CASE REPORT

The first novel influenza A (H1N1) fatality despite antiviral treatment and extracorporeal membrane oxygenation in Hong Kong

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We report the first fatality caused by novel influenza A (H1N1) infection despite having the diagnosis confirmed and being given antiviral treatment after hospitalisation. This patient was also the first with influenza A (H1N1) to be supported with extracorporeal membrane oxygenation in Hong Kong. Although extracorporeal membrane oxygenation is an effective means of supporting patients with refractory hypoxaemia on high mechanical ventilatory support, it is labour-intensive and technically demanding. We also discuss the challenges faced when managing this case.

Introduction

The novel influenza A (H1N1) pandemic began in Mexico in late March 2009. As of 13 August 2009, there have been more than 180 000 confirmed cases and nearly 1800 deaths worldwide.[1] In Hong Kong, more than 10 000 cases had been confirmed by 27 August 2009. Forty-four of these were reported to be in serious condition. Among them, four had died and 17 had recovered and been discharged.[2] It is expected that the number of confirmed and severe cases will continue to rise, which will increase the burden on the health care system in Hong Kong. We report the first fatality caused by novel influenza A (H1N1) infection, despite the use of antiviral treatment and extracorporeal membrane oxygenation (ECMO) as salvage therapy, in Hong Kong.

Case report

A 37-year-old Filipino woman who had enjoyed good past health and had given birth to a baby boy 6 months earlier arrived in Hong Kong at the end of June 2009. She was found to have fever the day after arrival during a routine medical check. She was commenced on antibiotics by her general practitioner but her fever persisted. She also complained of a runny nose, sore throat, and cough. She attended the Accident and Emergency Department of the United Christian Hospital 10 days after the onset of symptoms and was found to have severe pneumonia associated with severe hypoxaemia. Her initial chest X-ray (CXR) showed bilateral lung air-space consolidation (Fig 1a). She was admitted directly to the intensive care unit, put in respiratory isolation, and was supported by non-invasive mechanical ventilation. Her initial blood tests showed a normal white blood cell and lymphocyte count, type I respiratory failure and normal renal and liver function tests. A nasopharyngeal aspirate (NPA) was negative for influenza A and B rapid antigen, as was the real-time reverse-transcriptase polymerase chain reaction (RT-PCR) for novel influenza A (H1N1) on her throat and nasal swab. Urine streptococcal and Legionella antigens were also negative. She was commenced on imipenem/cilastatin and azithromycin but her condition deteriorated rapidly and she required intubation and invasive mechanical ventilatory support the day after admission. A tracheal aspirate was obtained for further investigation and the influenza A M-gene was detected by RT-PCR. Nonetheless, the RT-PCR for novel influenza A (H1N1) performed on the tracheal aspirate was negative so the original NPA specimen kept in the Department of Health laboratory was retrieved for RT-PCR for influenza A (H1N1). This came back positive. Influenza A (H1N1) infection was confirmed and oseltamivir 75 mg twice daily was started on day 3 of admission. The dose of oseltamivir was increased to 150 mg twice daily on day 4 of admission and was continued for 18 days. Zanamivir was also given as salvage therapy because the patient was critically ill and did not respond well to oseltamivir, and there was concern about oseltamivir resistance. She was given nebulised zanamivir 15 mg diluted in 2 mL normal saline for 4 doses over 3 days. It was then stopped as the patient could not tolerate it because of severe desaturation related to the loss of positive end-expiratory pressure (PEEP). Despite aggressive treatment, she had refractory hypoxaemia with a PaO_2 down to 52 mm Hg while receiving ventilatory support of fraction of inspired oxygen (FIO_2) 1.0, at an inspiratory pressure of 35 cm H_2O and PEEP of 20 cm H_2O. Veno-venous extracorporeal

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Antigens, viral; Extracorporeal circulation; Influenza A virus, H1N1 subtype; Influenza, human; Oxygenators, membrane

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香港首宗用抗病毒及體外膜肺氧合治療的新型H1N1流感死亡病例

本文報告首宗新型H1N1流感死亡個案，患者入院後被確診新型H1N1流感，隨即接受抗病毒治療，但最終死亡。這是首宗香港H1N1流感患者接受體外膜肺氧合治療的病例。接受體外膜肺氧合治療的病人要靠機械輔助呼吸，雖然對於低氧血症患者是有效的臨時措施，可是此技術需要大量人手，操作繁瑣。此外，本文會討論為患者治療時遇到的挑戰。

membrane oxygenation (VV-ECMO) was instituted on day 7 of her admission (Fig 1b). On commencement of VV-ECMO, the patient had no other vital organ failure and her oxygenation improved initially. Nonetheless, we failed to wean down the level of ventilatory support to reduce the risk of ventilator-induced lung injury (VILI). Serial CXRs showed bilateral diffuse interstitial infiltrates compatible with acute respiratory distress syndrome (ARDS) [Fig 1c]. The patient had clinical evidence of ventilator-associated pneumonia on day 12 of her admission with a fever spike, elevated white blood cell count, and increased infiltrates on her CXR. A tracheal aspirate grew *Candida albicans,* and amphotericin B was administered. After 12 days of hospitalisation, she was given linezolid empirically because she was at increased risk of hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection. She also developed septic shock requiring inotropic support on day 12 of her admission, and acute renal failure requiring intermittent renal replacement therapy. On day 21 of her admission, she developed a tension pneumothorax and a chest drain was inserted. She also suffered from haemolysis, which precluded the use of VV-ECMO, so this was ceased. She succumbed soon afterwards on that day. Viral cultures of the NPA, throat and nasal swab, and tracheal aspirate were negative but she had elevated antibody titres for influenza A, indicating a recent influenza A infection. A postmortem examination confirmed that the cause of death was pneumonia complicating influenza A (H1N1). A lung autopsy specimen revealed ARDS.

Discussion

This patient suffered the first fatality caused by novel influenza A (H1N1) infection despite the use of antiviral treatment in Hong Kong. A Filipino man who died of pneumonia earlier, tested positive for both community-acquired MRSA and influenza A (H1N1) after death.[3]

When we managed this patient, we experienced some diagnostic challenges at the beginning. We suspected that the patient had influenza A (H1N1) infection when she presented to us, as she complained of an influenza-like illness (ILI) and she had just arrived in Hong Kong from a country with a recent outbreak. Nevertheless, our patient's CXR did not show the classical radiological features of viral pneumonitis—diffuse, non-specific infiltrates—but instead showed air-space consolidation features indistinguishable from bacterial pneumonia.

Both the NPA rapid antigen test and the throat and nasal swab RT-PCR for influenza A (H1N1) were negative. At present the current influenza rapid antigen test is not sensitive. Studies have found that the sensitivity of the rapid antigen test for detecting influenza A (H1N1) virus ranges from 10 to 70%

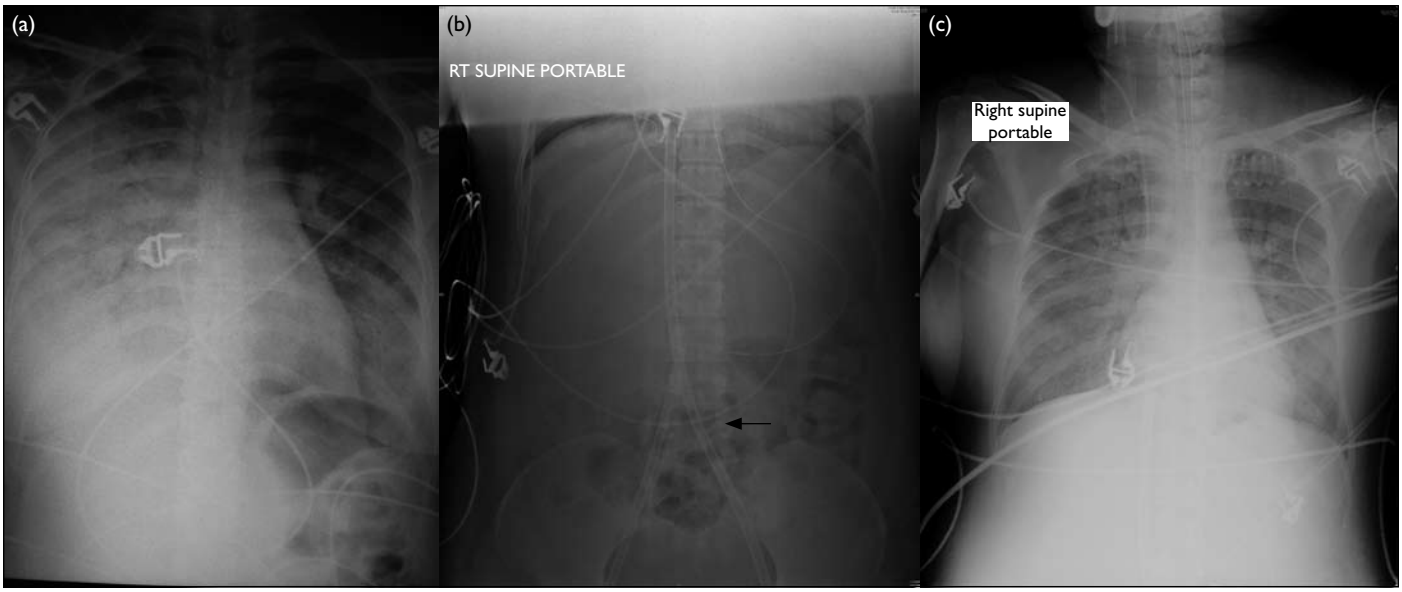

FIG 1. (a) Chest X-ray on admission; (b) abdominal X-ray after veno-venous extracorporeal membrane oxygenation catheters were inserted (arrow); (c) chest X-ray on day 10 of admission

FIG 2. Extracorporeal membrane oxygenation machine

compared to RT-PCR.[4] There are no major differences in the sensitivities of different commercially available rapid antigen test kits.[5] Our patient's negative throat and nasal swab RT-PCR can be explained by her late presentation and also by the propensity of this virus to involve the lower respiratory tract. It is therefore important for clinicians to maintain a high index of suspicion when dealing with this disease. It may be necessary to take specimens from both the upper and lower respiratory tract for simultaneous investigations in patients with suspected influenza A (H1N1) infection and severe pneumonia. Currently, the Hospital Authority Central Committee on Infectious Disease and Emergency Responses (CCIDER) recommends that NPA, a nasopharyngeal swab, or a combined oropharyngeal and nasal swab should be taken in patients with suspected influenza A (H1N1) infection. Physicians should also consider taking endotracheal aspirates or bronchoalveolar lavages to investigate patients who are intubated. Both RT-PCR and viral cultures for influenza A (H1N1) should be done.[6]

Our patient was also the first with influenza A (H1N1) to be supported by VV-ECMO in Hong Kong (Appendix). As our patient's oxygenation could not be maintained using high ventilatory support, we decided to institute ECMO (Fig 2) on day 7 of her admission. Veno-venous ECMO is an effective way to support patients with refractory hypoxaemia who fail to respond to conventional ventilatory strategies. By supporting the function of gaseous exchange, the ventilatory support can be weaned down to avoid further VILI, and thus 'rest the lung'. Although an early study on ECMO (1976) showed a cumulative survival rate of only 15%,[7] recent studies have yielded more promising results. Gattinoni et al[8] found a survival rate of 49% when combining the refined ECMO technique with low-frequency positive-pressure ventilation.[8] The CESAR trial[9] estimated a relative risk reduction of mortality or presence of severe disability of 0.69 in favour of ECMO (95% confidence interval, 0.05-0.97; P=0.03). Nehra et al[10] also reported a potential survival benefit of ECMO in carefully selected patients, with the highest survival rates in those with viral or bacterial pneumonia.

Extracorporeal membrane oxygenation is not a risk-free procedure. It can cause severe haemolysis, haemorrhage, and haemodynamic instability. Our patient was supported with ECMO for 14 days. Her oxygenation could be maintained only with the support of ECMO in conjunction with high mechanical ventilatory support. Therefore the 'rest-the-lung' strategy could not be instituted. We had to eventually stop the procedure because of haemolysis and her progressively deteriorating haemodynamic status. Extracorporeal membrane oxygenation is also labour-intensive and technically demanding. It is unrealistic and too costly to provide this procedure to every critically ill patient with influenza A (H1N1) in the midst of a pandemic when the demand for critical care service has already been stretched to the limit.

There are no reported data on the clinical benefits of antiviral treatment for novel influenza A (H1N1) infection as yet, and different authorities have different recommendations. The CCIDER has recommended that antiviral treatment should be given empirically to those patients with ILI who are at high risk of developing complications. Antiviral treatment should also be considered in patients with ILI who are aged below 6 years, current smokers, or obese; patients with no improvement in symptoms 48 hours after medical treatment; and patients who are confirmed to have influenza A (H1N1) infection.[11] The Centers for Disease Control and Prevention recommend that either oseltamivir 75 mg twice daily or inhaled zanamivir 10 mg twice daily should be given to all hospitalised patients with confirmed, probable, or suspected influenza A (H1N1) infection.[12] A higher dose of oseltamivir, up to 150 mg twice daily, can be considered in critically ill influenza A (H1N1) patients.[13] Nebulised zanamivir is

considered safe.[14] Steroids are not recommended as there is no evidence that steroids can improve ARDS outcomes.[15] Our patient presented 10 days after onset of her symptoms and oseltamivir was started 12 days after symptom onset. This probably explains the rapid downhill course of her illness, despite the aggressive treatment and maximal support she was given.

The novel influenza A (H1N1) virus can cause severe disease in previously healthy patients. World Health Organization data indicate that around 40% of severe cases occur in previously healthy children and adults, usually under the age of 50 years.[16] As the number of confirmed cases increases, it is expected that the number of those with serious novel influenza A (H1N1) infection and death rates will rise. Managing critical cases of novel influenza A (H1N1) infection remains a great challenge. Antiviral treatment, antibiotics and supportive care are the mainstay of treatment. The VV-ECMO is an effective supportive strategy but is costly, labour-intensive, and not without risks.

Appendix

Additional material related to this article can be found on the HKMJ website. Please go to <http://www.hkmj.org>, search for the appropriate article, and click on **Full Article in PDF** following the title.

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APPENDIX

Extracorporeal membrane oxygenation (ECMO) is a form of partial cardiopulmonary bypass used to support the respiratory and/or cardiac function. It involves connecting the patients' circulation to an external blood pump and the artificial lung (oxygenator).

There are two forms of ECMO: (1) venoarterial (VA-ECMO): draws deoxygenated blood from a central vein, pumps it through the oxygenator, then returns the oxygenated blood to the arterial side of the circulation. Beside the respiratory function, this form of ECMO also partially supports the cardiac output as blood flow through the ECMO circuit to the arterial circulation can increase the cardiac output. (2) Venovenous (VV-ECMO): draws blood from a central vein and returns oxygenated blood to the right atrium. This form of ECMO supports respiratory function only (Fig 3).

Extracorporeal membrane oxygenation is indicated to support respiratory or cardiac failure that is unresponsive to all other measures, and has reversible elements.

Complications are: tubing/circuit disruption, complications associated with catheter insertion or removal, bleeding, haemolysis, infection, metabolic disorders, hypothermia, haemodynamic instability.

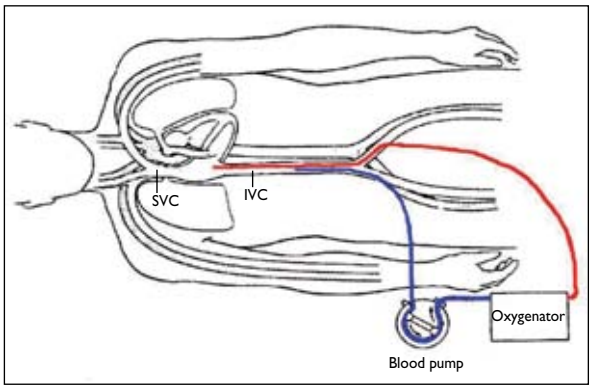

FIG 3. Veno-venous extracorporeal membrane oxygenation circuit
SVC denotse superior vena cava, and IVC inferior vena cava