Original Article

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Fatal cases of human infection with avian influenza A (H7N9) virus in Shanghai, China in 2013

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Summary **We retrospectively reviewed the medical records of 17 fatal H7N9 cases in Shanghai in 2013, analyzed clinical variables and described their clinical and epidemiologic characteristics. The median age was 73 years, and 82.4% had underlying medical conditions. The most frequent symptoms were fever (100%), followed by productive cough (47.1%) and dry cough (35.5%). Thirteen (76.5%) patients had dyspnea or respiratory distress, five (29.4%) had shock, and four (23.5%) had acute kidney injury. Seventeen (100.0%) patients had lymphopenia. Involvement of both lungs was found by chest radiography in 14 (82.4%) patients at presentation. Fifteen (88.2%) patients were hospitalized. The median times from illness onset to hospitalization and to diagnosis confirmation were both six days. Eleven (64.7%) patients were admitted to the intensive care unit. Sixteen (94.1%) patients were treated with oseltamivir. The median time from illness onset to oseltamivir treatment was six days. Among six patients for whom the duration of viral shedding was available, the median duration of viral shedding after oseltamivir treatment was 17 days. The median time from illness onset to death was 11 days. Refractory hypoxemia accounted for most deaths. The clinical and epidemiologic characteristics in the Shanghai fatal series of patients do not differ from other reports of H7N9 patients in China. This investigation reflects a delay in the diagnosis and antiviral treatment of H7N9 patients in the early stage of the epidemic in Shanghai. Late antiviral treatment and a long duration of viral shedding may be associated with a fatal outcome in these patients.**

Keywords: Avian influenza A (H7N9) virus, death, diagnosis, antiviral treatment

1. Introduction

The subtype H7N9 avian influenza virus has not been known to infect humans until only recently. On March 31, 2013, China confirmed the first three human cases of novel avian influenza A (H7N9) virus infection in Shanghai and Anhui, two of them have died (*1,2*). Novel reassortant H7N9 viruses were associated with severe and fatal respiratory disease in humans, most persons with confirmed H7N9 virus infection were critically ill (*1,2*). This increasing number of new H7N9 cases and high mortality has caused global concern and worries of spread outside of China (*3*). Since Shanghai reported the first case of human infection with H7N9

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virus at the end of March 2013, a total of 33 laboratory-confirmed human cases have been reported in Shanghai in 2013; 18 patients (54.5%) died while 15 were discharged from the hospital with full recovery (*4*). The majority of the Shanghai cases occurred between February and early April 2013 (*4*). To better understand the characteristics of severe influenza caused by this virus, we describe here the epidemiologic and clinical features in the fatal cases of human infection with avian influenza A (H7N9) virus in Shanghai, China in 2013.

2. Methods

2.1. *Ethics statement*

The study protocol was approved by the Shanghai Public Health Clinical Center Ethics Committee (SPHCCEC). Informed consent was waived by the SPHCCEC.

2.2. *Patients*

In our study, we used the case definitions of confirmed human infection with the novel H7N9 virus, which have been described by Li *et al*. (*2*). Laboratory confirmation of the novel H7N9 virus was performed with the use of the same protocols published previously (*1,2,5*). Only patients with laboratory-confirmed infection were enrolled in this study. In 2013, 18 fatal cases of human infection with avian influenza A (H7N9) virus have been reported in Shanghai. Clinical data were available for 17 of the 18 patients. The study population included the 17 fatal cases of laboratory-confirmed influenza A (H7N9) infection diagnosed in 2013. The 17 patients received treatment in nine hospitals in Shanghai. Most patients were treated in local hospitals, but some were referred to the special hospital (Shanghai Public Health Clinical Center, Fudan University) by first medical cares after the diagnosis was confirmed.

2.3. *Data collection*

Data were collected through a review of medical records. Clinical data for confirmed cases were abstracted from original medical records with use of a data abstraction sheet. We collected information on demographic characteristics, underlying medical conditions, clinical presentation, laboratory findings, the date of illness onset, visits to clinical facilities, hospitalization, treatment and clinical outcomes.

2.4. *Laboratory evaluation*

In this study, acute kidney injury (AKI) is defined as any of the following: increase in serum creatinine (SCr) by ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 h; or increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 mL/kg/h for 6 h.

Blood cultures were obtained from all patients on admission to the hospital. Blood cultures were performed for patients presenting with chills and shivering. Sputum or endotracheal aspirates were sent for identification of possible causative bacteria or fungi.

2.5. *Statistical analysis*

SPSS software for Windows (Version 11.5; SPSS Inc., Chicago, IL) was used for statistical analysis. Continuous variables were computed with standard methods and are presented as mean and standard deviations (SD) or medians (interquartile range, IQR). For categorical variables, the percentages of patients in each category were calculated.

3. Results

3.1. *Epidemiologic characteristics*

The epidemiologic characteristics of the 17 patients at presentation are shown in Table 1. In Patients 3, 7, 11 and 12, the diagnosis was confirmed by means of virus isolation. All the other diagnoses were confirmed by means of nucleic acid detection. The median age of the patients was 73 years (range, 27 to 88). Most confirmed cases occurred in males (76.5%), and 76.5% of the case patients were retirees. A total of 82.4% of the patients had one or more underlying medical conditions. Hypertension (58.8%) and diabetes (35.3%) were the most common underlying medical conditions. Four (23.5%) patients reported a history of recent live poultry exposure. The time of illness onset in nine (52.9%) patients was on or before the day when the first human infections with the novel influenza A/H7N9 virus were reported in Eastern China.

3.2. *Clinical and other features*

The most commonly reported symptoms were fever or history of fever (100.0%), followed by productive cough (47.1%), dry cough (35.5%), fatigue (17.6%) and sore throat (11.8%) (Table 1). Muscle pain, hemoptysis, runny nose and altered consciousness were reported in one patient, respectively. No patient had diarrhea, conjunctivitis, or a rash. Physical examination revealed crackles in 13 (76.5%) patients and wheezing in two (11.8%) patients on chest examination. Thirteen (76.5%) patients had dyspnea or respiratory distress, five (29.4%) had shock, and four (23.5%) had AKI. In all patients, there were marked abnormalities on chest radiography; involvement of both lungs was found by chest radiography in 14 (82.4%) patients at presentation. Bilateral ground-glass opacities and consolidation were the most common radiologic findings.

Table 1. Epidemiologic and clinical characteristics of the patients at presentation

Patient	Age, y/sex	Occupation	Time of illness onset	Underlying conditions	Exposure to poultry	Symptoms	Crackles	Shock	AKI	Abnormalities On chest radiography	Cause of death
1	87/M	Retiree	April 2	Smoker	No	Fever, fatigue, dyspnea	Yes	No	No	Both lungs	Hypoxemia
2	73/M	Farmer	March 31	None	Yes	Fever, dry cough, dyspnea	Yes	Yes	Yes	Both lungs	Hypoxemia
3	27/M	Butcher	February 27	Hepatitis B	No	Fever, productive cough	Yes	No	No	Both lungs	Hypoxemia
4	74/M	Retiree	April 5	HT, diabetes	Yes	Fever, fatigue, dry cough, dyspnea, alteredconsciousness	Yes	No	Yes	Both lungs	Multi-organ failure
5	49/M	Poultry worker	March 29	None	Yes	Fever, dyspnea, productive cough	Yes	No	No	Both lungs	Hypoxemia
6	77/M	Retiree	April 3	HT, CHD	Yes	Fever	Yes	Yes	No	Left lung	Hypoxemia
7	87/M	Retiree	February 19	HT, COPD	No	Fever, dyspnea, productive cough	Yes	No	No	Both lungs	Hypoxemia
8	63/M	Retiree	April 1	HT, diabetes	No	Fever, dyspnea	No	No	No	Right lung	Hypoxemia
9	51/F	Retiree	March 27	Diabetes	No	Fever, muscle pain, dry cough, dyspnea	Yes	Yes	No	Both lungs	Hypoxemia
10	67/F	Retiree	March 22	HT, CHD	No	Fever, dyspnea, productive cough	No	Yes	Yes	Right lung	Hypoxemia
11	63/M	Retiree	March 4	HT, smoker	No	Fever, dry cough, sore throat	No	Yes	No	Both lungs	Hypoxemia, AHF
12	74/M	Retiree	February 20	HT,CHD,COPD, diabetes, smoker	No	Fever, productive cough, sore throat, dyspnea	Yes	No	No	Both lungs	Hypoxemia
13	88/M	Retiree	April 10	HT, CHD, COPD, diabetes	No	Fever, productive cough, hemoptysis, fatigue, dyspnea	Yes	No	No	Both lungs	Multi-organ failure
14	83/F	Retiree	April 2	HT, diabetes	No	Fever, dry cough, dyspnea	Yes	No	No	Both lungs	Multi-organ failure
15	58/M	Worker	March 17	COPD, smoker, HT, hepatitis B	No	Fever, dyspnea, productive cough	Yes	No	Yes	Both lungs	Multi-organ failure
16	56/M	Retiree	April 2	None	No	Fever, dry cough	No	No	No	Both lungs	DIC, Shock
17	79/F	Retiree	April 11	CHD,COPD	No	Fever, productive cough, dyspnea, runny nose	Yes	No	No	Both lungs	AHF

NOTE: HT, hypertension; COPD, chronic obstructive pulmonary disease; CHD, coronary heart diseases; AHF: acute heart failure; AKI: acute kidney injury; DIC, disseminated intravascular coagulation

3.3. *Laboratory and microbiologic assessment*

The laboratory values of the 17 patients at presentation are shown in Table 2. Leukopenia was found in five (29.4%) patients, 17 (100.0%) had lymphopenia, two (11.8%) had neutropenia, and eight (47.1%) patients had thrombocytopenia. The ratios of CD4-positive cells to CD8-positive cells in Patients 2, 11, 13, 15, 16 and 17 were 8.8, 0.75, 2.04, 2.29, 3.10 and 2.20, respectively.

Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatinine levels were elevated in seven (41.2%), 14 (82.4%) and five (29.4%) of the 17 patients, respectively. Measurements of creatine kinase (CK) and lactate dehydrogenase (LDH) levels at presentation were available in 16 patients. CK levels were elevated in 12 (75.0%) of the 16 patients. LDH levels were elevated in 16 (100%) of them. C-reactive protein (CRP) levels were available in 13 patients and were elevated in 12 (92.3%) of them.

Blood cultures in Patient 6 were positive for *Candida albicans*, all the other blood cultures were negative. Sputum cultures on admission were all negative.

3.4. *Diagnosis and treatment*

The diagnosis and treatment of the patients with avian influenza A (H7N9) are summarized in Table 3. The median time from onset of symptoms to first medical care was two days (range, 0 to 5). Fifteen (88.2%) patients were hospitalized. The median time from illness onset to hospitalization was six days (range, 2 to 19). Eleven (64.7%) patients were admitted to the ICU (intensive care unit). The median time from illness onset to ICU admission was six days (range, 5 to 21). Patients 3 and 7 were the first two cases confirmed on March 31, 2013. The time from illness onset to diagnosis confirmation was 31 days in Patient 3 and 39 days in Patient 7. Patients 11 and 12 were retrospectively confirmed cases. The time from illness onset to diagnosis confirmation was 40 days in Patient 11 and 52 days in Patient 12. Among the other 13 patients, the median time from illness onset to diagnosis confirmation was six days (range, 5 to 21). Among all 17 patients, the median time from illness onset to diagnosis confirmation was six days (range, 5 to 52).

Sixteen (94.1%) patients were treated with the neuraminidase (NA) inhibitor oseltamivir. The median time from illness onset to oseltamivir treatment was six days (range, 2 to 19). Only two (12.5%) patient received oseltamivir within 48 h after illness onset. The median duration of oseltamivir treatment was six days (range, 1 to 30). The median dosage of oseltamivir was 150 mg per day (range, 150 to 300).

The duration of viral shedding after oseltamivir treatment was 9 days, ≥ 6 days, ≥ 13 days, 29 days, 30

Table 2. Laboratory values at presentation

Variable	Patient																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Leukocyte (per mm^3)	5380	5410	2100	2700	2900	7100	4670	5620	3290	3680	6210	7110	7050	4500	5380	5480	6590
Lymphocyte (per mm^3)	410	360	230	410	700	380	530	1490	180	210	750	170	840	410	130	1140	260
Neutrophil (per mm^3)	4330	4890	1900	2620	2000	6560	4110	3430	3040	2140	5270	6810	5870	4030	5090	3730	6190
Platelet (10^3 per mm^3)	186	71	58	192	71	102	78	94	155	162	390	67	166	121	75	137	79
Hemoglobin (g/liter)	110	147	143	124	168	149	131	118	136	131	114	129	135	113	119	130	129
CK (U/liter)	1883	170	2932	3889	1600	681	501	537	351	54	187	811	391	NA	772	290	170
LDH (U/liter)	911	886	1683	NA	2150	640	480	433	525	444	620	651	505	1529	906	146	1218
Creatinine (μmol/liter)	81.6	159.6	53	195	116	81	73	102	33	611	51	102	106.2	55	176.4	88.7	150.8
ALT (U/liter)	27	20	71	103	76	132	31	54	80	33	34	33	41	54	35	25	37
AST (U/liter)	110	86	156	519	258	239	77	159	100	38	57	35	57	137	74	19	202
CRP (mg/liter)	194	47	32	160	NA	192	114	NA	NA	4	134	220	196	NA	80.5	115	114
CD4:CD8 ratio	NA	8.80	NA	NA	NA	NA	NA	NA	NA	NA	0.75	NA	2.04	NA	2.29	3.10	2.20
Myoglobulin (ng/ml)	270	NA	119	NA	442	391	NA	229.4	54	NA	NA	NA	NA	NA	232	313	231
BNP (pg/ml)	1524	NA	158	301	871	423	7480	NA	327	NA	3000	10300	NA	NA	1309	194	7286
Serum amylase(U/liter)	198	NA	NA	240	74	NA	NA	NA	NA	NA	224	NA	122	NA	204	NA	76
Blood culture	–	–	–	–	–	CA	–	–	–	–	–	–	–	–	–	–	–
Sputum culture	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

NOTE: ALT, alanine aminotransferase; LDH, serum lactate dehydrogenase; AST, aspartate aminotransferase; CK, serum creatine kinase; CRP, C-reactive protein; BNP, brain natriuretic peptide; CA: *Candida albicans*; NA, not available; A plus sign denotes positive, and a minus sign negative.

Table 3. Diagnosis and treatment of patients infected with avian influenza A (H7N9) virus

Variable	Patient																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Days from onset of symptoms to first medical care	4	0	5	0	5	2	4	2	1	2	3	5	0	0	3	0	4
Hospitalization	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Days from illness onset to hospitalization	8	6	5	5	N/A	4	7	N/A	6	9	5	7	2	5	19	2	6
ICU admission	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Days from illness onset to ICU admission	8	6	7	5	N/A	N/A	8	N/A	N/A	9	N/A	N/A	6	5	21	6	6
Days from illness onset to diagnosis confirmation	8	6	31#	5	5	5	39#	6	5	10	40*	52*	6	8	21	6	5
Oseltamivir treatment	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Days from illness onset to oseltamivir treatment	8	5	7	4	N/A	5	7	2	3	8	6	7	6	7	19	2	5
Duration of oseltamivir treatment	9	5	4	2	N/A	6	6	4	1	11	2	4	13	7	29	30	21
Dosage of oseltamivir treatment (mg/d)	150	150	150	300	N/A	300	150	150	150	300	150	300	300	150	150	150	150
Days of viral shedding after oseltamivir treatment	9	≥ 6	NA	NA	N/A	NA	NA	NA	NA	NA	NA	NA	≥ 13	NA	29	30	21
Oxygen therapy on admission	Yes	Yes	No	Yes	N/A	No	Yes	N/A	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Mechanical ventilation on admission	Yes	Yes	No	Yes	N/A	No	Yes	N/A	Yes	Yes	No	Yes	No	Yes	Yes	No	No
Non-invasive mechanical ventilation during follow-up	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Invasive mechanical ventilation during follow-up	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ECMO during follow-up	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	Yes	Yes	No
Renal failure any time during follow-up	No	Yes	No	Yes	No	No	No	No	No	Yes	No	No	Yes	Yes	Yes	No	No
Continuous renal replacement therapy	No	No	No	Yes	No	No	No	No	No	Yes	No	No	Yes	Yes	Yes	No	No
Use of antibiotics before admission	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Use of antibiotics during hospitalization	Yes	Yes	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Use of corticosteroids any time during follow-up	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Intravenous immunoglobulin any time during follow-up	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vasopressors any time during follow-up	No	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	No	No	No
Days from onset of symptoms to death	19	11	11	6	5	11	13	6	7	22	8	11	19	38	75	85	109

NOTE: NA, not available; N/A, not applicable; # the first two cases; *cases confirmed retrospective; ECMO: extracorporeal membrane oxygenation.

days and 21 days in Patients 1, 2, 13, 15, 16 and 17, respectively. Influenza A (H7N9) RNA was detected in the clinical specimens using real-time reverse transcription polymerase chain reaction (rRT-PCR) 6 days and 13 days after oseltamivir treatment was intiated in Patients 2 and 13, respectively. The patients' samples were still positive for influenza H7N9 virus when the two patients died. Among the six patients for whom the duration of viral shedding was available, the median duration of viral shedding after oseltamivir treatment was 17 days.

Among the 15 hospitalized patients, 12 (80.0%) required oxygen therapy, and nine (60.0%) required mechanical ventilation on admission.

Fifteen (88.2%) patients were treated empirically with broad-spectrum antibiotics both before admission and during hospitalization. Sixteen (94.1%) patients received methylprednisolone during follow-up. Thirteen

(76.5%) patients received treatment with intravenous immunoglobulin, and vasopressors were used in eight (47.1%) patients during follow-up. Patients 2, 4, 10, 13, 14 and 15 developed renal failure during follow-up, and Patients 4, 10, 13, 14 and 15 received continuous renal replacement therapy.

The median time from onset of symptoms to death was 11 days (range, 5 to 109). Refractory hypoxemia accounted for most deaths (Table 1). Neither during the period when these patients were hospitalized nor subsequently was any illness reported in a health care worker or laboratory staff member.

4. Discussion

This report describes 17 fatal cases of human infection with avian influenza A (H7N9) virus in Shanghai. The investigation shows that the clinical and epidemiologic characteristics in the Shanghai fatal series of patients do not differ from larger reports of H7N9 patients in China (*2,5*). The majority of the patients were older men with preexisting medical conditions. The prominent clinical features on admission were those of a severe influenza syndrome with fever, cough, fatigue, and shortness of breath. The most striking laboratory findings were marked lymphopenia and thrombocytopenia. These clinical presentations were similar to those in the 2004 outbreak of influenza A (H5N1) in Vietnam, although diarrhea was a more prominent feature in the H5N1 patients (*6*). Our study shows that avian influenza A (H7N9) virus infection, characterized by multiple organ dysfunction, carries a high risk of death. The findings in this series of patients further demonstrates that novel H7N9 virus can cause severe and fatal disease in humans.

This investigation reflects a delay in the diagnosis of H7N9 patients in Shanghai. The H7N9 subtype virus has not been known to infect humans until only recently. A delayed diagnosis may be due to a weak knowledge among medical staff and the general public towards H7N9 virus associated diseases. This delay may compromise early management of patients with avian influenza A (H7N9).

This investigation also reflects a significant delay in antiviral treatment of H7N9 patients. Our previous report found that the risk of death was increased among H7N9 patients in whom antiviral therapy was initiated more than five days after illness onset (*5*). Our previous study also showed that the median time from the initiation of antiviral therapy to a negative test result on daily real-time RT-PCR assay was six days (*5*). In the current study, the median duration of viral shedding after oseltamivir treatment was 17 days. A study showed that reduction of viral load following antiviral treatment correlated with improved outcome of H7N9 patients (*7*). A study on timing of oseltamivir administration and outcomes in hospitalized adults with pandemic 2009 influenza A (H1N1) virus infection showed that time from onset of symptoms to oseltamivir administration was associated with a prolonged duration of fever, prolonged hospital length of stay, and higher mortality (*8*). A similar study showed that early oseltamivir treatment as an independent variable associated with reduced ICU mortality in critically ill patients with 2009 pandemic influenza A (*9*). Together with our study, these findings suggest that late antiviral treatment and a long duration of viral shedding may be associated with a fatal outcome in our case series. Therefore, early treatment of suspected or confirmed cases of avian influenza A (H7N9) is strongly recommended.

Most patients received methylprednisolone during follow-up in the current study. A study showed that emergence of NA Arg292Lys mutation in two avian influenza A (H7N9) patients who also received corticosteroid treatment led to treatment failure and a poor clinical outcome (*7*). The emergence of antiviral resistance in H7N9 viruses, especially in patients receiving corticosteroid therapy, is a concern. Controlled clinical studies are needed to assess the role of corticosteroids in the treatment of influenza A (H7N9) virus infections.

More aggressive treatments including oxygen therapy, mechanical ventilation, intravenous immunoglobulin, vasopressors, and continuous renal replacement therapy, have been used in patients with illness of greater severity. Most patients were treated empirically with broad-spectrum antibiotics. Antibiotic chemoprophylaxis should not be used where bacterial infection is not suspected. However, when pneumonia is present, antibiotic treatment is appropriate initially for community-acquired pneumonia.

There are some limitations to this study. First, the small case number prevents us from drawing any more conclusions. The study population is not representative of the entire H7N9 population and the results may not be generalizable. Second, the design of the study was observational, we were able to examine potential associations but were unable to assess causation. Further prospective clinical studies are needed for a better understanding of avian influenza A (H7N9) deaths.

In conclusion, the investigation shows that the clinical and epidemiologic characteristics in a Shanghai fatal series of patients do not differ from other reports of H7N9 patients in China. This investigation reflects a delay in the diagnosis and antiviral treatment of H7N9 patients in the early stage of the epidemic in Shanghai. Late antiviral treatment and a long duration of viral shedding may be associated with a fatal outcome in these patients. Strategies to facilitate rapid identification of cases and early antiviral treatment are urgently required.

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