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Concomitant severe influenza and cryptococcal infections

A case report and literature review

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Abstract

Background: Concomitant influenza and cryptococcal infections are rare. Herein, we describe an unusual case of an avian influenza A (H7N9) infection with several severe mixed bacterial infections and systemic super-infection with *Cryptococcus neoformans* presenting as ventilator-associated pneumonia (VAP) and bloodstream infection in a previously immunocompetent man during hospitalization.

Case presentation: A 58-year-old man was admitted to our hospital complaining of hyperpyrexia, dyspnoea, cough, and phlegm with blood. A chest computed tomography scan revealed multiple ground-glass opacities and consolidation in both lungs with right pleural effusion. An initial sputum test was positive for influenza A (H7N9) virus. After antiviral treatment and other supportive measures, the patient's condition improved. However, the patient's condition deteriorated again approximately 2 weeks after admission, and bronchoalveolar lavage fluid (BALF) and blood cultures were positive for *C. neoformans*. Therapy with intravenous liposomal amphotericin B and fluconazole was started. After a 2-week antifungal treatment, BALF and blood cultures were negative for *C. neoformans*. However, the patient had persistent lung infiltrates with severe pulmonary fibrosis with a prolonged course of disease. On hospital day 40, BALF and blood cultures were both positive for multidrug-resistant *Stenotrophomonas maltophilia*. Finally, the patient developed septic shock, disseminated intravascular coagulation and multi-organ failure and succumbed to treatment failure.

Conclusion: Cryptococcal infection can occur in patients with severe influenza during hospitalization with a more severe condition, and the clinician should be aware of this infection.

Abbreviations: ARDS = acute respiratory distress syndrome, BALF = bronchoalveolar lavage fluid, CAP = community-acquired pneumonia, CRP = C-reactive protein, CRRT = continuous renal replacement therapy, CT = computed tomography, DIC = disseminated intravascular coagulation, ECMO = extracorporeal membrane oxygenation, G = glucan, GM = galactomannan, HAP = hospital-acquired pneumonia, HIV = human immunodeficiency virus, IC = immunocompromised, IFN-γ = interferon gamma, IL = interleukin, LA = latex agglutination, LFA = lateral flow assay, LPM = live poultry market, MOF = multi-organ failure, MRSA = methicillin-resistant *Staphylococcus aureus*, MRSH = *Staphylococcus haemolyticus*, mTOR = mammalian target of rapamycin, NK = natural killer, $PaCO_2$ = pressure of carbon dioxide, PaO_2 = pressure of oxygen, PCT = procalcitonin, RICU = respiratory intensive care unit, RT-PCR = reverse transcription polymerase chain reaction, SMA = *Stenotrophomonas maltophilia*, Th = helper T, VAP = ventilator-associated pneumonia, VILI = ventilator-induced lung injury.

Keywords: avian, *Cryptococcus neoformans*, H7N9, influenza virus, ventilator-associated pneumonia

1. Background

Infections due to *Cryptococcus* species occur globally and can affect both immunocompromised (IC) and non-IC hosts.[1] To date, many cases of cryptococcal infection have been reported,[2–5] but only 3 cases of concomitant severe influenza and cryptococcal infections have been mentioned in the English and Chinese literature.[6–8] Herein, we describe an unusual case of an avian influenza A (H7N9) infection with several severe mixed bacterial infections and systemic super-infection with

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Cryptococcus neoformans presenting as ventilator-associated pneumonia (VAP) and bloodstream infection in a previously immunocompetent man during hospitalization. There is no report in the literature of concomitant infections of H7N9-influenza and disseminated cryptococcosis.

2. Methods

We describe the data of the case and extensively discuss the relation between severe influenza and cryptococcal infections during hospitalization. This study was approved by the ethics committee of Fuzhou Pulmonary Hospital of Fujian. Informed consent was obtained from a relative of the patient in the study.

3. Case presentation

On January 15, 2016, a 58-year-old man was admitted to our respiratory intensive care unit (RICU) complaining of hyperpyrexia for 7 days and dyspnoea, cough and phlegm with blood for 2 days. The patient had a history of hypertension for 2 years. His travel history revealed that he bought a chicken from a local live poultry market (LPM) and had poultry-related exposure 7 days before his symptom onset. The patient was diagnosed with community-acquired pneumonia (CAP) and was given antibacterial therapy alone for several days in a local community hospital; however, his condition failed to improve. A week after symptom onset, a chest computed tomography (CT) scan was obtained and revealed multiple ground-glass opacities and consolidation in both lungs with right pleural effusion (Fig. 1). Then, he was transferred to our hospital. The laboratory results showed increased C-reactive protein (CRP, >200 mg/L) and procalcitonin (PCT, 9.9 ng/mL) levels. Leukopenia and lymphopenia with significantly reduced T lymphocyte subgroups including CD3, CD4, and CD8 T cells in peripheral blood were also noted upon admission. A human immunodeficiency virus (HIV) antibody test was negative. Arterial blood gas analysis showed a pH of 7.46, a partial pressure of carbon dioxide ($PaCO_2$) of 24.5 mm Hg, and a partial pressure of oxygen (PaO_2) of 46.1 mm Hg while receiving 10 L/min inspired oxygen with a partial rebreathing mask. A bedside chest X-ray revealed multiple infiltrates in both lungs (Fig. 2). Severe acute respiratory distress

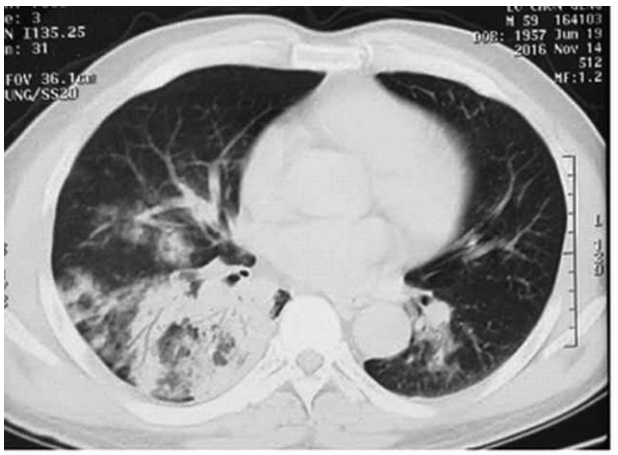

Figure 1. Chest computed tomography (CT) scan revealing multiple ground-glass opacities and consolidation in both lungs with right pleural effusion.

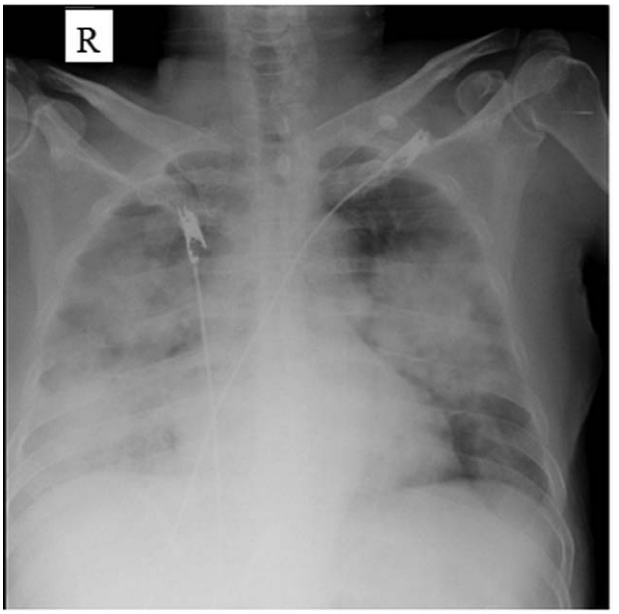

Figure 2. Chest X-ray revealing multiple infiltrates in both lungs.

syndrome (ARDS) led to endotracheal intubation and mechanical ventilation on the first day of hospitalization (Table 1), and initial antibiotic treatment with moxifloxacin and cefoperazone-sulbactam along with corticosteroids and continuous renal replacement therapy (CRRT) were also initiated. Then, the result of an initial sputum test obtained upon admission, which was performed as a qualitative assay and confirmed by the Fuzhou City Centre for Disease Control and Prevention, was positive for influenza A (H7N9) virus and negative for other prevalent strains of influenza by reverse transcription polymerase chain reaction (RT-PCR). Conversely, bacterial and fungal cultures of the patient's sputum and bronchoalveolar lavage fluid (BALF) were negative. He was diagnosed with avian influenza A (H7N9), and antiviral therapy with oseltamivir (150 mg twice daily) was immediately started. However, ARDS still progressively developed despite the treatment of lung recruitment and prone-position ventilation with a need for high pressure and F_iO_2 ventilation (Table 1), and veno-venous extracorporeal membrane oxygenation (ECMO) was required and started on hospital day 4 (11 days after symptom onset) because of the failure of invasive mechanical ventilation. Meanwhile, blood culture yielded *Staphylococcus haemolyticus* (MRSH) with a significant rise in PCT (85.0 ng/mL), suggesting bloodstream infection with MRSH, and vancomycin was started. Due to severe mixed infection and the use of ECMO, he was also administered imipenem/cilastatin and caspofungin at the same time. During this period, the BALF also yielded *Pseudomonas aeruginosa*. After this treatment, the serum levels of CRP and PCT gradually improved and decreased to normal levels, and a chest X-ray revealed an improvement of infiltrates in both lungs (Fig. 3). However, subcutaneous and mediastinal emphysemas emerged on hospital day 10; then, the ventilator parameters were decreased (Table 1), and the emphysemas were significantly relieved. BALF was retested on hospital day 14 (21 days after symptom onset), but the result was still positive for influenza A (H7N9) virus. On hospital day 16, the patient's condition

Table 1

Major ventilator settings and monitoring data and serial changes during RICU stay and ventilator support.

Hospital stay (days)	Major ventilator settings		Major monitoring data of the patient		
	IPAP (cmH_2O)	PEEP (cmH_2O)	TV (mL)	PIP (cmH_2O)	PaO_2 (mmH_2O)
1	20	18	400	32	44
2	20	20	380	31	39
3	18	20	370	31	40
4	15	15	330	31	70*
5	15	15	400	32	72
6	15	15	400	33	63
7	15	15	500	33	67
8	15	18	420	32	74
9	14	16	300	30	67
10	19	6	450	27	63†
11	19	6	400	26	66
12	19	6	600	30	63
13	20	6	350	27	70
14	16	6	320	26	66
15	18	6	300	28	54
16	18	7	350	30	49‡
17	20	7	250	27	45
18	25	6	300	26	51
19	32	10	150	33	53
20	32	10	150	37	51
21	35	10	150	37	61
22	32	9	140	38	41
23	32	9	150	38	42
24	32	9	200	35	50
25	32	8	230	34	50
26	32	10	160	34	43
27	32	10	160	36	46
28	32	10	130	38	54
29	32	10	130	38	46
30	32	10	130	37	40
31	32	10	160	35	47
32	32	10	220	32	40
33	20	10	200	35	42
34	20	10	200	35	41
35	20	13	170	36	43
36	20	13	160	34	44
37	20	13	160	34	45
38	21	13	260	32	45
39	19	15	170	32	41
40	20	12	200	32	43
41	19	12	180	33	46
42	19	15	200	36	45
43	19	15	200	35	44
44	23	12	200	35	46
45	23	12	200	34	44
46	23	12	180	32	49
47	23	12	190	32	43§

IPAP = inhale positive airway pressure, PEEP = positive end expiratory pressure, PIP = peak inflation pressure, TV = tidal volume.

* The start of ECMO support.

† The emergence of subcutaneous and mediastinal emphysemas.

‡ The super-infection of *C. neoformans*.

§ The date of death.

deteriorated again. A chest X-ray revealed the rapid progression of infiltrative lesions in both lungs (Fig. 4). Both a 1,3-β-D-glucan (G) test and a galactomannan (GM) test were negative. The patient was considered to have new bacterial co-infections, and several strong antibacterial drugs were successively administered

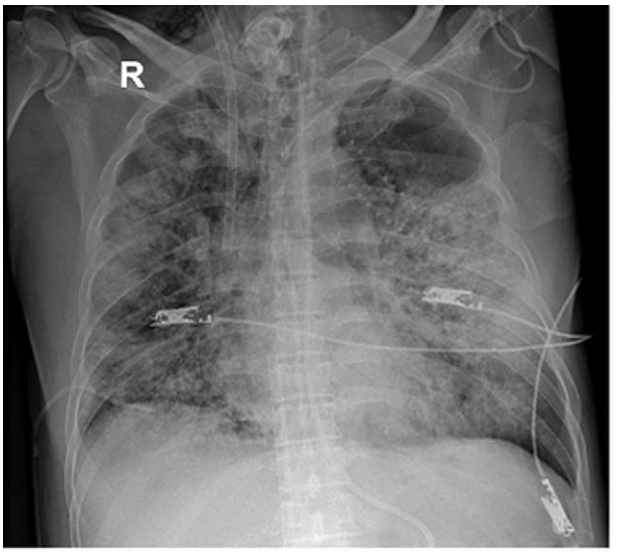

Figure 3. Chest X-ray revealing an improvement of infiltrates in both lungs.

for treatment of the aggravated infection without improvement. On hospital day 23, BALF and blood cultures were positive for *C. neoformans* (Fig. 5A, B, C, and D). The *C. neoformans* strain is sensitive to flucytosine, fluconazole, voriconazole, amphotericin B, and itraconazole. A serum cryptococcal capsular polysaccharide antigen test by lateral flow assay (LFA), which was performed as a qualitative assay, was positive. The patient was diagnosed with disseminated cryptococcal infection involving the lungs and bloodstream. Caspofungin was ceased, and intravenous liposomal amphotericin B (1 mg/kg of body weight) and fluconazole were started. Meanwhile, examinations of possible exogenous sources of cryptococcal infection, including various examination and treatment equipment (fibre bronchoscope, breathing machine, etc), indoor air and respiratory tract specimens from the other inpatients in the same period in RICU,

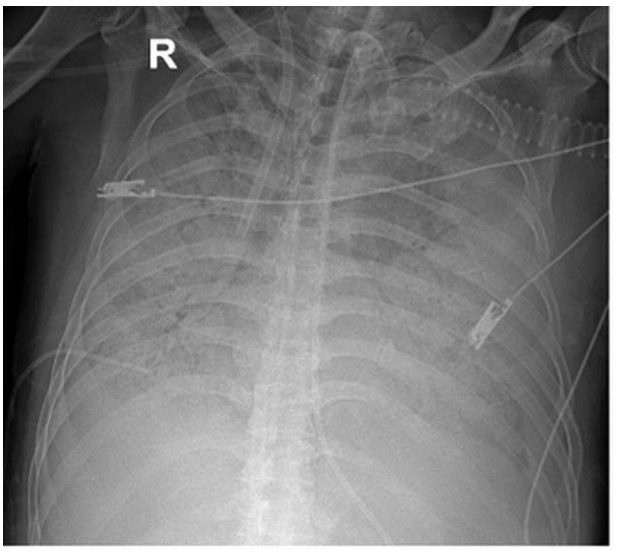

Figure 4. Chest X-ray revealing a rapid progression of infiltrative lesions in both lungs.

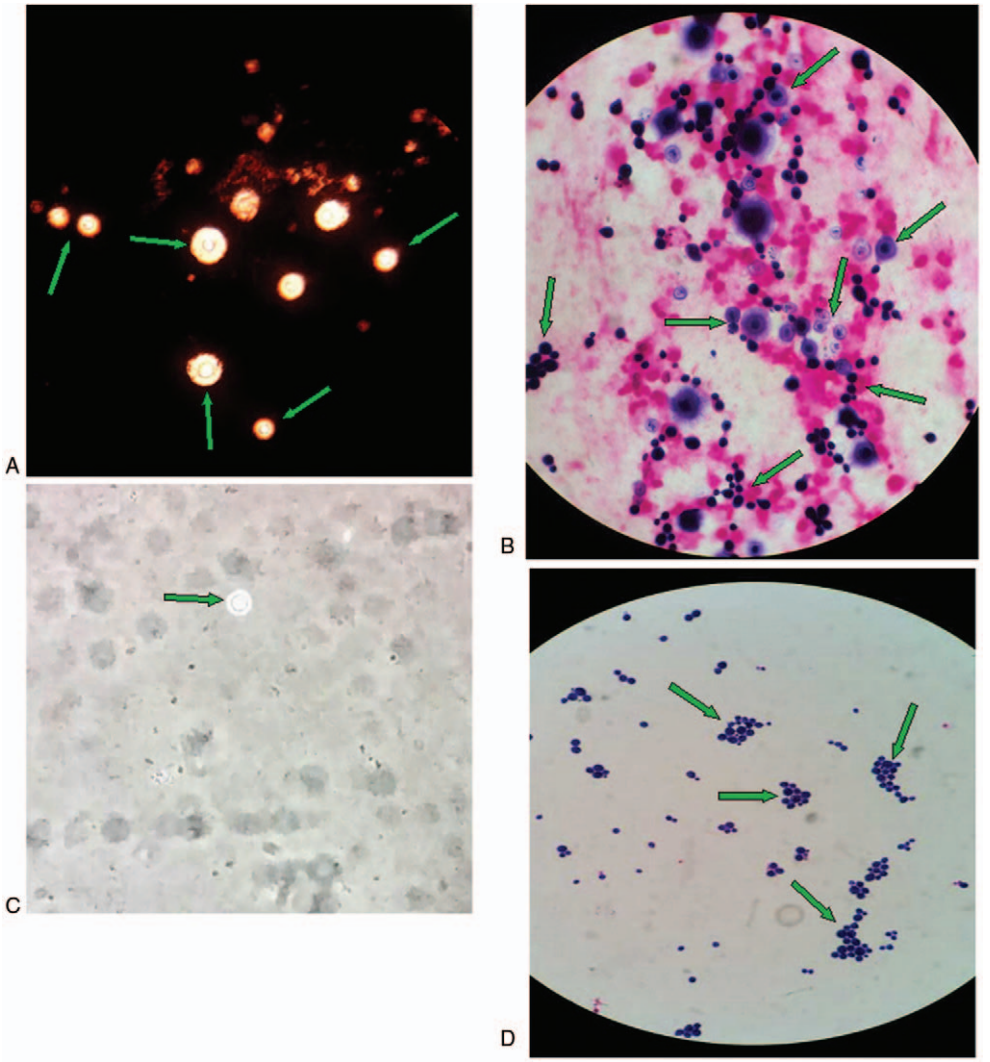

Figure 5. The findings for bronchoalveolar lavage fluid (BALF) culture specimens and blood culture specimens under oil immersion lenses. A: India ink examination of a BALF specimen demonstrating typical transparent thick capsule *Cryptococcus* spores (green arrows); B: Gram's stain smear of a BALF sample showing the yeast form of *C. neoformans* and that the capsules could be stained and found in some of them (green arrows). C: India ink examination of a blood specimen demonstrating the typical transparent thick capsule *Cryptococcus* spore (green arrow); D: Gram's stain smear of pure fungal colonies cultured from a blood sample showing *C. neoformans* without staining of the capsule (green arrows).

were performed, but the results were negative for *Cryptococcus* species. On hospital days 19 and 20 (26 and 27 days after symptom onset, respectively), BALF specimens were tested again, and the results were negative for influenza A (H7N9) virus. After a 2-week antifungal treatment, BALF and blood cultures were negative for *C. neoformans*. However, the patient had persistent lung infiltrates with progressive pulmonary fibrosis, and ventilator monitoring data showed a constant decrease in tidal volume (Table 1). On hospital day 40, BALF and blood cultures were both positive for multidrug-resistant *Stenotrophomonas maltophilia* (SMA). The patient's condition deteriorated, despite strong anti-infective therapy, with progressively increasing PCT from 1.7 to 20.7 ng/mL due to the new aggravated infection with SMA involving the lungs and bloodstream. Finally, the patient developed septic shock, disseminated intravascular coagulation (DIC) and multi-organ failure (MOF) and died on hospital day 47 (54 days after symptom onset).

4. Conclusion

In this study, the patient was diagnosed with H7N9-influenza first and then had complications with several severe bacterial mixed infections and disseminated cryptococcosis presenting as VAP and bloodstream infection with severe ARDS. This report showed that cryptococcal infection can occur in a patient with severe influenza during hospitalization with a severe condition, with the exception of the common emergence of bacterial co-infection.

5. Discussion and literature review

Generally, the fungal pathogens that cause super-infections are predominantly *Candida* spp. and *Aspergillus* spp., which are most commonly isolated in patients with influenza infection,[9–16] but *C. neoformans* has rarely been reported in such patients. Cryptococcosis is an invasive fungal infection that is more

common in immunocompromised (IC) hosts, while the principal predisposing factor is HIV infection.[17] The other susceptibility factors are the presence of long-term immunosuppressants or corticosteroid therapy, hematologic malignancies, severe diabetes mellitus, and other conditions that impair T cell mediated immunity.[18,19] In our case, there were several risk factors for cryptococcal infection after H7N9 virus infection. First, the BALF specimens were continuously positive for influenza A (H7N9) virus for more than 3 weeks after symptom onset despite antiviral treatment. A lengthy course of avian influenza virus infection may result in immunologic defects, impairment of normal ciliary function and leukopenia.[20] Usually, host defence against cryptococcal infection mainly depends on the host immune function and defensive response to infection,[21] and the cellular immune response is the main immune mechanism of cryptococcal infection control.[22,23] Previous reports have found that a prominent clinical feature of atypical influenza, including H7N9, H5N1, and H1N1, is lymphopenia,[24–26] which is similar to what occurred in our patient. Additionally, many studies of influenza infection have also revealed that the number of T lymphocyte subgroups, including CD3 cells, CD4 cells, CD8 cells, regulatory T (Treg) cells, helper T (Th) 17 cells, etc, declined dramatically,[27–30] along with alterations in the ratio of T cell subgroups, such as a decrease in CD4/CD8.[27,28] It has also been reported that the T lymphocyte subgroups including CD3, CD4, and CD8 T cells in peripheral blood and lung tissue were significantly decreased,[31] as well as peripheral blood monocytes,[32] natural killer (NK) cells, and NKT cells[28] being significantly reduced, suggesting a weakened immune status in patients with influenza infection. Furthermore, some antimicrobial cytokines such as interleukin (IL)-17 also decreased in influenza patients.[30] All the above studies indicated that obvious cellular immune dysfunction was primarily driven by viral-induced apoptosis of T lymphocytes,[31] which greatly increased the risk of cryptococcal infection and occurred in influenza patients, especially severe influenza patients. Second, in the early course, the patient's condition deteriorated progressively, and he developed severe ARDS requiring treatment with systemic steroids. Corticosteroid therapy should also result in an IC state and significantly increase the risk of fungal infection.[7,13,14] Finally, the use of several broad-spectrum antibiotics for the treatment of bacterial co-infection could cause bodily dysbacteriosis, which might result in secondary invasive fungal infection. Additionally, some studies described earlier found that *Cryptococcus* sp. invasion into the human body, including immunocompetent and immunosuppressive hosts, might also lead to Thl/Th2 cytokine imbalance; this imbalance presents as a decrease in Th1 cytokines, such as interferon gamma (IFN-γ), and enhancement of Th2 cytokines, such as IL-10, which is called "Th1/Th2 balance drift," with the domination of a Th2 cytokine response resulting in immune inhibition in the body, thus aggravating cryptococcal infection.[22,23,33] Due to all the risk factors mentioned above, a great potential possibility for the development of *C. neoformans* infection may occur in previously immunocompetent patients fatally infected with H7N9. Further studies are needed to clarify the complicated mechanisms of IC status after co-infection of atypical influenza and *C. neoformans* in the future.

Notably, *C. neoformans* usually causes a community-acquired infection; however, cryptococcal infection involving the lungs bilaterally and the bloodstream in our case occurred approximately 2 weeks after admission when the patient was treated by invasive mechanical ventilation with tracheotomy. There was no initial evidence of cryptococcal infection in our case, and the secondary fungal infection occurred more than 48 h after invasive mechanical ventilation during hospitalization, which was confirmed by positive cultures of *C. neoformans* from BALF and blood samples and positive results of serum cryptococcal antigen testing. There is no doubt that the present case was diagnosed as hospital-acquired cryptococcal infection, and cryptococcal pneumonia was considered as VAP according to the diagnostic criteria of VAP,[34] which was similar to what was observed in a previous report.[6] To date, a review of the medical literature revealed only 3 reported cases regarding concomitant hospital-acquired cryptococcal infection and severe influenza.[6–8] Adding our case to the review, the four cases are summarized in Table 2. All cases occurred in patients with severe influenza virus infection (2 cases with H1N1 and 2 cases with H7N9) from 7 to 25 days after admission. During the four patients' courses, there were 3 cases with cryptococcal pneumonia, 2 cases with cryptococcal fungemia, 1 case with cryptococcal pleurisy and 2 cases with cryptococcal meningitis, and 3 of them presented with disseminated cryptococcal infection. In the 3 cases with cryptococcal pneumonia, 1 case was diagnosed as hospital-acquired pneumonia (HAP), and 2 cases were VAP according to the diagnostic criteria of HAP and VAP.[34,35] As recognized, the pathogenic organisms of HAP and VAP are derived from either an endogenous or exogenous source.[35,36] Endogenous infection is the most frequent cause of HAP and VAP, and it can occur with either community-acquired or hospital-acquired pathogens that colonize the host.[37] Initial colonization of the respiratory tract with pathogens, especially colonization of the oropharynx, occurs most commonly.[37] Since *C. neoformans* is a ubiquitous organism that has a pulmonary portal of entry[38] and can persist in the human oropharynx on occasion, the pathogen may be an endogenous source of lung (aspiration) infections.[39] In our case, when cryptococcal infection occurred, examinations of possible exogenous sources of cryptococcosis in the RICU were performed, but the results were negative for *Cryptococcus* sp. There was no evidence for the pathogen from exogenous sources, such as medical equipment or other then-hospitalized patients. Therefore, the source of *C. neoformans* in our patient was considered to be from initial colonization of the respiratory tract before hospitalization. In general, *C. neoformans* is only conditionally pathogenic in healthy human hosts, but it causes important opportunistic infection in immunosuppressed hosts, as seen in the present patient.

In the early phase of the clinical course, due to severe mixed infection and the use of ECMO, the patient was treated with strong antibacterial drugs, while caspofungin was also used empirically for the treatment and prevention of *Candida* spp. infection, which is the most common invasive fungal infection.[40] Unfortunately, although caspofungin is an echinocandin antifungal agent that exhibits potent activity against most species of *Candida* and *Aspergillus*, *C. neoformans* is initially resistant to this antifungal drug.[41] Hence, the present antifungal therapy with an echinocandin drug for our patient failed to play a role in the timely and effective treatment of the subsequent *C. neoformans* infection, which was similar to what was observed in a previous report by Chen et al.[6] Due to the lack of awareness of hospital-acquired cryptococcal infection with delayed anti-Cryptococcus treatment, the cryptococcal infection in our case rapidly progressed and caused further injury to the lung tissue. Notably, in the patient, LFA was detected and

positive for cryptococcal antigen after the detection of *C. neoformans* in fungal cultures of blood and BALF. Actually, it has been reported that the serum cryptococcal antigen LFA has a very high accuracy for the diagnosis of cryptococcosis with a high level of agreement with latex agglutination (LA).[42] Thus, in such critically ill patients clinically suspected for invasive fungal infection, in addition to fungal culture and the conventional G and GM tests,[43] the cryptococcal capsular antigen test, which is conducive to early detection of cryptococcal infection and avoidance of delays in diagnosis and treatment, should be considered.

As observed in our patient, apart from systemic super-infection with *C. neoformans*, which obviously worsened the clinical condition, several mixed bacterial infections also occurred and had an important effect on the patient's prognosis. Generally, the most common pathogens of co-infection in patients with influenza infection are bacteria,[44] and super-infection with fungi is relatively less common. Many reports have shown that gram-positive cocci, which are predominantly *Staphylococcus aureus*, including methicillin-resistant *S aureus* (MRSA), *Streptococcus pneumoniae*, and *Streptococcus pyogenes*, were most commonly isolated in patients with influenza infection,[12,44–48] and gram-negative cocci, which were predominantly *Acinetobacter baumannii*, *P aeruginosa*, *Haemophilus influenzae*, and *Klebsiella pneumoniae*, were also commonly observed in influenza patients.[9,25,49,50] In our case, the pathogens causing bacterial co-infection were similar to those observed in the literature. MRSH was isolated at the early stage of influenza infection, and the subsequent isolated bacterial strains were *P aeruginosa* and SMA during prolonged invasive ventilator and ECMO support. The severe systemic infection of multidrug-resistant SMA occurred in the late course and obviously worsened the patient's condition, which was the main factor of death.

With respect to the infection chain of H7N9 influenza in the present case, a history of direct contact with live poultry in a local LPM before illness onset was considered to be the source of H7N9 influenza virus. As recognized, a majority of infected persons with the new H7N9 influenza A virus have live poultry exposure history before showing symptoms.[51] LPMs seem to have served as the main places where the H7N9 virus originally mutated, spread and thus infected human beings,[51,52] as observed in our patient. Since patients with influenza infection can deteriorate with ARDS in a short time,[26] it is necessary to provide effective therapy including antiviral drugs and other necessary medical measures as soon as possible to laboratory-confirmed influenza patients and highly suspected influenza patients, especially those with direct exposure to poultry. Thus far, the most vital therapeutic of atypical influenza infection is antiviral treatment with neuraminidase inhibitors, such as oseltamivir and peramivir, within 48 h after the onset of illness.[53,54] Severely ill patients with influenza infection still need to be treated with antiviral drugs even more than 48 h after onset.[53] Notably, a novel possible treatment method of influenza infection with a mammalian target of rapamycin (mTOR) inhibitor has been reported in recent years.[55,56] Wang et al found that oseltamivir combined with early adjuvant treatment with corticosteroids and an mTOR inhibitor (sirolimus) was associated with decreased viral titre and improvement in respiratory function in patients with severe H1N1 pneumonia.[55] Jia et al also reported that combined oseltamivir treatment with sirolimus as an adjuvant may be a promising immunomodulatory strategy for managing severe influenza by inhibiting lung immunopathologic injury.[56] However, some studies with different results showed that sirolimus treatment increased disease severity after influenza infection due to impairing virus clearance, suppressing T cell immunity and worsening lung inflammation.[57,58] Indeed, irrespective of whether an immunoregulator is being used or not, timely treatment with effective etiotropic antiviral drugs such as oseltamivir to depress viral load and reduce virus-induced cell death is always necessary during treatment of influenza infection.[56] It is well known that the use of immunosuppressant drugs such as sirolimus must be conducive to achieving homeostasis of the immune response, which not only inhibits an excessive immune response but also does not impede cellular and humoural responses to promote virus clearance.[56] Therefore, treatment of influenza with rapamycin inhibitor must be based on sufficient antiviral treatment, and we think it would be the best to administer a joint antiviral therapy such as oseltamivir in combination with one of the other direct-acting antiviral drugs that is proven safe and more effective than the use of a single drug such as oseltamivir monotherapy; moreover, the clinician must try to choose an appropriate window when the inflammatory response is particularly strong to administer the immunosuppressive medicine. Nonetheless, more data from animal and human studies of severe influenza infection are clearly needed before a rapamycin inhibitor (sirolimus or everolimus) can be recommended for the treatment of patients with severe influenza.[59]

Additionally, the emergence of prolonged viral replication despite antiviral treatment with oseltamivir after admission was another remarkable phenomenon in our patient. Previous studies have shown that prolonged viral infection can occur in patients with severe avian influenza A (H7N9) despite antiviral treatment,[60–63] and this effect might occur for up to 30 days,[63] which is similar to what was observed in our case. A recent multicentre study suggested that corticosteroid therapy and delayed antiviral treatment were associated with prolonged influenza A

Table 2

Literature review: concomitant severe influenza and cryptococcal infections.

References	Nation	Age, year/sex	Underlying disease	Type of influenza	Location of cryptococcal infection	Time of cryptococcal infection	Type of cryptococcal pneumonia	Prognosis
[6]	China	80/M	None	H7N9	Lung	25 days after admission	VAP	Died
[7]	America	52/M	None	H1N1	Brain and blood stream	25 days after admission	None	Recovered
[8]	India	34/M	HIV infection and history of PTB	H1N1	Lung, brain and pleura	7 days after admission	HAP	Died
Present case	China	58/M	Hypertension	H7N9	Lung and bloodstream	16 days after admission	VAP	Died

HAP = hospital-acquired pneumonia, HIV = human immunodeficiency virus, M = male, PTB = pulmonary tuberculosis, VAP = ventilator-associated pneumonia.

(H7N9) RNA shedding,[63] as observed in our patient. Wang et al reported that influenza A (H7N9) RNA shedding was shorter in survivors than in patients who died[63] and that there was an increase in the mortality hazard rate with each day of delay in initiation of treatment up to day 5 when compared with treatment initiated within 2 days of symptom onset.[64] In the present patient, the resulting continuous viral replication with ARDS as well as prolonged mechanical ventilation with ventilator-induced lung injury (VILI) caused severe pulmonary fibrosis and significantly prolonged the course of the disease.[61] During this period, the emergence of fatal fungal and bacterial co-infections might also have contributed to diffuse lung injury and result in progressive deterioration of the patient's condition. Although the treatment of secondary disseminated cryptococcal infection was considered successful, in the late course, the patient still succumbed to fatal multidrug-resistant bacterial mixed infection with severe septic shock, which was considered to be the only independent risk factor for mortality in H7N9 patients.[65] Due to the importance of early antiviral treatment, it is vital for clinicians to recognize the disease induced by avian influenza A (H7N9) virus and provide effective antiviral treatment early on. The early control of viral infection can be beneficial to shorten the course of the disease and to avoid mixed infection of highly resistant bacteria and fungi, which are associated with an increased risk of death.[62] Additionally, corticosteroids should be avoided except in clinical situations where they have proven benefit.[63]

In conclusion, cryptococcal infection can occur not only in the community but also in IC patients during hospitalization, especially in patients with severe influenza virus infection. Since patients with hospital-acquired cryptococcal infection (especially VAP and disseminated cryptococcosis) usually have a severe condition with high mortality,[6,7] the clinician should be aware of this infection and try to avoid a missed diagnosis. Unfortunately, in our case, successful therapy for the cryptococcal infection did not reverse the increased predisposition to secondary fatal bacterial co-infection due to progressive pulmonary fibrosis with a prolonged course of the disease. Finally, the patient succumbed to severe septic shock, DIC and MOF.

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Author contributions

Conceptualization: Heng Weng.
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Writing – original draft: Jinbao Huang, Hongyan Li, Changqing Lan.
Writing – review & editing: Heng Weng.

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