

Case Report

A human case died by avian influenza A (H5N6) infection in Jiangxi province, China: an epidemiological and clinical survey

Tianchen Zhang^{1*}, Yong Liao^{2*}, Weijie Fu¹, Yun Xie¹, Xiaoqing Liu¹

¹Jiangxi Province Center for Disease Control and Prevention, 555 Beijing East Road, Nanchang 330029, Jiangxi, China; ²Ganzhou Center for Disease Control and Prevention, 6 Zhangjiang North Road, Ganzhou 341000, Jiangxi, China. *Equal contributors and co-first authors.

Received February 9, 2016; Accepted February 24, 2016; Epub July 15, 2016; Published July 30, 2016

Abstract: Background: After the first case was laboratory-confirmed, a total of 9 human avian influenza A (H5N6) infection index cases were reported and treated in China as of January 28, 2016. The aim of this study was to analyze the epidemiological and clinical characteristics of the first fatal H5N6 case in Jiangxi province and provide scientific recommendations for control and prevention of this epidemic. Methods: Threal-time reverse-transcription polymerase chain reaction (RT-PCR) method was conducted to test for the presence of nucleic acid from the influenza A virus and its subtypes. RNA from throat swab specimens was extracted and reverse-transcribed to double-strand DNA. Embryonated chicken eggs were used to isolate the virus. Epidemiological and clinical information of this case were collected by the use of a standard questionnaire, which was recommended by the China Provincial Center for Disease Control and Prevention. Results: The onset of illness for this case began on December 12, 2014, where the patient then died from respiratory failure on December 21, 2014. On January 6, 2016, it was confirmed to be a case of human infection with the H5N6 virus. There were no secondary cases confirmed among the individual's close contacts. There was a clear history of avian exposure for this case and the avian influenza A (H5) nucleic acid was found in the patient's residence. Conclusion: The initial presentation of this case was similar to other avian influenza or influenza viruses, presenting as fever, cough, and other influenza-like illness symptoms. Similar to other human H5N6 infection cases reported previously, this case suffered from multiple organ failure and died from respiratory failure. A delay in initiating antiviral therapy was the main cause of death for this case. The epidemiological survey conducted in this case did not uncover any evidence to suggest human-to-human transmission of the infection.

Keywords: Avian influenza infection, H5N6, epidemiological survey, antiviral therapy

Introduction

In May 2014, the National Health and Family Planning Commission (HFPC) of China announced the first laboratory-confirmed human case of avian influenza A (H5N6) infection, where the patient had been infected in Sichuan Province [1]. By January 28, 2016, there were 9 laboratory-confirmed human H5N6 cases reported worldwide, where all cases had been infected in the China Mainland with a fatality rate of 55.6% (5/9). All 9 cases were found to be sporadic cases, with no family cluster or limited person-to-person transmission reported. During December 2015, 4 new laboratory-confirmed human cases of H5N6 infection were

reported in the Guangdong province of China, indicating that cross-species H5N6 infection has become a new emerging public health concern for humans.

On December 22, 2015, the Jiangxi Center for Disease Control and Prevention (CDC) detected influenza A (H5) nucleic acid in a throat swab specimen, which was collected from a patient with severe pneumonia who was admitted to the Ganzhou People's Hospital [2]. On January 6, 2016, the China CDC laboratory confirmed this to be the first H5N6 case in Jiangxi province, and the 8th laboratory-confirmed case worldwide. This patient was an imported case from Jieyang City, Guangdong Province, who

Avian influenza A (H5N6) infection in Jiangxi province

subsequently died from respiratory failure on December 21, 2015. This paper summarizes the clinical presentation, epidemiological information, laboratory results, and preventive and control measures of this case with accompanying recommendations.

Methods

The throat swab specimens were collected from this patient as a part of routine monitoring on December 21, 2015 by staffs at the Ganzhou People's Hospital, which were then sent to the relevant CDCs for laboratory testing. Real-time RT-PCR was conducted to test for the presence of nucleic acid from the influenza A virus and its subtypes. RNA from the throat swab specimens was extracted and reverse-transcribed to double-strand DNA. Embryonic chicken eggs were used to isolate the virus from throat swab specimens.

Epidemiological and clinical information were collected by the use of a standard questionnaire, which was recommended by the China CDC. The survey collected the following information: basic information about the case and his family, past medical history, the places he had visited and who he had contacted, recent exposure history to avian animals and live poultry markets, clinical manifestations, laboratory results and imaging diagnosis, therapeutic schemes, and clinical outcomes.

"Close contacts" was defined individuals anyone who the case had interaction with without any effective means of protection against transmission of the infection, such as his family members and medical staff within 2 weeks before the onset of his illness until the day that the patient died. All close contacts were medically monitored for 2 weeks and throat specimens were collected.

Results

The patient in this study was a 42-year-old male vegetable peddler, who was a resident of Huichang, Jiangxi Province. He had lived near an agricultural trade market in the town of Jieyang, Guangdong for a long period. His past medical history included calcification in his right liver lobe, calculus of the bile duct, coronary heart disease, diabetes, and hypertension.

Clinical history

On December 12, 2015, the case began to develop a fever (39.5°C) and a cough, had slight difficulty in his breathing (not related to his body position), and other symptoms of influenza-like illness (ILI). He was then treated in 2 rural clinics (the specific drugs used were unknown). On December 14, 2015, the patient was moved to Lancheng District People's Hospital of Jieyang City due to the worsening of his condition. Upon admission, the patient presented with the following: a temperature of 39.5°C, a blood pressure of 162/102 mmHg, a rapid blood glucose of 18.4 mmol/L, a white blood cell (WBC) count of $5.98 \times 10^9/L$ with 90.5% neutrophils, and a negative dengue NS1. The computed tomography (CT) chest scan showed right upper pulmonary lobar pneumonia. Of note, the patient's chest CT images were destroyed by his relatives before the survey was conducted. He was treated with penicillin sodium, amoxicillin and clavulanate potassium, and levofloxacin sodium chloride; however, the symptoms mentioned above still did not improve. At 9:00 PM on December 18, 2015, the patient was driven back to Huichang from the Lancheng District People's Hospital by his relatives, and was admitted to the Huichang County People's Hospital with respiratory failure, pulmonary infection, hypertension, and diabetes mellitus. Upon admission, his WBC count was $1.12 \times 10^9/L$ with 75.5% neutrophils, 21.5% lymphocytes, 2.7% monocytes, and 0.1% eosinophils. Two rapid tests for the influenza A antigen were performed and both were positive. Levofloxacin and cefotaxime sodium, which were used for anti-infection, and antipyretic symptomatic treatment were administered; however, the patient's cough and expectoration did not improve and his dyspnea became aggravated. At 11:00 PM on that day, the case was transferred to Ganzhou People's Hospital, and was admitted to the Department of Respiratory Medicine at 4:32 AM on December 19, 2015. The results of his physical examination upon admission were, as follows: a body temperature of 36.0°C, a pulse of 101 beats/min, a breathing rate of 22 breathes/min, a blood pressure of 101/68 mmHg, an enhanced pectoral fremitus on his right side, double lung voiceless percussion and the use of a stethoscope displayed attenuated breathing sounds and moist rales from his right side.

Avian influenza A (H5N6) infection in Jiangxi province

Table 1. Summary about the results of related blood biochemical indices

Items	Reference Value	Unity	14 th	18 th	19 th 09:35	19 th 14:52	20 th 07:00
C-reaction protein	0.0-8.00	mg/L	-	-	261.00	-	-
Lactate dehydrogenase	80-285	U/L	-	-	901.00	-	-
Creatine kinase	0-190	U/L	-	-	779.40	-	-
Creatine kinase MB isoenzyme	0.00-25.00	U/L	-	-	23.65	-	-
Alpha-hydroxybutyrate dehydrogenase	76.00-218.00	U/L	-	-	830.00	-	-
WBC counts	3.5-9.5	10 ⁹ /L	5.98	1.12	1.31	1.29	-
Ratio of neutrophils	40-75	%	90.5	75.5	71.80	86.01	-
Ratio of lymphocytes	20-50	%	-	21.5	24.40	7.82	-
Ration of Lymphomonocyte	3-10	%	-	2.7	3.80	5.40	-
Ratio of eosinophil granulocyte	0.4-8.0	%	-	0.1	0.00	0.80	-
Neutrophils counts	1.8-6.3	10 ⁹ /L	-	-	0.94	1.11	-
Lymphocytes counts	1.1-3.2	10 ⁹ /L	-	-	0.32	0.10	-
Mononuclear cell counts	0.1-0.6	10 ⁹ /L	-	-	0.05	0.07	-
Eosinophil granulocyte counts	0.02-0.52	10 ⁹ /L	-	-	0.00	0.01	-
Red blood cell counts	4.3-5.8	10 ¹² /L	-	-	5.10	4.62	-
Platelet counts	125-350	10 ⁹ /L	-	-	70	70	-
Mean platelet volume	6.5-12.0	fL	-	-	13.5	12.4	-
Platelet distribution width	9.0-17.0	%	-	-	19.7	18.4	-
Bilirubin total	5.10-19.00	umol/L	-	-	20.00	-	9.90
Bilirubin direct	0.0-6.80	umol/L	-	-	7.70	-	3.70
Indirect bilirubin	3.40-14.00	umol/L	-	-	12.30	-	6.20
Glutamate-pyruvate transaminase	9-50	U/L	-	-	73.00	-	67.00
Glutamic oxalacetic transaminase	15-40	U/L	-	-	172.00	-	171.00
Alpha-L-fucosidase	5.00-40.00	U/L	-	-	14.30	-	18.80
Total protein	60.00-85.00	g/L	-	-	49.50	-	44.80
Albumin	35.00-55.00	g/L	-	-	29.30	-	26.80
Globulin	20.00-40.00	g/L	-	-	20.20	-	18.0
Urea nitrogen	2.3-7.6	mmol/L	-	-	8.25	-	17.76
Creatinine	53-123	umol/L	-	-	85.10	-	135.00
Fibrinogen	2.0-4.0	g/L	-	-	5.20	-	-
Activated partial thromboplastin time	20-40	s	-	-	30.4	-	-
Thrombin time	14-24	s	-	-	17.30	-	-

The related results of the blood biochemical analysis are summarized in **Table 1**. The Ganzhou People's Hospital immediately organized a consultation about this case, and the panel's conclusion was that this patient had viral pneumonia (with the possibility of an influenza A viral infection). Piperacillin and tazobactam were given as antiviral therapy, and methylprednisolone sodium succinate was given as an anti-inflammatory therapy; however, the patient's respiration did not significantly improve. In the meantime, his liver function became impaired, his myocardial enzyme level increased, and he experienced multiple organ

failure. The chest CT conducted on December 19, 2015 demonstrated that lesions had significantly and rapidly developed in comparison to the chest CT performed previously (**Figure 1**). The lesions were found in both lungs; and, mainly in the right lung. On the same day, this case was transferred to Intensive Care Unit of Ganzhou People's Hospital for further care. The case was given medical treatment in isolation by the use of tracheal intubation and ventilator therapy (with a tidal volume of 450 mL, positive end expiratory pressure of 16 cmH₂O, and a fractional concentration of inspired oxygen of 100%). In the meantime, transfusion of albu-

Avian influenza A (H5N6) infection in Jiangxi province

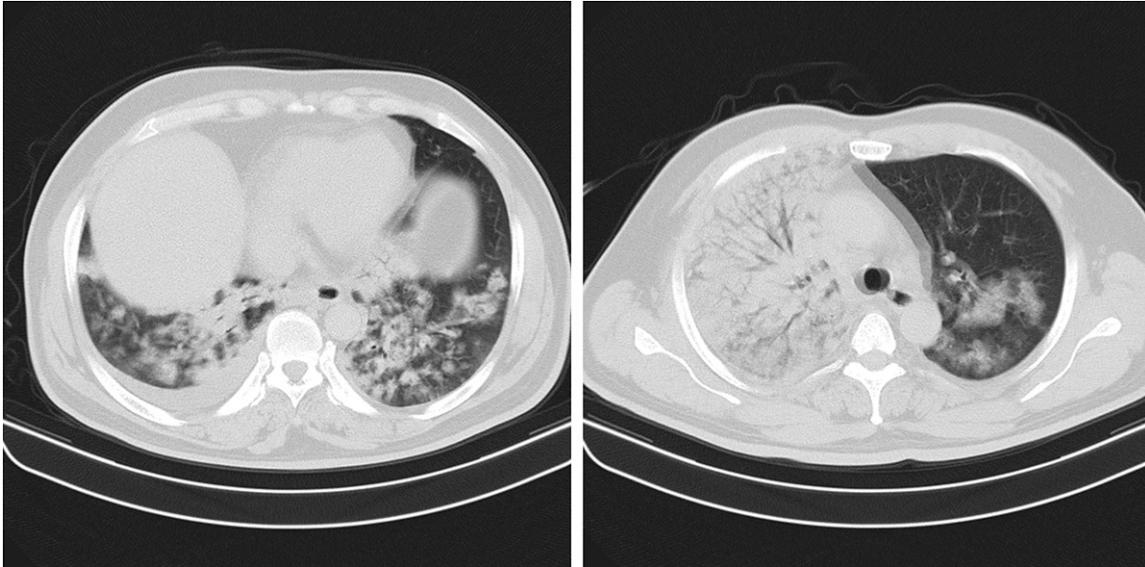


Figure 1. Chest CT images from the patient, which were conducted on December 19, 2015. A large area of patchy and globular shadows or mutation can be seen in the right lung and left lower lung, with an air bronchus and pleural effusion detected.

Table 2. Summary on the results of the blood gas analysis under the condition of Vt 450 ml, PEEP 16 cmH₂O and FiO₂ 100%

Items	Reference Value	Unity	19 th				20 th				
			04:36	12:02	14:14	20:42	00:07	06:12	14:42	21:09	23:15
Ph	7.35-7.45	-	7.42	7.30	7.35	7.43	7.41	7.43	7.37	7.37	7.41
PaO ₂	83-108	Mmhg	46	42	54	37	35	36	38	29	26
PaCO ₂	35-45	Mmhg	32	41	35	35	36	36	37	33	35
Na	135-145	Mmol/L	127	128	131	130	132	133	136	138	137
K	3.5-5.5	Mmol/L	4.0	4.2	3.8	4.3	4.5	4.6	4.6	3.6	4.3
Ionized Ca	1.15-1.35	Mmol/L	0.98	1.13	1.08	1.18	1.21	1.22	1.28	1.17	1.32
BG	3.9-6.1	Mmol/L	12.4	19.3	18.2	14.7	12.0	10.5	15.0	14.2	14.9
Haematocrit	35-51	%	50	45	34	35	37	37	36	31	38
Total CO ₂	22-29	Mmol/L	21.8	21.5	20.4	24.3	23.9	25.0	22.5	20.1	23.3
Buffer Base	-3-3	Mmol/L	-3.7	-6.2	-6.3	-1.1	-1.8	-0.4	-3.9	-6.2	-2.4
BE	-2.3-3	Mmol/L	-2.7	-5.9	-5.7	-0.8	-1.5	-0.1	-3.5	-5.5	-2.0
Oxygen Saturation	95-98	%	83	71	86	73.0	68	71	70	53	49
Bicarbonate	18-23	Mmol/L	20.8	20.2	19.3	23.2	22.8	23.9	21.4	19.1	22.2
Hemoglobin	11.7-17.4	G/Dl	15.5	14.0	10.5	10.9	11.5	11.5	11.2	9.6	11.8

BG: blood glucose; BE: base excess; PaCO₂: CO₂ partial pressure; PaO₂: O₂ partial pressure.

min was performed to relieve the patient's edema, ceftazidime was given to treat infection, oseltamivir was given as an antiviral therapy and other therapeutic regimens were conducted according to other reported symptoms; however, his blood oxygen saturation was still poor (at about 80%), with a large amount of bloody secretions in his airway, and a blood pressure of only 85-92/42-56 mmHg. The results of the blood gas analysis are summa-

ized in **Table 2**. At 6:00 AM on December 21, 2015, this patient died from respiratory failure. The timeline for the clinical course of this patient is presented in **Figure 2**.

Epidemiological survey

Occupational exposure history: Before the onset of his illness, this patient worked as a vegetable peddler in an agricultural trade mar-

Avian influenza A (H5N6) infection in Jiangxi province

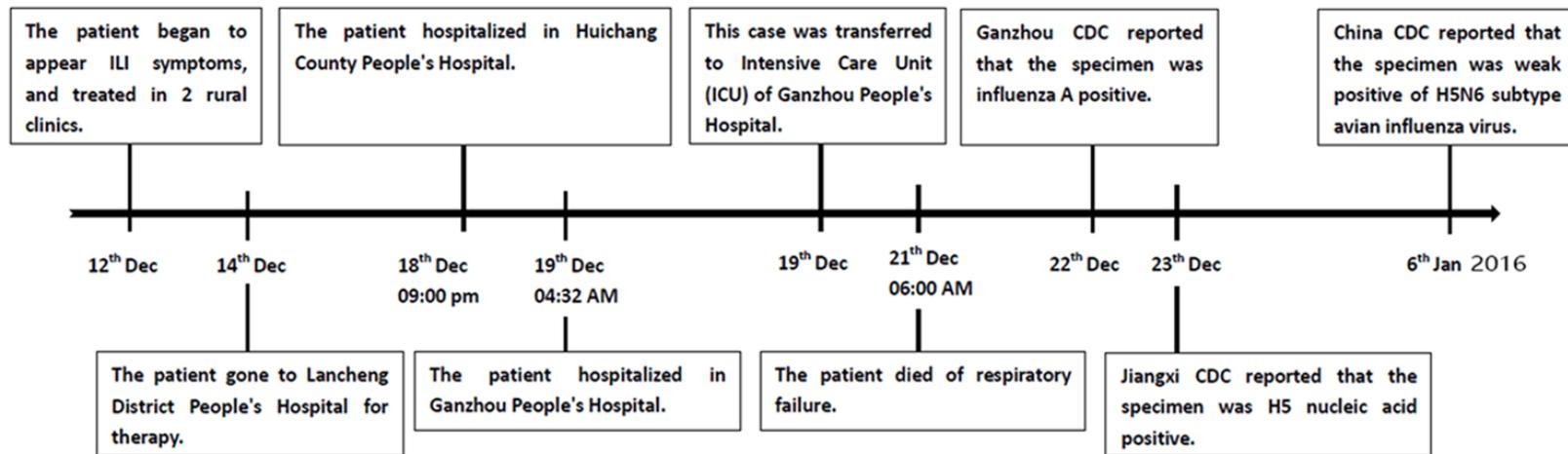


Figure 2. The patient's clinical course timeline.

Avian influenza A (H5N6) infection in Jiangxi province

ket in a town in Jieyang, Guangdong for many years, and there were 7 live poultry stalls in that market. Two weeks before the onset of his illness, no poultry had died as a result of disease and no ILI symptoms were reported in the stall owner of the live poultry. Family members of the paper denied that he had contacted any individuals with ILI symptoms and stated his travel history 14 days before the onset of his illness.

Residence environment survey: The patient lived near the 2nd floor of that agricultural trade market and the surrounding environment was very poor. There was a slaughter zone for chickens, ducks and other poultry downstairs and a rubbish-dealing site nearby. Only the patient and his wife lived in his home for a long period of time, and they raised 14 chickens on the balcony (none of the chickens died of disease). During the period from the onset of his illness to his death, his wife did not display any suspicious symptoms.

Close contact monitoring: According to the epidemiological survey, 35 individuals, including the case's family members and medical staff at the hospitals the case had visited, were defined as close contacts and all of them were medically monitored. Following a medical observation period of 2 weeks, no close contact developed a fever or cough, except one of the medical staff from the Emergency Department at Lancheng District People's Hospital. During the full medical observation period, all of the close contacts had a throat swab specimen collected for analysis, and no suspected cases of severe pneumonia or avian influenza infection were found.

Laboratory testing

Testing of throat swab specimens from the case and his close contacts: On December 21, 2015, the Ganzhou People's Hospital sent the throat swab specimens from this case as routine monitoring specimens to the Ganzhou CDC for laboratory testing. On December 22, 2015, the Ganzhou CDC reported that the specimen was influenza A universal primer positive; however, the specific subtype was unidentified. On the next day, the Jiangxi province CDC reported this specimen that was sent by the Ganzhou CDC as H5 nucleic acid positive. On January 6, 2016, the China CDC reported the test result

for this specimen was weakly positive for the H5N6 virus as detected by the real-time RT-PCR method. Deep sequencing uncovered a partial influenza virus fragment. However, the content of the virus was too low to get enough sequence data; therefore, further analysis could not be conducted. The virus isolation test demonstrated a negative result for the E1 generation by the use of the specific pathogen free chicken embryo. The throat swab specimen collected from the medical staff with ILI symptoms mentioned above was negative for the influenza A nucleic acid by the use of real-time RT-PCR.

Environmental testing for suspicious exposure: On December 24, 2015, the Jieyang CDC collected 20 environmental samples from the 7 live poultry stalls in the market mentioned above. From the Jieyang CDC testing, one sample was H5 nucleic acid positive, four samples were H9 nucleic acid positive, ten samples were influenza A universal nucleic acid positive, and the remaining samples were influenza A nucleic acid negative. Because all of the 14 chickens fed by this patient were disposed of by his relatives, no specimens from these chickens were collected successfully.

Preventive and control measures

After the outbreak of this epidemic, the Jiangxi CDC had timely reported it to the Jiangxi provincial HFPC, and notified the Guangdong provincial CDC. In order to be certain of the diagnosis, the specimen was sent to the China CDC for further testing at the same time. The Jiangxi CDC, Ganzhou CDC, Guangzhou CDC, Jieyang CDC, and related hospitals had conducted preventive and control measures as follows: 1, they performed a survey on the clinical and epidemiological features of this case to investigate the possible infection source and risk factors; 2, they tracked, investigated, and medically monitored the close contacts of this case to observe and report the abnormal situation in a timely manner; 3, they disinfected the agricultural trade markets of Jieyang and the hospitals where this case had visited; 4, they guided the medical staff on how to personally protect themselves from infection and performed nosocomial infection control; 5, they actively searched for patients with similar symptoms, and strengthened the surveillance of patients with ILI and unexplained pneumonia in related

Avian influenza A (H5N6) infection in Jiangxi province

hospitals and communities; and 6, they timely reported the suspected cases with severe pneumonia and collected specimens for laboratory testing.

Discussion

In 1996, the H5N1 virus was first detected in geese within China. During the past 20 years, H5 subtype viruses continuously evolved and underwent reassortment, generating multiple virus clades [3]. Recent research reported that the virus reassortment in clade 2.3.4.4 has given rise to some novel H5 highly pathogenic avian influenza virus subtypes, including the H5N2, H5N6 and H5N8 virus, which has widely spread in Asia, Europe, and North America among wild birds or poultry [4-9]. In 1975, García et al. were the first to isolate the H5N6 virus from mallards in North America [10]. In March 2014, the H5N6 virus outbreak caused the death of 457 birds in Laos. Since 2013, the H5N6 subtype virus has been found in ducks or chickens in some areas of Jiangxi, Guangdong, and Sichuan province, indicating that the H5N6 virus is circulating in China [11, 12]. Recently, it is believed that cross-species infection with the H5N6 influenza can occur for humans [13]. In early 2014, the Chinese national HFPC reported the first human H5N6 virus infection case in Nanchong City, Sichuan Province [14]. After the first case was confirmed, a total of 9 human cases of H5N6 influenza viral infection were reported in Guangdong province, Yunnan province, and Jiangxi province. Nowadays, this infection has been considered as a newly emerging public health problem in China [15].

The clinical presentation of this case displayed similar classical signs and symptoms to the other highly pathogenic avian influenza virus infections, such as H7N9 and H10N8. This includes fever, cough, and respiratory discomfort as the initial symptoms, with the development of severe pneumonia where acute respiratory distress syndrome (ARDS) with leucopenia and lymphopenia decreased rapidly. Similar to H1N1 infection in humans, this case presented with liver and heart damage. Related tests demonstrated that the levels of aspartate transaminase (AST), lactate dehydrogenase (LDH), and hydroxybutyrate dehydrogenase (HBDH) were increased, and levels of total protein and albumin were decreased. This clinical

presentation was similar to other human cases of H5N6 influenza infection as Pan et al. [16]. previously reported. The fatality of this case might be due to 3 major reasons. The first is the delay in administering antiviral therapy. From the first day of the onset of the illness on December 12, 2015, to the day that the patient was transferred to the Ganzhou People's Hospital on December 19, 2015, no antiviral therapy was administered to this patient. Previous studies have shown that when antiviral therapy was given to patients with an avian influenza virus infection within the first 3 days, this can shorten the duration of viral shedding and reduce the incidence of mortality [17, 18]. The second reason is the lack of awareness of avian influenza virus infection in the primary hospitals. In the first 6 days, the clinics or hospital where the patient was treated did not consider the possibility of avian influenza virus infection, and the rapid test for the avian influenza virus was not conducted. The third reason is that oseltamivir was administered too late. For this case, oseltamivir was given on day 8 of his illness. Oseltamivir is widely recommended to be used as an antiviral drug for classical and new atypical avian influenza virus infection. The correct treatment regimen for H5N6 influenza virus infection is still unclear and is currently being explored. Previous indexed cases did not prove that oseltamivir was effective against H5N6 infection. However, the use of oseltamivir is still recommended as an effective therapy for avian influenza virus infection with no drug resistance detected [19, 20].

The epidemiological survey of this case demonstrated that there was a clear exposure history to poultry, and H5 nucleic acid was detected in the environment where the patient lived. According to the results of the medical monitoring of the close contacts, no evidence was found suggesting that human-to-human transmission occurred. Because there are only 9 patients with H5N6 infection in China, and that all of them are sporadic cases with no epidemiological association, the possible human-to-human transmission of H5N6 should not be excluded and further investigation should be conducted.

According to the results of this survey, and the background information pertaining to the frequent outbreaks of H5N6 infection in humans,

Avian influenza A (H5N6) infection in Jiangxi province

this study puts forward the following recommendations: 1, strengthen the surveillance of human avian influenza infection and environmental monitoring of the avian influenza virus, especially for a new avian influenza virus; 2, reinforce the use of technology for diagnosis and treatment and increase the knowledge of medical staff in regards to the prevention and control of avian influenza infection in order to reduce the severity of infection cases and resulting mortality to a great extent; 3, strengthen the information exchange between the agriculture department, industry department, and other related departments, and timely grasp the epidemic situation.

Conclusion

The first symptoms of this case were similar to other avian influenza or influenza virus infections, which presented as fever, cough, and other ILI symptoms. Similar to previously reported cases of human H5N6 infection, this case suffered from multiple organ failure and subsequently died from respiratory failure. A delay in the initiation of antiviral therapy was a main cause for death for this case. The epidemiological survey for this case did not uncover any evidence of human-to-human transmission.

Acknowledgements

We thank China CDC for the technical assistance supported.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xiaoqing Liu, Jiangxi Province Centre for Disease Control and Prevention, 555 Beijing East Road, Nanchang 330029, Jiangxi, China. Tel: +86 791 88156385; E-mail: jxcdcliuxiaoqing@163.com

References

- [1] Yu Z, Gao X, Wang T, Li Y, Xu Y, Chu D, Sun H, Wu C, Li S, Wang H, Xia Z, Lin W, Qian J, Chen H, Xia X and Gao Y. Fatal H5N6 Avian Influenza Virus Infection in a Domestic Cat and Wild Birds in China. *Sci Rep* 2015; 5: 10704.
- [2] Human infection with avian influenza A(H5N6) virus-China, WHO reopred. [Online] Available from: <http://www.who.int/csr/don/11-january-2016-avian-influenza-china/en/>. [Accessed on 13th January, 2014].
- [3] Mok CK, Da Guan W, Liu XQ, Lamers MM, Li XB, Wang M, Zhang TJ, Zhang QL, Li ZT, Huang JC, Lin JY, Zhang YH, Zhao P, Lee HH, Chen L, Li YM, Peiris JS, Chen RC, Zhong NS and Yang ZF. Genetic Characterization of Highly Pathogenic Avian Influenza A(H5N6) Virus, Guangdong, China. *Emerg Infect Dis* 2015; 21: 2268-2271.
- [4] Bae YJ, Lee SB, Min KC, Mo JS, Jeon EO, Koo BS, Kwon HI, Choi YK, Kim JJ, Kim JN and Mo IP. Pathological Evaluation of Natural Cases of a Highly Pathogenic Avian Influenza Virus, Subtype H5N8, in Broiler Breeders and Commercial Layers in South Korea. *Avian Dis* 2015; 59: 175-182.
- [5] Conraths FJ, Sauter-Louis C, Globig A, Dietze K, Pannwitz G, Albrecht K, Horeth-Bontgen D, Beer M, Staubach C and Homeier-Bachmann T. Highly Pathogenic Avian Influenza H5N8 in Germany: Outbreak Investigations. *Transbound Emerg Dis* 2016; 63: 10-13.
- [6] Saito T, Tanikawa T, Uchida Y, Takemae N, Kanehira K and Tsunekuni R. Intracontinental and intercontinental dissemination of Asian H5 highly pathogenic avian influenza virus (clade 2.3.4.4) in the winter of 2014-2015. *Rev Med Virol* 2015; 25: 388-405.
- [7] Harder T, Maurer-Stroh S, Pohlmann A, Starick E, Horeth-Bontgen D, Albrecht K, Pannwitz G, Teifke J, Gunalan V, Lee RT, Sauter-Louis C, Homeier T, Staubach C, Wolf C, Strebelow G, Hopper D, Grund C, Conraths FJ, Mettenleiter TC and Beer M. Influenza A(H5N8) Virus Similar to Strain in Korea Causing Highly Pathogenic Avian Influenza in Germany. *Emerg Infect Dis* 2015; 21: 860-863.
- [8] Adlhoch C, Gossner C, Koch G, Brown I, Bouwstra R, Verdonck F, Penttinen P and Harder T. Comparing introduction to Europe of highly pathogenic avian influenza viruses A(H5N8) in 2014 and A(H5N1) in 2005. *Euro Surveill* 2014; 19: 20996.
- [9] Jung MA, Nelson DI, Centers for Disease C and Prevention. Outbreaks of avian influenza A (H5N2), (H5N8), and (H5N1) among birds-United States, December 2014-January 2015. *MMWR Morb Mortal Wkly Rep* 2015; 64: 111.
- [10] Garcia M, Suarez DL, Crawford JM, Latimer JW, Slemons RD, Swayne DE and Perdue ML. Evolution of H5 subtype avian influenza A viruses in North America. *Virus Res* 1997; 51: 115-124.
- [11] Shen H, Wu B, Chen Y, Bi Y and Xie Q. Influenza A(H5N6) Virus Reassortant, Southern China, 2014. *Emerg Infect Dis* 2015; 21: 1261-1262.
- [12] Bi Y, Mei K, Shi W, Liu D, Yu X, Gao Z, Zhao L, Gao GF, Chen J and Chen Q. Two novel reassortants of avian influenza A (H5N6) virus in China. *J Gen Virol* 2015; 96: 975-981.

Avian influenza A (H5N6) infection in Jiangxi province

- [13] Joob B and Viroj W. H5N6 influenza virus infection, the newest influenza. *Asian Pac J Trop Biomed* 2015; 5: 434-437.
- [14] Yang ZF, Mok CK, Peiris JS and Zhong NS. Human Infection with a Novel Avian Influenza A(H5N6) Virus. *N Engl J Med* 2015; 373: 487-489.
- [15] WHO. Influenza research at the human and animal interface: report of a WHO working group. Geneva: WHO; 2006. [Online] Available from: http://www.who.int/csr/resources/publications/influenza/WHO_CDS_EPR_GIP_2006_3/en/index.html [Accessed on 13th January, 2014].
- [16] Pan M, Gao R, Lv Q, Huang S, Zhou Z, Yang L, Li X, Zhao X, Zou X, Tong W, Mao S, Zou S, Bo H, Zhu X, Liu L, Yuan H, Zhang M, Wang D, Li Z, Zhao W, Ma M, Li Y, Li T, Yang H, Xu J, Zhou L, Zhou X, Tang W, Song Y, Chen T, Bai T, Zhou J, Wu G, Li D, Feng Z, Gao GF, Wang Y, He S and Shu Y. Human infection with a novel, highly pathogenic avian influenza A (H5N6) virus: Virological and clinical findings. *J Infect* 2016; 72: 52-59.
- [17] Ling LM, Chow AL, Lye DC, Tan AS, Krishnan P, Cui L, Win NN, Chan M, Lim PL, Lee CC and Leo YS. Effects of early oseltamivir therapy on viral shedding in 2009 pandemic influenza A (H1N1) virus infection. *Clin Infect Dis* 2010; 50: 963-969.
- [18] Adisasmito W, Chan PK, Lee N, Oner AF, Gasimov V, Aghayev F, Zaman M, Bamgboye E, Dogan N, Coker R, Starzyk K, Dreyer NA and Toovey S. Effectiveness of antiviral treatment in human influenza A(H5N1) infections: analysis of a Global Patient Registry. *J Infect Dis* 2010; 202: 1154-1160.
- [19] Wiwanitkit V. Current research on drugs and vaccines for fighting bird flu. *Trans R Soc Trop Med Hyg* 2007; 101: 1171-1172.
- [20] Schirmer P and Holodniy M. Oseltamivir for treatment and prophylaxis of influenza infection. *Expert Opin Drug Saf* 2009; 8: 357-371.