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Glucocorticoid treatment of suspected organizing pneumonia after H7N9 infection

A case report

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Abstract

Rationale: H7N9 infection causes acute respiratory distress syndrome with high mortality. The use of glucocorticoids in the acute phase lessened inflammatory responses. Some case reports suggested that secondary organizing pneumonia (SOP) could occur at the recovery stage of the influenza virus infection, and the treatment with glucocorticoid was effective. However, the reports of organizing pneumonia after H7N9 infection are lacking. This study reported a patient with H7N9 virus infection who presented a suspected SOP during the recovery stage.

Patient concern: A 68-year-old woman who was diagnosed with H7N9 viral pneumonia. After standard antiviral treatment, venous-venous extracorporeal membranous oxygenation (VV-ECMO) and other supportive treatment, the antigen in the alveolar lavage fluid turned negative, and the shadow in the lung was partially absorbed. However, the imaging manifestations were deteriorated at 3 weeks after disease onset, presented as exudation and consolidation shadow distributed under the pleura and along the bronchial vascular bundles. The oxygenation could not be improved. Repeated sputum, alveolar lavage fluid, and blood pathogen examinations showed negative results. Broad-spectrum anti-infective treatment was ineffective. However, the autoantibodies (ANA, anti-SSA/Ro60, anti-SSA/Ro52) were detected.

Diagnosis: SOP was considered.

Interventions: Glucocorticoid treatment begun at week 4 from the disease onset. The regimen was methylprednisolone at an initial dose of 40 mg twice a day for 1 week, tapering within 70 days until total withdrawal.

Outcomes: The oxygenation was rapidly improved after initiation of methylprednisolone. The shadow in the lung gradually resolved, and the patient was discharged after improvement of the disease condition. The clinical disease course, imaging findings, and treatment effects in the previous cases of SOP after influenza virus infection were similar to those in this case, suggesting the occurrence of SOP after H7N9 virus infection.

Lessons: Organizing pneumonia might occur during the recovery stage of influenza virus infection. When the clinical symptoms do not improve and the shadow in the lung shows no obvious absorption after elimination of the H7N9 influenza virus, or the clinical symptoms are aggravated again after improvement, the probability of transforming into the organizing pneumonia should be taken into consideration.

Abbreviations: DAD = diffuse alveolar damage, SOP = secondary organizing pneumonia.

Keywords: avian influenza/H7N9, case report, extracorporeal membranous oxygenation, glucocorticoids, organizing pneumonia

1. Introduction

The H7N9 influenza is a single-stranded and highly pathogenic RNA virus that belongs to the Orthomyxoviridae family. The first case of H7N9 infection occurred in Shanghai in 2013, which caused 5 outbreaks in the major provinces and cities of China, especially Shanghai, Jiangsu, Zhejiang, and Jiangxi.[1] The incidence of H7N9 infection was relatively high.[2] H7N9 infection can be asymptomatic or show mild symptoms, such as fever, cough, fatigue, and muscle soreness. However, it also can lead to severe lung inflammation, especially it can progress rapidly to acute respiratory distress syndrome (ARDS) within 1 week or even multiple organ dysfunction and death in elderly patients.[3] Of the currently diagnosed 1567 cases, 615 cases (40%) succumbed to mortality.[1] The mortality rate in patients with severe ARDS, who required venous-venous extracorporeal membranous oxygenation (VV-ECMO) for supportive treatment, was >60%.[4]

The therapeutic strategies for H7N9 infection primarily included 3 aspects: antiviral treatment (such as oseltamivir) to

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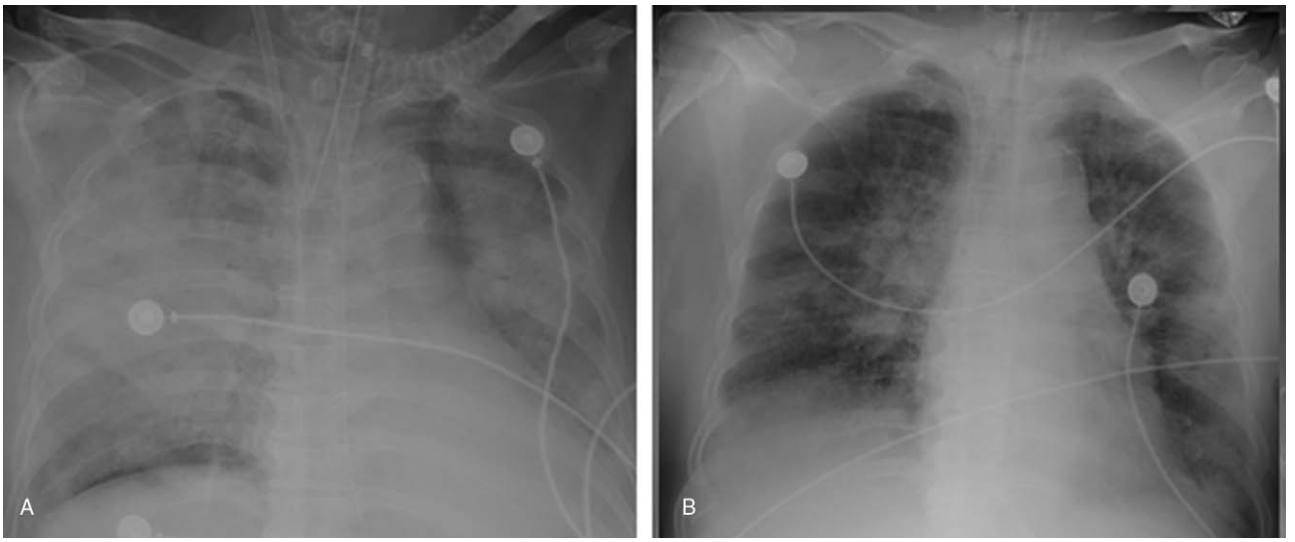

Figure 1. A. At 1 week from disease onset (on d 1 of admission, February 10, 2018), the chest radiography showed patchy, roundish, and sheet-like blurred shadow. B. After treatment, the chest radiography of the patient suggested that the lung shadows were significantly absorbed as compared with that before the treatment (at 3 weeks from disease onset, on d 14 of admission, February 23, 2018).

reduce alveolar epithelial damage caused by viral replication and spread, immune regulation, and strengthening the respiratory support and organ protection at the acute stage.[3,5]

As an anti-inflammatory drug, glucocorticosteroid was widely used in the acute phase of severe influenza virus infection to reduce the immune injury to the host, especially in patients with ARDS, and the utilization rate was 50% to 80%.[6] However, none of the studies have yet addressed the treatment of glucocorticoids in the recovery stage of H7N9 infection.

Interestingly, abnormal tissue repair is observed during the recovery stage of pulmonary infection. The pathological manifestation was organizing pneumonia, which if not treated promptly with glucocorticosteroids, might result in pulmonary interstitial fibrosis.[7,8] The nucleic acid of influenza A virus in the lung tissue turned to negative within 3 weeks from the disease onset, which is termed the pathogen elimination stage during infection.[9] And then, the immune response in host tissue entered into the stage of inflammatory repair. However, it is currently unclear whether glucocorticosteroides have good application value in patients with prolonged pulmonary inflammation and obstinate radiographic shadow after viral infection. Most of the time they were treated with antibiotics for clinically suspected superinfections, while they might have actually encountered abnormal tissue repair manifested pathologically as organizing pneumonia that called for glucocorticosteroids.

This article reported a case of severe A (H7N9) infection that benefitted from the glucocorticoid treatment beginning at 1 month after disease onset of infection. Informed consent was obtained from the patient before presenting the case report.

2. Case presentation

The patient was a 68-year-old woman with a previous history of hypertension and cholecystectomy. One week before admission, the patient had been exposed to live poultry, which might have resulted in a dry cough accompanied by fatigue, chills, and fever that gradually progressed to shortness of breath and dyspnea. Chest radiography suggested pneumonia of the bilateral lower lungs. The alveolar lavage fluid was assessed by fluorescent polymerase chain reaction, which detected 1.84×10^6 copies/mL of the H7N9 virus RNA, and the nucleic acid of Epstein-Barr virus (EBV) was positive. The resulting diagnosis was H7N9 viral pneumonia. In the local hospital, the disease condition of the patient was aggravated after treatment with ventilator support, blood purification, moxifloxacin combined with imipenem for anti-infection, oral oseltamivir for antiviral treatment, and methylprednisolone for anti-inflammatory treatment. The local hospital contacted the ECMO team and established the VV-ECMO pathway. The patient was transferred to the intensive care unit of a higher authority hospital on February 10, 2018 (1 week after the disease onset).

Examinations were carried out at the time of admission. Blood routine showed white blood cell count being 19.76×10^9/L and neutrophil percentage 90.2%. The procalcitonin was 0.29 ng/m. The chest radiography showed patchy, roundish, and sheet-like blurred shadow in bilateral lungs (Fig. 1A). The anticardiolipin antibodies, the anti-nuclear autoantibodies (ANA), the neutrophil cytoplasmic autoantibodies, blood culture, sputum culture, alveolar lavage fluid culture, and mid-stream urine culture were negative.

The patient was subjected to piperacillin tazobactam for antibacterial treatment, oseltamivir combined with peramivir for antiviral treatment, gamma globulin and thymosin for immune regulation immunity, low-dose glucocorticoid (D3–D10) for anti-inflammatory treatment, component transfusion, appropriate sedation and ventilator, VV-ECMO, continuous venous-venous hemofiltration, and other respiratory and circulation supportive treatments. *Candida albicans* was found in the sputum culture of the patient at a late stage, and the blood routine was significantly elevated. The fluconazole and vancomycin were added on D7 and D9 for antifungal and anti-Gram-positive cocci treatment, respectively, after admission. During treatment, the re-examination of nuclei acids of H7N9 and EBV virus in the alveolar lavage fluid showed gradually decreased titer. From D12, 3 times detection of the alveolar lavage fluid showed negative results for the nucleic acid of the H7N9 virus. Thus, oseltamivir and peramivir were ceased on D14 and D15, respectively. On D13, the ECMO oxygen supply tube was

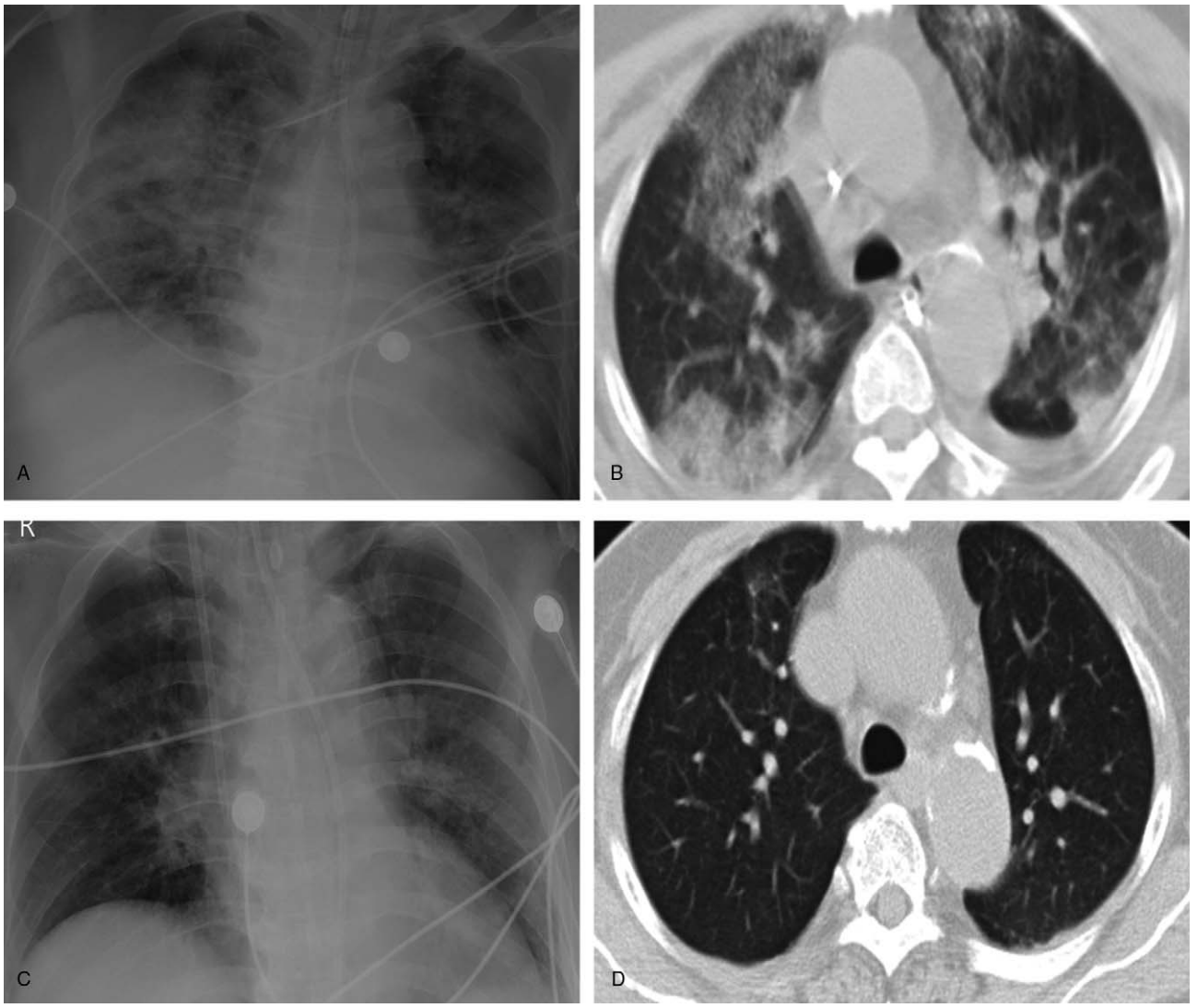

Figure 2. From week 3, the lung shadows of the patient in the chest radiography were gradually increased, and after the initiation of glucocorticoid treatment, the chest radiography showed that the lung shadows were gradually absorbed. A. At 5 weeks from disease onset (on day 25 of admission, March 6, 2018, before the initiation of glucocorticoid treatment), the chest radiography suggested that the lung shadows were significantly progressed as compared with that before the treatment, which was obvious in the lateral band of the bilateral lungs with grid-like changes. B. At 3 weeks from the disease onset (on day 18 of admission, February 27, 2018), the chest CT showed, for the first time, scattered, patchy, grid-like shadows in the bilateral lungs, common under the pleura and around the bronchial vascular bundle. C. At 7 weeks from disease onset (on day 40 of admission, March 20, 2018, 2 weeks after the initiation of glucocorticoid treatment), the chest radiography showed significant absorption of lung shadows. D. At 8 months from disease onset (October 9, 2018), reexamination of chest CT showed significant absorption of lung shadows, and only a few cord-like fibrous lesions were remaining. CT=computed tomography.

clamped, and the oxygenation of the patient could be maintained. On D14, the ECMO was removed.

However, the patient still needed high concentrations of oxygen (FiO_2 60–70%) and high ventilator parameters (positive end-expiratory pressure [PEEP] 8–10 cmH_2O, pressure support [PS] 18 cmH_2O), and the partial arterial pressure of oxygen (PaO_2) fluctuated between 80 and 100 mmHg. In addition, fever repeatedly occurred in the patient (maximal temperature, 39.1°C), and the absorption of shadows in the lung was not obvious. On D19, the piperacillin-tazobactam and fluconazole was upgraded to meropenem and micafungin, respectively, for anti-infection treatment, followed by continued vancomycin treatment. On D24, vancomycin was replaced with linezolid.

Subsequently, a regular re-examination of imaging showed that the shadows in the lung were significantly absorbed (Fig. 1B) but then gradually increased day-by-day (Fig. 2A, B). The oxygenation index was not significantly improved during this period (PaO_2 62 mmHg, FiO_2 80%, PEEP 8 cmH_2O, PS 20 cmH_2O). The re-examinations of sputum, alveolar lavage fluid, urine, blood, and deep vein catheter tip culture were negative. Only on D34, the genetic testing of alveolar lavage fluid found Burkholderia, while the genetic testing of blood detected the human herpesvirus type I. On D24, D26, and D31, the re-examination of autoantibodies suggested that ANA, anti-SSA/Ro60, and anti-SSA/Ro52 were positive with an elevated titer. On D29, the anti-β2 glycoprotein antibody was positive. No significant increase in the white blood cell count, neutrophil ratio, and procalcitonin level were detected, thus bringing the suspicion of comorbidity with autoimmune interstitial pneumonia. On D26, the methylprednisolone was added for the anti-inflammatory treatment. The regimen was

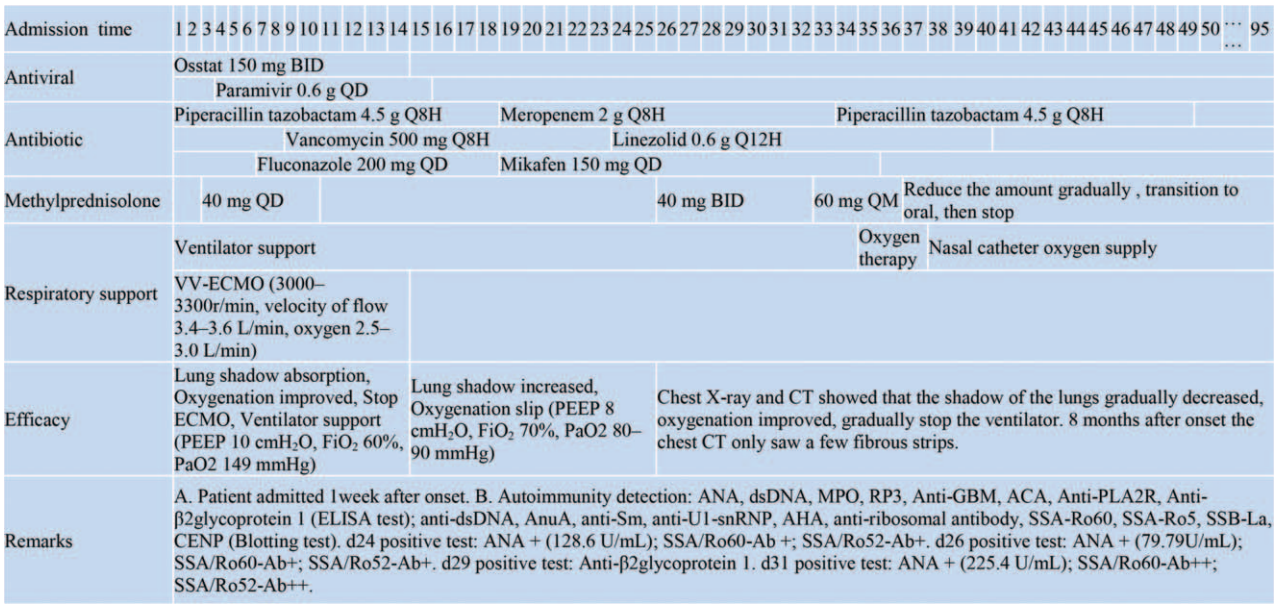

Figure 3. Disease evolution and altered therapeutic regimen in the patient after admission.

methylprednisolone at an initial dose of 40 mg twice a day for 1 week, tapering within 70 days until total withdrawal (Fig. 3). Subsequently, the shadows in the lung of the patient were gradually reduced, and the oxygenation index was improved daily. On D35, the patient was transitioned to high-flow oxygen therapy (PaO_2 101 mmHg, FiO_2 50%, 50 L/min) and changed to nasal catheter oxygen inhalation (PaO_2 103–170 mmHg, oxygen flow rate 5 L/min) on D38. The imaging re-examination showed that the shadows in the lung were significantly absorbed (Fig. 2C). Furthermore, the meropenem antibiotic was degraded to piperacillin-tazobactam on D34, while the administration of micafungin and linezolid was ceased on D36 and D41, respectively. On D50, administration of piperacillin-tazobactam was stopped because intertrigo combined with obvious pruritus occurred in the 2 lower extremities of the patient; the delayed drug allergy could not be excluded. Subsequently, the patient did not use any antibiotics although there were occasional low fever and an elevated level of hemogram index. Consequently, the diseased condition of the patient was stable, and the level of hemogram index was declined spontaneously. On D95, the administration of oral methylprednisolone was stopped, and the patient was discharged on D101.

At 8 months after disease onset, the follow-up of chest computed tomography (CT) showed a significant absorption of lung shadows, and only a few cord-like fibrous lesions remained (Fig. 2D).

3. Discussion

The theoretical basis of glucocorticoid treatment for ARDS caused by severe influenza A infection was that the influenza virus could induce excessive host immune response in patients with specific genotypes (e.g., IFN-induced transmembrane protein 3, IFITM-3) or underlying diseases. Excessive immune reaction triggered cytokine storms and recruitment of inflammatory cells that damage the pulmonary vascular endothelial cells and alveolar epithelial cells, leading to diffused alveolar damage, interstitial edema, and alveolar hemorrhage, which increased the mortality. On the other hand, inflammatory factors lead to relative hypoadrenocorticism or steroid resistance. The body requires additional glucocorticoids for supplementation.[10–12] Autopsy showed that the detected amount of viral antigen in alveolar epithelial cells was low, and the colonization site in the alveolar epithelium did not match the location of the diffused alveolar lesions and alveolar hyaline membrane formation, suggesting that the virus-associated pneumonia was partially attributed to the host immune response damage but not caused by the direct cytotoxic damage of the virus.[13]

Presently, the timing, dosage, and treatment course of glucocorticoids were not clarified, and the overdose or inadequate treatment might result in a non-uniform standard for the clinical application of glucocorticoids.[6,10] Limited observational studies have shown that the initial application of glucocorticoids was usually within 3 days since admission into the hospital or within a median of 7 days (interquartile range, 5.0–9.4 d) of the onset of illness according to the current clinical practice.[14] Moreover, the course of treatment was <2 weeks (median time, 1 week) with a low-medium dose. This regimen might prolong the time of virus clearance and increase the rate of superinfection for patients with influenza A, thereby increasing the mortality rate.[9,14–19]

The ARDS caused by viral infection primarily occurs during the period of viral clearance. Also, the excessive immune response in this period would aggravate the local tissue damage. After viral clearance, the survivors would enter into the repair phase, during which, the necrotic tissues were cleared by mucociliary transport or macrophage phagocytosis. As a result, the epithelial barrier was repaired, leading to the rapid recovery of the alveolar respiratory function within a few days. In addition to adjacent epithelial and precursor cells, the inflammatory cells (such as innate lymphocytes) also secrete extracellular matrix and growth factors that are involved in the post-infection repair process.[7,20]

Generally, in the case of patients with disease duration longer than 3 weeks, the disease was supposed to enter into the tissue repair stage. However, concerning patients in this subset, when

Table 1

Case reports of organizing pneumonia secondary to influenza viral infection.

Author/y	Subtype of influenza	Gender/Age	Comorbidity	BAL	Pathology	Time to restart glucocorticoid treatment	GCs regime	Outcome	Follow-up
AlfonsTorrego (2010)[25]	H1N1	F/55	Asthma	NA	Multiple areas of organizing pneumonia and alveolar cells with viral cytopathic changes	4 w	Prednisone (0.75 mg/kg/d)	Improved	1 m
Alejandro Gómez-Gómez (2011)[28]	H1N1	F/44	Non	65% macrophage, 26% lymphocyte, 6% neutropenia, 1.8% eosinophilia	Granulous tissue, fibroblasts and myofibroblasts filling in the alveoli	3 w	GCs 1 mg/kg×1W, tapering in 2.5m	Improved	2.5 m
Alejandro Gómez-Gómez (2011)[28]	H1N1	M/66	NA	68% macrophage, 25% lymphocyte, 5% neutropenia, 1.4% eosinophilia	Organized pneumonia	3 w	GCs 1 mg/kg×1W, tapering in 2.5 m	Improved	2.5 m
Rodrigo Cornejo (2012)[29]	H1N1	F/52	Osteoarthritis, smoking	Etiology negative	Organized pneumonia	8 d	Methylprednisolone 500 mg/d, tapering in 6 m	Improved	8 m
Rodrigo Cornejo (2012)[29]	H1N1	M/36	Diabetes mellitus	Etiology negative	Organized pneumonia	17 d	Methylprednisolone 500 mg/d, tapering in 6 m	Improved	8 m
Claudia Otto (2013)[26]	HIN1	F/66	Pulmonary fibrosis, lung transplantation	Etiology negative	Acute fibrogenic organizing pneumonia	11 d	Methylprednisolone + mycophenolate mofetil	Death	NA
Wang C. Kwok (2016)[27]	B	F/45	Non	Etiology negative	Patchy paraseptal fibroblastic proliferation with edematous stroma compatible with organizing pneumonia	5 d after initial improvement	Prednisolone 30 mg daily on d 44	Improved	1 y
Nobuhiro Asai (2017)[30]	B	F/23	None	Etiology negative	Lymphocytic alveolitis, intra-alveolar granulation tissue with myofibroblasts consistent with organizing pneumonia	NA	Corticosteroid 30 mg (0.5 mg/kg) daily	Improved	5 m
Huijiao L (2018)	H7N9	F/58	Hypertension	Etiology negative	NA	4 w	Prednisolone (40 mg BID), tapering in 2 m	improved	8 m

BAL = bronchial alveolar lavage, F = female, GCs = glucocorticoids, H1N1 = Hemagglutinin 1 NeuramNIidase 1, M = male, NA = not available.

the clinical manifestations or imaging cannot be improved continuously, the specific application of glucocorticoid treatment is yet to be elucidated.

Previous studies have shown that the repair of lung tissues after viral infection might involve an abnormal type II immune response, forming a Th2 cytokine environment which facilitated chemotaxis of neutrophils and activation of M2 type macrophages. Through the release of cytokines, such as transforming growth factor-β, epidermal growth factor, and fibroblast growth factor-2, neutrophils and macrophages promoted the transformation of epithelial cells into mesenchymal cells and activated the fibroblasts. Substantial amount of collagen fibers was deposited, and ultimately led to fibrosis.[7,8,21,22] This phenomenon was consistent with the results of clinical studies. In the case of patients who died after Hemagglutinin 1 NeuramNIidase 1 infection, autopsy revealed pathological change of the exudative diffuse alveolar damage (DAD) to proliferative DAD as disease course elongated. Although alveolar edema, fibrous exudation, and hyaline membrane formation were alleviated as disease proceeded, the interstitial inflammation was gradually aggravated accompanied by moderate-to-severe granulation tissue repair. Subsequently, fibrotic changes were detected, and most of the patients died within 1 week due to exudative DAD, while those that died after 1 week were ascribed to hyperplastic DAD.[23]

Nevertheless, the mechanism underlying the abnormal tissue repair after influenza virus infection is yet unclear. Currently, it is speculated that the influenza virus did not cause chronic infection. However, some studies have shown that, even after standard antiviral therapy and clearance of pathogenic virions, the viral antigens (such as RNA, nuclear proteins, or polypeptides treated by antigen-presenting cells) can still be detected in the lung tissues (especially in type I alveolar epithelium and macrophages) up to 38 days since infection.[13,20,23,24] But these antigens requires more sensitive tools to detect. An early antiviral treatment did not seem to prevent the delayed organizing pneumonia.[25] On the other hand, endogenous proteins that were oxidized or nitrated after influenza virus infection, such as heat shock proteins, could activate the autoimmune inflammation through damage-related molecular receptors.[8] The residues of viral antigens or inflammatory-modified endogenous proteins can be recognized by toll-like receptors on the membranes of innate lymphocytes and structural cells (e.g., alveolar epithelial cells, fibroblasts, and smooth muscle cells), which in turn, activated the downstream pathways, resulting in the formation of local Th2 cytokine environment. The type I immune response at acute phase was then altered into type II immune response at repair phase, resulting in a persistent chronic inflammatory state or scar repair.[8,21]

This patient successfully passed the VV-ECMO supportive treatment for almost 2 weeks, and no clear bleeding complications occurred. However, after 3 weeks of disease onset and the virus nucleic acid turned negative, the inflammation in the lungs was still not improved, necessitating high-parameter mechanical ventilation support. Nonetheless, the evidence of clinical infection was insufficient. Subsequently, the clinical symptoms were rapidly improved after the initiation of glucocorticoid treatment, and the lung shadows were gradually absorbed, suggesting the abnormal repair process in the body (Fig. 3).

Hitherto, only sporadic cases of organizing pneumonia after influenza virus infection have been reported (Table 1).[25–30] The disease was more common in women than in men (F:M = 6:2) and mainly occurred 2 to 3 weeks after infection. It was manifested as progressive dyspnea, dry cough, and fever for a second time after

improvement of clinical symptoms, accompanied by an elevated level of inflammatory indicators, and the lung shadows recurred. Alternatively, the clinical symptoms persisted and did not improve after active treatment; also, the lung shadows were not absorbed, while the pathogen detection of alveolar lavage fluid was negative. The chest CT was characterized by exudation shadows and consolidation shadows distributed along the subpleural space or bronchial vascular bundles. A bronchoscopy lung biopsy confirmed the diagnosis of organizing pneumonia. The disease condition of this subset of patients was significantly improved (except for 1 case of death [26]) after treatment with glucocorticoids. The re-examination of CT showed that the lung shadows were gradually absorbed and no recurrence was observed during the follow-up.

But none of the cases above had tested autoantibodies. In this patient, the positive autoantibodies were the anti-β2-glycoprotein 1 antibody, the anti-SSA/Ro60 antibody, and the anti-SSAS/Ro52 antibody. However, they were not regularly followed up after discharge as it was for the chest computer tomography in our case. As a consequence, we could not tell whether after corticosteroids treatment the titer of these autoantibodies turned to negative or not. But the positive autoantibodies indicated autoimmune response after H7N9 infection. They can be found positive in most auto-immune diseases. But none of them was specific for a certain type of auto-immune diseases. And the exact functions of the corresponding antigens were not well clarified. Lung was a common victim of connective tissue diseases, mostly manifested as interstitial pulmonary diseases including organizing pneumonia. We assumed that viral infection led to cell damage and exposed the intracellular proteins (e.g., cytoplasmic ribonucleoproteins) that had not been submitted to the host immune system for immune toleration, or that the viral remnants might bind to host glycoproteins as haptens to form holoantigens. Autoantibodies were then produced by activated lymphocytes, causing auto-immune response to the lung tissue. Molecular mimicry might also play a role in autoimmunity especially when the viral remnant persisted in the lung tissue. However, these non-organ-specific auto-antibodies might probably be the results rather than the causes of the persistent inflammation in the lung. Moreover, we did not found any papers citing the relationship between autoantibodies and organizing pneumonia secondary to viral infections, or papers studying the underlying mechanisms of autoimmunity in influenza viral infection.

Currently, there were no reports of organizing pneumonia after H7N9 infection. This patient was the first case of suspected organizing pneumonia after H7N9 infection with positive autoantibody results. But lung biopsy was not performed due to concerns about complications such as pneumothorax that might exacerbate the patient's oxygenation. Despite its lack of histopathological support from lung biopsy, the clinical manifestation, radiographic features, and response to glucocorticoid treatment were consistent with the organizing pneumonia after influenza A virus infections reported previously. Although the interpretation of this case was currently at the level of clinical theoretical conjecture, it alerted the clinicians about the possibility of combined organizing pneumonia during the recovery period of influenza virus infection.

4. Conclusion

The recovery period of influenza virus infection begun generally 3 weeks after infection and might encounter abnormal tissue repair manifested as organizing pneumonia, albeit with an unclear mechanism. In clinical practice, it is necessary to focus on the possibility of organizing pneumonia in addition to secondary bacterial infection, when patients in the recovery stage of H7N9 infection showed non-improved clinical symptoms or lung shadows after the clearance of influenza virus, or when the symptoms were aggravated again after initial improvement. The imaging manifestations of organizing pneumonia were exudation and consolidation shadows under the pleura or along the bronchial vascular bundles. The alveolar lavage and bronchoscopic lung biopsy were recommended for a definite diagnosis. Glucocorticoids are effective for organizing pneumonia.

Author contributions

Conceptualization: Huijiao Liu, Jiahao Su.
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Formal analysis: Huijiao Liu, Jianwei Li, Miaolian Chen, Jiahao Su.
Funding acquisition: Jiahao Su.
Investigation: Huijiao Liu.
Methodology: Huijiao Liu.
Project administration: Jiahao Su.
Writing – original draft: Huijiao Liu.
Writing – review & editing: Jianwei Li, Miaolian Chen, Jiahao Su.

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