Case Report

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

Luca Marchetti¹, Claudia Gandolfo², Enivarco Maglioni¹, Martina Contorni¹, Fabio Arena³ and Maria Grazia Cusi²*

¹ Cardiothoracic Anesthesia and Intensive Care Unit, Siena University Hospital, Siena, Italy.
² Microbiology Unit, Department of Medical Biotechnologies, University of Siena, Le Scotte Hospital, Siena, Italy.
³ Department of Medical Biotechnologies, University of Siena, Siena, Italy.

Running title: Influenza B infection and myocarditis

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.

Keywords: Influenza B virus, myocarditis, flu, ECMO

*Corresponding author: Prof. Maria Grazia Cusi. UOC Microbiologia e Virologia; Azienda Ospedaliera Universitaria Senese; Dipartimento Biotecnologie Mediche, Università degli
Studi di Siena. V.le Bracci, 1. 53100 Siena. E-mail: cusi@unisi.it. Tel +39 0577 233871; fax +39 0577 233870
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 O2 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 above [http://www.who.int/influenza/gisrs_laboratory/molecular_diagnosis_influenza_virus_humans_update_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 $6.72 \times 10^3$/ml 8 (0.90-4.50) and $17.93 \times 10^3$/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


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

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