Clinical practice

Clinical variability in onset of influenza A (H7N9) infection

WANG Shu-ying, REN Shu-hua, HUANG Mei-xian, YU Dao-jun, SHEN Qiang, ZHAO Hong-feng, LÜ Qiao-hong and QIAN Shen-xian

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Clinical information of infections with the novel avian influenza A (H7N9) have been described elsewhere,[1] but clinical variability, especially changes of mental status in the onset of infection, has rarely been reported in patients infected with H7N9. In this report, the initial clinical manifestations of three confirmed cases are summarized. Two of the patients were in critical condition. In addition, two of the patients experienced changes in mental status, one of which was believed to be the first published case with Brugada syndrome associated with H7N9 infection in China. We suggest that this H7N9 virus causes various signs and symptoms in the early stages of infection. Detailed knowledge of its clinical features can assist in the decision-making of physicians facing this emerging infectious disease.

We report three cases of influenza A (H7N9) infection hospitalized in the Affiliated Hangzhou Hospital of Nanjing Medical University (Hangzhou First People's Hospital, Zhejiang), China. For diagnosis of H7N9 virus infection, we followed the criteria published by the National Health and Family Planning Commission of China.[2] Two throat swabs of each patient suspected to be infected with the H7N9 virus (suspected because of fever and rapidly progressing pneumonia and no response to antibiotic therapy) were transported to the Hangzhou Center for Disease Control. Nucleic acids of H7N9 avian influenza virus in throat swabs were detected by real-time reverse-transcriptase polymerase chain reaction (RT-PCR).

The clinical characteristics and laboratory results of the three cases are summarized in Table 1. Additional information is provided in the case reports.

Case 1

Patient 1, a 69-year-old man, was hospitalized because of fever and chills for 5 days, and cough and hemoptysis for 1 day. He also had diarrhea, passing watery stools thrice per day. A chest radiograph showed lower left lobe pneumonia. Laboratory tests showed hyponatremia, hypoproteinemia and hypoxemia. Elevated levels of creatine kinase and C-reactive protein were observed. Treatment with cefoperazone/sulbactam, acyclovir, oseltamivir (75 mg/12 hours) and intravenous glucocorticoid (methylprednisolone, 40 mg/d) was initiated. The patient developed acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. The first test of nucleic acids of influenza H7N9 virus from his throat swab specimens upon hospital admission was negative, but repeated tests of throat swab specimens were positive 2 days later. He died 3 days later of multiorgan failure.

Case 2

Patient 2, a 42-year-old man, was hospitalized because of fever with cough for 3 days. Laboratory tests showed hypoxemia. A thoracic computed tomography scan revealed infections in the right lower lung. He was treated with cefoperazone/sulbactam, methylprednisolone (40 mg/d), and oseltamivir (75 mg/12 hours). He was febrile (40.5°C) and progressed to confusion, and was delirious on day 2 after hospital admission. He became unable to answer questions or recognize his family. A complete neurological examination and lumbar puncture were difficult to perform because the patient was not cooperative. Plain and diffusion-weighted magnetic resonance imaging (MRI) of the brain showed no obvious abnormality. The treatment of oseltamivir and glucocorticoid was continued. He improved and regained consciousness after 24 hours. The results of RT-PCR of throat swab specimens were positive for influenza H7N9 on day 4 after admission. He had a slow but successful recovery, and he was discharged home after 15 days of treatment. His mental status had returned to baseline.

Case 3

Patient 3, a 37-year-old man without prior history of coronary artery disease, was hospitalized because of fever with cough for 20 days, tightness and pain in the chest for 4 days, and one episode of syncope. He experienced loss of consciousness when he waited outside the physician's office, but regained consciousness about 1 minute later. He was febrile (39.8°C) and was admitted. His creatinine kinase levels and serum electrolytes were all normal. Chest radiography showed suspected infections in the right lower

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Department of Nosocomial Infection Management (Wang SY, Ren SH, Shen Q, Zhao HF and Lü QH), Department of Infectious Diseases (Huang MX), Department of Clinical Laboratory (Yu DJ), Department of Hematology (Qian SX), Affiliated Hangzhou Hospital of Nanjing Medical University, Hangzhou First People's Hospital, Hangzhou, Zhejiang 310006, China
Correspondence to: QIAN Shen-xian, Department of Hematology, Affiliated Hangzhou Hospital of Nanjing Medical University, Hangzhou First People's Hospital, Hangzhou, Zhejiang 310006, China (Fax: 86-571-87923830. Email: sxqian_88@163.com)

Table 1. Clinical features and laboratory results of three cases with H7N9 virus infection

Parameters	Case 1	Case 2	Case 3
Age (years)	69	42	37
Time from disease onset to hospital admission (days)	5	3	20
Epidemiology	Currently working in poultry market	Bought a live hen in the market 10 days before disease onset	No
Disease history	Surgical treatment due to varicose veins in the lower extremities	Extracorporeal lithotripsy for kidney stones	No
History of smoking	>50 years of smoking 10–20 cigarettes per day	No	>20 years of smoking 20 cigarettes per day
Fever	Remittent fever, with highest body temperature of 39.2°C	Remittent fever, with highest body temperature of 40.5°C	Remittent fever, with highest body temperature of 39.8°C
Cough	+	+	+
Phlegm production	+	+	+
Hemoptysis	+	+	–
Chest tightness	+	–	+
Difficulty in breathing	+	+	–
Abnormal state of consciousness	No	+	+
Diarrhea	+	–	–
Wet rales	+	+	+
White blood cells ($\times10^9$ cells/L)	4.8	5.3	4.3
Lymphocytes ($\times10^9$ cells/L)	0.6	0.9	1.0
Neutrophils ($\times10^9$ cells/L)	3.9	4.3	2.8
C-reactive protein (mg/L)	125	120	8
Alanine aminotransferase (U/L)	36	14	27
Albumin (g/L)	29.7	41.6	43.4
Creatinine (μmol/L)	78	100	63
Lactate dehydrogenase (U/L)	556	463	168
Creatine kinase (U/L)	2742	89	93
Sodium (mmol/L)	128	138	138
PaO_2 (mmHg)	53.0	54.0	88.0
$PaCO_2$ (mmHg)	20.0	36.0	36.0

lobe. Electrocardiogram (ECG) demonstrated anteroseptal ST-segment elevation and Brugada pattern (Figure 1). He was treated with piperacillin, levocarnitine and adenosine cyclophosphate. The RT-PCR results of his throat swab specimens were positive for influenza H7N9 on day 2 after admission and oseltamivir (75 mg/12 hours) was initiated. The patient had a successful recovery with no additional syncopes.

We identified three cases with laboratory-confirmed H7N9 avian influenza virus infection. As demonstrated in this and other reports, fever and cough were the most common symptoms, the white cell count was normal and the radiographic features were consistent with pneumonia.[1,2] The clinical presentation of H7N9 infections can be mild, or can be as severe as ARDS.

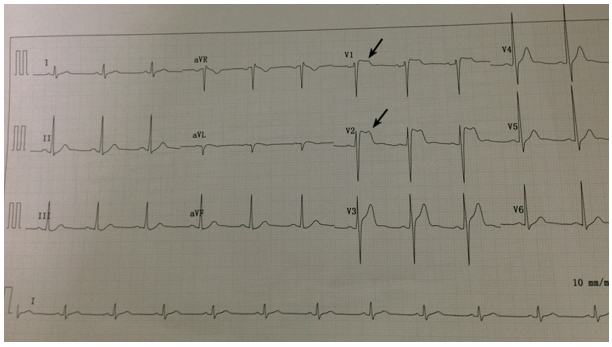

Figure 1. Electrocardiogram shows ST-segment elevation consistent with Brugada pattern in two of the right precordial leads of case 3 (V1–V3) (arrows).

In cases 1 and 2, the disease progressed rapidly from day 3 to day 5 after disease onset, and both patients had hemoptysis and obvious hypoxemia. Intestinal symptoms, hyponatremia, hypoproteinemia and elevated levels of creatine kinase were noted in case 1. The patient developed ARDS and rapidly deteriorated, while the disease in case 3 was relatively mild and progressed slowly. Although case 3 had fever and cough for 20 days, the pneumonia was slight and the arterial blood gas analysis result of the patient was normal. Changes of mental status, which have rarely been reported in patients infected with H7N9, were observed in two cases. One (case 2) presented with acute febrile encephalopathy and the other (case 3) presented with one episode of syncope.

Encephalopathy is more common in pediatric than adult influenza patients.[3] Cases in adults are infrequently reported and remain poorly characterized, although the more complex clinical scenarios in adults may have hindered case recognition. Lee et al[4] reported acute encephalopathy associated with influenza A infection in three adults who recovered without sequelae. They found no evidence of viral neuroinvasion, but reported high concentrations of CXCL8/IL-8, CCL2/MCP-1, IL-6, and CXCL10/IP-10 in cerebrospinal fluid and plasma. In our patients, case 2 was delirious on day 2 after admission. The symptom lasted for 24 hours and responded to therapy. Further study of significant implications for unusual presentations of this novel virus is needed.

In case 3, the patient was admitted because of fever, cough

and one episode of syncope. ECG demonstrated T-segment elevation in leads V1–V3, consistent with Brugada pattern. His family history was significant for sudden, recurrent syncopes of his mother and his sister. Therefore, Brugada syndrome was diagnosed. The syndrome is a clinical entity first described in 1992, and most patients with the syndrome are asymptomatic. It predisposes to malignant ventricular arrhythmias and can be unmasked by physiologic stress, including fever.[5] The subsequent ECG of the patient, recorded after the fever had resolved, showed normal ventricular repolarization. These findings suggest that the fever due to H7N9 influenza infecion may play an important role in the changes of the case's ECG manifestations.

Based on these case reports, patients with H7N9 influenza virus infection from symptom onset to laboratory confirmation showed variable findings in clinical manifestation. Patients with H7N9 infection present variable symptoms: fever, cough, phlegm production, hemoptysis, chest tightness, diarrhea, and disturbance of consciousness. Detection of the nucleic acids of H7N9 virus in the throat swab specimens may show negative results in the early stage. Clinicians should remain vigilant to the possibility of H7N9 infection associated with neurological and cardiovascular complications, because the novel virus may unmask some underlying diseases. Documentation of these atypical cases will facilitate a better understanding of this emerging infection.

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