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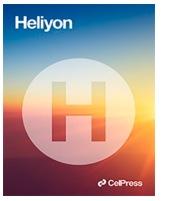

Spectre of COVID-19 infection confounding myocarditis related to cytomegalovirus mononucleosis syndrome and hyperinflammatory syndrome

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ABSTRACT

Viral infections have multiple mechanisms of affecting internal and external organs by direct invasion or by molecular mimicry. They have also been described as triggers for inflammatory processes like hyperinflammatory syndrome (HIS), Adult-onset Stills Disease (AOSD), and myocarditis [1].

Here we report an interesting case of a young adult with recent infection with SARS-CoV-2 (COVID-19) who presented with myocarditis requiring circulatory support in the cardiac care unit. During the admission, he was found to have concurrent cytomegalovirus (CMV) mononucleosis syndrome and presentation consistent with HIS resembling AOSD. This patient had multiple etiologies that could have caused myocarditis: CMV infection, COVID-19 infection, and HIS. As noted, viral infections have been proposed as potential triggers for the onset of HIS and AOSD with unknown mechanisms. We aim to add to the literature regarding CMV infection in an immunocompetent host causing myocarditis and HIS with features of AOSD with recent history of COVID-19 infection.

1. Introduction

Viral diseases have pleomorphic manifestations and are being explored as potential triggers for inflammatory processes such as Adult-onset Still's Disease (AOSD), hyperinflammatory syndrome (HIS), myocarditis [1–7]. We report a case of a patient who presented with myocarditis as a complication of cytomegalovirus (CMV) mononucleosis and HIS with recent COVID-19 infection. Although viral infections have been proposed as potential triggers for HIS and AOSD, the exact mechanisms are unknown and warrant further studies to understand the same [1,8–10].

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2. Case presentation

A 26-year-old male was in his usual state of health in late summer until he developed anosmia, ageusia, and positive test result for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing mild symptoms of coronavirus disease 2019 (COVID-19). In the emergency room, he denied receiving any COVID-19 vaccinations or booster doses. Given his immunocompetent status and stable oxygenation on room air, the patient was discharged home and instructed to quarantine for 10 days. The patient had a past medical history of asthma and attention deficit hyperactivity disorder. Family history included a maternal uncle who passed away from heart failure at the age of 40 years old. He had no known drug allergies and was not taking any medications at home. Social history is remarkable for tobacco use, daily marijuana use, and occasional alcohol consumption. He noted being monogamous with one female sexual partner, worked as a construction worker, and had a pet hamster. He had no travel history, exposure to other animals, or consumption of uncooked foods.

He developed chest and back pain accompanied by fever and rash approximately three weeks after his visit and presented to the emergency room again. On arrival, his vital signs included temperature of 39.9 °C, blood pressure 91/59 mm Hg, respiratory rate 32 breaths per minute, heart rate 107 beats per minute, oxygen saturation 98 % on 2 L of nasal cannula supplemental oxygen. On physical exam, patient was a well-developed man who appeared tired with left submandibular lymphadenopathy, tachycardia with regular rhythm, no obvious cardiac murmur on auscultation, no lower extremity edema, and no jugular venous distention. He had no swollen or erythematous joints. He was noted to have a non-blanching and non-pruritic maculopapular, reticular rash on the trunk extending to his abdomen and thighs.

Initial laboratory studies included lactic acid 4.5mmol/L, ultra-sensitive troponin 214ng/L (peaking at 493ng/L), erythrocyte sedimentation rate 130mm/hr, and C-reactive protein greater than 200mg/L. Electrocardiogram revealed sinus tachycardia with nonspecific T wave changes, and an echocardiogram revealed an ejection fraction of 25–30 % with mild to moderate mitral regurgitation, moderate tricuspid regurgitation, and minimal pericardial effusion. Given worsening hypotension with lactic acidosis, the patient was triaged to the cardiac care unit and placed on inotropic support with dobutamine and epinephrine infusions. He was later cannulated for veno-arterial extracorporeal membrane oxygenation (VA-ECMO) on hospital day 5.

In the cardiac care unit, heart failure and infectious disease services were consulted to assist with heart failure management and extensive infectious work-up was negative (Table 1). The patient continued to have maculopapular rash and new diffuse arthralgias. Skin biopsy done by dermatology consult service was consistent with viral exanthem and/or drug eruption. Rheumatology was consulted for inflammatory etiologies of myocarditis and patient was initially diagnosed with HIS with features of AOSD fulfilling the following criteria: fever for at least one week, arthralgias for more than two weeks, leukocytosis with neutrophilic predominance, lymphadenopathy, hepatomegaly, negative ANA and rheumatoid factor, elevated transaminases, and maculopapular salmon-colored truncal rash [11]. He also demonstrated typical features of AOSD with classic quotidian fevers, elevated ferritin (peak 2200 ng/mL), and Koebner phenomena of the skin [12]. Subsequent results from endomyocardial biopsy on admission showed acute/chronic

Table 1
Initial infectious Workup (serum).

Test Name	Result
Acute Viral Hepatitis Panel[a]	Negative
Anaplasma IgM and IgG	Negative
Babesia IgM and IgG	Negative
COVID-19 PCR	Negative
Coxiella IgM and IgG	Negative
Coxsackie B Virus IgM and IgG	Equivocal
Ehrlichia IgM and IgG	Negative
Epstein Barr Virus IgM	Negative
Heterophile Antibodies (Monospot Test)	Negative
HIV Ag/Ab 4th Generation Test	Negative
HIV-1 RNA PCR	Negative
Leptospira IgM	Negative
Lyme IgM and IgG	Negative
Respiratory Viral Panel (BioFire® assay)[b]	Negative
Rocky Mountain Spotted Fever IgM and IgG	Negative
Rapid Plasma Reagin (RPR) Test	Negative

Footnotes:

[a] Acute viral hepatitis panel includes: Hepatitis A IgG, Hepatitis B core IgM, Hepatitis B surface Ag, Hepatitis B surface IgM, Hepatitis C Ab IgG.

[b] BioFire® assay includes: Adenovirus, Coronavirus 229E, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Human Metapneumovirus, Human Rhinovirus/Enterovirus, Influenza A virus, Influenza A virus A/H1, Influenza A virus A/H3, Influenza A virus A/H1-2009, Influenza B virus, Parainfluenza virus, Parainfluenza virus 2, Parainfluenza virus 3, Parainfluenza virus 4, Respiratory syncytial virus Bordetella parapertussis, Bordetella pertussis, Chlamydia pneumonia, Mycoplasma pneumoniae.

inflammation with no amyloid deposits. Due to tissue quality, no further viral stains could be performed on this specimen.

After multidisciplinary discussion regarding infectious and immunologic risks, patient was started on pulse-dose steroids and anakinra for suspected AOSD on hospital day 5 to prioritize treatment of hyperinflammatory syndrome with infectious risks to be mitigated if they arose given negative infectious work-up. Four days after anakinra initiation, serum cytomegalovirus (CMV) quantitative polymerase chain reaction (PCR) was found to be increased from 1271 copies/mL (3.10 log copies/mL) up to 24,475 copies/mL (4.39 log copies/mL) along with positive CMV IgM and IgG serologies. A diagnosis of CMV mononucleosis syndrome was made as possible associated trigger for myocarditis and HIS with features of AOSD for this patient and he was started on IV ganciclovir. He experienced rapid improvement in arthralgias and abdominal pain with resolution of fevers on hospital day 16. Anakinra was briefly held to assist with CMV clearance and was restarted on hospital day 20 (Fig. 1).

Patient continued to improve and decannulated from VA-ECMO on hospital day 11. Repeat echocardiogram revealed a recovered ejection fraction of 55–60 % on hospital day 12 (Table 2). After being weaned from inotropic support, the patient was transferred to cardiology floors to where he was continued on a steroid taper and anakinra. Intravenous ganciclovir was continued, and he was transitioned over to oral valganciclovir when CMV PCR decreased to <137 copies/mL (Fig. 1). Given plans for ongoing immunosuppression on discharge, he was discharged with valganciclovir 900mg daily, prednisone 5 mg daily, and anakinra 100mg daily.

During outpatient follow-up with rheumatology, interleukin-2 (IL-2) alpha receptor was found to be 511 IU/mL, compared to 2738.1 IU/mL during his hospitalization. During an outpatient visit with infectious disease, he continued to have undetected CMV viral load three months after discharge and valganciclovir was discontinued. He was planned for continued cardiology follow-up given these events.

3. Discussion

Myocarditis is a state of inflammation of the myocardium associated with myocyte degeneration and necrosis of non-ischemic origin [13]. Manifestations of myocardial injury include symptomatic chest pain, elevated cardiac biomarkers, and echocardiographic evidence of cardiomyopathy in the absence of diseased coronary arteries. Myocarditis can be caused by various insults to the myocardium including infectious pathogens, immune-mediated processes, toxins, medications, hormones, or physical agents (Table 3). It can also present as component of hyperinflammatory syndrome with or without other organ involvement. COVID-19 can cause myocarditis, affecting 25–30 % of infected individuals with complications such as acute respiratory distress syndrome and shock [7]. CMV has also been described as an infectious cause of myocarditis and can cause mononucleosis syndrome without prodromal pharyngitis [4,6].

Given minimal prodromal symptoms and lack of overt exposures in our patient, differential diagnoses included Coxsackievirus, EBV, CMV, COVID-19 disease, Lyme disease, collagen vascular disorder, Kawasaki-disease or alcohol-induced cardiomyopathy. In human myocarditis, viral and autoimmune mechanisms with or without genetic predisposition induce myocyte necrosis and macrophage activation with the release of cytokines such as interleukin-1, interleukin-2, Tumor Necrosis Factor alpha (TNF-α) and interferon gamma which decrease myocardial contractility leading to a low cardiac output and heart failure [7]. Direct cytopathic injury, apoptosis, activation of the innate and adaptive immune system, and cardiac remodeling also play a role in the pathogenesis of viral myocarditis [3]. Diagnosis of viral etiology may not always be revealed by endomyocardial biopsy with histopathologic examination.

Our patient experienced hyperinflammatory state with features consistent with AOSD. AOSD usually affects young male adults in a bimodal distribution at ages 15–25 years old and 36–46 years old and remains a diagnosis of exclusion based on the presence of symptoms described in Yamaguchi criteria [11]. AOSD can affect any area of the heart with pericarditis being more common than myocarditis; however it is important to note that myocarditis carries a poor prognosis [10,14]. In Table 4, we outline different features our patient had during hyperinflammatory state compared to Yamaguchi criteria. Given presence of CMV and recent COVID-19, our patient met one exclusion criteria for AOSD. Overall, he improved with steroid and anakinra treatment.

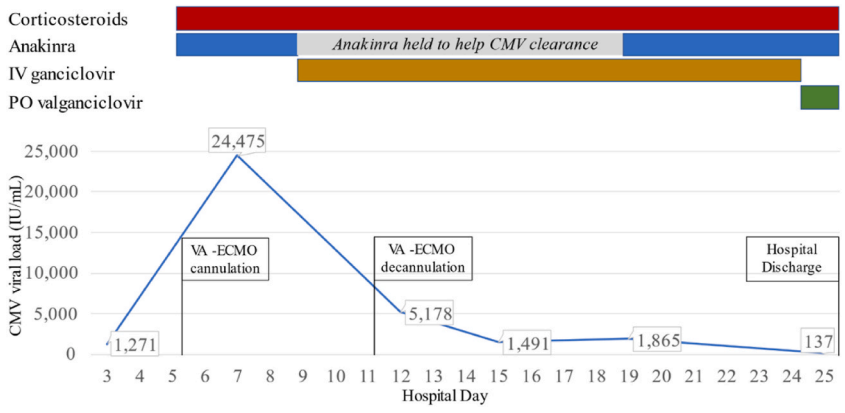

Fig. 1. Timeline of CMV viral load and treatments.

Table 2
Transthoracic echocardiogram parameters through hospitalization.

Feature	At presentation	Hospital Day 12
Left ventricular ejection fraction	25–30 %	55–60 %
Left ventricular systolic dysfunction	Global, moderate to severely decreased	Normal
Right ventricular systolic function	Mildly reduced. TAPSE = 1.4 cm	Normal
Valvular structure	Normal	Normal
Additional Comments	Intermediate diastolic dysfunction	Grade 1 diastolic dysfunction

Table 3
Table of infectious and non-infectious causes of myocarditis.

Infectious Causes	Non-infectious Causes
Bacterial	**Chemicals or Drugs**
Actinomyces, Brucella, Francisella, Gonococcus, Haemophilus, Legionella, Meningococcus, Mycobacterium spp., *Mycoplasma, Nocardia, Pneumococcus,* Psittacosis*, Salmonella, Staphylococcus, Streptococcus, Tropheryma whippleii,*	Alcohol, Anthracyclines, Arsenic, Carbon monoxide, Cardiotoxins, Catecholamines, Cocaine, Cyclophosphamide, Heavy metals (copper, lead, iron)
Viral	**Inflammatory conditions**
Adenovirus, Arbovirus, Arenavirus, Coxsackie, Epstein–Barr virus, COVID-19, Cytomegalovirus, Dengue, Echovirus, Encephalomyocarditis virus, Hepatitis B, Hepatitis C, Human Herpes Virus 6, Human Immunodeficiency Virus, Influenza virus B, Measles, Mumps Rubella, Parvovirus B19, Rabies, Respiratory Syncytial Virus, Vaccinia, Varicella, Variola virus	Auto-Immune (GPA), Collagen vascular disorders, Inflammatory Bowel Disease, Kawasaki disease, Sarcoidosis, Thyrotoxicosis,
Fungal	**Other conditions/exposures**
Aspergillus, Blastomyces, Candida spp., *Coccidioides, Cryptococcus, Histoplasma, Sporothrix*	Hypersensitivity reactions, Radiation, Snake bite
Rickettsial	
Rocky Mountain Spotted Fever, *Q fever, Scrub typhus, Typhus*	
Spirochetal	
Borrelia, *Leptospira*, Relapsing fever, Syphilis	
Protozoal	
Entamoeba, Malaria, *Trypanosoma, Toxoplasmosis*	
Helminthic	
Strongyloides, Cysticercosis*, Echinococcus, Schistosoma, Toxocara, Trichinella*	

Adapted from UpToDate.

Table 4
Patient symptoms and findings in comparison to Yamaguchi criteria.

Features		Present in Patient
Major Criteria	Fever of at least 39C for at least a week	Yes
	Arthralgia or arthritis for at least 2 weeks	Yes
	Non pruritic salmon colored rash on trunk/extremities	Yes
	Granulocytic leukocytosis (10,000/miclroL or greater)	Yes
Minor Criteria	Sore throat	No
	Lymphadenopathy	Yes
	Increased serum aminotransferase or lactate dehydrogenase levels (after other causes have been excluded)	Equivocal as he had cardiogenic shock
	Negative IgM rheumatoid factor and ANA	Yes
Exclusion Criteria	Infections	Yes
	Malignancy	No
	Other rheumatic disease	No

Viral infections such as rubella, CMV, EBV, and Human Herpes Virus 6 (HHV-6) have been proposed as potential triggers for AOSD, but the exact mechanisms underlying AOSD onset remain unknown [9]. As described by Jia J et al., patients with AOSD had higher levels of anti-CMV IgM and IgG antibodies and CMV DNA copies, indicating that CMV infection was associated with new-onset and reactive AOSD [8]. On the other hand, there have been very few case reports that describe AOSD-like hyperinflammatory syndrome as a post-COVID complication where a misdirected immune response against SARS-COV-2 potentially triggered onset of AOSD [10]. Both diseases seem to be mediated by Interleukin-1 (IL-1) as evidenced by the role of targeting IL-1 to reduce hyperinflammatory response to COVID-19 infection. AOSD has been thought to be mediated by IL-1 that further activates neutrophils, macrophages, and mast cells.

Symptomatically, the treatment of heart failure due to myocarditis is similar to treatment for non-myocarditis induced heart failure. To prevent further immune-mediated myocardial injury, treatment will include immunosuppressive agents such as corticosteroids, immunoglobulins, azathioprine, and cyclosporine. Immunosuppressant therapy may be continued for five to six months after the acute episode [1,7–10,15,16]. Our patient continued corticosteroids for 3 months with ongoing improvement and recovery of cardiac output.

More cases of CMV myocarditis in the immunocompetent host are emerging. Previous case reports and series reveal favorable

response to intravenous ganciclovir or oral valganciclovir [5]. Current challenges remain about the duration of treatment that potentially prevents progressive myocardial injury by viral clearance while balancing medication adverse effects such as leukopenia and renal toxicity [3]. Our patient improved with intravenous ganciclovir as induction therapy for 10 days followed by maintenance oral valganciclovir through 3 months after acute presentation. Given our patient's mild COVID-19 disease and reported recovery, it is unclear if this viral infection played a role in presentation of myocarditis. No specific antiviral therapy has been described to aid in the treatment of COVID-related myocarditis.

In conclusion, CMV and COVID-19 infection have been described as causes of viral myocarditis. It is important for physicians to be aware that CMV myocarditis can occur in immunocompetent hosts with favorable response to antivirals. Viral infections have also been proposed as triggers for immune-mediated disease such as HIS and AOSD. This case highlights an unusual presentation of myocarditis associated with CMV mononucleosis syndrome and HIS with features of AOSD in the setting of recovery from recent COVID-19 infection.

Consent

Verbal and written informed consent were obtained from the patient for publication of this case report.

Data availability statement

All data in this case report are available within the paper and its Supplementary Information. No datasets were generated or analysed during the current study.

CRediT authorship contribution statement

Blanca Simon Frances: Writing – review & editing, Writing – original draft, Resources, Conceptualization. **Namitha Nair:** Writing – original draft, Visualization, Conceptualization. **Aahana Gaur:** Writing – original draft, Supervision, Conceptualization. **Benjamin Plotz:** Writing – original draft. **Anjali Majumdar:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e21383.

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