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HEART FAILURE AND CARDIOMYOPATHIES

CASE REPORT: CLINICAL CASE

Myocarditis Associated With Anti-IgLON5 Autoimmune Disease Following Immune Checkpoint Inhibitor Therapy

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ABSTRACT

Myocarditis is an inflammatory injury of the myocardium. Viral infections are the most common etiology, but less frequently, inflammatory myocardial injury can result from systemic autoimmune diseases. We present the first reported case of myocarditis in a patient with anti-IgLON5 disease. (JACC Case Rep 2024;29:102467) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 68-year-old man with lymphocytic thyroiditis presented with atypical chest pain occurring at rest and bilateral lower extremity swelling. Six months before cardiovascular consultation, he had a sudden onset of unusual behavior characterized by cognitive and behavioral changes, hallucinations, myoclonus, gait dysfunction, features of impulse control disorder, and sleep changes including dream enactment behaviors. Symptoms commenced following initiation of immune checkpoint inhibitor (ICI) therapy with pembrolizumab for metastatic renal cell carcinoma. Subsequent cerebrospinal fluid studies were seropositive for IgLON5 IgG. A diagnosis of anti-IgLON5 autoimmune encephalitis secondary to ICI therapy was made after formal evaluation by neurology department.

Upon cardiovascular evaluation, he noted chest pain and intermittent bilateral leg swelling. High sensitivity troponin was above 99th percentile at 49 ng/L (normal range ≤15 ng/L) and C-reactive protein was elevated at 3.5 mg/L (normal range <2.0 mg/L).

LEARNING OBJECTIVES

- To emphasize the complexity of diagnosing myocarditis in patients with concurrent anti-IgLON5 autoimmune encephalitis and recent immune checkpoint inhibitor therapy.
- To establish that effective management of myocarditis in such patients may require a multidisciplinary approach and a combination of immunosuppressive therapies.

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ABBREVIATIONS AND ACRONYMS

CT = computed tomography

ICI = immune checkpoint inhibitor

OSA = obstructive sleep apnea

PET = positron emission tomography

Positron emission tomography (PET) computed tomography (CT) showed a low ejection fraction at 20% with a moderate-size perfusion defect involving the apical and inferior wall from mid to apex as well as basal anterior septal wall with corresponding abnormal fluorodeoxyglucose uptake consistent with an active inflammatory myocardial process (Video 1, **Figure 1**).

PAST MEDICAL HISTORY

The patient has a medical history that includes metastatic clear cell renal cell carcinoma, type 2 diabetes mellitus, hypertension, hyperlipidemia, lymphocytic thyroiditis, symptomatic premature ventricular contractions, and obstructive sleep apnea (OSA) managed with continuous positive airway pressure. Additionally, the patient has major depressive disorder and anti-IgLON5 autoimmune encephalitis.

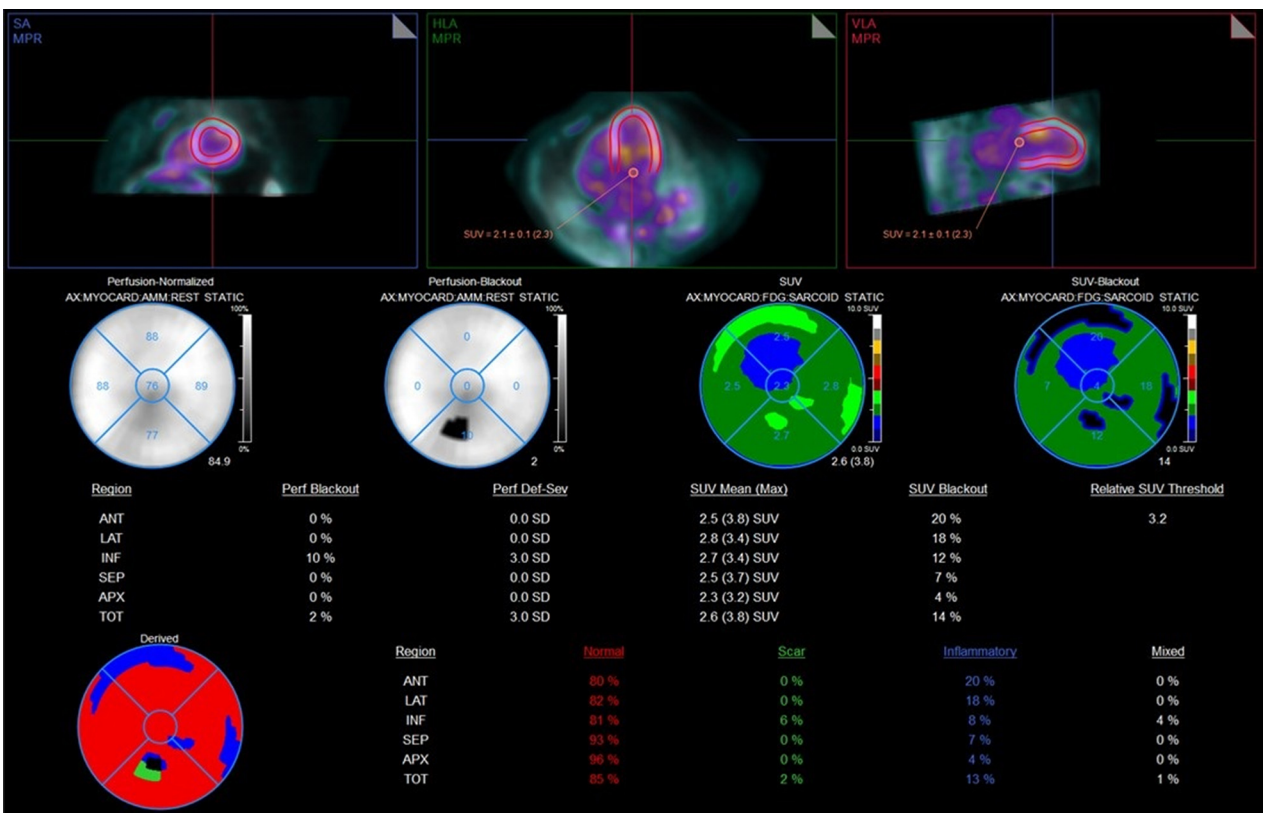
DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes ICI-associated myocarditis vs a novel case of paraneoplastic antibody-mediated myocarditis secondary to anti-IgLON5 disease.

INVESTIGATIONS

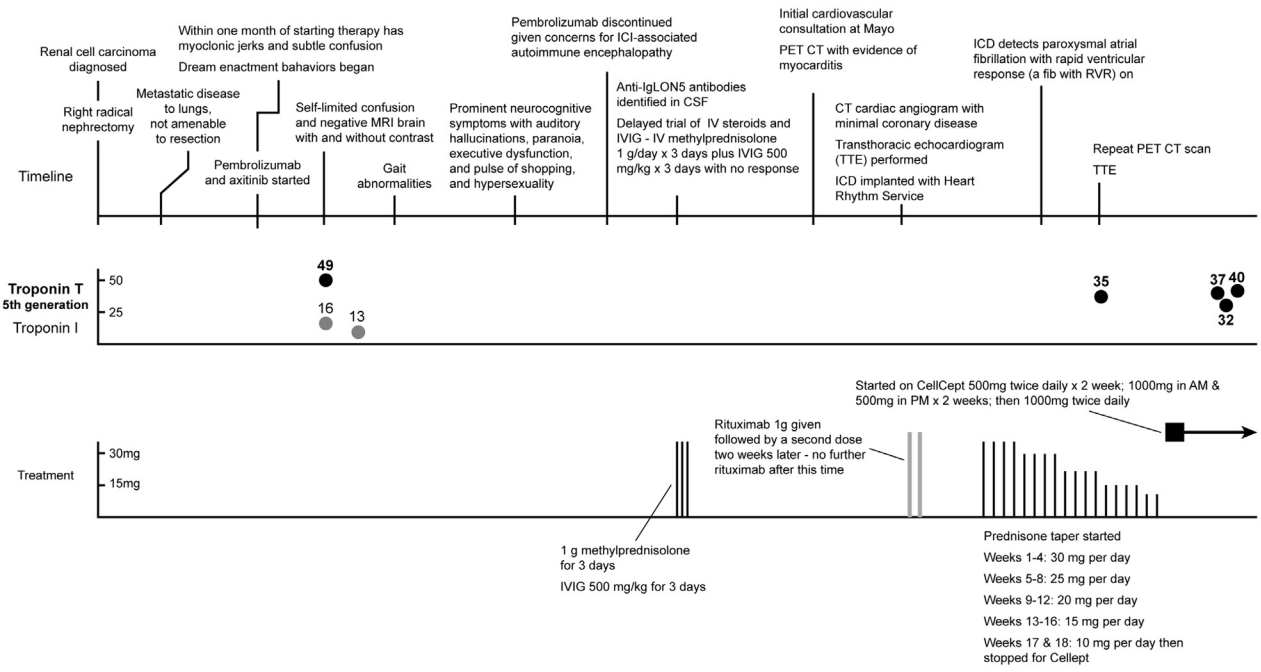
CT cardiac angiogram with intravenous contrast showed only mild coronary artery stenosis (Supplemental Figure 1). An electrocardiogram revealed 1st degree atrioventricular block accompanied by new right bundle branch block (Supplemental Figure 2). Transthoracic echocardiogram showed a left ventricular ejection fraction of 40% (Videos 2 and 3). Given the significant amount of myocardial inflammation, markedly reduced ejection fraction, prior reports of IgLON5-related ventricular tachycardia, and the potential for subsequent ventricular

FIGURE 1 Initial Myocardial Inflammatory Assessment



Abnormal fluorodeoxyglucose (FDG) uptake is observed in the apical and inferior walls from mid to apex, as well as in the basal anterior septal wall, indicating active inflammation.

FIGURE 2 **Clinical Course, Troponin Trends, and Therapeutic Interventions**



The patient's significant clinical events are outlined chronologically for reference. All available troponin data and treatment interventions have been included.
A fib = atrial fibrillation; CSF = cerebrospinal fluid; CT = computed tomography; ICD = implantable cardioverter-defibrillator; ICI = immune checkpoint inhibitor; IVIG = intravenous immunoglobin; MRI = magnetic resonance imaging; PET = positron emission tomography; RVR = rapid ventricular response; TTE = transthoracic echocardiogram.

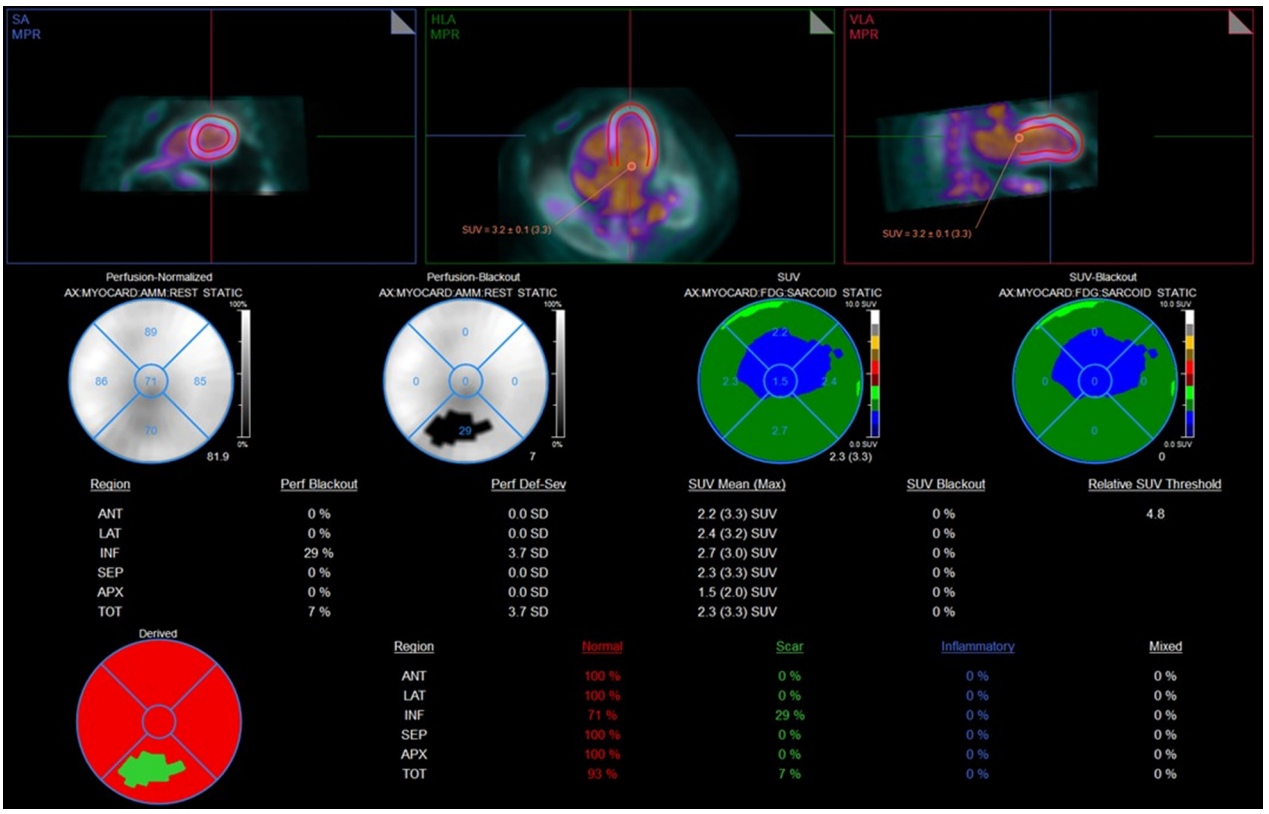
arrhythmias during the treatment and recovery periods, a dual chamber implantable cardioverter-defibrillator was placed for the primary prevention of sudden cardiac death. The progressive and uncertain nature of his disease, coupled with limited knowledge of this unique scenario and uncertainty regarding recovery, further supported this decision. After Cardio-Oncology consultation, it was felt this was an unusual presentation and less likely to represent a case of ICI-associated myocarditis. After multidisciplinary discussion with Interventional Cardiology and Cardiac Pathology, endomyocardial biopsy was deferred as this would not help differentiate between ICI-associated myocarditis and anti-IgLON5-related myocarditis. Holter monitor showed decreased premature ventricular contraction burden <2% with new paroxysmal atrial fibrillation with rapid ventricular response.

Broad rheumatologic laboratory evaluation included rheumatoid factor, 25-hydroxyvitamin D2 and D3, angiotensin-converting enzyme, complement levels, anti-cyclic citrullinated peptide, and double-stranded DNA antibodies were negative. X-rays of the bilateral hands and feet showed no signs of rheumatoid arthritis.

MANAGEMENT

Pembrolizumab was discontinued, and there was no improvement with steroids and intravenous immunoglobulin. He was given a trial of rituximab for management starting with1,000 mg of rituximab every 2 weeks followed by a prednisone taper starting at 30 mg by mouth daily for his anti-IgGLON5 autoimmune encephalitis and myocarditis of uncertain etiology, respectively (Figure 2). Guideline-directed medical therapy was also initiated with metoprolol succinate 12.5 mg by mouth daily. His home valsartan was switched to sacubitril-valsartan 24 to 26 mg twice daily. Repeat transthoracic echocardiogram performed 4 months later (on metoprolol succinate 75 mg daily and sacubitril valsartan 24-26 mg) showed

FIGURE 3 Myocardial Inflammatory Assessment



Decreased fluorodeoxyglucose (FDG) uptake compared with study values obtained during initial evaluation.

increased left ventricular ejection fraction to 38% (Videos 4 and 5). Repeat PET CT showed interval improvement in the inflammatory burden (Video 6, **Figure 3**) while remaining on prednisone taper (currently down to 10 mg by mouth daily). Metoprolol succinate was uptitrated to a target dose of 200 mg daily, and empagliflozin was eventually added.

After multidisciplinary discussion with Cardiology, Rheumatology, and Neurology in line with European Society of Cardiology cardio-oncology guidelines,[1] the decision was made to discontinue rituximab and prednisone (treated for 4 months) and transition to mycophenolate mofetil for ongoing management of ICI myocarditis. He remains on mycophenolate mofetil 1,000 mg by mouth twice daily with plans for repeat cardiovascular imaging. A comprehensive timeline of the patient's clinical course is provided for reference (**Figure 2**).

OUTCOMES AND FOLLOW-UP

Patient continues mycophenolate mofetil 1,000 mg twice daily with repeat PET-CT and transthoracic echocardiogram pending. He continues to have profound neurologic impairment and is working closely with physical/occupational and speech therapy teams.

DISCUSSION

Myocarditis is an inflammatory injury of the myocardium.[2] The most common etiology is viral infection, and patients can often present with gastrointestinal or flu-like symptoms before cardiovascular manifestations. Other causes include systemic autoimmune diseases, cardiac sarcoidosis, myopathic genetic variants, and medication-induced

myocarditis, among others.[3] We present an atypical case of myocarditis in a patient with anti-IgNOL5 disease that was newly diagnosed after starting ICI therapy for metastatic renal cell carcinoma.

The differential diagnosis includes myocardial inflammation secondary to an anti-IgLON5 paraneoplastic phenomenon vs $CD8^+$ T-cell ICI-mediated myocarditis. With a prior history of lymphocytic thyroiditis, the patient may have had increased risk for checkpoint inhibitor immune-related adverse events.[4] In patients with cancer, ICI-associated myocarditis has been noted in up to 1% of patients.[5] The biggest risk factor is combination treatment with CTLA-4-targeted therapy (OR: 4.3 [95% CI: 2.9-6.4]).[5] Chest pain, the chief complaint for our patient, is present in 14% to 37% of ICI-associated myocarditis.[5] Median time from exposure to ICI to myocarditis was 30 days (Q1-Q3: 18-60 days).[5] Cardiac magnetic resonance with T1 parametric mapping improves diagnostic performance for ICI myocarditis and is included in the Lake Louise Criteria.[6] ICI myocarditis typically presents with elevation in $CD8^+$ T cells, which has been demonstrated in both experimental and biopsy studies. Though speculative, peripheral fluorescence-mediated cell analysis may be have been utilized in our case to detect a monoclonal $CD8^+$ cell population and aid in diagnosis.[7] Overall, it was felt that history, chest pain presenting 2 months after initiation of pembrolizumab, and radiographic findings would be atypical for ICI-associated myocarditis alone.

Another possibility is a novel case of anti-IgLON5 paraneoplastic-mediated myocarditis. Interestingly, anti-IgLON5 disease has been associated with renal malignancy, which was diagnosed in 2015 for our patient.[8] Anti-IgLON5 disease was first discovered in 2014.[9] Initially, a small cohort of 8 patients from Barcelona were all found to have abnormal sleep movements/behaviors and OSA. All patients had antibodies against IgLON5, a cell adhesion molecule. Other features that preceded sleep disorder included gait instability, dysarthria, and dysphagia in 2 of the original 8 patients described.[9] Three years later, a retrospective cohort study was completed by the same research group and included 22 patients with parasomnias, OSA, and antibodies to IgLON5. All patients had sleep problems, and 86% of patients' partners described vocalizations, limb movements, and purposeful gestures with snoring and apneas.[10] Only 4 had suspected autonomic cardiac dysfunction. Two had ventricular tachycardia, 1 had symptomatic bradycardia requiring pacemaker placement, and 1 had Takatsubo cardiomyopathy.[10] With both neurodegenerative and autoimmune components contributing to anti-IgLON5 disease, immune injury to the myocardium is plausible. In our case, cognitive decline likely led to delayed cardiovascular evaluation leading to long-standing untreated myocarditis resulting in inflammatory cardiomyopathy.

CONCLUSIONS

Myocarditis and inflammatory cardiomyopathy may occur in the presence of, and be potentiated by, anti-IgLON5 disease.

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The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Lyon AR, Fernandez TL, Cough LS, et al. ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43(41):4229-4361.

2. Tschöpe C, Ammirati E, Bozkurt B, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol*. 2021;18:169-193.

3. Ammirati E, Moslehi JJ. Diagnosis and treatment of acute myocarditis: a review. *JAMA*. 2023;329(13):1098-1113.

4. Chennamadhavuni A, Abushahin L, Jin N, Presley CJ, Manne A. Risk factors and biomarkers for immune-related adverse events: a practical guide to identifying high-risk patients and rechallenging immune checkpoint inhibitors. *Front Immunol*. 2022;13:779691.

5. Salem J, Manouchehri A, Moey M, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol*. 2018;19:1579-1589.

6. Kramer C, Hanson C. CMR parametric mapping in immune checkpoint inhibitor myocarditis: novel

noninvasive tools in a lethal condition. *J Am Coll Cardiol*. 2021;77(12):1517-1519. https://doi.org/10.1016/j.jacc.2021.01.043

7. Cunningham MW, Cooper LT. PD-1 checkmate and the 2-edged sword of the immune system: what next? *JACC Basic Transl Science*. 2023;8(12):1518-1520.

8. Rauf EHU, Krahn AB, Paulus W. Anti-IGLON5-syndrome presenting fasciculations and oculomotor palsy associated with renal neoplasia. *Eur J Neurol*. 2020;(suppl S1):1176.

9. Sabater L, Gaig C, Gelpi E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. *Lancet Neurol*. 2014;13(6):575-586.

10. Gaig C, Graus F, Compta Y, et al. Clinical manifestations of the anti-IgLON5 disease. *Neurology*. 2017;88(18):1736-1743.

KEY WORDS anti-IgLON5 disease, autoimmune myocarditis, ICI toxicity, immune checkpoint inhibitor therapy, inflammatory cardiomyopathy, myocarditis, novel presentation

APPENDIX For supplemental figures and videos, please see the online version of this paper.