

## Case Report

# A Patient with Fulminant Primary Influenza Pneumonia Which Developed into Secondary Bacterial Pneumonia

Masafumi SEKI,<sup>1,2,3</sup> Kohji HASHIGUCHI,<sup>1,4</sup> Kosuke KOSAI,<sup>1,2,3</sup> Yasuhito HIGASHIYAMA,<sup>2,3</sup> Katsunori YANAGIHARA,<sup>3</sup> Shintaro KURIHARA,<sup>3</sup> Koichi IZUMIKAWA,<sup>2,3</sup> Yoshitsugu MIYAZAKI,<sup>2,3</sup> Yoichi HIRAKATA,<sup>2,3</sup> Takayoshi TASHIRO,<sup>3</sup> Shigeru KOHNO<sup>2,3</sup>

<sup>1</sup> Kitakyushu City Yahata Hospital, Kitakyushu City, Fukuoka, Japan

<sup>2</sup> Department of Molecular Microbiology and Immunology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

<sup>3</sup> Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan

<sup>4</sup> The Japan Red Cross, Nagasaki Atomic Bomb Hospital, Nagasaki, Japan

An 88-year old man was admitted to our hospital because of severe respiratory disturbance and fever, but no sputum. We found diffuse reticular shadow on chest X-ray, and detected influenza virus antigen from nasopharyngeal swab. Primary influenza pneumonia was suspected and oseltamivir was prescribed. Data were improved after adding steroid; however, hemoptysis appeared on day 9, and the patient died 2 days later. We suspected the recurrence of primary virus pneumonia with alveolar damage, but *Staphylococcus aureus* was cultured from the hemospitum after his death despite oral administration of antibiotics. Subsequent secondary bacterial pneumonia as well as severe primary influenza virus pneumonia was finally suspected in this case. It was a rare case that not only fulminant primary virus pneumonia but also different type of severe influenza pneumonia were found in one patient. We need to observe influenza patients carefully, even if antibiotics were administered.

ACTA MEDICA NAGASAKIENSIA 51: 121 - 124, 2006

**Keywords:** Influenza virus; Primary influenza virus pneumonia; Secondary bacterial pneumonia; *Staphylococcus aureus*

## Introduction

Influenza virus infection is a major respiratory infectious disease that generally induces bronchitis.<sup>1-3</sup> It causes an acute febrile illness with malaise, and respiratory failure is sometimes lethal in the elderly if the bronchitis develops into pneumonia.<sup>4</sup>

Influenza pneumonia has been classified into primary influenza virus and bacterial infection-related types of pneumonia.<sup>4-8</sup> The former type is influenced by virus itself. Patients with this type usually complain short of breath, but no sputum. Chest X-ray findings show reticular shadows, and respiratory disturbances rapidly progress. Steroid is usually used for treatment to improve inflammation of the lung.<sup>5,6</sup> The latter type is due to superinfection and/or secondary bacterial infection. The symptoms, including cough and sputum are almost similar to those of bacterial pneumonia, and infiltrative shadows appear on chest X-rays.<sup>7,8</sup> Synergic effects between the influenza virus and bacteria have been suggested, and severe pneumonia fre-

quently results in such patients.

Here, we describe a patient who died of severe influenza pneumonia. The patient was initially diagnosed as having primary influenza virus pneumonia and was administered anti-microbial drugs. Addition of steroid improved his symptoms. However, massive pneumonia with hemoptysis due to bacterial infection developed subsequently and the patient died despite intensive treatment.

## Case Report

An 88-year old man was admitted to the emergency ward in our hospital on December 16, 2003 because of dyspnea, vomiting and chills due to high fever which he had from 5 days before. A physical examination upon admission revealed a high body temperature (39.6 °C), moist rales on both anterior chest walls, but no sputum. Respiratory disturbance was obvious and SpO<sub>2</sub> was 88% under O<sub>2</sub> 7L

**Address correspondence:** Masafumi Seki, M.D., Ph.D., Second Department of Internal Medicine, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501 JAPAN

TEL: +81-(0)95-849-7273, FAX: +81-(0)95-849-7285, E-mail: seki@nagasaki-u.ac.jp

Received May 1, 2006; Accepted November 17, 2006

mask conditions. Laboratory findings indicated slight inflammation as follows: white blood cells (WBC)—9,640/mm<sup>3</sup>; neutrophils—81.1 % and C-reactive protein (CRP)—0.8 mg/dL (Table 1). KL-6 was also elevated. We found a massive reticular shadow on bilateral lung fields (Figure 1) and detected influenza virus type-A antigen from a nasopharyngeal swab. The patient was suspected as having primary influenza virus pneumonia and was administered 150 mg of oral oseltamivir for 5 days with intravenous meropenem trihydrate of 1.0 g/day (Figure 2).

However, the fever persisted and clinical laboratory findings on December 18 revealed a WBC count of 8,460/mm<sup>3</sup> and CRP of 21.9 mg/dL, indicating deterioration. Since anti-microbial drugs did not

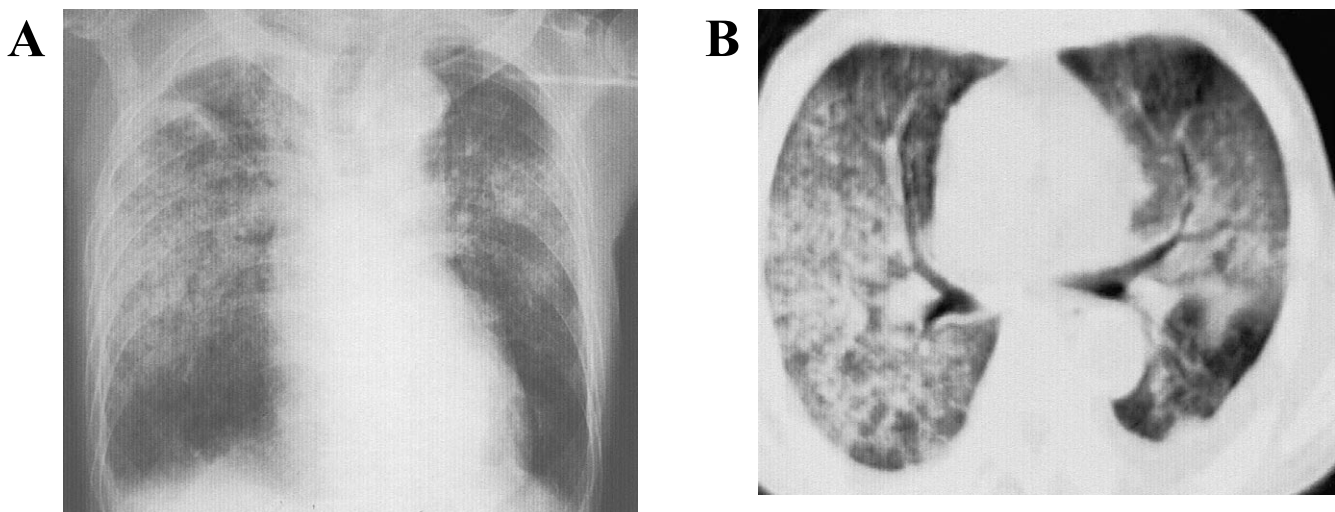
work, we added intravenous methylprednisolone sodium succinate of 250 mg/day to improve inflammation of the lung. Levels of WBC and CRP were decreased to 6,840/mm<sup>3</sup> and 3.4 mg/dL, respectively, and chest X-ray findings became almost clear on December 21. Intravenous administration of steroid was discontinued and was replaced by the oral administration of 300 mg/day cefditoren pivoxil on December 22.

However, his body temperature increased again, and hemoptysis appeared on December 24. On the following day, laboratory findings worsened: WBC—9,480/mm<sup>3</sup> and CRP—15.9 mg/dL. Massive infiltrates in bilateral lung fields appeared and we suspected the recurrence of primary virus pneumonia with alveolar haemorrhage/

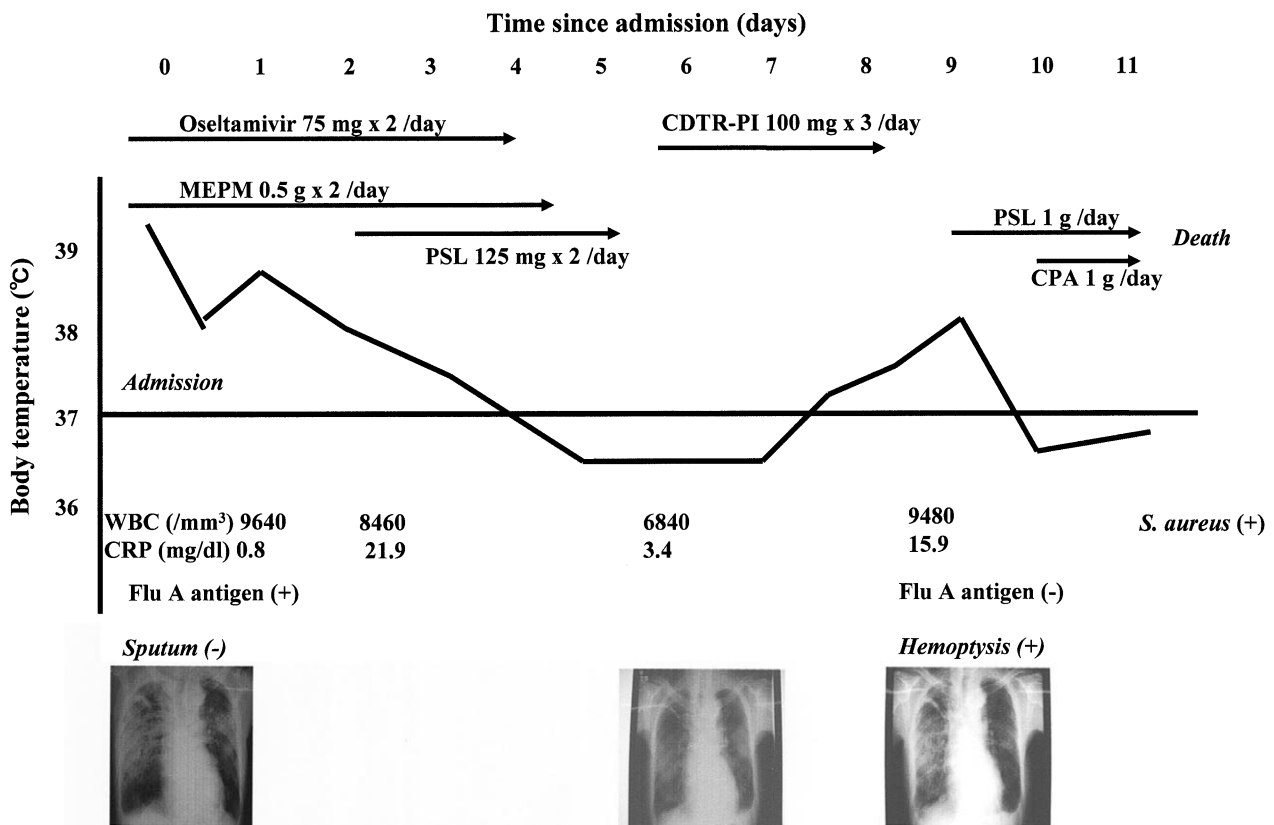
**Table 1.** Laboratory findings on admission

Parameters	Measurements	Parameters	Measurements	Parameters	Measurements	Parameters	Measurements
<i>Hematology</i>		<i>Chemistry</i>		<i>Serology</i>		<i>Blood gas analysis</i> (O <sub>2</sub> 7L mask)	
WBC <sup>a</sup>	9640/mm <sup>3</sup>	TP	6.2 g/dL	KL-6 <sup>a</sup>	887 U/mL	pH	7.411
Neu <sup>a</sup>	17.5%	TB	0.3 mg/dL	RF	(-)	PaO <sub>2</sub>	72 Torr
Mo	1.0%	AST	17 IU/L	ANA	(-)	PaCO <sub>2</sub>	38.3 Torr
Eo <sup>a</sup>	0.3%	ALT	8 IU/L	HBsAg	(-)	HCO <sub>3</sub> <sup>-</sup>	26.3 mEq/L
Ba	0.1%	LDH	184 IU/L	HCVAb	(-)	BE	2.7
Hb	10.7g/dL	CPK	94 IU/L	Mycoplasma antibody	<40(-)		
Plt	28.1×10 <sup>4</sup> /mm <sup>3</sup>	Amy	95 IU/L	β-D-glucan	(-)		
		BUN	19.8 mg/dL	Aspergillus antigen	(-)		
		Cr	0.9 mg/dL	IgE	313 IU/mL		
		Na	143 mEq/L	IgG	3420 mg/dL		
		K	3.6 mEq/L	IgA	539 mg/dL		
		Cl	108 mEq/L	IgM	123 mg/dL		
		Ca	9.1 mEq/L				
		CRP <sup>a</sup>	0.8 mg/dL				

<sup>a</sup>The measurements were out of normal range.



**Figure 1.** Chest X-ray (A) and chest CT (B) of the patient on admission. A. Diffuse reticular shadows are seen in both lung fields. B. Ground glass opacity is evident in both lung fields, but pleural effusion is absent.



**Figure 2.** The clinical course of the patient after admission. CPA=cyclophosphamide; *S. aureus*=*Staphylococcus aureus*; PSL=methylprednisolone sodium succinate; MEPM=meropenem trihydrate; and CDTR-PI=cefditoren pivoxil.

pulmonary vasculitis. However, influenza virus antigen was not detected from a nasopharyngeal swab taken at that time. We administered methylprednisolone sodium succinate (1 g/day) again and cyclophosphamide (1 g/day) as same as the treatment for pulmonary vasculitis. But he died of respiratory failure on December 27. *Staphylococcus aureus* (*S. aureus*) of  $1 \times 10^5$  CFU/mL was cultured from hemoptisum and we observed phagocytosed *S. aureus* thereafter. Secondary bacterial pneumonia was finally diagnosed.

## Discussion

Influenza A virus accounts for significant morbidity and mortality despite major efforts in prevention and treatment.<sup>1,2,4</sup> Morbidity and mortality have been attributed to the development of respiratory complications including pneumonia. Rapid diagnostic tests have recently allowed confirmation of a tentative diagnosis of influenza virus pneumonia in patients with pneumonia acquired from the community.<sup>1,2,4,9</sup>

Here, a rapid detection kit identified the influenza virus antigen from a nasopharyngeal swab taken upon admission. The patient had no sputum and chest X-ray findings showed a reticular shadow, and therefore, primary influenza pneumonia was suspected. The results of urinary antigen test for *Streptococcus pneumoniae* (*S. pneumoniae*)

and *Legionella* spp. were negative. Treatments by anti-viral drugs with antibiotics did not work well, while addition of steroid was effective.

Primary influenza pneumonia is rare and its pathological changes frequently include severe bronchiolocentric exudation of histiocytes, obliterative bronchiolitis with organizing pneumonia and diffuse alveolar damage with necrosis and haemorrhage.<sup>5,6</sup> The mechanisms of viral pathogenesis are most likely complex. In addition to direct viral replication in epithelial cells, proinflammatory cytokine release<sup>10</sup> and abnormalities in the interferon system<sup>11</sup> might contribute to the morbidity and mortality. In this case, we tried to perform bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) by bronchoscopic method to analyze the inflammatory cells and tissue damage, but we could not do because of his severe respiratory condition on admission.

Despite transient improvement and administration of oral antibiotics, the condition of this patient worsened again and he finally died only few days after the recurrence of pneumonia. Ineffectiveness of oral antibiotics and appearance of hemoptysis made us suspect the recurrence of primary virus pneumonia with alveolar haemorrhage/pulmonary vasculitis, which, however, differed from the first one in that sputum (hemoptisum) was present and he was negative for the influenza antigen. Furthermore, *S. aureus* was later collected from the sputum. These data suggested the patient developed bacterial

pneumonia with alveolar damage. Cultured *S. aureus* was sensitive to antibiotics including amoxicillin and first-/second- generation cephalosporin. We administered antibiotic orally after improvement of the first pneumonia but could not prevent further bacterial infection. Ineffectiveness of antibiotics in this case might be due to poor physical status of the aged patient. Cyclophosphamide was used to improve hemoptysis as same as the treatment for pulmonary vasculitis<sup>12</sup>; however, we should have used antibiotics intravenously with steroid when pneumonia relapsed.

Influenza virus-related bacterial pneumonia is about three times more frequent than primary viral pneumonia.<sup>7</sup> The most commonly involved bacteria are *S. aureus*, *S. pneumoniae* and *Haemophilus influenzae*. The reported fatality rate of *S. aureus* co-infection is about 42%.<sup>7</sup> Virus infection in the respiratory tract appears to favor growth conditions for bacteria and some *S. aureus* strains might secrete a protease that exerts a decisive influence on the outcome of influenza virus infection by cleavage activation of viral hemagglutinin.<sup>8</sup> These data suggest that an extant influenza virus infection plays a key role in the pathogenesis of these lethal lung diseases, and in synergic effects between viral and bacterial infections.<sup>13,14</sup>

In conclusion, we identified a patient with probably severe primary influenza virus pneumonia which developed into secondary bacterial pneumonia. These two types of influenza pneumonia might have different pathogenesis, but both can be severe and fatal despite careful therapy including antibiotics administration. Further studies of the pathogenesis and treatment of viral and bacterial pneumonia are required.

## References

1. Infectious Diseases Society of America. Practice guidelines for the management of community-acquired pneumonia in adults. *Clin Infect Dis* 31: 347-382, 2000
2. American Thoracic Society. Guidelines for management of adults with community-acquired pneumonia. *Am J Respir Crit Care Med* 63: 1730-1754, 2001
3. Woodhead M, Blasi F, Ewig S et al. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J* 26: 1138-1180, 2005
4. Glezen WP, Greenberg S, Atmar RL et al. Impact of respiratory virus infections on persons with chronic underlying conditions. *JAMA* 283: 499-505, 2000
5. Gerberding JL, Morgan JG, Shepard JA et al. Case 9-2004 ? An 18-year-old man with respiratory symptoms and shock. *N Engl J Med* 350: 1236-1247, 2004
6. Yeldandi AV, Colby T. Pathologic features of lung biopsy specimens from influenza pneumonia cases. *Hum Pathol* 25: 47-53, 1994
7. Robertson L, Caley J, Moore J. Importance of Staphylococcus aureus in pneumonia in the 1957 epidemic of influenza A. *Lancet* 2: 233-236, 1958
8. Tashiro M, Ciborowski P, Klenk HD et al. Role of Staphylococcus protease in the development of influenza pneumonia. *Nature* 325: 536-537, 1987
9. Marcante R, Chiumento F, Palu G et al. Rapid diagnosis of influenza type A infection: comparison of shell-vial culture, directigen flu-A and enzyme-linked immunosorbent assay. *New Microbiol* 19: 141-147, 1996
10. Hayden FG, Fritz R, Lobo MC et al. Local and systemic cytokine responses during experimental human influenza A virus infection: relation to symptom formation and host defense. *J Clin Invest* 101: 643-649, 1998
11. Katze MG, He Y, Gale M Jr. Viruses and interferon: a fight for supremacy. *Nat Rev Immunol* 2: 675-687, 2002
12. Channick R, Rubin L. Pulmonary vasculitis and primary pulmonary hypertension. In *Textbook of Respiratory Medicine, 4th ed* (Mason R, Broaddus V, Murray J, Nadel J eds.; Elsevier Saunders Publishers, Philadelphia) pp.1459-1464, 2005
13. Seki M, Yanagihara K, Higashiyama Y et al. Immunokinetics in severe pneumonia due to influenza virus and bacteria coinfection in mice. *Eur Respir J* 24: 143-149, 2004
14. Seki M, Higashiyama Y, Tomono K et al. Acute infection with influenza virus enhances susceptibility to fatal pneumonia following Streptococcus pneumoniae infection in mice with chronic pulmonary colonization with Pseudomonas aeruginosa. *Clin Exp Immunol* 137: 35-40, 2004