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CASE REPORT

Favorable outcome after life-threatening meningococcal disease complicating influenza A(H1N1) infection

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Abstract
Purpose Neurological complications of influenza A(H1N1) have been reported in several patients since the onset of the pandemic in 2009. However, meningococcal disease complicating influenza A(H1N1) has not been reported.
Patients Two patients were admitted to an intensive care unit (ICU) for altered mental status, fever, and rapidly spreading petechial purpura. They were diagnosed with meningococcal meningitis and/or meningococcemia and influenza A(H1N1) co-infection.
Conclusions Meningococcal disease presenting as meningitis and/or meningococcemia is among the potential complications of influenza A(H1N1) infection. Physicians should be aware of this co-infection, as it must be detected and treated promptly with antibiotics in addition to supportive care.

Keywords Meningococcal disease · Meningitis · Influenza A(H1N1) infection · Intensive care unit · Coma

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Introduction

Neurological complications of influenza A(H1N1) have been described in several patients since the onset of the pandemic in 2009 [1]. We report on two patients who presented with altered mental status, fever, and rapidly spreading petechial purpura related to meningococcal disease and influenza A(H1N1) co-infection.

Case 1

A 35-year-old woman with an unremarkable medical history was found at home in the morning by her husband with impaired consciousness, headache, and vomiting. She was last seen on the previous evening, when she complained of cough and chills. Upon examination at home, she had a Glasgow Coma Scale (GCS) score of 10, mental confusion, neck stiffness, and a skin rash with pinpoint red spots and a few purple bruise-like areas suggesting petechial purpura. Her body temperature was 40°C, blood pressure 113/79 mmHg, heart rate 119 beats/min, SpO_2 96%, and respiratory rate 12 breaths/min. She received intravenous cefotaxime (2 g) <10 min after the arrival of the mobile emergency team. She was admitted to the intensive care unit (ICU), where the physical examination showed spreading of the purpura, without necrosis, and worsening consciousness impairment (GCS of 9). Her hemodynamic parameters and ventilation were stable. Intravenous dexamethasone (10 mg) was given immediately. Computed tomography revealed discrete meningeal-vessel contrast enhancement. Cerebrospinal fluid analysis indicated purulent meningitis with turbidity, Gram-negative diplococci, 1,800 cells/μL (97% neutrophils), 4.2 g/L protein, and 2.75 mmol/L glucose. Her simultaneous blood glucose

level was 8.1 mmol/L. A purpuric skin lesion was biopsied for microscopy and culture. Arterial blood tests under mechanical ventilation with 60% FiO_2 were as follows: pH, 7.36; $PaCO_2$, 44 mmHg; PaO_2, 194 mmHg; bicarbonate, 24 mmol/L; and lactate, 3.7 mmol/L. Renal function tests were normal. White blood cell count was 19.8 g/L (95% neutrophils), platelet count was 116 g/L, prothrombin time 74%, and fibrinogen 3.65 g/L.

Less than 1 h after ICU admission, her consciousness impairment progressed to coma (GCS of 7) and she experienced cardiovascular collapse that was unresponsive to fluid challenge. She promptly received endotracheal mechanical ventilation. She required vasopressor support of up to 0.75 mg/h of norepinephrine. Cefotaxime was continued (2 g every 4 h). Adjunctive drotrecogin alfa treatment was given. The purpuric rash stopped spreading a few hours after ICU admission. Her hemodynamic parameters improved, and norepinephrine was stopped on day 2. Sedation was discontinued, allowing full recovery of consciousness. She was successfully extubated on day 3. Cultures of blood, cerebrospinal fluid, and a purpuric skin lesion were negative. Nevertheless, specific polymerase chain reaction (PCR) for the detection and genogrouping of *Neisseria meningitidis*, performed on cerebrospinal fluid and skin lesions, confirmed the diagnosis of meningitis caused by *N. meningitidis* serogroup B [2].

Once extubated (day 2), cough and fever persisted. The chest radiographs showed the generalization of parenchymal infiltrates during the first ICU week (Fig. 1). Microscopic examination and quantitative cultures of a protected bronchial sample were negative. Her husband also complained of fever, cough, and sore throat the day before her admission and their children had experienced similar symptoms the week before. Real-time reverse transcriptase PCR on a nasopharyngeal swab specimen from the patient was positive for influenza A(H1N1). Given the late diagnosis of influenza A(H1N1) pneumonia, no antiviral agent was given. The pneumonia resolved rapidly. She achieved full recovery and was discharged at home on day 11.

Case 2

A 17-year-old man with a recent history of acne treated by doxycycline developed fever, myalgia, and cough. One week later, he presented to the emergency department with

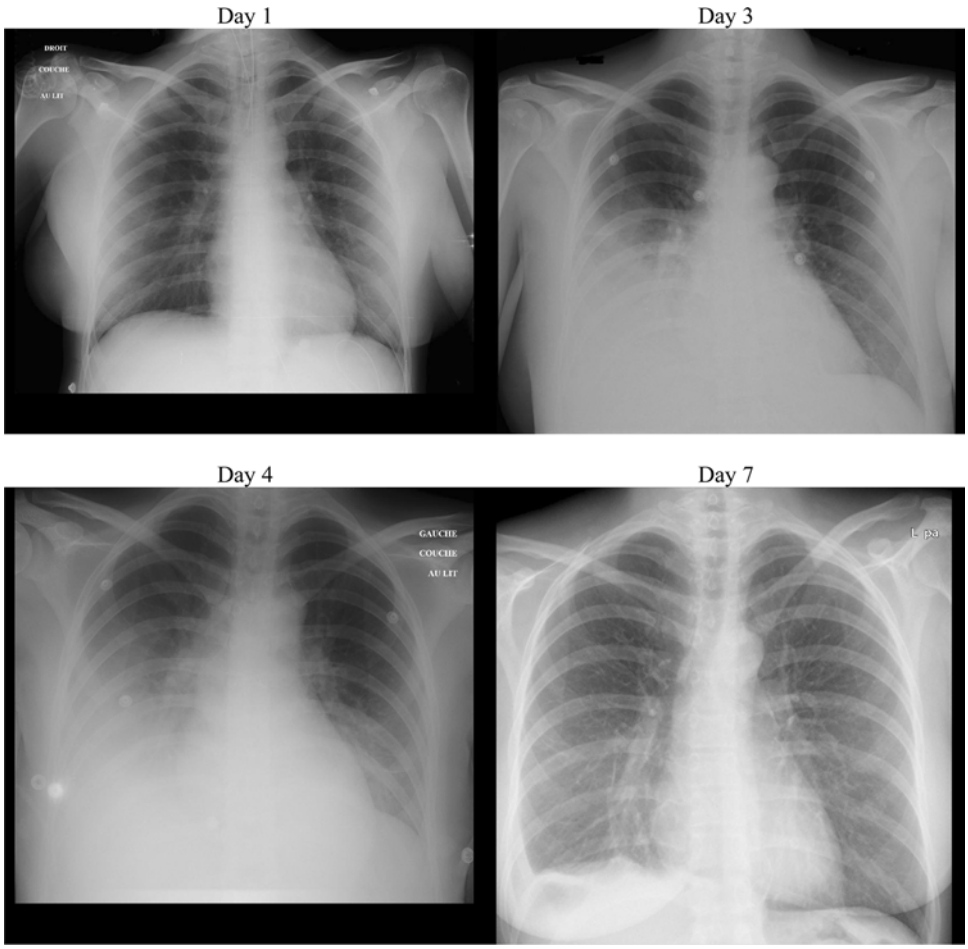

Fig. 1 Chest radiographs from day 1 to day 7 in the intensive care unit (ICU)

persistent fever (body temperature of 40°C), headaches, vomiting, and abdominal pain. His hemodynamic parameters were altered, with a blood pressure of 80/40 mmHg. Arterial blood lactate was 10 mmol/L, platelet count 137 g/L, prothrombin time 36%, and factor V 34%. His initial troponin level was 1.74 ng/mL, and cumulated at 11.8 ng/mL. Plasma creatinine was 200 µmol/L. Consciousness was normal and neck stiffness was not found. His respiratory rate and SpO_2 were normal. Chest X-ray and abdominal computed tomography were unremarkable. Real-time reverse transcriptase PCR on a nasopharyngeal swab specimen was positive for influenza A(H1N1). He received an intravenous combination of amoxicillin and clavulanic acid, associated with oseltamivir, and was transferred to the ICU.

On ICU admission, physical examination revealed neurological impairment with drowsiness and severe headache. His blood pressure was 90/65 mmHg. Petechial purpura appeared in the velum, at the bases of the thighs and neck. A transthoracic echocardiogram showed latero-septo-apical hypokinesia and a left ventricular ejection fraction of 35–40%. Two blood cultures yielded *N. meningitidis* serogroup B. Lumbar puncture was not deemed necessary given the coagulation test abnormalities. He was treated with intravenous cefotaxime injection with a loading dose of 2 g, followed by continuous administration at 15 g/day until day 7. Oseltamivir was discontinued at day 5. His clinical and biological parameters rapidly improved and he was successfully discharged home on day 11.

Case discussion

In contrast to previously reported cases of neurological involvement during influenza A(H1N1) infection, the two patients reported herein presented with meningococcal disease associated with influenza A(H1N1). When this pattern of co-infection occurs, prominent influenza symptoms of fever, sore throat, headache, myalgia, vomiting, and diarrhea may lead to the meningococcal disease being missed [3, 4]. A simultaneous outbreak of meningococcal disease and influenza occurred in 1972 among elderly nursing home residents [5]. A large increase in meningococcal disease was noted 2 weeks after an influenza A outbreak in England and Wales during the winter of 1989 [6]. Patients with meningococcal disease were significantly more likely to have positive serological tests for recent influenza A infection than age-matched controls [6]. In a French surveillance database extending from 1985 to 1990, the incidence of meningococcal disease was significantly associated with the incidence of influenza-like illness during the five previous weeks, and geographic spread was similar for the two diseases [7]. Meningococcal disease was more severe in the 2-month periods during and after influenza outbreaks, when mortality was 26% [7]. Meningococcal disease occurred a few weeks after an influenza outbreak in five children who shared a school bus in the US in 1991 [8] and in 15 Air Force recruits in Greece in 1996 [9]. Population-based data including 3,072 cases of meningococcal disease in The Netherlands from 1997 to 2003 revealed a significant association between influenza and meningococcal disease in children and adults [10]. Other studies found no association between meningococcal disease and other respiratory viruses, such as adenovirus, parainfluenza virus, respiratory syncytial virus, or rhinovirus [11, 12], which suggests that a specific pathophysiological process would be in play for influenza virus–meningococcus interactions. In a study of epithelial cell cultures, Rameix-Welti et al. [13] found that a direct interaction between the influenza A virus neuraminidase and the *N. meningitidis* capsule enhanced bacterial adhesion to respiratory epithelial cells. This effect may promote *N. meningitidis* dissemination via the bloodstream [14]. Other potential mechanisms include influenza virus-mediated immune dysregulation of phagocytic function and/or cytokine production [15], influenza virus-mediated upregulation of cellular receptors for *N. meningitidis* [16], and influenza virus-infected cell binding of bacterial sialic acids [17].

In conclusion, neurological complications of influenza A(H1N1) infections are rare but life-threatening. Meningococcal disease presenting as meningitis and/or meningococcemia should be add to the list of neurological complications of influenza A(H1N1). Physicians should be aware of this co-infection, as it must be detected and treated promptly with appropriate antibacterial and antiviral agents, in addition to supportive care.

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Conflict of interest None.

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