Novel treatment (new drug/intervention; established drug/procedure in new situation)

Successful management of fulminant influenza A subtype H1N1 myocarditis

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Summary

The outbreak and spread of the new influenza A subtype H1N1 reached pandemic levels during 2009, with greater numbers of cases reported daily and numerous complications described. The present report concerns an atypical manifestation of the disease in a previously healthy middle-aged patient who presented with severe, refractory cardiogenic shock 4 days after being diagnosed as having influenza A. The patient was considered for emergency heart transplant. Successful treatment involved the use of a left ventricular assist device, extracorporeal membrane oxygenation, intravenous immunoglobulin and peramivir as therapeutics and bridging therapies for transplant. This case is a report of H1N1 fulminant myocarditis and illustrates the usefulness of a multidisciplinary approach in the care of these patients.

BACKGROUND

Influenza is an acute and recurring respiratory disease known since ancient times, occurring, most often during the winter months, effecting public health worldwide.¹⁻² It is associated with morbidity and mortality in people of all ages, particularly in children, adults over 60 years old, individuals with chronic illnesses and pregnant women.³⁻⁴

On 11 June 2009, the WHO declared a global pandemic of influenza A (H1N1).² The USA continues to report the largest number of H1N1 cases of any country worldwide.⁵ The H1N1 virus subtype differs in its pathogenicity from seasonal influenza, in that it is most virulent in children and young adults, likely due to minimal or no pre-existing immunity to the virus, and in its propensity to infect the lower respiratory tract causing rapidly progressive pneumonia and adult respiratory distress syndrome.⁶

Influenza infection has been estimated to cause up to 36 000 deaths annually in the US.⁷ Mortality is most often related to the development of pneumonia, toxic shock syndrome or cardiac complications.¹ The frequency of myocardial involvement in influenza infection is variable, with incidences as high as 10% reported in the literature.⁸⁻¹¹

The following case report describes a patient with influenza-associated cardiogenic shock who was successfully managed with the use of extracorporeal membrane oxygenation (ECMO), intravenous immunoglobulin and peramivir.

CASE PRESENTATION

A previously healthy 60-year-old woman, with a recent travel history to South America and the USA, developed flu-like symptoms in late October 2009. The patient was seen by her primary care doctor and a rapid test was positive for influenza A, initially treated with oseltamivir 75 mg orally every 12 h. Then, 3 days later she was admitted to a community hospital with progressive worsening dyspnoea,

chest pain, hypotension and tachycardia. A cardiac catheterisation revealed an ejection fraction of 10% with severe left ventricular dysfunction. No evidence of coronary artery occlusive disease was evident. An intra-aortic balloon pump (IABP) was placed at this time to maintain her blood pressure. The patient was intubated and ventilated due to respiratory distress and oseltamivir treatment was continued at the same dose. Due to suspicion of an overimposed bacterial infection empiric broad-spectrum antibiotic treatment was initiated with vancomycin and piperacillin/tazobactam.

Over the subsequent 2 days the patient remained hypotensive despite the use of the IABP and the administration of dobutamine, vasopressin, norepinephrine and milrinone infusions. A percutaneous left ventricular assist device (LVAD) (Impella 2.5; Abiomed-Impella CardioSystems GmbH, Aachen, Germany) was placed for additional support. The patient's status continued to deteriorate despite this aggressive management, prompting the transfer to our tertiary referral centre for further care including possible emergency heart transplantation.

Upon arrival the patient was determined to have multi-system failure with oligoanuric acute renal failure, acute liver failure and respiratory failure. There was evidence of cardiogenic shock: with the Impella LVAD providing 2.4 litres/min of circulatory assistance and with the vasopressor treatment described above, the cardiac index was only 2.1 litres/min/m². An echocardiogram showed global hypokinesis of the left ventricle, inferior wall akinesis, dilated left atrium, dilated inferior vena cava, moderate mitral regurgitation, mild tricuspid regurgitation, mild aortic regurgitation, a small pericardial effusion and a right ventricular systolic pressure of 35–39 mm Hg.

Upon arrival at our centre the dose of oseltamivir was increased to 150 mg orally every 12 h. Due to lack of clinical improvement the Centers for Disease Control and

Prevention (CDC) were contacted for compassionate release of peramivir, a novel intravenous neuraminidase inhibitor. Within 24 h of admission oseltamivir was discontinued and the patient was given peramivir 600 mg intravenously every 24 h for a total of 10 days.

Prior to initiating peramivir treatment, the patient's blood and urine were cultured and found to be negative for bacterial growth. HIV by ELISA and HIV PCR viral loads, were obtained to rule out acute retroviral syndrome. Serology testing for legionella, mycoplasma, chlamydia, coxsackie virus A and B, respiratory syncytial virus, and influenza A, subtype H1N1 reverse transcriptase (RT)-PCR were obtained. All results were negative including viral respiratory cultures.

Considering the patient's rapid clinical deterioration, a decision was made to empirically administer intravenous immunoglobulin (Flebogamma 5%) 10g intravenous over 8 h in attempts to boost the innate immunity and control the infection as part of the management of acute viral myocarditis.

The LVAD and vasopressor treatment were continued for haemodynamic support. Within 24 h of the patient's transfer to our institution the LVAD (which had been in place for 5 days) malfunctioned and its flow gradually decreased to 1.4 litres/min despite maximal speed. The LVAD was removed and full venoarterial ECMO (flow=3.1 litres/min) was initiated by cannulating the right common femoral artery and vein. Vasopressors were weaned quickly after ECMO was initiated.

OUTCOME AND FOLLOW-UP

On day 5 of hospitalisation, an echocardiogram showed complete recovery of left ventricular function with normal left and right ventricular wall motion, a left ventricular ejection fraction of 50% and a small but clinically insignificant pericardial effusion. In light of these findings, plans to streamline treatment began: on day 6 of hospitalisation ECMO was discontinued, on day 7 the antibiotics were discontinued, on day 8 the patient was placed on intermittent haemodialysis and on day 9 she was extubated. The patient successfully completely recovered her renal and cardiac function and was discharged home, where she continues to do well.

DISCUSSION

Rapid influenza diagnostic tests (RIDTs) are antigen detection tests that detect influenza viral nucleoprotein antigen. When influenza viruses are circulating in a community, a positive test result indicates that influenza virus infection is likely present in the specimen, and the specificity of RIDTs is generally high.² The diagnosis of H1N1 influenza in this case was based on clinical history and the positive rapid influenza A test; according to the CDC influenza activity remained elevated in the USA and over 99% of all subtyped influenza A viruses being reported to the CDC were 2009 influenza A (H1N1).² According to the WHO, as of 1 November 2009, there was intense and persistent influenza transmission in North America, and 100% of patients who tested positive for influenza at the sentinel doctor visit had the pandemic H1N1 2009 strain.²

The negative RT-PCR for influenza H1N1 is likely due to the antiviral treatment prior to admission, which could

have controlled or decreased the level of circulating virus. Moreover, the patient's PCR test was performed 9 days after her initial presentation, when viral shedding tends to be low, and a false negative result may occur if inadequate numbers of organisms are present or if the specimen is improperly collected, transported or handled.¹²

The myocardial damage seen in our patient is presumably the result of a combination of the direct effects of the virus at the tissue level and the patient's immune response with massive cytokine release to control the infection. This might also explain her severe presentation despite the lack of evidence of respiratory viraemia by RT-PCR.

The use of intravenous immunoglobulin for influenza A H1N1 is controversial; however immunoglobulin has been used for years in severe cases of influenza. During the influenza pandemic of 1918, severely ill patients received whole blood, plasma or serum from convalescent survivors.¹³ Luke *et al*,¹⁴ in a meta-analysis of eight studies published from 1918 to 1925 concluded that patients with Spanish influenza (H5N1) pneumonia who received convalescent human blood products experienced significant reduction of the mortality risk. To date, the WHO does not recommend immunoglobulin unless in the context of prospective clinical and virological data collection, but given the severity of the patient's clinical status we felt the potential benefit outweighed the risks associated with this treatment.

Peramivir is a novel neuraminidase inhibitor that may be effective in treating influenza H1N1. The drug's efficacy is still being evaluated in clinical trials for efficacy as an intravenous agent for treating influenza. On 23 October 2009, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for peramivir allowing hospitals to use this drug under special circumstances. Data regarding its use in seriously ill patients with H1N1 influenza are very limited, and the probability of its effectiveness is based on the drug's demonstrated activity as a neuraminidase inhibitor and the treatment benefit in patients with acute, uncomplicated influenza.¹⁵ The use of peramivir in this patient was decided after careful multidisciplinary discussion. Although we could not detect levels of H1N1 virus in nasopharyngeal wash, the patient never had a myocardial biopsy performed and we could not determine if the myocarditis was a result of direct viral effects in the myocardium or a consequence of the massive cytokine release and severe inflammatory response. Considering that the patient had clinically failed prior antiviral treatment with oseltamivir and was mechanically ventilated the only alternative antiviral treatment at that point was intravenous peramivir.

Few cases of influenza-associated myocarditis have been reported in the literature,^{16–21} and to the best of our knowledge, none associated with the 2009 pandemic H1N1 strain. In one series, five patients with influenza myocarditis had cardiac involvement occurring between 4 and 9 days after the onset of influenza symptoms, with worsening dyspnoea being the most common presenting symptom.²² Patients either recovered with complete restoration of myocardial function or died within 2 weeks of developing symptoms.²³

Cardiogenic shock has been described in cases of influenza induced myocarditis and left ventricular support measures including inotropic support, IABP and ventricular

assist devices have been described.^{17 21–24} The use of ECMO during the 2009 H1N1 pandemic has been described in a recent series for patients with respiratory failure yet no cases have reported its use in primary cardiogenic shock.²⁵

This case illustrates the utility of percutaneous LVADs as a temporising measure when ECMO is not readily available. When the initial LVAD failed, we decided to institute ECMO as it provided reasonable short-term support given her haemodynamic instability, permitted recovery of multi-organ injury and would allow time to complete a transplant evaluation before long-term circulatory support with an implantable LVAD was considered.

This is the first reported case of successful treatment of H1N1 influenza-related fulminant myocarditis with a multidisciplinary state of the art approach using all resources available of an intensive care unit including LVAD, ECMO, intravenous immunoglobulin and peramivir. The successful clinical course in this patient is most likely the result of multiple interventions rather than any of them by themselves. Randomised, controlled trials are needed to determine if alternative therapies improve outcomes in severe cases of influenza infection.

Learning points

- ▶ Influenza H1N1 may present as a fulminant form of myocarditis.
- ▶ Aggressive, early treatment with haemodynamic support including the use of left ventricular assist device (LVAD) may be warranted in these cases.
- ▶ Immunoglobulin may be useful as an adjuvant treatment in very severe cases.
- ▶ These patients should be transferred to a tertiary centre where invasive haemodynamic support is available and transplant consideration should be given if they fail to respond to treatment.

Competing interests None.

Patient consent Not Obtained.

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