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Case Report

Myo-Pericarditis in the Context if MIS-A Syndrome: A Short Review Based on a Miscellaneous Case Following COVID-19 Infection

Maria Ioannou[1]*, Angeliki Mouzarou[3], Maria Skarpari[2], Elena Xenofontos[2], Andreas Kostis[2], Aristos Aristodimou[2] and Elena Leonidou[1]

[1]*Department of Cardiology, General Hospital Limassol, State Health Organization Services, Limassol, Cyprus*
[2]*Department of Internal Medicine, General Hospital Limassol, State Health Organization Services, Limassol, Cyprus.*
[3]*Department of Cardiology, General Hospital Paphos, State Health Organization Services, Paphos, Cyprus.*

ABSTRACT

Myo-pericarditis is characterized by inflammation that affects the myocardium and extends to the pericardium. This heart condition can vary in severity and requires a comprehensive diagnostic approach due to numerous potential causes. This is particularly challenging in the context of coronavirus disease (COVID-19) infection, due to the related potential complications that may emerge. In response to COVID-19, the immune system has already been associated with an explosion of powerful inflammatory alarm signals that trigger inflammation. Multisystem inflammatory syndrome in adults (MIS-A syndrome) is an under-recognized hyperinflammatory condition that occurs during or after the infectious period of COVID-19. This manifestation can affect multiple organs, including the heart, and can also cause myo-pericarditis. We present a complex case marked by intricate clinical presentation, extensive diagnostic evaluation, and multiple therapeutic interventions, highlighting the need for ongoing re-assessment of the diagnosis. Additionally, a brief literature review examines the pathologies complicating our diagnostic approach, aiming to elucidate the challenges inherent in diagnosing febrile myo-pericarditis. Given the diverse manifestations and overlapping symptoms, a refined diagnostic strategy is essential for accurate identification and effective management.

Keywords

Pericarditis, Myocarditis, Coxiella Burnetti, COVID-19, MIS-A syndrome.

Corresponding Author Information

Maria Ioannou, MD, MSc
Department of Cardiology, General Hospital Limassol, Cyprus, Tel: 00357-99199600.

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Introduction

The coronavirus disease (COVID-19) pandemic has posed significant challenges to the medical community, particularly in diagnosing and managing its associated complications, especially those affecting the cardiovascular system. Our case report details the clinical journey of a patient, for whom written informed consent was obtained, initially suspected of having myocarditis in the context of COVID-19 pneumonia. Through a comprehensive assessment of clinical presentation, laboratory results, and imaging findings, our diagnostic focus shifted towards pericarditis, potentially complicated by a bacterial infection with Coxiella burnetii. Despite various antibiotic regimens, the patient's clinical condition and laboratory parameters remained unchanged, casting doubt on the diagnosis. A notable improvement with intravenous immunoglobulin (IVIG) and methylprednisolone, coupled with the exclusion of other potential diagnoses, strengthened our suspicion of a hyperinflammatory condition, specifically Multisystem Inflammatory Syndrome in Adults (MIS-A). This case, along with

the following brief literature review, underscores the diagnostic complexity of febrile myopericarditis in the setting of COVID-19, highlighting the intricate interplay of infectious and inflammatory processes in such presentations.

Case Report

A 26-years-old Egyptian patient, without any known medical history, presented to Emergency Department (ED), due to abdominal pain and episodes of vomiting. Accompanying symptoms were chest pain, non-productive cough, arthralgia in the last 10 days. At ED, he was febrile with a temperature of 38° C. He had abdominal rigidity and bilateral lower extremity edema. Nothing else was reported abnormal during the initial physical examination. Laboratory testing showed elevated inflammatory markers (WBC #12, PMN #10, CRP:300mg/L) and d-dimers (38.799μg/L, normal range up to 500μg/L). The first electrocardiogram (ECG) showed sinus tachycardia, while Troponin I was positive (19ng/ml, normal range up to 0.5ng/ml). A bedside transthoracic echocardiogram (TTE) was done, showing diffuse wall hypokinesia with left ventricular ejection fraction (LVEF) 40-45%. Computed tomography (CT) of the abdomen and CT pulmonary angiogram (CTPA) were performed, presenting hepatosplenomegaly and numerous centrilobular/tree in bud nodular infiltrates with bilateral hilar lymph nodes enlargement. The polymerase chain reaction (PCR) test for COVID-19 was positive. Therefore, the patient was admitted in the COVID-19 Clinic, with the suspicion of myocarditis in the context of COVID-19 pneumonia for further investigation and treatment.

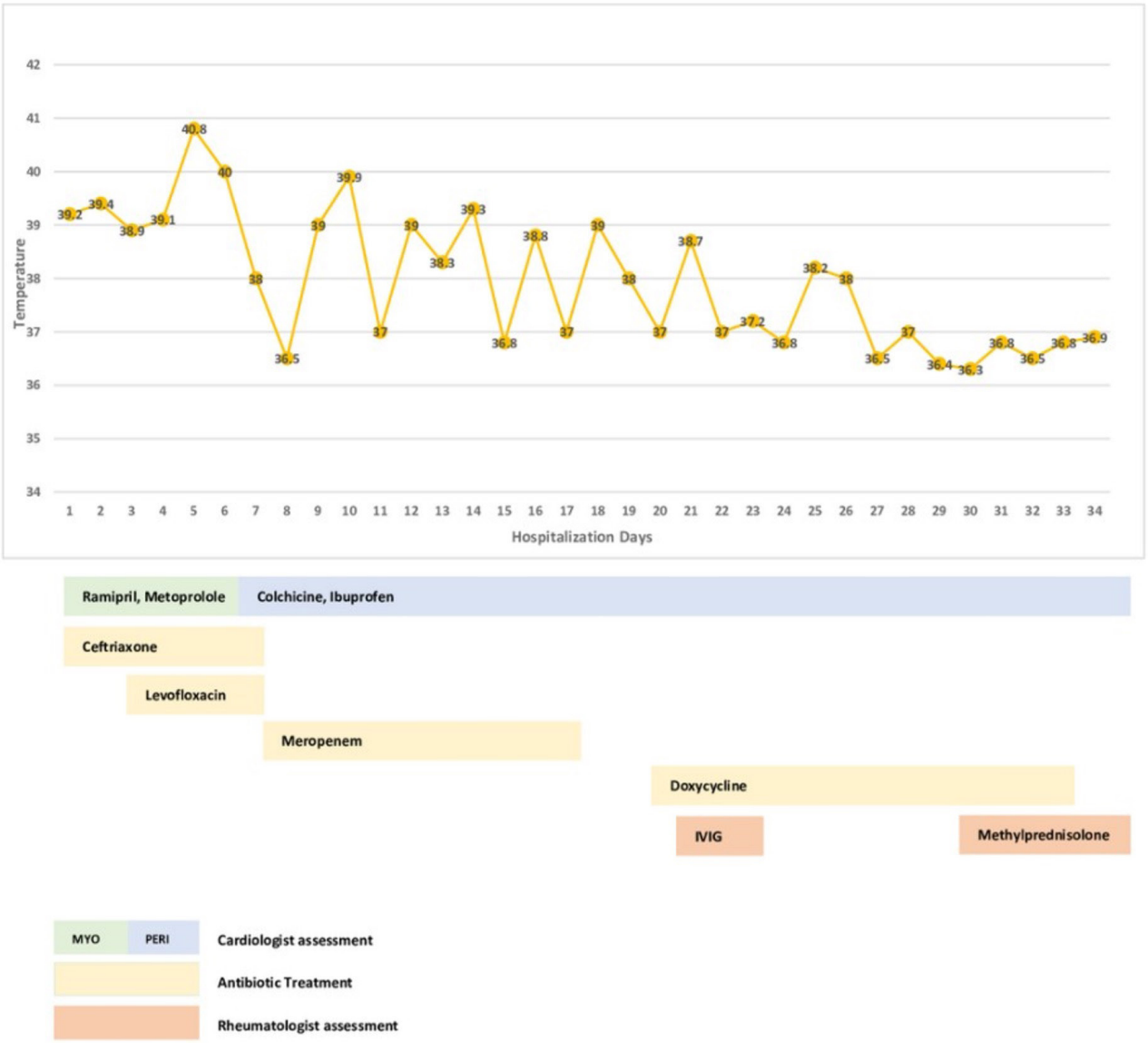
Upon admission, we administered low dose angiotensin-converting enzyme (ACE) inhibitors (ramipril) and β-blocker (metoprolol) for myocarditis, and remdesivir, enoxaparin and ceftriaxone for the COVID-19 infection (blood, urine cultures and procalcitonin had been preceded). During hospitalization, his clinical condition was progressively deteriorating, with quotidian fever (2 episodes per day, up to 40° C), and lab tests (inflammatory markers) were getting worse, resulting to the addition of levofloxacin on his treatment. Three days after his admission, the troponin testing was negative, following three previous positive measurements. The 5th day of his hospitalization, pericardial friction rub was heard, while serial ECGs, demonstrating, the typical sequence of ECG findings seen in acute pericarditis. A series of TTE studies that followed, showed improvement in contractility (LVEF >60%), and the emerge of a mild to moderate amount of pericardial fluid (10-15mm). The findings above, led to reconsideration of our working diagnosis, setting the diagnosis of pericarditis in the context of a COVID-19 infection with a probable bacterial superinfection (given the positive procalcitonin). Due to the new twist, the treatment was modified, adding colchicine and NSAIDs (ibuprofen) for the pericarditis and switching the previous administered antibiotics (ceftriaxone and levofloxacin) to meropenem, a broader-spectrum antibiotic, covering the possible bacterial infection.

Considering persistent febrile episodes and elevated inflammation biomarkers, a comprehensive infectious work-up (with repeated blood and urine cultures) and intensification of antibiotic therapy were performed. Due to the negative cultures, the antibiotic treatment was omitted, while the monitoring of clinical and laboratory presentation ensued. It performed also, an extensive viral, immunologic, and thyroid work-up, with unremarkable findings. Testing for specific bacteria (atypical or intracellular) and parasites was negative too. A Mantoux test, as well as acid-fast bacilli stain, culture and PCR in sputum samples excluded Mycobacterium tuberculosis infection. The suspicion of Sarcoidosis, due to the hilar lymphadenopathy, was eliminated based on the normal urine calcium values and the negative ACE test. Given the persistent, unrelieved fever and the patient's complicated status, a repeated whole-body CT scan was conducted, ruling out an abscess or an eventual malignancy. The new CT scan, that performed 14 days after his admission, revealed regression of infiltrations, presence of pericardial, pleural effusion and hepatosplenomegaly. A bronchoscopy was carried out, without suspicious findings, as well as a bone marrow biopsy, setting aside some hematological diseases. The 15th day of hospitalization, he underwent gastroscopy and colonoscopy, excluding malignancy. In subsequent TTE studies, an echogenicity change of the pericardial fluid was observed, containing echogenic fibrinous strands, without an increase in the amount of pericardial fluid or any effect on the heart's contractility. Taking to account this finding, as well as the initial reduced LVEF, it was decided to perform a cardiac magnetic resonance imaging (CMR), to exclude eventual constrictive bacterial pericarditis or myocarditis. The CMR revealed only moderate pericardial effusion mainly in the inferolateral wall and fibrinous strands within in it. He had also normal coronary arteries, ruling out coronary artery disease as a cause of initial systolic dysfunction.

Regardless any therapeutic intervention, the patient was maintaining an unchanged clinical and laboratory status, with fever and increased inflammatory biomarkers. So, on 20th day, it was decided to start doxycycline, covering a more extended spectrum, including intracellular microbes. Repeated laboratory tests for specific microbes were preceded, the results of which, indicated positive test for Coxiella Burnetti. Pending immunofluorescence (IFA) results, a rheumatological assessment was performed, with the recommendation to start IVIG as a treatment for possible MIS-A syndrome. During the three-day administration of IVIG, in addition to a doxycycline regimen, the patient experienced symptom remission, which relapsed after discontinuation of IVIG. The IFA results revealed titers of phase II IgG 1:1024, compatible with acute infection. Despite of doxycycline regimen, he continued to present the pre-existing symptomatology fever, chest and abdominal pain, myalgias and arthralgias. On 30th day of his hospitalization, a rheumatologist's reassessment, suggested starting of corticosteroids (methylprednisolone), initially intravenously and therefore orally. The patient remained afebrile, hemodynamically stable, under methylprednisolone and doxycycline. He received doxycycline for 14 days. The 34th day, he was discharged with instructions for corticosteroid oral treatment tapering and follow-up at Internist's and Cardiologist's Outpatient Clinic two weeks later.

During the follow-up, the patient was afebrile, under orally

Figure 1: Medical Treatment During Hospitalization and Fever Response



treatment with methylprednisolone. He denied any of his previous symptoms. The physical examination and lab re-testing were normal. The TTE showed only a trace of pericardial effusion, without other abnormal findings. So, the patient continued his treatment with gradual tapering of corticosteroids.

Discussion

The novel coronavirus disease 2019 (COVID-19) is a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 can lead to acute and chronic cardiovascular manifestations. Among them: acute coronary syndrome, left ventricular heart failure, rhythm disturbances, myocarditis, and acute and subacute pericarditis with or without pericardial effusion [1]. A recent retrospective cohort across 23 hospitals in the United States and Europe showed that the acute myocarditis prevalence among hospitalized patients with COVID-19 was 2.4 per 1000 hospitalizations considering definite/probable and 4.1 per 1000 considering possible acute myocarditis [2].

Several potential pathophysiological mechanisms may contribute to COVID-19-induced myocarditis. The most possible causes of myocarditis could be: direct cellular injury attributed to the presence of Ace2 in cardiomyocytes, and T-cell cytotoxicity targeting the myocardium. Myocarditis pathogenesis involves IL-6, a cytokine implicated in recruiting inflammatory cells to the

myocardium [3]. IL-6 is also a primary mediator of the cytokine storm, triggering T-lymphocyte activation and further release of inflammatory cytokines, creating a vicious cycle resulting in myocardial injury [4]. This inflammatory process can be intensified also by endothelial cells insult, increasing the risk of thrombus formation, due to platelet activation and elevated clotting factors. Furthermore, myocardial injury may be exacerbated by myocardial hypoxia, driven by increased oxygen demands in the setting of COVID-19 pneumonia. Consequently, myocardial inflammation results from the combination of hypoxemia, thrombus-induced ischemia, and the migration of proinflammatory cytokines and immune cells to the area [3].

TTE constitute a useful tool for evaluating the structural and functional status of the heart, but it may not provide specific indications of myocarditis. For a definitive diagnosis, CMR is considered the optimal non-invasive test. The interpretation of CMR images relies on Lake Louise criteria, focusing on three aspects of myocardial inflammation: oedema, hyperaemia and necrosis and/or fibrosis [5]. CMR should be conducted within 2 to 3 weeks from symptom onset for reliable ruling in or ruling out of myocardial inflammation [6]. While endomyocardial biopsy (EB) using the Dallas criteria remains the gold standard for confirmation, the majority of COVID-19-induced myocarditis cases are diagnosed primarily based on CMR findings [5].

The initial echocardiographic assessment in the ED revealed diffuse hypokinesia with mildly-reduced EF of approximately 45-50%. Interestingly, these findings completely reversed five days later, prompting reconsideration of the initial diagnosis of myocarditis. Myocarditis typically has a more prolonged course and may result in permanent myocardial damage. Additionally, even though CMR performed at the appropriate time, did not show previously reported findings, indicative of myocarditis, further diminishing its likelihood as a diagnosis. A literature search directed our attention to an alternative cardiomyopathy known as sepsis-related cardiomyopathy. This condition is characterized by reversible myocardial dysfunction, with three key features: (1) left ventricular dilation (2) impaired ejection fraction and (3) recovery within 7–10 days [7]. Sepsis-related cardiomyopathy is also defined as an "EF < 50% and a ≥ 10% decrease in the patient's baseline LVEF" [8]. The myocardial injury is thought to stem from increased nitric oxide production, which suppresses cardiomyocyte's response to calcium, induces mitochondrial dysfunction and downregulates the heart's β1-adrenergic receptors. A case series study demonstrated that 33% of COVID-19 patients developed this type of reversible cardiomyopathy [7].

The subsequent clinical course of our patient, along with laboratory and imaging findings, prompted a reevaluation of the working diagnosis to pericarditis in the context of COVID-19 pneumonia with a potential bacterial infection. Limited published data exist on cases of COVID-19 leading to acute pericarditis, with most reported cases associated with myocardial involvement [9]. In a recent meta-analysis of 2676 hospitalized COVID-19 patients, the pooled prevalence of pericardial effusion on chest CT was 3% [10]. Ghantous et al. highlights that pericardial effusion is prevalent in hospitalized patients with COVID-19, but rarely attributable to acute pericarditis [11]. Pericarditis is diagnosed, when a patient presents two of the following four criteria: (1) Chest Pain, (2) Auscultation of pericardial friction rub, (3) Serial ECG changes, (4) Echocardiographic demonstration of pericardial effusion. ECG changes evolve through four stages: Stage 1 – widespread concave ST elevation and PR depression through most of the leads, with reciprocal changes in avR; Stage 2 – normalization of ST changes, generalized T wave flattening; Stage 3 – flattened T wave become inverted; Stage 4 – ECG returns to normal [12]. The Spodick's sign observed in our case, characterized when at least two leads had TP downslopping at least 1mm. Although this sign was first described by David H. Spodick in 1974, it remained relatively unevaluated until a recent retrospective analysis in 2020. Witting et al. found that Spodick's sign occurred in 29% of patients with pericarditis and 5% of patients with STEMI [13]. The patient fulfilled all required criteria and received the mainstay anti-inflammatory therapy for acute pericarditis, a combination of NSAIDs with colchicine [14].

Despite following appropriate regimens for COVID-19 and acute pericarditis, the patient's clinical condition progressively worsened, marked by daily fever, chills, myalgias, and arthralgias, accompanied by elevated inflammation biomarkers. It appears that the sepsis-related cardiomyopathy and pericarditis in this case were not solely attributed to COVID-19 pneumonia but potentially linked to a concurrent bacterial infection, supported by laboratory findings. Despite an intensified antibiotic regimen, the patient's clinical presentation remained unchanged. Extensive diagnostic examinations and repetitive testing for specific microbes were conducted, leading to the detection of a positive test for Coxiella Burnetii.

Q fever (also known as Query fever) is an acquired infectious disease caused by the obligate intracellular gram-negative bacterium Coxiella burnetiid [15-17]. The typical primary reservoirs of C. burnetii include ruminant animals like cattle, goats, and sheep, with infections easily transmitted to humans from these infected animals [18]. The primary modes of transmission involve direct or indirect exposure to aerosolized materials from infected animals or birth products, as well as the ingestion of unpasteurized milk. Individuals at major risk include those regularly in contact with animals, such as livestock farmers, slaughterhouse workers, veterinarians, meat processing workers, and laboratory workers [19].

C. burnetti infection is usually asymptomatic. The most common presentation is a self-limited febrile illness (91%) occurring after an incubation period of 2-3 weeks. Symptoms may include headache, cough, myalgia, arthralgia, abdominal pain and diarrhoea. Headache may be severe, accompanying by confusion. Faget's sign, a pulse-fever dissociation, is frequently observed in Q fever [20], in contrast to our patient who presented tachycardia during febrile episodes. Severe cases may exhibit atypical pneumonia, hepatitis (without or with hepatomegaly, as observed in our patient), endocarditis, or neurological manifestations such as meningitis or meningoencephalitis. Myocarditis or pericarditis can be acute

complications. Thirty-one patients among the 2434 patients included in one study analysis (1.3%) had pericarditis [21]. Q fever pericarditis can manifest as acute or chronic disease, accounting for 1% of cases of acute Q fever. However, its true incidence is likely underestimated, as diagnosis depends on local physicians' interest and the availability of specialized laboratories capable of performing serological tests [22].

The diagnosis of primary (acute) infection relies on the association between clinical symptoms and evidence of microbial infection, primarily interpreted through serological studies. While various serological techniques are available, the indirect immunofluorescence assay (IFA) has become the reference technique. Particularly, a detection of a 4-fold increase in phase II IgG or IgM antibodies between two serum samples taken 3 to 6 weeks apart, could be diagnostic [23]. Cut-offs values for a positive serological titer can vary between countries. Generally, titers of phase II IgG >200 and/or IgM >50 are considered significant for the diagnosis of primary Q fever infection [23,24]. Seroconversion typically occurred 7 to 15 days after the onset of clinical symptoms [23], potentially explaining our initial negative serologic test. The majority of patients develop antibodies by the third week after infection, as also detected in our patient, and then decrease within 3 to 6 months [24]. In contrast, the diagnosis of persistent C. burnetii focal infection is based on recently updated criteria, including the persistence of clinical symptoms for more than 3 months and the identification of an infectious focus using imaging tools such as TTE and positron emission tomography (PET). The term "chronic Q fever" is no longer recommended, as the serologic response in such cases is strain-dependent [21].

Doxycycline is considered the gold standard treatment for C. burnetii in humans [25]. Administering tetracycline within the first 3 days of illness has been shown to reduce the duration of fever by up to 50% [26]. In cases where doxycycline is poorly tolerated due to adverse effects, fluoroquinolones such as levofloxacin or moxifloxacin can be used as an alternative. Co-trimoxazole is recommended for pregnant women. For chronic disease, the standard antibiotic regimen is a combination of doxycycline and hydroxychloroquine for a duration exceeding 18 months [27]. In the presented case, despite receiving levofloxacin as part of the intensified antibiotic regimen, the patient did not respond to treatment regarding his symptoms. It's crucial to consider the existence of different strains of C. burnetii with distinct characteristics, including varying cellular antibiotic uptake, which may result in resistance to different antibiotics [28]. Wielders et al. demonstrated that early treatment of primary infection, before antibody positivity, did not influence the subsequent IgG II response [29]. Adding to the diagnostic uncertainty, the patient received optimal doses of doxycycline for 2 weeks without significant symptom remission. Interestingly, the patient was afebrile during the three days of IVIG administration along with the doxycycline regimen. However, upon discontinuation of IVIG, the patient resumed presenting pre-existing symptoms, including fever, chest and abdominal pain, myalgias, and arthralgias.

The patient's clinical condition was becoming increasingly concerning. The likelihood of C. burnetii infection diminished, given the absence of Faget's sign, but more significantly due to the lack of response to treatment. A multidisciplinary approach was performed, involving healthcare providers from various specialties, pursuing the most plausible diagnosis for our patient. Our focus shifted towards investigating a systemic pathology with multiorgan involvement, potentially linked to the previous COVID-19 infection. A thorough reassessment of clinical, laboratory, and imaging findings led us to consider MIS-A syndrome.

MIS-A syndrome is an uncommon and under-recognized manifestation that occurs during or in the postinfectious period of COVID-19 infection. Typically, affected patients are young or middle-aged, previously healthy. A systematic review revealed that among 221 patients with MIS-A, the median age was 21 years old (interquartile range [IQR], 19-34), 70% of the patients were men, 36% were non-Hispanic Black individuals, and 58% had no underlying comorbidity [30]. In addition to high fever and myalgia, MIS-A syndrome exhibits numerous extrapulmonary manifestations, encompassing cardiac, gastrointestinal, neurological, and dermatological involvement [31]. In the previously reported review, myocarditis was documented in 30%, and pericardial effusion in 25% of the patients [30]. The majority of acute myocarditis occurs in the absence of pneumonia and is often complicated by hemodynamic instability [2]. Common symptoms of MIS-A include daily fever, headaches, myalgia, arthralgia, abdominal pain, vomiting, diarrhoea, neck pain or sore throat, and a widespread rash [31]. For the diagnosis, a positive SARS-CoV-2 test for current or recent infection is required. Additionally, the presence of laboratory evidence of inflammation, including CRP, ESR, ferritin, procalcitonin and IL-6 is necessary [32]. MIS-A syndrome can mimic common conditions such as sepsis [31]. A recent study highlighted that LDH/lymphocyte ratio (LLR) above 0.24 predicted MIS-A development with 70% sensitivity and 65.2% specificity [33]. The patient in our case report fulfilled the majority of the Centers for Disease Control and Prevention's (CDC) Criteria for MIS-A syndrome.

At present, the optimal treatment for MIS-A is unclear. IVIGs, steroids, and other immunomodulatory agents have been employed to treat suspected cases of MIS-A, with clinical improvement noted in some instances [34]. Recent evidence suggests resistance to IVIG in some cases with MIS-C (related to children), thereby questioning the benefit of immunomodulators such as IL-1 or IL-6 blocking agents [35]. Our patient demonstrated a positive response to IVIG and corticosteroids, leading to symptoms remission. While most patients seem to respond well to corticosteroid therapy, the failure of clinicians to recognize this recently identified phenomenon could potentially delay diagnosis and treatment [31].

Conclusion

Myo-pericarditis constitutes a complex heart condition with a broad spectrum of possible causes, demanding a thorough diagnostic approach to accurately determine the specific cause. This is particularly challenging in the context of COVID-19, where each diagnostic strategy can be complicated by potential complications,

such as the MIS-A syndrome. This clinical manifestation necessitated a comprehensive work-up. A timely diagnosis and a specific management plan, considering a constellation of symptoms arising from multiple organ involvement, typically lead to a complete recovery.

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