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CASE REPORT

Myocarditis requiring extracorporeal membrane oxygenation support following Influenza B infection: a case report and literature review

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SUMMARY

Seasonal influenza A (IA) and B (IB) viruses co-circulate every year, causing respiratory tract infections in individuals of all ages. Recently, the association between laboratory-confirmed influenza infection and acute myocardial infarction has been clearly demonstrated. However, most of the reported cases of fulminant myocarditis had been associated with influenza virus type A infection.
Here we report the case of a 44 y/o man who experienced myocarditis with cardiogenic shock [requiring percutaneous extracorporeal membrane oxygenation (ECMO) support], following influenza B virus infection, which circulated widely in Italy in 2017-18.

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INTRODUCTION

During the 2017-18 flu season, both influenza virus types A and B co-circulated (with prevalence of type B viruses) in European countries. The majority of severe cases admitted to non-ICU hospital wards occurred in adults infected with influenza type B viruses (http://ecdc.europa.eu/en/seasonal-influenza). In this report we describe a case of myocarditis associated with Influenza B infection, requiring ECMO support. Retrospectively reviewing the scientific literature, we noted a recent increase (starting in 2017) in the number of reports of severe cardiac damage related to Influenza B. This observation should draw the attention of physicians and public health authorities to the importance of influenza vaccination as a strategic tool to avoid serious complications.

CASE REPORT

In December 2017, a 44-year old man was admitted to the Grosseto Hospital (Italy) with acute heart failure associated with two previous days of malaise and fever. After a few hours, the patient was transferred to the Cardiac Intensive Care Unit of the Santa Maria alle Scotte Hospital (Siena, Italy) due to cardiogenic shock (hypotension, tachycardia, dyspnea, low O_2 saturation notwithstanding oxygen therapy, mental confusion and oliguria). The patient had a history of non-Hodgkin Lymphoma (thirteen years before), smoking, familial hypercholesterolemia; no history of drug abuse. He wasn't vaccinated against influenza.
At ICU admission, a Chest X-Ray revealed signs of pulmonary congestion. A coronary angiography showed diffuse coronary artery disease and absence of critical obstructive lesions. An echocardiogram showed severe biventricular hypokinesis with an estimated ejection fraction (EF) of 15%, associated with minimal circumferential pericardial effusion. Due to the absence of clinical response to dobutamine and norepinephrine administration, the patient was sedated, intubated orotracheally, and subjected to mechanical ventilation. A mechanical circulatory support was implemented as a 'bridge to decision' with veno-arterial extracorporeal membrane oxygenation (V-A ECMO), according to ELSO guidelines. Heparin treatment (100UI/kg bolus) and then Unfractioned Heparin (UFH), in continuous infusion, were initiated, and the Activated Partial Thromboplastin Time (APTT) test was used to monitor anticoagulation therapy.
On hospital day 2, inotropic support with epinephrine was reduced and Levosimendan therapy was associated with norepinephrine for 24 hours; on hospital day 4, a mechanical support with intra-aortic balloon pump (IABP) was initiated to support circulation.
Empiric antibiotic therapy with vancomycin and piperacillin-tazobactam was administered. Microbiology samples including blood cultures obtained at hospital admission, bronchoalveolar lavage and urine cultures resulted negative for bacterial and fungal pathogens.
The pharyngeal swab resulted positive for influenza virus type B by polymerase chain reaction (PCR) performed as described [http://www.who.int/influenza/gisrs_laboratory/molecular_diagnosis_influenza_virus_humans_up-

Key words:
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Table 1 - *Case reports of severe cardiac damage associated with Influenza B infection (https://www.ncbi.nlm.nih.gov/pubmed/) until October 2018.*

Year	*Age (years)*	*Sex*	*Clinical presentation*	*LVEF*	*Mechanical circulatory support*	*Treatment*	*Hospital survival*	*First author*
2018	34	F	Cardiogenic shock	NA	No	No	No	Dickey *et al.*
2018	57	F	Cardiac tamponade	NA	No	No	No	Roto *et al.*
2018	89	F	Takotsubo cardiomyopathy	24%	No	Oseltamivir	Yes	Elikowski *et al.*
2018	13	F	Cardiogenic shock	severely decreased	ECMO	Oseltamivir, Antithymocyte Globulin	Yes	Piccininni *et al.*
2017	22	F	Cardiogenic shock	10%	No	Oseltamivir	Yes	Siskin *et al.*
2016	≤18 years	NA	NA	NA	NA	NA	NA	Matsuura *et al.*
2016	43	M	Acute myocarditis and ARDS	60%	No	Oseltamivir	Yes	Chang *et al.*
2013	52	F	Cardiogenic shock	10%	ECMO	Oseltamivir	Yes	Taremi *et al.*
2013	7	F	Cardiogenic shock	NA	No	Oseltamivir	Yes	Moon *et al.*
2010	5	F	Cardiac arrest	10%	No	No	No	Frank *et al.*
2009	15	M	Mimicking acute coronary syndrome	63%	No	No	Yes	Muneuchi *et al.*
2004	4	F	Cardiogenic shock	severely decreased	ECMO	NA	Yes	Tabbutt *et al.*
1997	6	F	Cardiogenic shock	NA	No	No	No	Craver *et al.*
1989	34	F	Cardiogenic shock	severely decreased	LVAD	Ribavirine	No	Ray *et al.*

date_201403.pdf]. The sample was extracted using a QIAamp viral RNA mini kit (Qiagen), according to the manufacturer's instructions; 5µl of purified RNA were employed for reverse transcription (RT) using the SuperScript III One-Step RT-PCR with Platinum Taq (Invitrogen) for one cycle of reverse transcription at 50°C for 30 min and at 94°C for 5 min followed by 45 cycles of PCR (20 sec at 94°C; 30 sec 60°C). Parvovirus B19, HHV6, HSV1-2, Enteroviruses, EBV and CMV were all negative by PCR on whole blood. Serology showed the presence of Influenza B IgA (58.10 UI/ml) and specific IgG (33.40 IU/ml). On hospital day 5, the patient underwent right ventricle endomyocardial biopsy under echocardiographic guide. The endomyocardial biopsy analysis confirmed the presence of a modest lymphocyte and macrophage inflammatory infiltrate. Direct detection of influenza B virus by PCR on myocardial tissue extract was negative. It should be noted that viral myocarditis is usually characterized by a focal infiltration, predominantly in the lateral free wall of the left ventricle; therefore, there may be false negative results when right ventricle biopsies are analyzed (Mahrholdt *et al.*, 2004). During the acute phase, the patient's immune response profile showed a simultaneous increase of lymphocytes and neutrophils with peaks of 6.72 x10^3/ml 8 (0.90-4.50) and 17.93 x10^3/ml (1.8-7.0), respectively (presumably ten days after onset of the infection). In the following days, these cell populations progressively decreased. While lymphocytes are an index of viral infection, neutrophils may contribute to disease severity (Camp and Jonsson, 2017), being involved in response to viral infection, and may respond to viruses with specific effector functions, influencing the microenvironment and contributing to disease severity. However, disease severity is influenced not only by direct damage by cardiac myocytes but also by overproduction of cytokines, severe inflammatory response and cellular damage through intracellular signal transduction upon viral infection (Mamas *et al.*, 2008; Guarner *et al.*, 2006; Pan and Kido, 2011).

The time elapsed between the onset of symptoms and the diagnosis was longer than five days; therefore, the patient was not treated with antiviral therapy.

Afterwards, hemodynamic parameters improved, cardiac function recovered and, on hospital day 12, the patient was weaned from the ventilator and extubated.

The patient's condition gradually improved; the transthoracic echocardiogram showed complete recovery of left ventricle function with an estimated EF of 65%, absence of regional wall motion abnormalities, normal dimensions and right ventricle function. On day 17, he was discharged from the Intensive Care Unit. At the 90-day follow-up visit, the patient was alive without significant cardiologic abnormalities.

Clinical data regarding risk factors and complications of influenza B are still limited, although a clear association between acute respiratory infections, particularly influenza, and acute myocardial infarction has been shown (Rezkalla and Kloner, 2010; Kwong *et al.*, 2018).

Although we were unable to confirm the presence of influenza B virus in the myocardial tissue, the recent clinical history, the positivity for influenza B virus of the patient's pharyngeal swab, and the presence of specific IgA and IgG, together with the absence of other causes of myocardial damage, were all elements supporting a direct correlation between influenza B infection and acute myocarditis. As shown in a recent literature review (Hékimian *et al.*, 2018), myocarditis associated with influenza B had rarely been reported before 2017 (10 published cases from 1989 to 2017; 3 requiring mechanical circulatory support). Four other cases of severe myocardial damage following influenza B have been described in 2018, underscoring the increasing relevance of the phenomenon. In fact, influenza B virus circulated heavily during the 2017-18 winter

season (https://ecdc.europa.eu/en/seasonal-influenza). A summary of the main features of influenza B cases associated with severe cardiac damage, published up to October 2018, is presented in *Table 1*. The majority of published cases occurred in female patients. 50% of cases were described in pediatric patients (age ≤18 years).
The increasing trend of severe myocarditis cases associated with influenza B is a cause for serious concern and should attract the attention of physicians and public health authorities to the importance of influenza vaccination.

Conflict of interest: The authors declare the absence of conflict of interest.

Ethical standards: The study has been performed in accordance with local ethics committee requirements and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.
Written informed consent was obtained from the patient for publication of this case report.

References

Camp J.V., Jonsson C.B. (2017). A role for neutrophils in viral respiratory disease. Frontiers in Immunology. **8**, 1-17.

Craver R.D., Sorrells K., Gohd R. Myocarditis with influenza B infection. (1997). *Pediatr Infect Dis J.* **16**, 629-630.

Chang H.-L., Hsu J.-F., Tsai Y.-M., Lin S.-Y., Kuo H-F., Yang C.-J. (2016). Acute respiratory distress syndrome and acute myocarditis developed in a previously healthy adult with influenza B. *BMC Pulm Med.* **16**, 1.

Dickey T., Schweir M., Hysell M. (2018). Fatal Influenza B Myocarditis in a 34-Year-Old Female. *Clin Pract Cases Emerg Med.* **3**, 219-222.

Elikowski W., Małek-Elikowska M., Lisiecka M., Trypuć Z., Mozer-Lisewska I. (2018). Takotsubo cardiomyopathy triggered by influenza B. *Pol Merkur Lekarski.* **45**, 67-70.

Frank H., Wittekind C., Liebert U.G., Siekmeyer M., Siekmeyer W., Schuster V., et al. (2010). Lethal influenza B myocarditis in a child and review of the literature for pediatric age groups. *Infection.* **38**, 231-235.

Guarner J., Paddock C.D., Shieh W.J., et al. (2006). Histopathologic and immunohistochemical features of fatal influenza virus infection in children during the 2003-2004 season. *Clin Infect Dis.* **43**, 132-140.

Hékimian G., Jovanovic T., Bréchot N., et al. (2018). When the heart gets the flu: Fulminant influenza B myocarditis: A case-series report and review of the literature. *J Crit Care.* **47**, 61-64.

Kwong J.C., Schwartz K.L., Campitelli M.A., Chung H., et al. (2018). Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. *N Engl J Med.* **378**, 345-353.

Mamas M.A., Fraser D., Neyses L. (2008). Cardiovascular manifestations associated with influenza virus infection. *Int J Cardiol.* **130**, 304-309.

Mahrholdt H., Goedecke C., Wagner A., Meinhardt G., Athanasiadis A., et al. (2004). Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. *Circulation.* **109**, 1250-1258.

Matsuura H., Ichida F., Saji T., Ogawa S., Waki K., Kaneko M., et al. (2016). Clinical Features of Acute and Fulminant Myocarditis in Children- 2nd Nationwide Survey by Japanese Society of Pediatric Cardiology and Cardiac Surgery. *Circ J Off J Jpn Circ Soc*. **80**, 2362-2368.

Moon J.-H., Na J.-Y., Kim J.-H., Yum M.-K., Oh J.-W., Kim C.-R., et al. (2013). Neurological and muscular manifestations associated with influenza B infection in children. *Pediatr Neurol.* **49**, 97-101.

Muneuchi J., Kanaya Y., Takimoto T., Hoshina T., Kusuhara K., Hara T. (2009). Myocarditis mimicking acute coronary syndrome following influenza B virus infection: a case report. *Cases J.* **2**, 6809.

Pan H.-Y., Kido H. (2011). Effects of inhibitors of Toll-like receptors, proteases-activated receptor-2 signallings and trypsin on influenza A virus replication and upregulation of cellular factors in cardiomyocytes. *J Med Invest.* **58**, 19-28.

Piccininni J.A., Richmond M.E., Cheung E.W., Lee T.M., Law S.P., Addonizio L.J., Zuckerman W.A. (2018). Influenza Myocarditis Treated With Antithymocyte Globulin. *Pediatrics.* pii: e20180884.

Ray C.G., Icenogle T.B., Minnich L.L., Copeland J.G., Grogan T.M. (1989). The use of intravenous ribavirin to treat influenza virus-associated acute myocarditis. *J Infect Dis.* **159**, 829-836.

Rezkalla S.H., Kloner R.A. (2010). Influenza-related viral myocarditis. *Wisconsin Medical Journal.* **4**, 209-213.

Roto D., Malnoske M.L., Winters S., Georas S.N. (2018). A Fatal Case of Influenza B Myocarditis with Cardiac Tamponade. *Case Rep Crit Care.* **2018**, 802631.

Siskin M., Rao S., Rapkiewicz A., Bangalore S., Garshick M. (2017). A Case of Cardiogenic Shock Secondary to Complement-Mediated Myopericarditis From Influenza B Infection. *Can J Cardiol.* **33**, 1335.e1-1335.e3.

Tabbutt S., Leonard M., Godinez R.I., Sebert M., Cullen J., Spray T.L., et al. (2004). Severe influenza B myocarditis and myositis. *Pediatr Crit Care Med.* **5**, 403-406.

Taremi M., Amoroso A., Nace H.L., Gilliam B.L. (2013). Influenza B-induced refractory cardiogenic shock: a case report. *BMC Infect Dis.* **13**, 452.