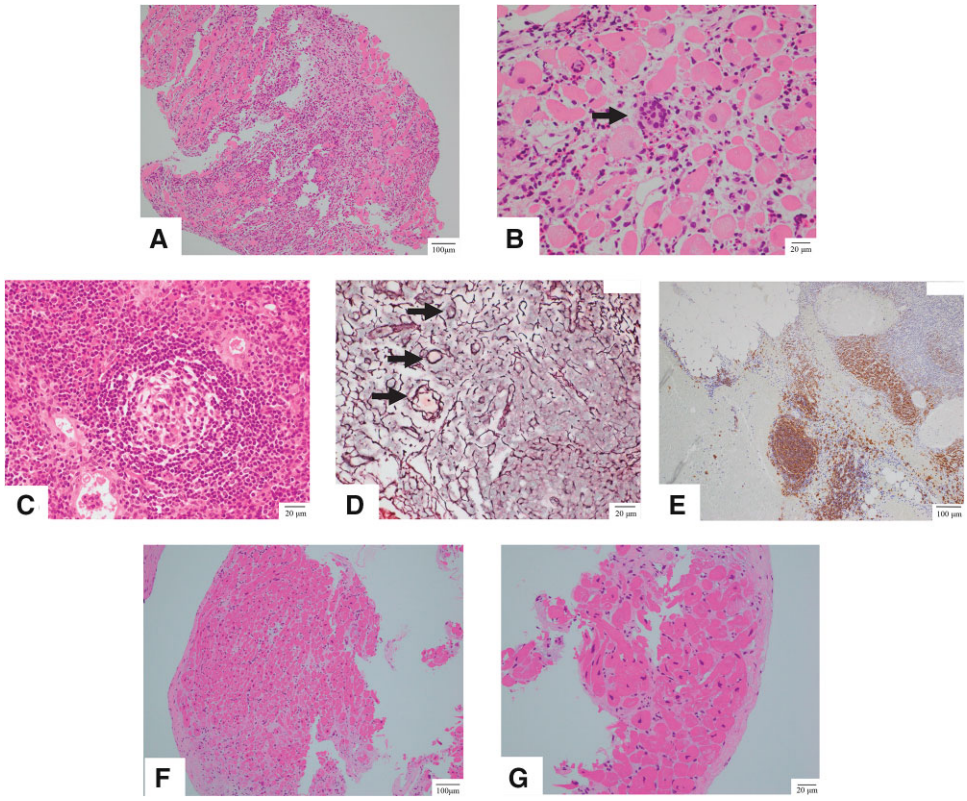

Figure 2 Histopathological findings. (*A* and *B*) On the day of admission, the histological findings of the initial biopsy of the right ventricular septum are shown. Diffuse myocardial necrosis with infiltration by lymphocytes, eosinophils, and multinucleated giant cells (indicated with a black arrow) were observed (*A*: haematoxylin and eosin staining, scale bar 100 μm; *B*: haematoxylin and eosin staining, scale bar: 20 μm). (*C*–*E*) Histological findings of the resected thymus, which showed no evidence of thymoma. (*E*) The findings of the lymphoid follicle are shown. (*D* and *E*) The aggregation of postcapillary venule (black arrows) and the lymphoid follicle consisting of B lymphocytes, which is a characteristic finding for myasthenia gravis patients, respectively are shown (*C*: haematoxylin and eosin staining, scale bar 20 μm; *D*: Silver statin, Watanabe's method, scale bar 20 μm; *E*: immune stain for CD20, scale bar 20 μm). (*F* and *G*) Histological findings of the follow-up endomyocardial biopsy on Day 80, which revealed no infiltration of eosinophils and multinucleated giant cells with replacement fibrosis. This finally resulted in a diagnosis of resolving myocarditis under the CYA-based immunosuppressive therapy with oral steroids (*F*: haematoxylin and eosin staining, scale bar 100 μm; *G*: haematoxylin and eosin staining, scale bar 20 μm).

The mechanism of the onset of GCM is not fully elucidated, but its development may be associated with various non-cardiac autoimmune disorders, such as MG, inflammatory bowel diseases, and thyroid diseases.[1,2,9] Our patient discontinued maintenance therapy for several autoimmune diseases at the time of GCM onset, such that the disease activities were not under control. The clinical course of the present patient may suggest a meaningful association between the activation of autoimmunity and the development of GCM.

With respect to the association between MG and GCM, Suzuki *et al.*[2] described that all patients with MG who developed myocarditis were complicated with thymoma and seropositive to the anti-muscular voltage-gated potassium channel (Kv1.4) antibody; this is one of the anti-striational antibodies that bind to the heart muscle. In the present patient, no muscle-related antibodies, including the Kv1.4 antibody, were detected, and there was no thymoma in the resected thymus. To our knowledge, this is the first report of the development of fulminant GCM in MG patients despite the absence of thymoma or any muscle-related antibodies and concomitant with UC and AD.

The therapeutic strategy for GCM with consideration for concomitant autoimmune disorders has not been established yet. Thymectomy is an effective treatment for MG with or without thymoma.[9,10] However, a previous report, which was based on a small number of cases, suggested that thymoma resection in MG may influence the secondary onset of GCM.[11] In the present case, extended thymectomy was safely performed as the treatment for MG at the same time as the LVAD explantation under median sternotomy, and recurrence of GCM was not observed.

We describe the case of a fulminant GCM patient requiring extracorporeal BiVAD with multiple autoimmune diseases who did not show the known anti-striational antibodies associated with the onset of GCM in MG patients. The patient successfully recovered after early CYA-based immunosuppressive therapy and extended

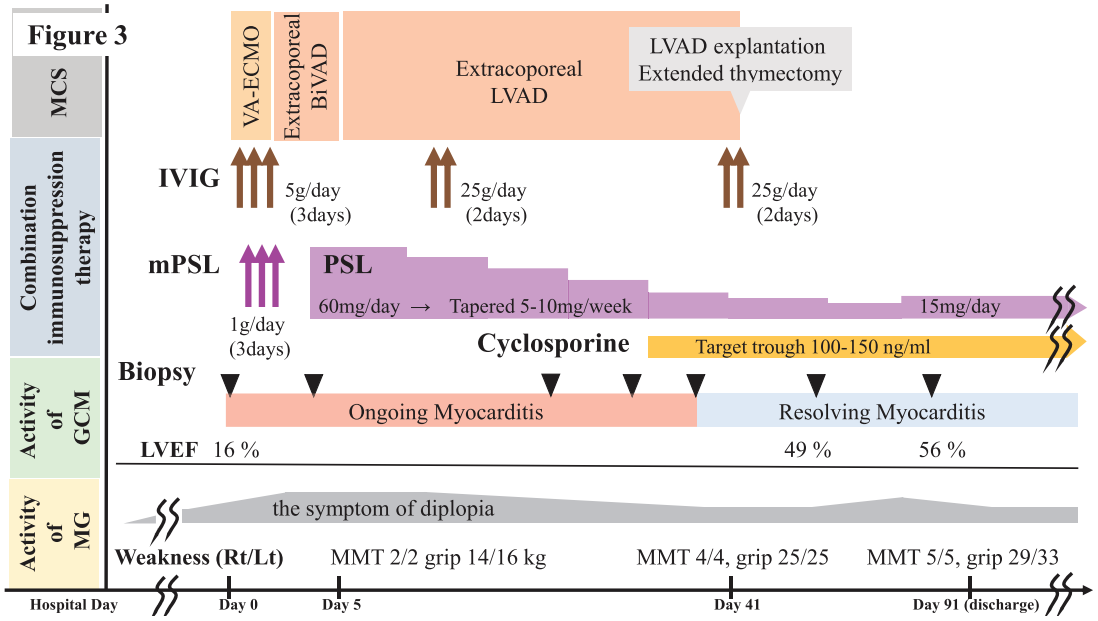

Figure 3 The clinical course. This figure shows the clinical state of diseases described in this case report as well as the implemented therapeutic strategy. The patient's right ventricular assist device was removed on Day 5 (i.e. postoperative Day 3 following biventricular assist device implantation). Following this, the patient was prescribed a steroid therapy regimen of oral prednisolone (60 mg daily), which was subsequently reduced by 5 or 10 mg/day every week until tapering. Cyclosporine was started on Day 40 when oral steroids were tapered to 20 mg/day. BiVAD, biventricular assist device; GCM, giant cell myocarditis; IVIG, intravenous immunoglobulin; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MG, myasthenia gravis; MMT, manual muscle test; mPSL, methylprednisolone; PSL, prednisolone; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

Table 1 The presence of anti-striational antibodies associated with giant cell myocarditis (GCM) in myasthenia gravis (MG) patients

Associated striational antibodies in myasthenia gravis	Result	Titers	Unit	Normal range
Acetylcholine receptor-binding antibody	Positive	6.3	nmol/L	<0.3
Muscle-specific tyrosine kinase antibody	Negative	<0.01	nmol/L	<0.02
Anti-titin antibody	Negative	0.48	arb.units	<1.0
Anti-muscular voltage-gated potassium channels antibody	Negative	0.45	arb.units	<1.0

Only an acetylcholine receptor-binding antibody was detected. The presence of anti-muscular voltage-gated potassium channel antibody, which may be associated with the onset of GCM in patients with MG, was negative in the present patient. GCM, giant cell myocarditis; MG, myasthenia gravis.

thymectomy. This case may provide a new possibility that unknown autoimmunity is involved in the pathogenesis of GCM and may likewise provide another immunotherapy option for patients with fulminant GCM who require MCS.

Lead author biography

Nobuichiro Yagi graduated from Kyoto Prefectural University of Medicine, Japan and acquired the MD degree in 2013. He has worked as a cardiovascular fellow at the Department of Transplant Medicine, National Cerebral and Cardiovascular Center, Japan from 2019. His principal field of interest is heart transplantation, ventricular assist device, cardiomyopathy, and echocardiography.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

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References

1. Cooper LT, Berry GJ, Shabetai R. Idiopathic giant cell myocarditis—natural history and treatment. *N Engl J Med* 1997;**336**:1860–1866.
2. Suzuki S, Utsugisawa K, Yoshikawa H, Motomura M, Matsubara S, Yokoyama K et al. Autoimmune targets of heart and skeletal muscles in myasthenia gravis. *Arch Neurol* 2009;**66**:1334–1338.
3. Nakajima-Doi S, Mochizuki H, Iwasaki K, Kuroda K, Watanabe T, Tadokoro N et al. Mechanical circulatory support combined with immunosuppression for the treatment of giant cell myocarditis—a single-center experience in Japan. *Circ J* 2020;**84**:815–819.
4. Patel PM, Saxena A, Wood CT, O'Malley TJ, Maynes EJ, Entwistle JWC et al. Outcomes of mechanical circulatory support for giant cell myocarditis: a systematic review. *JCM* 2020;**9**:3905.
5. Ekstrom K, Lehtonen J, Kandolin R, Räisänen-Sokolowski A, Salmenkivi K, Kupari M. Long-term outcome and its predictors in giant cell myocarditis. *Eur J Heart Fail* 2016;**18**:1452–1458.
6. Kandolin R, Lehtonen J, Salmenkivi K, Räisänen-Sokolowski A, Lommi J, Kupari M. Diagnosis, treatment, and outcome of giant-cell myocarditis in the era of combined immunosuppression. *Circ Heart Fail* 2013;**6**:15–22.
7. Koul D, Kanwar M, Jefic D, Kolluru A, Singh T, Dhar S et al. Fulminant giant cell myocarditis and cardiogenic shock: an unusual presentation of malignant thymoma. *Cardiol Res Pract* 2010;**2010**:185896.
8. Maleszewski JJ, Orellana VM, Hodge DO, Kuhl U, Schultheiss H-P, Cooper LT. Long-term risk of recurrence, morbidity and mortality in giant cell myocarditis. *Am J Cardiol* 2015;**115**:1733–1738.
9. Gondim FA, Oliveira GR, Araújo DF, Souza MH, Braga LL, Thomas FP. Two patients with co-morbid myasthenia gravis in a Brazilian cohort of inflammatory bowel disease. *Neuromuscul Disord* 2014;**24**:999–1002.
10. Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A et al. Randomized trial of thymectomy in myasthenia gravis. *N Engl J Med* 2016;**375**:511–522.
11. Joudinaud TM, Fadel E, Montpreville VT, Mussot S, Flecher EM, Dartevelle PG et al. Fatal giant cell myocarditis after thymoma resection in myasthenia gravis. *J Thorac Cardiovasc Surg* 2006;**131**:496–497.