

PROLONGED SHEDDING OF INFLUENZA A(H1N1)v VIRUS: TWO CASE REPORTS FROM FRANCE 2009

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We observed a prolonged shedding of virus 14 and 28 days after symptom onset in two patients with pandemic H1N1 influenza, who did not have immunodepression and were treated with neuraminidase inhibitor. This prolonged shedding was not associated with the emergence of resistance mutation H275Y in the viral neuraminidase gene.

From 1 May until the beginning of October 2009, the virology laboratory in Bordeaux received more than 1,200 nasopharyngeal samples from the southwest of France for diagnosis of influenza A(H1N1)v virus by realtime RT-PCR, 186 of which were found positive. For five pandemic H1N1 influenza cases, we had the opportunity to monitor the duration of viral shedding and present here two cases of prolonged shedding.

Case report A

Case A was a man in his mid-fifties with body mass index (BMI) <30 and without relevant medical history. He developed fatigue and cough at the beginning of July 2009, shortly after his arrival to France from California, United States (US). On the day after symptom onset, he was admitted to the university hospital of Bordeaux with a fever of 39.4°C and breathing difficulties. Values of partial pressure of oxygen (PO₂) and of carbon dioxide (PCO₂) were at 7 kPa and 5.6 kPa, respectively, and the patient was transferred to an intensive care unit. A nasopharyngeal swab was taken and found positive on day 1 after symptom onset for influenza A(H1N1)v by realtime RT-PCR, and a treatment with oseltamivir was initiated at 150 mg/day. Since the patient's clinical condition improved rapidly, he was transferred to the infectious diseases department on 7 July. Oseltamivir treatment was continued and the presence of the virus was monitored via PCR from nasopharyngeal swabs. The signal remained positive during the following five days despite the patient's excellent clinical condition; oseltamivir was replaced by zanamivir on day 11. In five samples taken over the following seven days, influenza A(H1N1)v virus was still detected. The PCR was finally negative on day 15, and the patient was discharged. In order to exclude an immunodepression, we investigated biological parameters including IgG subclasses. Total IgG and subclass serum immunoglobulin levels were normal.

Case report B

Case B was a woman in her late twenties with a BMI >40 who had returned to France from holidays in Spain. On 25 July 2009,

the day of the symptom onset, she consulted the outpatient clinic of her local hospital in France, where typical influenza symptoms were diagnosed. After staying at home for five days, she experienced severe breathing difficulties and was admitted to an intensive care unit. On 31 July, RT-PCR for influenza A(H1N1)v was positive and oseltamivir treatment was started at 150 mg/day. In the following days, she developed acute respiratory distress syndrome (ARDS) and required mechanical ventilation and subsequently extracorporeal membrane oxygenation (ECMO). The oseltamivir dose was increased to 300 mg/day from 2 August, and RT-PCR for influenza A(H1N1)v was positive in 13 samples (in deep respiratory secretions but interestingly not in nasopharyngeal swabs) for 19 days and negative on days 31 and 34 after symptom onset. In the meantime, the patient fully recovered and was discharged from the hospital at the beginning of September. No cellular or humoral immunodepression could be diagnosed by quantitation of IgG subclasses and B cell and T cell phenotyping.

Discussion

In two of our patients with confirmed pandemic H1N1 influenza who were treated with oseltamivir, the duration of viral shedding was prolonged. As confirmed by RT-PCR, starting from symptom onset, the shedding was 14 days in patient A and 28 days in patient B. For each patient, the neuraminidase N1 gene was amplified from a positive viral sample at the end of the shedding period and sequenced. No H275Y resistance mutation associated with oseltamivir-resistance was observed.

Viral shedding of seasonal influenza A viruses is estimated to occur over a period between five and seven days [1]. In humans experimentally infected with influenza A/Texas/36/91 (H1N1) virus, oseltamivir administration shortened the median duration of viral shedding from 107 to 58 hours [2]. Prolonged shedding of seasonal influenza viruses has been demonstrated in immunocompromised patients even when treated with antiviral drugs, potentially leading to the emergence of viral resistant mutations [3-5]. Similarly, most patients with pandemic H1N1 influenza infection may be shedding virus from one day before the onset of symptoms until five to seven days after the onset of symptoms [6]. For infections with the pandemic influenza A(H1N1)v virus, prolonged viral shedding has been reported in immunocompromised patients treated with oseltamivir, in association with emergence of viral resistance to the drug [7].

Our observations, although limited to PCR detection without an attempt to culture the virus, are noteworthy because long-term shedding of influenza A(H1N1)v occurred in two patients without immunodepression, who were treated with oseltamivir and in whom the virus did not develop resistance to the drug. However, it seems plausible that prolonged viral shedding in our patients was more likely to be associated with the rather severe clinical course in both cases. We cannot provide data on how frequently prolonged shedding for more than seven days occurred in our series because we only have the necessary data for few patients. However, in some non-severe clinical cases of pandemic H1N1 influenza where a longitudinal study was undertaken, the viral PCR was negative within five to seven days after symptom onset, which is clearly different from the observation presented here.

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