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EDITORIAL COMMENT

# Rare Causes of Autoimmune Myocarditis

## Finding Needles in a Shifting Haystack*

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Although the diagnostic criteria for identifying myocarditis are well described, in clinical practice the approach to evaluation remains highly variable. Several factors contribute to these variations in clinical approach to patients with suspected myocarditis. Patient-related factors include the highly variable clinical manifestations of myocarditis, which can range from mild chest pain and various arrhythmias to fulminant heart failure with cardiogenic shock, and can mimic other noninflammatory common cardiovascular disorders such as acute coronary syndrome. Health care system factors include clinician index of suspicion and availability of and expertise using diagnostic tools such as cardiac biopsy (typically endomyocardial biopsy, EMB) and cardiac magnetic resonance imaging (CMR) used to identify the presence of myocardial inflammation. A definitive diagnosis of myocarditis requires histologic confirmation after EMB and is recommended when the results are likely to change management, in particular when immunosuppressive therapy is being considered.[1] However, many patients do not undergo EMB when a diagnosis of clinically suspected myocarditis is made using clinical criteria including characteristic signs and symptoms and the presence of a probable cause (and absence of other conditions that could explain the patient's presentation) along with noninvasive diagnostic test results suggesting that myocardial inflammation is present, the most robust being T1- and T2-based imaging by CMR. Numerous causes of myocarditis have been identified, with the main etiologic categories being infection, toxin, or autoimmune disease associated.[1]

Similar variability exists regarding the management of myocarditis. The treatment of complications such as heart failure and arrhythmia are generally in line with their management in the absence of myocarditis. Whether or not to treat with immunosuppression represents a key decision point in the management of myocarditis. Immunosuppression therapy is recommended only in the setting of confirmation of an autoimmune disorder, typically by EMB and/or diagnosis of a systemic autoimmune disorder known to cause myocarditis. Numerous autoimmune diseases have been associated with myocarditis, with commonly known examples including sarcoidosis, giant cell arteritis, and eosinophilic myocarditis, in addition to connective tissue diseases such as systemic lupus erythematosus and rheumatoid arthritis. Empiric use of immunosuppression is considered reasonable when there is a high index of suspicion for immune-mediated myocarditis complicated by severe clinical manifestations such as cardiogenic shock or malignant and/or refractory arrhythmias, conditions that may complicate the performance of EMB or CMR; however, subsequent confirmation of autoimmune disease after clinical stabilization is recommended when possible. When the decision to use immunotherapy is made, variability in clinical practice also exists regarding the agent(s), dose, duration, and approach to follow-up monitoring and surveillance. Although these decisions are naturally influenced by etiology and clinical response, in general there remains a lack of evidence to guide such management decisions in many settings.

It is against this background that we consider the 2 interesting cases of autoimmune myocarditis presented in this issue of *JACC: Case Reports*. Kuyama

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et al[2] describe 2 patients with diagnoses of anti-Kv1.4 antibody-associated myocarditis occurring in the absence of thymoma and myasthenia gravis with anti-acetylcholine receptor antibody (AChR-Ab) seropositivity. Myasthenia gravis is an autoantibody-mediated autoimmune disease, most often associated with thymic hyperplasia or thymoma.[3] The diagnosis is typically established by the patient's history (including muscular weakness involving ocular, bulbar, or proximal limb muscles), electromyography, and detection of autoantibodies interfering with the acetylcholine receptor.[4] Patients who are AChR-Ab negative often have other autoantibodies directed against the muscle-specific receptor tyrosine kinase or other postsynaptic neuromuscular junction components. Kv1.4 is a subunit of the voltage-gated potassium channel located in myocardium and skeletal muscle.[3] Anti-Kv1.4 antibody is an antistriational antibody that has been associated with the occurrence of thymoma and AchR-Ab positive myasthenia gravis (and has correlated with the severity of presentation) accompanied by myocarditis and/or myositis, and predominantly in patients of Japanese descent.[3,5]

The first case described by the authors describes a patient presenting with diplopia and ptosis with subclinical left ventricular dysfunction who went on to experience decompensated heart failure. EMB and CMR could not be performed because of the patient's clinical instability; however, skeletal muscle biopsy demonstrated inflammatory myositis. Whereas the ocular symptoms and creatinine kinase levels improved with empiric steroid therapy, progressive heart failure and respiratory muscle weakness developed, requiring the addition of a calcineurin inhibitor and intravenous immunoglobulin therapy. Anti-titin antibody (which is also an antibody directed against straited muscle antigen and is associated with myasthenia gravis) was positive; however, the diagnostic criteria for myasthenia gravis were not met.

The second case was of a patient with a recent diagnosis of polymyositis and interstitial lung disease, previously treated with a calcineurin inhibitor and corticosteroid, who presented with acute decompensated heart failure and new left ventricular systolic dysfunction. The patient's condition improved with the addition of heart failure medical therapy and another pulse treatment of corticosteroids. Both EMB and CMR demonstrated myocarditis, in the absence of thymoma or evidence of myasthenia gravis.

What can we learn from these unique and, according to current knowledge, very rare cases? Primarily, these cases demonstrate that our understanding of the clinical significance of anti-Kv1.4 antibodies is limited. These autoantibodies have been principally linked to the presence of thymoma and AChR-Ab-positive myasthenia gravis; however, these cases suggest that the association may not be as specific as previously believed and that a more general association with systemic neuromuscular diseases may exist. It is unknown how often this autoantibody is screened for in patients presenting with myocarditis and/or myositis without thymoma or AChR-Ab-positive myasthenia gravis, or how often it occurs in non-Japanese patients, and it may be more common than previously thought. This raises questions about its significance in clinical practice, especially regarding its importance for diagnosing the cause and the subsequent treatment of patients with autoimmune myocarditis. The authors speculate that patients who are anti-Kv1.4 antibody positive may have an improved therapeutic response to calcineurin inhibitor therapy, basing their speculation on the response of the first patient in their report, whose heart failure continued to worsen until tacrolimus and intravenous immunoglobulin were introduced, and on a prior report describing the benefit of calcineurin inhibitor therapy in a patient with myasthenia gravis who was anti-KV1.4 antibody positive.[6] However, our understanding of anti-Kv1.4 antibodies is currently too limited to recommend this approach to management more broadly, and it is noted that the second patient in the report by Kuyama et al[2] had previously been treated with tacrolimus for polymyositis before the development of heart failure. Perhaps the intravenous immunoglobulin treatment was of greater relative clinical benefit than tacrolimus for the first patient presented? These details emphasize how much we still have to learn about this autoantibody.

Otherwise, this case report illustrates some of the more general ongoing challenges faced in clinical practice for patients presenting with myocarditis, in particular autoimmune myocarditis. For example, despite having relatively similar diagnoses and presenting to the same medical center, the 2 patients described by Kuyama et al[2] had significant differences in their diagnostic evaluation, with 1 patient undergoing both EMB and CMR and the other neither. This comment is not intended as a criticism—far from it—but rather as an example of how a one-size-fits-all approach to the evaluation of acute myocarditis does not work. The same can be said for the use of immunosuppression strategies in these 2 patients, with the sole unifying approach being the use of high-

dose corticosteroid therapy, particularly in the acute phase. Last, an important element not commented on in the current report is the importance of multidisciplinary shared care and decision making in the treatment of patients with rare multisystem diseases (including, but not limited to, patients with autoimmune myocarditis with multisystem involvement). Treatment with immunosuppression therapy illustrates the importance of this element because there are multiple agents that could be used without clear consensus on dose and duration, which frequently are patient specific and influenced by response to therapy, risk for and development of treatment toxicities, and ongoing disease activity surveillance. Specialists from different disciplines may prefer approaches that differ, and therefore direct and ongoing communication and collaboration is critical for ensuring that patients, particularly those with more severe and/or complex clinical courses (which are relatively more common among patients with autoimmune diseases) receive an optimal management plan based on a systemic rather than organ-specific treatment response for those with multisystem manifestations.

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## REFERENCES

**1.** McDonagh TA, Metra M, Marianna Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2022;24:4–131.

**2.** Kuyama N, Takashio S, Nagakura T, et al. Anti-Kv1.4 antibody without myasthenia gravis: a rare cause of autoimmune myocarditis and myositis. *J Am Coll Cardiol Case Rep*. 2023;9:101734.

**3.** Caforio ALP, Adler Y, Agostini C, et al. Diagnosis and management of myocardial involvement in systemic immune-mediated diseases: A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Disease. *Eur Heart J*. 2017;38:2649–2662.

**4.** Berrih-Aknin S, Le Panse R. Myasthenia gravis: A comprehensive review of immune dysregulation and etiological mechanisms. *J Autoimmun*. 2014;52:90–100.

**5.** Suzuki S, Baba A, Kaida K, et al. Cardiac involvements in myasthenia gravis associated with anti-Kv1.4 antibodies. *Eur J Neurol*. 2014;21:223–230.

**6.** Nagane Y, Suzuki S, Suzuki N, Utsugisawa K. Factors associated with response to calcineurin inhibitors in myasthenia gravis. *Muscle Nerve*. 2010;41:212–218.

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