

Fatal Myocarditis Relapse in a Patient with Myasthenia Gravis Treated with Efgartigimod Alfa: A Case Report

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Abstract

Myasthenia gravis (MG) is an autoimmune neuromuscular disorder primarily caused by autoantibodies against acetylcholine receptors (AChR), leading to muscle weakness. In 2021, efgartigimod was FDA-approved as the first neonatal Fc receptor (FcRn) blocker for generalized MG, reducing pathogenic IgG autoantibodies and improving symptoms. We present a 39-year-old woman with AChR-positive generalized MG and a history of resolved inflammatory myocarditis. Owing to persistent weakness despite intravenous immunoglobulin, she transitioned to efgartigimod. Efgartigimod induced significant neuromuscular improvement, reducing her myasthenia gravis activities of daily living (MG-ADL) score from 9 to 4. However, 3 months later, she developed fatal fulminant heart failure (LVEF 20%–25%) without concurrent skeletal muscle weakness. Despite emergency intervention with veno-arterial extracorporeal membrane oxygenation, the patient died after anoxic brain injury. Although efgartigimod effectively reduces pathogenic IgG, it may not adequately suppress cellular or cytokine-mediated inflammation driving MG-associated myocarditis. Clinicians should exercise caution and maintain cardiac monitoring when prescribing FcRn blockers to patients with a history of myocardial involvement.

Key Words: myasthenia gravis, efgartigimod, myocarditis, adverse effect

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INTRODUCTION

Myasthenia gravis (MG) is a chronic autoimmune disorder characterized by fluctuating weakness of voluntary muscles, due to autoantibodies targeting components of the neuromuscular junction, most commonly

the acetylcholine receptor (AChR), leading to impaired synaptic transmission.^{1,2}

In 2021, the FDA approved efgartigimod, the first neonatal Fc receptor (FcRn) blocker for AChR-positive generalized MG. By accelerating IgG catabolism, efgartigimod reduces pathogenic autoantibodies and improves clinical outcomes.³

We report a fatal case of myocarditis relapse during efgartigimod therapy in a patient with generalized MG.

CASE PRESENTATION

A 39-year-old woman was diagnosed with AChR antibody-positive generalized MG, after presenting during the 36th week of her ninth pregnancy as a myasthenic crisis, requiring emergency intubation. She was treated with high-dose corticosteroids, plasmapheresis (PLEX), and azathioprine. Owing to the severity of her respiratory failure, she underwent an urgent delivery, and her newborn was delivered in good health. She subsequently underwent thymectomy, with histopathological evaluation revealing a WHO type B3 thymoma. The patient's disease course and treatment phases are summarized chronologically (Fig. 1).

Despite initial improvement, after 3 weeks, the patient developed progressive shortness of breath and tachycardia. ECG demonstrated sinus tachycardia with T-wave inversions in the lateral leads. Echocardiography revealed a dilated left ventricle with severely reduced systolic function (left

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Written informed consent was obtained for the publication of this case.

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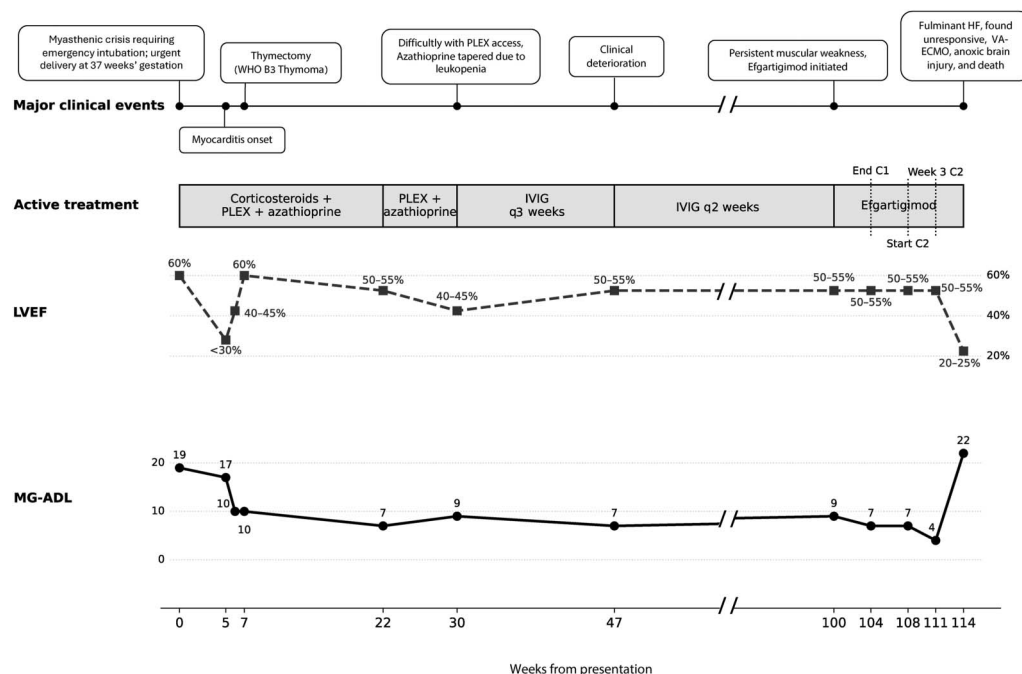


FIGURE 1. Clinical trajectory of AChR-positive generalized myasthenia gravis complicated by myocarditis. The timeline correlates major clinical events and treatment durations with the longitudinal progression of both neuromuscular disease severity (MG-ADL score) and cardiac function (left ventricular ejection fraction, LVEF). MG, myasthenia gravis; MG-ADL, myasthenia gravis activities of daily living; PLEX, plasmapheresis; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; WHO, World Health Organization.

ventricular ejection fraction [LVEF] < 30%). Troponin levels were elevated (643.45 ng/L), prompting initiation of an ACE inhibitor and Ivabradine. Right heart catheterization and endomyocardial biopsy confirmed the diagnosis of inflammatory myocarditis, with histopathological evaluation demonstrating characteristic inflammatory infiltrates. Anti-titin antibodies were negative. After treatment, the patient showed clinical and functional improvement, with LVEF increasing to 40%–45%.

Despite treatment with corticosteroids, azathioprine, and maintenance PLEX every 3 weeks, the myasthenic symptoms remained poorly controlled. Due to difficulties with PLEX access, the patient was switched to intravenous immunoglobulin (IVIg), and azathioprine was tapered after she developed leukopenia. Her generalized symptoms worsened after this change, accompanied by a decline in cardiac function. In response, the frequency of IVIg administration was

increased to every 2 weeks, which led to improved cardiac function (LVEF 50%–55%); however, she continued to experience significant proximal weakness. Given her persistent muscular weakness despite optimized IVIg therapy, maintenance treatment was switched to efgartigimod.

After the first 4-week treatment course of efgartigimod, the myasthenia gravis activities of daily living (MG-ADL) score decreased from 9 to 7. After a 4-week interval, the second cycle was initiated, during which, by week 3, the score further improved to 4, with the patient regaining strength and adequate control of her MG.

Three months after efgartigimod initiation, despite sustained improvement of muscle weakness, she developed shortness of breath, which she initially attributed to anxiety. There was no accompanying muscle weakness; however, after 10 days of dyspnea, she was found unresponsive and cyanotic. She was intubated and transferred to the

emergency department with hypotension and desaturation. Evaluation revealed severe heart failure, with a troponin level of 2042.65 ng/L and echocardiography showing a dilated left ventricle (estimated LVEF 20%–25%) with moderate to severe mitral regurgitation.

Despite treatment with veno-arterial extracorporeal membrane oxygenation (VA-ECMO) and improvement in cardiac function, the patient sustained a presumed cardiac arrest resulting in severe anoxic brain injury and subsequently passed away.

DISCUSSION

Myocarditis is a rare but life-threatening complication of MG, caused by immune-mediated damage to cardiac tissue through both humoral and cellular mechanisms. MG autoantibodies, primarily against AChR, target the neuromuscular junction, but cross-reactivity with myocardial antigens has been proposed as a mechanism relating to the association of MG with myocarditis.^{1,4–6} Although anti-titin antibodies were negative in this case, they are commonly found in patients with thymoma or late-onset MG and are associated with an increased risk of myocarditis, reflecting broader autoimmune involvement.^{7–9} Among Japanese, Korean, and Chinese cohorts, 68%–93% of patients have been reported to be test positive for anti-titin antibodies.^{7,10} In addition to autoantibodies, other contributors to myocarditis in myasthenia gravis include T-cell-mediated inflammation, thymoma, and dysregulated cytokines. T cells and cytokines play a central role in the pathogenesis of MG, with Th17 and Tfh cells, as well as cytokines such as IL-17 and IL-21, being upregulated and associated with disease severity and inflammation, which can extend to cardiac tissue.^{11,12} Thymoma is a well-established risk factor for both MG and myocarditis, likely due to its role in immune dysregulation and the generation of autoreactive lymphocytes.^{6,11,13}

Histopathologically, myocarditis in MG typically reveals lymphocytic infiltration,

myocyte necrosis, and interstitial edema, all of which were observed in the myocardial biopsy of the patient.⁶ In severe cases, multinucleated giant cells may be present, a finding associated with poor prognosis and limited reversibility, especially in thymoma-associated disease, indicating a robust cellular immune response. These features are consistent with the broader understanding of autoimmune myocarditis, where both humoral and cellular mechanisms contribute to myocardial injury.^{6,14,15} Clinically, alternative etiologies including viral, drug-induced, and peripartum cardiomyopathy (given the temporal association with pregnancy) were considered; however, the biopsy definitively supported an immune-mediated process.^{16,17} Myocarditis in MG is often underrecognized due to overlapping symptoms but can cause severe heart failure, arrhythmias, and high morbidity. Because MG-associated myocarditis is rare, often overlaps with myasthenic symptoms, and carries high morbidity, maintaining a high index of suspicion is essential, particularly in patients with risk factors such as thymoma or poorly controlled disease.

Conventional immunomodulatory treatments such as high-dose corticosteroids, azathioprine, PLEX, and IVIG broadly suppress both cellular and humoral immune responses.^{18–20} In this patient, these therapies effectively controlled the myocarditis, likely by dampening T-cell-mediated inflammation and cytokine dysregulation. While both IVIG and PLEX are effective in managing MG by reducing circulating autoantibodies, IVIG also exerts additional immunomodulatory benefits regarding T-cell activation, cytokine balance, and complement scavenging, which may be relevant to myocarditis.^{19,21–23} Furthermore, IVIG may be better tolerated hemodynamically than PLEX in patients with heart failure.^{22,24} Conversely, efgartigimod specifically targets FcRn to reduce circulating IgG autoantibodies. While highly effective for neuromuscular symptoms, its impact on cellular immunity is limited. Because myocarditis pathogenesis involves T-cell and macrophage activation beyond IgG-mediated

mechanisms, highly targeted therapies such as efgartigimod may not adequately prevent or treat myocarditis.

Although this mechanistic difference may explain why the patient's myocarditis remained quiescent under broad immunosuppression but flared during efgartigimod therapy, the precise etiology remains uncertain, and alternative contributing factors cannot be excluded. Therefore, while efgartigimod is effective in controlling neuromuscular symptoms, this case raises concern regarding its use in patients at risk for myocarditis. Moreover, this case highlights the potential importance of routine cardiac monitoring in patients with MG, alongside assessment of classical neuromuscular signs and symptoms.

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