First Case of Acute Myocarditis Caused by Metapneumovirus in an Immunocompromised 14-year-old Girl

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Abstract

Background: Human metapneumovirus (hMPV) is a paramyxovirus, well known as a causative agent of respiratory tract infections. Non-respiratory manifestations, including cardiac impairments, remain rare. Only two cases of myocarditis caused by hMPV have been described in adults.

Case description: We present the case of a 14-year-old female suffering from Burkitt leukemia and diagnosed with severe myocarditis caused by hMPV, based on results from real-time polymerase chain reaction (RT-PCR) and magnetic resonance imaging (MRI). She was successfully treated by venoarterial extracorporeal membrane oxygenation and intravenous immunoglobulins. She was discharged from pediatric intensive care unit (PICU) 3 weeks later.

Conclusion: This is the first pediatric case of hMPV myocarditis requiring venoarterial extracorporeal membrane oxygenation.

Keywords: Intraavenous immunoglobulin, Myocarditis, Venoarterial extracorporeal membrane oxygenation.

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Introduction

Myocarditis, defined as inflammation of the myocardium, is one of the primary etiology of acute heart failure (HF) in children.1 Most often, myocarditis results from common viral diseases such as enteroviral, influenza, and adenoviral infections. Less commonly, myocarditis may result from other pathogens, toxic drug reactions, giant-cell myocarditis, or sarcoidosis.2

The hMPV, a paramyxovirus related to the respiratory syncytial virus, was first isolated in 2001.3 This virus is well known as a causative agent of respiratory tract infections. However, non-respiratory manifestations including cardiac impairments are rare. Acute myocarditis secondary to hMPV has only twice been described in adults,4,5 and only one pediatric case with acute respiratory distress syndrome has been reported in the literature.6

We report the first case of hMPV myocarditis, without respiratory manifestations, in a child who was successfully treated with venoarterial membrane extracorporeal oxygenation (VA–ECMO) and intravenous immunoglobulins (IVIg).

Case Description

A 14-year-old girl suffering from Burkitt leukemia presented to the emergency room with chest pain, dyspnea, and mild cough, without fever. She was diagnosed with Burkitt leukemia 4 months earlier and treated with chemotherapy (120 mg/m² of doxorubicin and 5,700 mg/m² of cyclophosphamide, both known as cardiotoxic drugs).7

In the emergency room, her vital signs were listed as follows: Heart rate of 144 beats/minutes, blood pressure of 59/45 mm Hg, body temperature of 37.2°C, respiratory rate of 40/min, and oxygen saturation level of 100% on room air. The physical examination was remarkable for signs of hypoperfusion (prolonged capillary refill time, mottling) and mild respiratory distress. Chest X-ray showed cardiomegaly and perihilar infiltration. Electrocardiogram showed ST–T waves abnormalities in leads V4, V5, and V6. Myocardial biomarkers, as listed in the following, were increased on admission: Brain natriuretic peptide 349 pmol/L (Normal <28.9 pmol/L); Troponin I 353 ng/L (Normal <15.6 ng/L), increasing to 9,953 ng/L 72 hours later. Echocardiography showed a severely depressed left ventricular ejection fraction (LVEF) of 10–15% with a moderate pericardial effusion, establishing the diagnosis of HF. The patient was transferred to the PICU to be placed under mechanical ventilation. An inotropic support by catecholamines was initiated. Rapidly, a refractory cardiogenic shock was diagnosed due to increasing lactic acidosis and the patient was placed under VA–ECMO. After an initial improvement of myocardial function, a decrease in LVEF associated with an elevation of myocardial biomarkers (7 days after admission) were observed. Therefore, a treatment by IVIg was started (2 gm/kg) for 2 days. After 10 days of VA–ECMO, the patient...
gradually recovered and LVEF was normalized on day 11. Pericardial effusion disappeared and myocardial biomarkers decreased to normal values. She was weaned from VA–ECMO support on day 16 and was discharged from the PICU on day 23.

Regarding the etiologic diagnosis, a RT-PCR in bronchoalveolar lavage identified hMPV. The other main causes of myocarditis (blood PCR testing for enteroviruses, adenoviruses, Epstein–Barr virus, human herpes virus 6, cytomegalovirus, parvovirus B19, hepatitis C virus, human immunodeficiency virus, influenza, dengue, and chikungunya virus; multiplex respiratory PCR testing for respiratory syncytial virus, influenza A, influenza B, parainfluenza, adenovirus, coronavirus, chlamydia, and mycoplasma pneumoniae; toxins and autoimmune diseases) were ruled out, and the blood cultures remained negative. Endomyocardial biopsy was not performed because the patient’s condition was unstable and because of predominant left HF. A cardiac MRI was performed 30 days after the admission: Left ventricular ejection fraction was normal with high signal intensity of the myocardium in T2-weighted STIR sequences, and a delayed myocardial enhancement in T1-mapping was suggestive of myocardial inflammation (Fig. 1).

The diagnosis of acute myocarditis secondary to hMPV was finally established, with a large body of evidence such as timing of recovery, frequency, imaging findings, and identification of hMPV, already known as a causative agent of myocarditis. For note, the cardiac function after completion of chemotherapy was normal with a LVEF >50%, without regional kinetic wall motion abnormalities.

**Discussion**

The hMPV is a recently discovered pathogen, which is a member of the Paramyxovirus family, and is worldwide distributed. Although it is well known to cause various upper and lower respiratory diseases, the full spectrum of clinical manifestations may not be limited to the respiratory tract and needs to be further characterized. We hereby report a rare case of isolated cardiac impairment due to hMPV, without respiratory manifestations.

Since our patient was administered cardiotoxic drugs for the treatment of her Burkitt leukemia, the differential diagnosis was toxic drug-induced myocarditis. Indeed, she had received a cumulative dose of 120 mg/m² of doxorubicin (toxic threshold >500 mg/m²) and 191 mg/kg of cyclophosphamide (toxic threshold >150 mg/kg). However, this hypothesis was rejected due to the prolonged time interval between treatment administration and the onset of myocarditis. Moreover, the short recovery time was not consistent with a drug-induced myocarditis.

![Figs 1A to D: (A to C) High signal intensity of the myocardium in T2-weighted STIR imaging and (D) A delayed myocardial enhancement in T1-mapping suggesting myocardial inflammation](image-url)
Myocarditis Caused by Metapneumovirus in Children

It is known that hMPV infections are more common and more severe in immunocompromised patient. Since our patient have had an immunosuppression induced by chemotherapy (especially Rituximab, an anti-CD20 inhibitor), we initiated a prompt treatment by IVIg therapy. We could not find any dosing recommendations for IVIg in children with viral myocarditis, especially under VA–ECMO. The dosage of immunoglobulins was chosen arbitrarily and several assays were performed. According to a Cochrane review in 2015, no benefit was found concerning the use of IVIg in adults with viral myocarditis. Nevertheless, a recent review of the literature did not confirm those results. Indeed, this meta-analysis suggests that IVIg therapy is associated with a decrease in in-hospital mortality and an improvement of LVEF recovery, compared to a conventional treatment. In our patient, we noticed an improvement of LVEF 3 days following IVIg therapy. The LVEF was measured at 45% and the cardiac index increased to 2.7 L/min/m² when ECMO flow was less than 1 L/min. An increase in pulse pressure, mean and systolic arterial pressure values were obtained concomitantly.

Only three cases of myocarditis caused by hMPV have been described in the literature. The first case of hMPV myocarditis was described in 2015 in a 25-year-old man without any past medical history. He presented with severe HF after 2 weeks of respiratory illness and hMPV infection was diagnosed. He was successfully treated with diuretics and inotropic agents. He was discharged home 7 days after hospitalization. Another 73-year-old woman, with underlying diabetes mellitus and hypertension, was admitted with fever, cough and progressive dyspnea. She was diagnosed with pneumonias and myocarditis with moderate HF secondary to hMPV infection. She was treated with supportive care and recovered without any sequelae in 7 days. The third recent case of hMPV myocarditis concerned a healthy 2.5-month-old boy. He presented with acute respiratory distress syndrome and myocarditis secondary to hMPV. A treatment by positive inotropic agents and IVIg were given. Left ventricular ejection fraction rapidly increased and the child was discharged after 16 days. Our case differs from the previous descriptions in several points. First, our patient was a child and was immunocompromised. Second, she had severe HF without respiratory manifestations, unlike the three previous cases. Finally, this was the first case of hMPV-associated myocarditis requiring the use of VA–ECMO.

**CONCLUSION**

To our knowledge, this is the first pediatric case of hMPV-associated myocarditis requiring the use of VA–ECMO.

**REFERENCES**

1. Panda S, Mohakud NK, Pena L, Kumar S. Human metapneumovirus: review of an important respiratory pathogen. Int J Infect Dis 2014;25:45–52. DOI: 10.1016/j.ijid.2014.03.1394.
2. Beijiqi R, Retkoceri R, Maloku A, Mustafa A, Beijiqi H, Beijiqi R. The diagnostic and clinical approach to pediatric myocarditis: a review of the current literature. Open Access Maced J Med Sci 2019;7(1):162–173. DOI: 10.3889/oamjms.2019.010.
3. van den Hoogen BG, de Jong JC, Groen J, Kuiken T, de Groot R, Fouchier RA, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001;7(6):719–724. DOI: 10.1038/89098.
4. Choi MJ, Song JY, Yang TJ, Jeon JH, Noh JY, Hong KW, et al. Acute myopericarditis caused by human metapneumovirus. Infect Chemother 2016;48(1):36–40. DOI: 10.3947/ic.2016.48.1.36.
5. Weinreich MA, Jabbar AY, Malguria N, Haley RW. New-onset myocarditis in an immunocompetent adult with acute metapneumovirus infection. Case Rep Med 2015;2015:814269. DOI: 10.1155/2015/814269.
6. Yakut K, Varan B, Erdoğan İ, Tokel KÇ. Acute respiratory distress syndrome and myocarditis caused by human metapneumovirus in a child. Bzilemlek Science 2020;8(2):212–214. DOI: 10.14235/bas-galenos.2020.3919.
7. Zamorano JL, Lancellotti P, Muñoz DR, Aboyans V, Asteggiiano R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines. Kardiol Pol 2016;74(11):1193–1233. DOI: 10.5603/ki.2016.0156.
8. Finet JE, Tang WHW. Protecting the heart in cancer therapy. F1000 Res 2018;7:F1000. DOI: 10.12688/f1000research.15190.1.
9. Maisch B, Alter P. Treatment options in myocarditis and inflammatory cardiomyopathy: Focus on i. v. immunoglobulins. Herz 2018;43(5):423–430. DOI: 10.1007/s00059-018-4719-x.
10. Robinson J, Hartling L, Vandermeer B, Klassen TP. Intravenous immunoglobulin for presumed viral myocarditis in children and adults. Cochrane Database Syst Rev 2015;5:CD004370. DOI: 10.1002/14651858.CD004370.pub3.
11. Huang X, Sun Y, Su G, Li Y, Shuai X. Intravenous immunoglobulin therapy for acute myocarditis in children and adults: a meta-analysis. Int Heart J 2019;60(2):359–365. DOI: 10.1536/ihj.18-299.