A previously healthy 45-year-old male with respiratory insufficiency caused by H1N1 pneumonitis

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Abstract · We present the case of a previously healthy patient who suffered from severe respiratory insufficiency based on an H1N1v pneumonitis. He was admitted to ICU, intubated and mechanically ventilated. Eventually the patient recovered. Three months after discharge he was still suffering from restrictive lung disease.

Keywords · novel H1N1 influenza, pneumonitis, respiratory insufficiency, ICU

Introduction
Since the emergence of the novel H1N1 influenza (H1N1v) strain in March 2009, the virus has spread around the globe creating a pandemic. Most infected patients have only mild, influenza-like symptoms, but in high risk groups, e.g. patients with heart failure, chronic obstructive pulmonary disease or the elderly, influenza may follow a less benign course [1]. We present the case of a previously healthy male with respiratory insufficiency caused by H1N1v who required mechanical ventilation and who eventually recovered.

Case Report
A previously healthy, 45-year-old male was admitted to the pulmonary ward with fever and dyspnoea. He was born in Surinam, South America and of Native American descent. He had lived in the Netherlands for more than 10 years. He had not travelled outside the Netherlands in the preceding months. His brother had had an episode of influenza-like illness 10 days earlier. On admission to the pulmonary ward the patient had been having episodes of fever as high as 40°C, myalgia and shortness of breath for one week. He had a non-productive cough. His symptoms were progressively worsening.

Physical examination on admission to hospital revealed a blood pressure of 125/75mmHg, a heart rate of 90/minute, a temperature of 40°C, a respiratory rate of 20/minute and an oxygen saturation of 90% without supplementary oxygen. Crackles were heard over both basal and mid-thoracic lung fields, as well as in both axillas. Further physical examination showed no abnormalities.

Arterial blood gas analysis taken while the patient received 5 litres per minute oxygen supplementation via a nasal cannula showed pH 7.44, PaCO2 4.6 kPa, bicarbonate 22 mmol/litre, base excess -1.1 mmol/litre, PaO2 10.0 kPa, oxygen saturation 94%. Further laboratory results are displayed in Table 1.

The first bedside chest X-ray showed marked bronchovascular bundles and patchy consolidation of the lower regions of both lungs (Figure 1-a). Blood cultures taken on admission were negative. Results from a nasopharyngeal swab taken on admission were positive for H1N1v influenza the following day. A Legionella pneumophila antigen test was negative.

The patient was initially treated for severe community-acquired bilateral pneumonia with cefuroxim and erythromycin. Although H1N1v pneumonia was considered upon admission, antiviral therapy was not started because the patient had been symptomatic for more than 48 hours. His clinical condition worsened, however, and on day 4 after admission to hospital he was hypoxaemic (pO2 7.4 kPa) despite being treated with 15 litres oxygen/minute via a non-rebreathing mask. He was transferred from a general ward to the intensive care unit (ICU) because of imminent respiratory failure and the need for mechanical ventilation. On arrival in the ICU the patient had a respiratory frequency of 30/minute and an oxygen saturation of 88% with 15 litres oxygen/minute oxygen via a non-rebreathing mask and was promptly intubated and mechanically ventilated, with tidal volumes of 6-8 ml/kg and pressure-controlled ventilation with a PEEP level of 20.4 cmH2O. Inspiratory oxygen fraction was as high as 100% to have arterial saturations of 91% and an arterial pO2 of 8.5 kPa. Prone positioning did not improve oxygenation. Permissive hypercapnia was used. The patient was sedated with propofol, midazolam and morphine and paralyzed with pancuronium when on coughing, saturations dropped below 80%. This was frequently necessary during the first days of mechanical ventilation. Cefotaxim, selective decontamination of the digestive tract and prednisolon 25mg twice daily were started and a restrictive fluid strategy was used. Oseltamivir (Tamiflu®) was started because the patient...
A previously healthy 45-year-old male with respiratory insufficiency caused by H1N1 pneumonitis had progressive respiratory failure and was considered to have H1N1v pneumonitis. Bronchoalveolar lavage (BAL) of the middle lobe was performed. Cultures from the bronchoalveolar fluid remained negative (see Table 1). Microscopic examination revealed no Pneumocystis jiroveci or bacteria. H1N1v was reconfirmed by PCR in the bronchoalveolar fluid. This isolate was later shown to be oseltamivir susceptible. PCR tests for Chlamydia pneumoniae and P. psittaci, M. pneumoniae, influenza B virus, para-influenza 1-4 virus, rhinovirus, human metapneumovirus and respiratory syncitial virus A and B were all negative. Serology was used to rule out Coxiella burnetii. Human immunodeficiency virus (HIV) test was also negative.

After three days on the ICU the patient’s condition was improving. Steroids were tapered off and stopped (Figure 2). Oseltamivir was stopped after 5 days on the ICU because elevated liver enzyme tests led to fears of oseltamivir-induced hepatotoxicity. However, on the ninth day after ICU admission, the patient’s condition deteriorated. Chest X-ray showed a progressive airspace consolidation in all lobes of both lungs with air bronchogram (Figure 1-b). A high resolution computed tomography (HR-CT) scan of the chest showed bilateral patchy ground-glass opacities, a combination of consolidation and reticulation and some bronchial wall thickening, findings indicating viral pneumonitis (Figure 1-c). BAL of the middle lobe was still positive for H1N1v influenza (Table 1). Other cultures again remained negative. Pending the results of the BAL, the patient was treated with broad spectrum antibiotics, antifungal and antiviral medication. Steroids and oseltamivir were restarted. Liver enzyme tests showed no elevation and oseltamivir was continued. The patient slowly recovered from day 17.

On day 18 a tracheostomy was performed to facilitate weaning. On day 19 a third BAL was performed, which still was positive for H1N1v (Table 1). On day 30 oseltamivir was stopped and mechanical ventilation was withdrawn. On day 32 the tracheostomy tube was removed. After 33 days on the ICU the patient was transferred to the pulmonary ward. A chest X-ray taken on day 44 still showed a lot of parenchymal abnormalities including airspace consolidation and reticulation (Figure 1-d). He was discharged to a rehabilitation clinic after 58 days in hospital, and continued to require oxygen suppletion during exercise for approximately two more months. Spirometry done more than 3 months after discharge showed restrictive lung disease, as his vital capacity was 2.79 litres (66% of predicted) and the forced expiratory volume in 1 second was 2.48 litres (74% of predicted). Diffusion capacity of the lung for carbon monoxide testing (DLCO) was decreased (43%), the KCO (corrected for the alveolar volume) was normal (83%).

**Discussion**

The novel H1N1 Influenza (H1N1v) was the first pandemic virus in humans for 40 years. Most patients have mild influenza-like symptoms and recover within a week without medical treatment. In 0.1%-0.9% of patients hospitalization is needed [2,3]. In a small group of patients, H1N1v influenza causes severe respiratory insufficiency caused by rapidly progressive lower respiratory tract disease. Respiratory failure leading to hospitalization and mortality mostly occurs in patients with underlying conditions or who are pregnant. Other identified risk factors for severe disease include age over 65 years, obesity, and cardiovascular disease.

**Table 1. Laboratory and microbiology results**

<table>
<thead>
<tr>
<th></th>
<th>DAY 1</th>
<th>DAY 4</th>
<th>DAY 13</th>
<th>DAY 19</th>
<th>NORMAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (mmol/L)</td>
<td>9.5</td>
<td>9.1</td>
<td>7.2</td>
<td>6.8</td>
<td>8.4-10.9</td>
</tr>
<tr>
<td>Leukocyte count (10E9/L)</td>
<td>5.8</td>
<td>6.5</td>
<td>13.5</td>
<td>11.2</td>
<td>3.5-11.0</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>96</td>
<td>179</td>
<td>313</td>
<td>19</td>
<td>0-10</td>
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<tr>
<td>Creatinine (umol/L)</td>
<td>104</td>
<td>75</td>
<td>74</td>
<td>72</td>
<td>62-115</td>
</tr>
<tr>
<td>Aspartate transaminase (U/L)</td>
<td>83</td>
<td>149</td>
<td>63</td>
<td>56</td>
<td>0-37</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/L)</td>
<td>537</td>
<td>1181</td>
<td>390</td>
<td>303</td>
<td>0-250</td>
</tr>
<tr>
<td>Creatine kinase (U/L)</td>
<td>1293</td>
<td>1706</td>
<td>44</td>
<td>46</td>
<td>0-200</td>
</tr>
</tbody>
</table>

Results from bronchoalveolar lavage fluid

<table>
<thead>
<tr>
<th></th>
<th>Right middle lobe</th>
<th>Left lower lobe</th>
<th>Right middle lobe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza A virus rt-PCR1</td>
<td>Positive (Ct 31.4)</td>
<td>Positive (Ct 39.7)</td>
<td>Positive (Ct 44.0)</td>
</tr>
<tr>
<td>HLA PCR2</td>
<td>Ct 29.8 (100%)</td>
<td>Ct 31.5 (31%)</td>
<td>Ct 38.7 (&lt;1%)</td>
</tr>
</tbody>
</table>

1 Influenza A rt-PCR results of the three BAL samples with Cycle-threshold (Ct) values as a measure of positivity (lower = more positive). As a reference the Human Leucocyte

2 Antigen (HLA) PCR is given to correct for the quantity of human cells in each sample, relative to the first BAL. There is a decrease of viral load in each consecutive sample although the lower cell count suggests that the results could be influenced by the quality of the samples.

Cultures for bacteria and fungi as well as microscopy for Pneumocystis jiroveci were negative in all three bronchoalveolar fluid samples.
factors are obesity, children younger than 2 years of age and a history of asthma or COPD [1]. However, respiratory failure has also been reported in previously healthy individuals in all age groups, as is illustrated by this case [4]. The reasons why some patients develop lower respiratory tract infection and respiratory failure are not yet understood. In patients admitted to ICU with respiratory failure, mortality rates between 11 and 41% have been reported [5-9]. Secondary bacterial infections have been reported in 4% of all patients admitted to hospital with H1N1v and in 6.8%-24.4% of patients admitted to ICU [5-9].

To confirm the diagnosis, a sample of the upper or lower respiratory tract should be collected for testing. There are several diagnostic tests available, however, real-time reverse transcriptase PCR is the most sensitive and specific. Testing should be limited to hospitalized patients, including pregnant women in labour, who are suspected of infection [10].

Initially, our patient did not receive antiviral therapy because he had been ill for 10 days and was considered moderately ill. At that time, this was in accordance with the guidelines in our hospital. Oseltamivir, an oral neuraminidase inhibitor, was first started when his condition deteriorated, 36 hours after the diagnosis of H1N1v was established. Nowadays there is growing evidence that prompt treatment (within 48 hours after onset of illness) with the antiviral drugs oseltamivir and zanamivir (Relenza®), reduces the severity of illness and improves outcome [11]. Current guidelines advise the initiation of treatment in patients who are more than mildly ill, even without a confirmed diagnosis or if illness has been present for more than 48 hours [10]. Patients requiring hospitalization should be treated with antiviral therapy for at least five days and antiviral treatment can be prolonged if a patient has a severe infection [10-12]. However, the optimal duration of therapy is unclear in the case of severe pneumonia and clinicians tend to use higher doses of oseltamivir and for a longer duration. In our case, the patient’s condition appeared to deteriorate when the oseltamivir was discontinued after five days [10-12].

Initially, very little resistance to oseltamivir was reported in H1N1v influenza virus. However, due to the use of oseltamivir for chemoprophylaxis and treatment of the H1N1v, the first sporadic cases of oseltamivir-resistance were reported at the end of July 2009 [13]. Oseltamivir resistance is usually caused by a histidine to tyrosine mutation at residue 275 of the neuraminidase protein (H275Y) [13,14]. It can be detected using real-time PCR with H275Y discrimination assay [15]. This mutation has been detected in oseltamivir-resistant strains in Europe, China, the United States, Oceania, South East Asia, South Africa and Canada. There is an association between the use of oseltamivir and the appearance of this mutation, although spontaneous mutations have also been reported [13,16]. There is no evidence that oseltamivir-resistant H1N1v causes different or more severe forms of illness. Viruses resistant to oseltamivir remain sensitive to zanamivir. Zanamivir, which is administered via inhalation, is also a good alternative if oseltamivir cannot be administered orally [10]. The only intravenous alternative is peramivir. This has been authorized by the Food and Drug Administration for emergency use in the US, if neither oseltamivir nor zanamivir can be used. The 275Y

Figure 1a. Chest X-ray on admission (day 1) showing marked bronchovascular bundles and patchy consolidation of the lower regions of both lungs.

Figure 1b. Chest X-ray on day 16 showing progressive airspace consolidation of all lobes of both lungs with air bronchogram.
neuraminidase mutation causes resistance to both peramivir and oseltamivir [17].

In patients with renal impairment, the clearance of the active metabolite oseltamivir decreases linearly with creatinine clearance, therefore dose reductions should be made at a creatinine clearance of 10 - 30 ml/min [18,19]. No recommended dosage regimens for oseltamivir are available for patients with a creatinine clearance < 10 ml/min. Zanamivir is not absorbed after oral inhalation, therefore no dose adjustments are necessary in patients with renal impairment [19]. When using peramivir in patients with renal impairment, as in oseltamivir, dosage adjustments should be made [20]. In patients with mild and moderate hepatic impairment no dosage adjustment is required for oseltamivir. The safety and pharmacokinetics of oseltamivir have not been evaluated in patients with severe hepatic impairment and acute liver failure [18,21]. Zanamivir and peramivir are not protein bound and not hepatically metabolized, therefore dose adjustment in patients with hepatic impairment is not required [19,22].

The use of steroids in acute respiratory failure is still subject

Figure 1c. HR-CT on day 19 showing bilateral patchy ground-glass opacities, a combination of consolidation and reticulation and some bronchial wall thickening.

Figure 1d. Chest X-ray on day 43 showing a lot of parenchymal abnormalities including airspace consolidation and reticulation.

Figure 2. Course of LDH, CRP and leukocyte count in time in relation to use of prednisone, oseltamivir and mechanical ventilation.
of debate, however a majority of patients with respiratory failure admitted to ICU with confirmed H1N1 v infection received steroids [23,24].

Extracorporeal membrane oxygenation (ECMO) can be used in critically ill patients as an important rescue therapy for the treatment of refractory hypoxaemia, hypercapnia, or both, which occurred despite mechanical ventilation and rescue ARDS therapies. If ECMO is expected to be needed, referral to a specialized centre should occur early [12,25].

References

22. Administration USFaD. Emergency use authorization of peramivir iv fact sheet for health care providers.

Conclusion

This case illustrates the course of a previous healthy patient, who suffered from severe respiratory insufficiency based on an H1N1v pneumonia. As in most patients, his disease started with an influenza-like illness, however progression of his disease led to ICU admission, intubation and mechanical ventilation. No other pathogens that could have caused his respiratory insufficiency were found. Three months after discharge our patient was still suffering from restrictive lung disease.”