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HEART FAILURE AND CARDIOMYOPATHIES

CLINICAL CASE

Fulminant Myocarditis After mRNA COVID-19 Vaccine Evolving to Giant Cell Myocarditis

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ABSTRACT

BACKGROUND Pediatric inflammatory multisystem syndrome (PIMS-TS) is a rare entity observed in children with postinfectious hyperinflammatory syndrome. Cases have been reported, although rarely, after the mRNA SARS-CoV-2 (COVID-19) vaccine.

CASE SUMMARY We present a case of a young man who developed PIMS-TS with fulminant myocarditis after a first dose of COVID-19 vaccination, with persistent evidence of inflammation despite multiple lines of therapy over the course of 2 years. He then experienced fulminant myocarditis that was resistant to anti-inflammatory therapies. Repeat endomyocardial biopsy was consistent with giant cell myocarditis.

DISCUSSION Cases of giant cell myocarditis after COVID-19 vaccination have been reported in the past, however to our knowledge, none have been reported 2 years after a single dose and with intercurrent diagnosis of PIMS-TS myocarditis. This raises the question of a possible pathophysiologic association between the 2 diseases and immune dysregulation.

TAKE-HOME MESSAGE This case illustrates the importance of repeating the investigation and questioning the diagnosis when the progression of the disease is not typical. (JACC Case Rep. 2025;30:105078) © 2025 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 AND PAST MEDICAL HISTORY

This is the case of a 16-year-old African American man with no prior medical history who presented to the emergency department with a 5-day history of fever, retrosternal chest pain, cough, and dyspnea progressing to respiratory distress.

DIFFERENTIAL DIAGNOSIS

Four weeks before the onset of symptoms, the patient had received the BNT162b2 (Pfizer-BioNTech) mRNA SARS-CoV-2 (COVID-19) vaccine. Given the recent vaccine administration, a diagnosis of pediatric inflammatory multisystem syndrome (PIMS-TS) temporally associated with the COVID-19 vaccine was entertained.

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ABBREVIATIONS AND ACRONYMS

FDG-PET = fluorodeoxyglucose-positron emission tomography

GCM = giant cell myocarditis

IVIg = intravenous immunoglobulin

LVEF = left ventricular ejection fraction

MMF = mycophenolate mofetil

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PIMS-TS = pediatric inflammatory multisystem syndrome

TNF = tumor necrosis factor

TTE = transthoracic echocardiography

INVESTIGATIONS

Initial bloodwork was remarkable for elevated high-sensitivity troponin T of 4,215 ng/L (reference: <14 ng/L) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) of 15,164 ng/L, with evidence of end-organ hypoperfusion. Transthoracic echocardiography (TTE) revealed severe diffuse systolic dysfunction, with a left ventricular ejection fraction (LVEF) of 25% and a normal end-diastolic diameter. A diagnosis of cardiogenic shock was promptly established, for which inotropic support was initiated and intubation performed. Inflammatory markers were significantly elevated, with a C-reactive protein above the laboratory's maximum threshold of 190 mg/L and ongoing fevers despite a negative infectious work-up. A right ventricular endomyocardial biopsy was performed and showed normal myocardium.

MANAGEMENT

A diagnosis of fulminant myocarditis with cardiogenic shock was established, for which inotropic support and mechanical ventilation were initiated. The patient received a course of pulse corticosteroid therapy and intravenous immunoglobulin (IVIg), given the suspicion of PIMS-TS. The combination of those led to rapid recovery, with normalization of cardiac and inflammatory markers as well as cardiac function on repeat TTE (**Figure 1**). Upon clinical recovery, fluorodeoxyglucose-positron emission tomography (FDG-PET) revealed abnormal uptake in the left ventricular inferolateral wall, suggestive of persistent active inflammation. Cardiac magnetic resonance imaging showed normal biventricular function, with late gadolinium enhancement and edema in the inferior, inferolateral, and anterior territories, also suggesting persistent inflammation.

The patient was discharged on prednisone 35 mg/d with a tapering plan, during which an asymptomatic rise in cardiac and inflammatory biomarker levels was observed once he reached 15 mg/d. A repeat FDG-PET scan demonstrated increased uptake in the inferolateral wall and new intense uptake in the basal septum. PET scan-guided left and right ventricular endomyocardial biopsies (a total of 9 samples) were again unremarkable. Prednisone was increased to 50 mg/d, and mycophenolate mofetil (MMF) was initiated.

TAKE-HOME MESSAGES

- This case illustrates the complexity of GCM in patients with prior immune dysregulation. An initial inflammatory process may in part be responsible for the activated pathological pathways leading to the development of GCM.
- This case underlines the role of repeating endomyocardial biopsy in patients with unexpected or atypical clinical presentation to target therapy and improve prognosis.

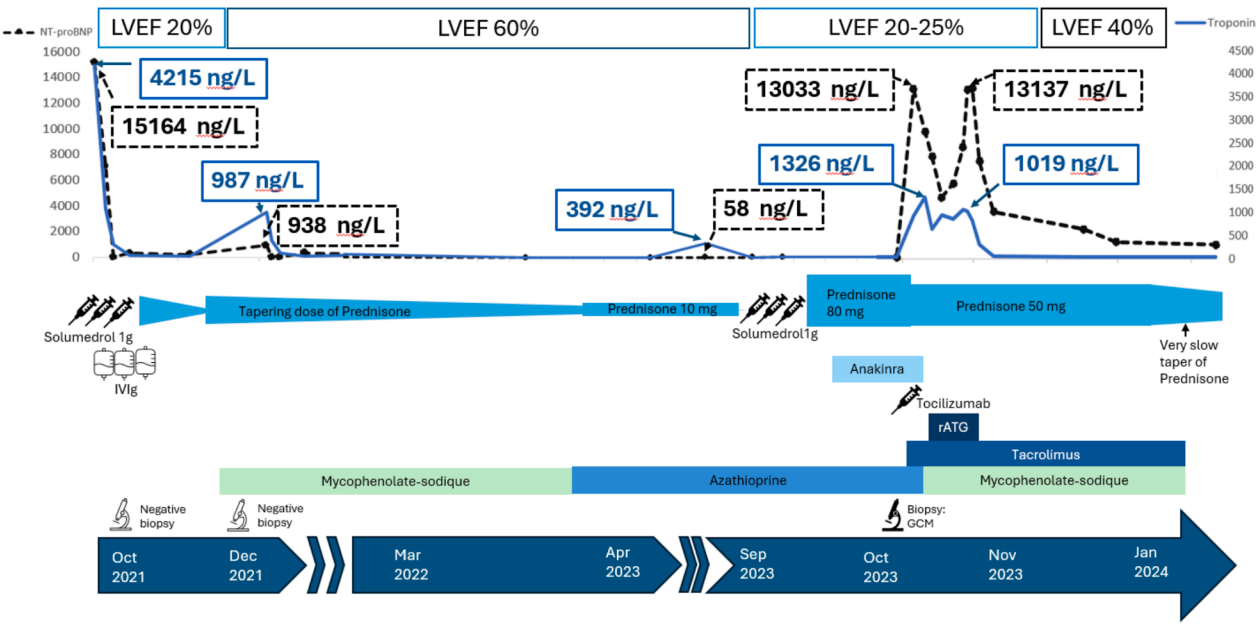
PROGRESSION OF THE CASE

Over the next 2 years, the patient had similar intermittent asymptomatic recurrences manifesting as rising troponin levels with progressive increased inflammation on FDG-PET scans, while NT-proBNP levels and LVEF remained stable. These episodes responded well to intensified corticosteroid therapy, MMF, and colchicine. The patient's noncompliance to twice-daily MMF dosing was thought to be at least partly responsible for these relapses, and MMF was replaced with azathioprine (once-daily dosing).

A little over 2 years from his initial presentation, the patient was admitted to the hospital with flu-like symptoms, pleuritic chest pain, frequent nonsustained ventricular tachycardia, and increased troponin and NT-proBNP levels of 1,326 and 13,033 ng/L, respectively. His outpatient medical regimen consisted of prednisone 10 mg daily, azathioprine 150 mg daily, and colchicine 0.6 mg daily. TTE revealed a LVEF of 20% with a cardiac index of 1.8 L/min/m^2. FDG-PET showed the highest cardiac uptake recorded, involving the entire left ventricle and left atrium. Cardiac magnetic resonance imaging showed extensive late gadolinium enhancement, with signs of diffuse left ventricular edema (**Figure 2**). Pulse steroids and IVIg were given. There were initial signs of improvement, unfortunately followed by rapid clinical deterioration requiring inotropic support.

Anakinra was attempted to target the excess activation of proinflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor (TNF) seen with fulminant myocarditis, without any notable improvement.[1] The monoclonal antibody against the IL-6 receptor, tocilizumab, was attempted to target a different pathological pathway. After an initial dose, the first significant improvement in myocardial injury with reduced troponin and NT-proBNP levels

FIGURE 1 Evolution of LVEF, Biomarkers, and Medication Over Time



(Upper Half) Timeline showing the fluctuation in LVEF, troponin, and NT-proBNP. (Lower Half) A visual representation of the different immunosuppressive regimen used over the 2-year period and timing of the biopsies. IVIg = intravenous immunoglobulin; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

was achieved (Figure 1). In parallel, we had decided to repeat an endomyocardial biopsy given the severity of recurrence presenting as fulminant disease with lack of clinical improvement. The biopsy revealed a pathological diagnosis of giant cell myocarditis (GCM) for the first time after multiple previous negative biventricular endomyocardial samples (Figure 2). Tocilizumab was discontinued, and a 3-day course of rabbit antithymocyte globulin was given along with tacrolimus for maintenance therapy. Within the next few days, the patient's clinical status improved significantly; LVEF improved to 30%, and guideline-directed medical therapy for heart failure was progressively optimized. He received a subcutaneous implantable cardioverter-defibrillator before discharge given the heavy burden of nonsustained ventricular tachycardia monitored during his hospital stay.

The patient's outpatient regimen included prednisone 50 mg/d, tacrolimus, and MMF. Repeat PET-FDG 6 weeks later showed complete resolution of inflammation along with improved LVEF to 40% on TTE. Additionally, genetic testing showed a variant of unknown significance in *RAF1*. He is currently being evaluated in the advanced heart failure clinic, undergoing a slow prednisone taper.

DISCUSSION

PIMS-TS. Epidemiology and pathophysiology. PIMS-TS was initially described before the advent of vaccination. Postvaccine PIMS-TS with or without myocarditis has since been reported, although much more rarely, with a rate of 2.9 per million vaccinated children.[2] Increased risk of PIMS-TS has been associated with male sex, teenage years, and Hispanic or Black race.[2] The pathophysiology of PIMS-TS is not well understood, but it is hypothesized to be an immune dysregulation through IL-1β pathway upregulation and downstream activation of a cytokine storm with release of IL-6, IL-8, and TNF-α.[1]

Clinical course and management. PIMS-TS symptoms include but are not limited to fever, asthenia, as well as mucocutaneous and gastrointestinal manifestations. Up to half of patients can present with septic shock-like syndrome,[1] and more than half of them will have significant cardiovascular involvement such as myocarditis.[1] Endomyocardial biopsies have historically rarely been performed in the pediatric population, but autopsy reports have shown nonspecific signs of

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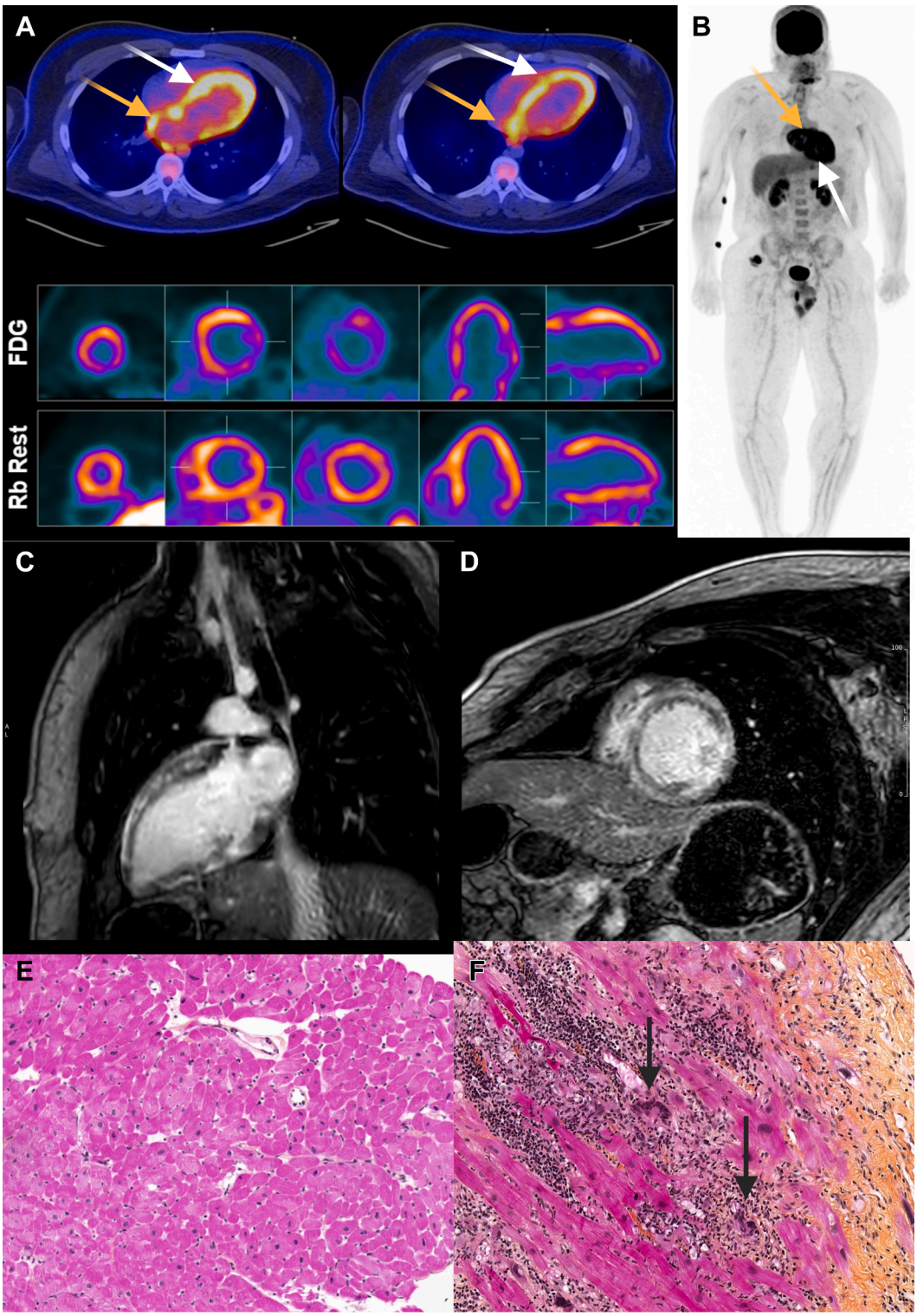
FIGURE 2 Multimodality Imaging and Pathology for Diagnosis



FDG-PET axial (A, Top) and whole-body (B) scans showing intense left ventricle (white arrows) and left atrium (orange arrows) uptake compatible with myocardial inflammation. (A, Bottom) TEP-Rubidium images showing no significant perfusion defect. Cardiac magnetic resonance imaging (C) long-axis and (D) short-axis views showing diffuse late gadolinium enhancement compatible with significant inflammation. Histologic images showing (E) the normal myocardium from the 2021 biopsy and (F) multinucleated giant cells (arrows) from the 2023 biopsy. FDG-PET = fluorodeoxyglucose-positron emission tomography.

myocarditis.[3] Management of PIMS-TS initially consists of inflammation reduction using corticosteroids and IVIg.[1] For refractory cases, immunomodulatory therapies such as anakinra may be used for cytokine storm downregulation.[1] With treatment, outcomes are favorable in most cases, with clinical and biochemical recovery.[2]

GIANT CELL MYOCARDITIS. Epidemiology and pathophysiology. GCM is a rare disease, with an estimated incidence between 0.007% and 0.051%; most cases occur in healthy individuals.[4] Interestingly, up to 20% of patients have an underlying autoimmune disorder before GCM being diagnosed, which may relate to the sequence of events in our case.[4] GCM itself is thought to be an autoimmune disorder mediated by T-cell and macrophage activity.[4] CD4 T lymphocytes produce inflammatory cytokines, leading to giant cell formation, macrophage stimulation, and production of nitric oxide and TNF, perpetuating the inflammatory cascade and leading to hemodynamic instability, acute myocardial injury, and eventually fibrosis.[4] Inhibition of IL-6 prevents CD4 T lymphocyte differentiation and regulatory T-cell inhibition, which are central factors in the pathogenesis of autoimmune diseases.[5] This could explain why there was initial clinical and biochemical improvement after a dose of tocilizumab.

Clinical course and management. Although a minority of patients may present with an indolent course, most patients with GCM will present with definite clinical heart failure, usually characterized by an acute onset, cardiogenic shock, and ventricular arrhythmias.[4] TTE will show wall motion abnormalities with decreased LVEF, and cardiac magnetic resonance imaging will reveal evidence of inflammation, although there is no pathognomonic imaging finding for GCM.[4] Diagnostic confirmation with endomyocardial biopsy is necessary to show multinucleated giant cells surrounded by an inflammatory infiltrate.[6] Management aims at reducing inflammation and myocardial destruction, with an initial course of pulse corticosteroids followed by a very slow taper used concomitantly with more potent immunosuppressive medications used long-term to prevent recurrence.[4]

Two case reports of GCM diagnosed after COVID-19 vaccination have been published. The first case described a 48-year-old female patient who developed fulminant myocarditis from GCM 4 days after receiving a second dose of heterologous COVID-19 vaccine.[7] The second case described a middle-aged woman presenting with cardiogenic shock a few weeks after her third COVID-19 vaccination.[8] In response to mRNA exposure, some autoantibodies may develop after COVID-19 infection and trigger abnormal innate and acquired immune activation in genetically predisposed patients, also known as the "two-hit theory."[9]

CONCLUSIONS

In this presented case, GCM was diagnosed 2 years after a first and single COVID-19 vaccination followed by a long-standing course of waxing and waning myocardial injury and inflammation, with biventricular endomyocardial biopsies yielding negative pathological results. To the best of our knowledge, this is the first reported case of mRNA COVID-19 vaccine-related myocarditis or PIMS-TS evolving into GCM. It seems unlikely that biopsy samples missed identifying giant cells, given the extent of myocardial involvement on imaging and the patient's initial fulminant presentation. In addition, the most recent hospital admission was remarkable for nonsustained ventricular tachycardia, more intense inflammation on imaging, and lack of response to anti-inflammatory therapy, supporting a different pathological process. We hypothesize that the heterologous mRNA vaccine and subsequent inflammatory process may in part be responsible for the activated pathological pathways and immune response alterations leading to the development of GCM. Additionally, the patient's initial noncompliance to immunosuppressive therapy may have potentiated this process. Finally, this also raises the question whether the identified *RAF1* variant, known to be involved in RASopathies, may have played a pathological role in this case.[10] This case illustrates the complexity of GCM in patients with prior immune dysregulation, as well as the potential for genetic fragilization in patients with genetic variants of unknown clinical significance.

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KEY WORDS **acute heart failure, autoimmune, cardiac magnetic resonance, inotropes, positron emission tomography, reduced ejection fraction**