Case Report

Fulminating Influenza Pneumonia in the Elderly: A Case Demonstration

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An 82-year-old male Bangkokian with hypertension, diabetes mellitus, end-stage renal disease, and coronary artery disease for many years, was hospitalized due to deterioration of a 3-day influenza-like-illness with one-day chest oppression and respiratory failure. At the emergency room, oxygen saturation was 79% on room air. Chest X-ray revealed bilateral diffuse pulmonary infiltrates. He was intubated and hemodialysis was initiated. Emergency coronary angiography revealed patent coronary artery. Sputum gram stain revealed numerous leukocytes with no bacteria. On day three of hospitalization, empiric treatment with oseltamivir and clarithromycin was administered. Seventy-two hours later his clinical condition began to improve and fever subsided 7 days later. Rapid test of tracheal secretion with immunofluorescence assay was positive for moderate amount of influenza A virus. Viral isolation yielded influenza A virus subtype H_1N_1. Review of in-patient records at this hospital using ICD-10 codes as J10 and J11 during 1995-2005, discovered 32 cases with claim diagnosis of influenza. However, this is the first case with proven influenza pneumonia that was given empiric oseltamivir. Rapid deterioration of influenza-like illness due to human influenza virus in the elderly and pathogenesis of pulmonary in this case are discussed to alert physicians to recognize this dreadful illness and treat it in timely fashion.

Keywords: *Influenza A virus, Influenza pneumonia, Influenza, Oseltamivir*

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Influenza is among one of the most common infections every physician encounters in Thailand[1,2]. Its serious complication such as pneumonia with respiratory failure is well known worldwide but rarely recognized in developing countries where diagnostic procedures are limited, deemed sophisticated and considered expensive.

The authors recently encountered a proven case of fulminating influenza pneumonia in an elderly man who was given empiric oseltamivir together with other supportive treatments and consequently made a rapid and impressive recovery. When the authors asked their colleagues in many medical schools about how often the diagnosis of primary human influenza pneumonia especially in the elderly has been made, it is seldom recognized. Empiric treatment with neuraminidase inhibitor is even never given except when avian influenza is suspected. Thus, the authors wish to report this classical case and confirm the benefit of timely treatment with oseltamivir. The present report should alert general physicians, infectious disease specialists, pulmonologists and critical care activists to recognize this deadly complication in order to save more lives of such patients.

Since early 2004 avian influenza A/H5N1 outbreak in Asia, this report should also serve to increase

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public awareness of the threat of an influenza pandemic and hopefully early detection of pandemic influenza is achieved if it may ever occur in Thailand as Asian countries are anticipated to be the starting points.

Case Report

An 82-year-old man was admitted to the hospital because of shortness of breath, productive cough, chest oppression, and high-grade fever for one day. Three days prior to the hospital admission, he developed mild fever, myalgia, headache, running nose and frequent non-productive cough. Chest roentgenogram revealed normal lung parenchyma (Fig. 1). He was treated with co-amoxiclav, antipyretic and cough suppressant but without any improvement. Two days later, he became dyspneic and arrived at the emergency department. Chest roentgenogram revealed bilateral diffuse pulmonary infiltrates (Fig. 2). He was intubated with ventilatory support and admitted to an intensive care unit. His medical history was notable for diabetes mellitus, hypertension, ischemic heart disease and end-stage renal disease on hemodialysis thrice a week. His current medication included nifedipine, captopril, trimetazidine dihydrochloride, metoprolol, clopidogrel, atorvastatin, fenasteride, aspirin isosorbide, dinitrate and erythropoietin injection on a regular basis.

Physical examination revealed an elderly man in severe respiratory distress and drowsiness with a blood pressure of 126/70 mm Hg, pulse rate of 100 beats per minute and respiratory rate of 36 breaths per minute. He was febrile with a pulse oxygen saturation of 79% on room air. He did not have any rash or lymphadenopathy. The jugular venous pressure was elevated. Diffuse rhonchi and coarse crepitations were audible in both lungs. He had a regular pulse rate and rhythm. No murmur, gallop or pericardial rub were appreciated. The abdomen, lower extremities and neurological examination were unremarkable.

Laboratory test results showed hematocrit of 33.3%, leukocyte count of 10,280/cu.mm with 86% of neutrophil, and platelet count of 239,000/cu.mm. Findings from a comprehensive electrolyte panel, alanine aminotransferase, and coagulation factors were normal. Renal function was impaired with blood urea nitrogen of 44 mg/dL and creatinine of 3.6 mg/dL. Electrocardiography showed inverted T waves in V_4-V_6. Cardiac troponin-T and CK-MB were 0.5 ng/mL and 3.91 ng/mL, respectively. An arterial blood gas revealed pH 7.43, PCO_2 32.2 mm Hg, PO_2 80.2 mm Hg, and oxygen saturation of 96.3% on a 40% O_2 supplement with mechanical ventilator. Sputum gram-stain revealed numerous PMN without any bacteria. Echocardiogram showed fair left ventricular function (ejection fraction 55%), mild hypokinesia at anteroseptal and inferoseptal walls, abnormal ventricular relaxation, no atrial thrombus, normal pericardium. APACHE II at admission was calculated to be 25.

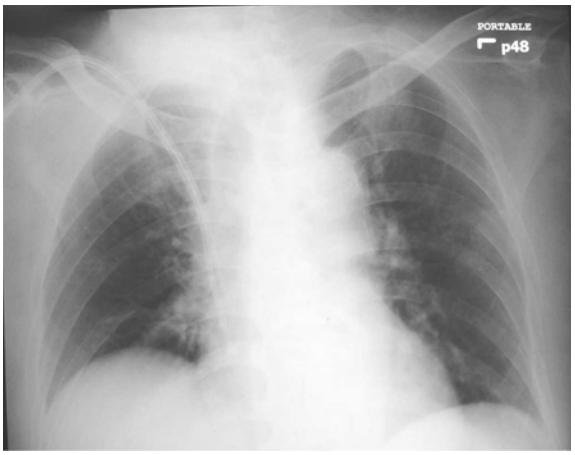

Fig. 1 Chest roentgenogram on the first day of influenza-like illness. Lung parenchyma was clear

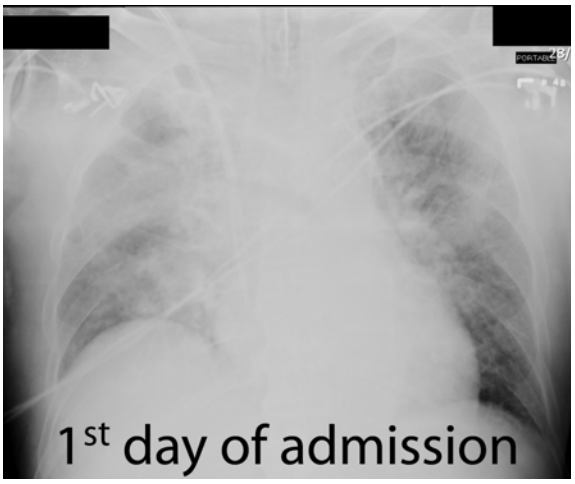

Fig. 2 Chest roentgenogram on the third day of influenza-like illness or the first day of admission. Lung parenchyma shows bilateral ground-glass and reticular patterns of pulmonary infiltrates

Hospital course

The patient was intubated on the first day of hospitalization to correct severe respiratory distress and hypoxemia. Coronary angiography was performed

to rule out recurrent thrombosis and revealed double-vessel disease at left anterior descending branch and left circumflex branch without significant stenosis. Enoxaparin was started to treat acute non-ST elevated myocardial infarction. Hemodialysis was initiated to alleviate volume overload and congestive heart failure. Piperazillin/tazobactam were prescribed to cover possible gram-negative nosocomial pneumonia. Chest roentgenogram after hemodialysis revealed persistent bilateral ground-glass density and reticular pattern on both lower lungs (Fig. 3) and the patient remained in respiratory distress on the second day of hospitalization. An infectious disease physician was consulted and prescribed oseltamivir 75 mg twice daily and clarithromycin 500 mg twice a day due to provisional diagnosis of atypical pneumonia especially influenza pneumonia because gram stain of tracheal secretion revealed numerous leukocytes without detectable bacteria and this case lived in Bangkok and had preceding upper respiratory symptoms or influenza-like illness. The patient's hospital course was further complicated by pulseless ventricular tachycardia on the third day of admission, which was treated with electrical cardioversion and intravenous atropine sulphate. Thereafter, his EKG converted to normal sinus rhythm. On the fifth day, direct immunofluorescent assay was positive for influenza A virus and viral culture of tracheal secretion subsequently yielded influenza A virus (subtype H_1N_1). His blood and tracheal secretion cultures for bacteria were reported to be negative. Hence, piperazillin/tazobactam and clarithromycin were discontinued on the fifth day. A chest roentgenogram obtained on the third hospital day, revealed ground glass pattern of bilateral pulmonary infiltrates (Fig. 4) which gradually diminished and disappeared on the fifth hospital day (Fig. 5, 6). He became afebrile 72 hours after oseltamivir treatment and was extubated on the seventh hospital day. Oseltamivir was continued for a total of 7 days. He was transferred to a general ward on the tenth hospital day and made a very successful recovery.

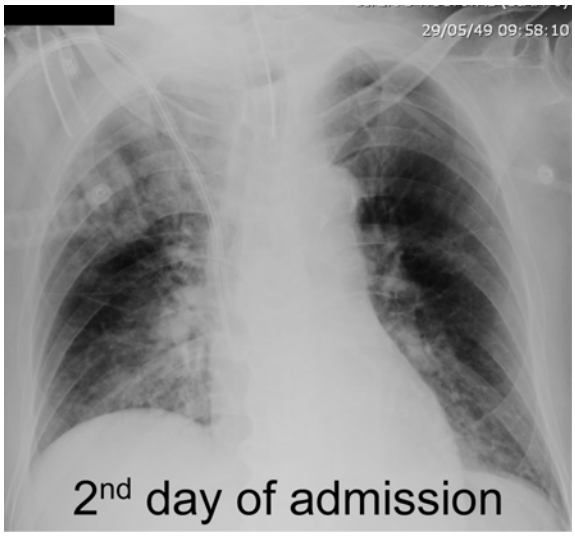

Fig. 3 Chest roentgenogram on second day of admission after hemodialysis. Reticular pattern of pulmonary infiltrate is seen predominantly on both lower lobes with minimal alveolar infiltration

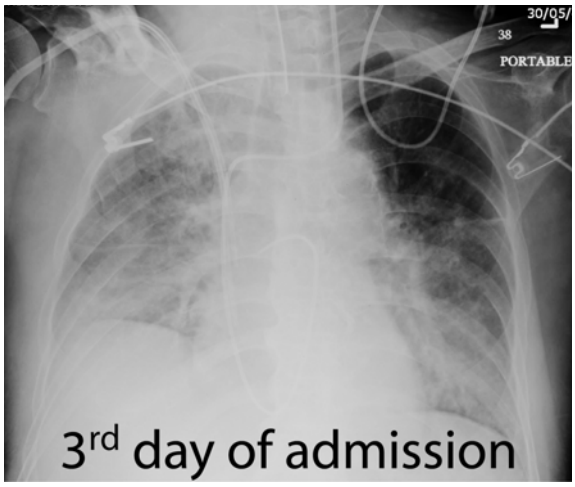

Fig. 4 Chest roentgenogram on third day of admission shows ground glass haziness on both lower lobes

Review of in-patient case records at this hospital

In-patient case records diagnosed as influenza or influenza pneumonia were retrieved from the Department of Medicine at Siriraj Hospital, using ICD-10 codes as J10 and J11 from 1995-2005. This hospital is a tertiary medical care where 2,400 beds are available with an annual admission of approximately 60,000 cases. The claim diagnosis was reviewed if it was confirmed by laboratory investigation and empiric treatment with oseltamivir or zanamivir if given, was also noted. During this period, forty-five records were retrieved but only 32 records met the diagnostic criteria. The other 13 records were excluded due to the following reasons: diagnosis of avian influenza in two cases, duplicated case with unconfirmed diagnosis in one case, miscoding of *H. influenzae* type B infection for influenza in three cases, coding error for influenza in other two cases, three cases gave only a history of URI during

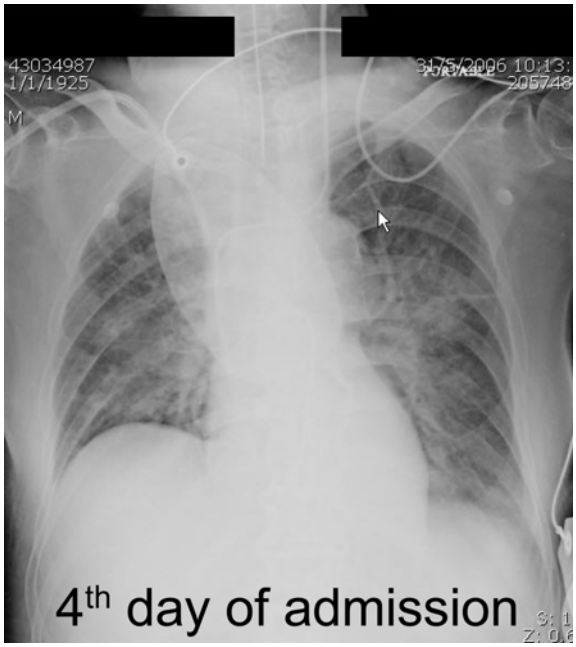

Fig. 5 Chest roentgenogram on fourth day of admission shows a mixture of reticular and alveolar patterns of pulmonary infiltrate on both lungs

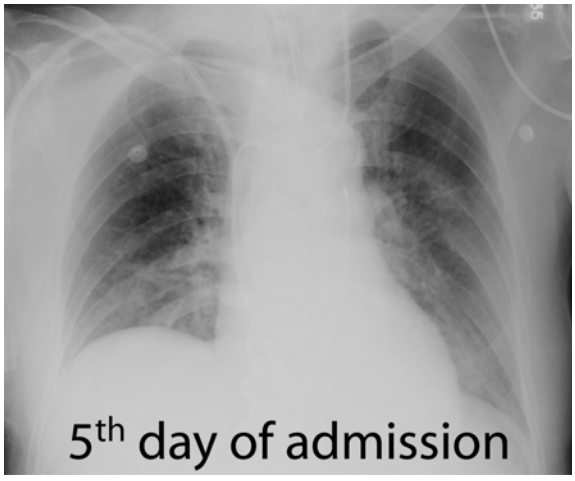

Fig. 6 Chest roentgenogram on the fifth day of admission shows clearing of pulmonary infiltrates in both lungs

the preoperative period, remote viral myocarditis and influenza was clinically suspected without laboratory investigation in one case, suspected avian influenza but not confirmed by investigation in one case. The details of confirmed cases are shown in Table 1. The authors also contacted pulmonologists or infectious

Table 1. Demographic data, clinical features and treatment with neuraminidase inhibitor in 32 case records diagnosed as influenza or influenza pneumonia

Parameter	Number	(%)
Male	14	(43.8%)
Age (year, mean, range)	23.7	(0.5-83)
Co-morbid illness	10	(31.3%)
Preceding history of influenza-like illness	20	(62.5%)
Fever before admission (day) (mean, range)	3.1	(1-9)
Pneumonia	6	(18.8%)
Complication other than pneumonia	3	(9.4%)
Influenza confirmed by investigation	11	(34.4%)
Initial empiric treatment with		
Antibacterial agents	17	(53.1%)
Oseltamivir	1	(3.1%)

disease specialists in other medical schools and found out that primary influenza pneumonia was seldom diagnosed and empiric treatment with neuraminidase inhibitors (oseltamivir or zanamivir) was not recalled in any case.

Discussion

This elderly man with co-morbid illnesses suddenly developed near-fatal pneumonia and respiratory failure two days after acquiring influenza-like-illness. Fortunately, he received prompt investigations and aggressive treatments for concurrent pulmonary congestion and edema, acute non-ST elevation myocardial infarction, possible volume overload due to renal failure. Increased vascular permeability induced by influenza pneumonia also aggravated pulmonary edema, which resulted in acute respiratory failure. Restriction of fluid intake and prompt hemodialysis kept lung parenchyma dry with leftover bilateral pulmonary infiltrate purely due to influenza pneumonitis (Fig. 3). Oseltamivir was given empirically due to negative gram-stain of tracheal secretion for bacteria. He responded dramatically 72 hours after initiation of antiviral therapy. At a private hospital during 2005-2006 surveillance of human influenza, avian influenza, and SARS, Sawang Saenghirunvattana[3] also shared a similar experience when he found two elderly patients with chronic obstructive pulmonary disease who developed acute respiratory distress syndrome due to influenza A virus. Both of them were intubated in the intensive care unit and survived due to early administration of oseltamivir. Hence, the three Thai cases are good samples to illustrate rapid clinical response to a timely given antiviral

drug. Clinical manifestation of this case is classified as rapidly progressive diffuse viral pneumonia as described by Louria et al[4]. Comorbid conditions, such as chronic obstructive airway disease (COPD), heart disease, renal disease, diabetes mellitus, and immunosuppression, could contribute to the severity of influenza pneumonia[5,6]. Thus, physicians need high suspicion of influenza pneumonia in other cases with similar scenario in order to take proper action and save more lives of the elderly. In addition, proper antiviral treatment can also shorten duration of hospitalization and save costs[7].

Pulmonary edema was initially suspected as the sole cause of respiratory failure and led physician's attention to focus on hemodialysis rather than treatment of influenza pneumonia. After the lung was "dried up" and pulmonary infiltrates remained at lower lung bases (Fig. 3), it was thought to be solely due to influenza pneumonia. Then he was given empiric oseltamivir and lung lesions though gradually expanded (Fig. 4, 5), diminished and returned to their normal pattern in 72 hours after antiviral treatment. Fluid accumulation in the alveoli is a result of viral attack at alveolar cell lining which result in increased vascular permeability. The present case illustrated sequentially the roentgenographs of edematous lung (Fig. 2), "dried up" lungs (Fig. 3), influenza pneumonia (Fig. 4, 5) and normal lung (Fig. 6). If antiviral drug is not initiated timely, then the untreated influenza infection could even aggravate the inflammation and lead to greater chance of disability and mortality. Perhaps this may explains partly why management of influenza pneumonia is more difficult if pathophysiology of respiratory failure and viral sepsis is not clearly understood and the mortality rate remained high even in the present day of the medical era[8]. Increased alveolar permeability also explains the roentgenograghic findings of influenza pneumonia. It consists mainly of patchy or diffuse ground-glass opacity with or without consolidation and reticular areas of increased opacity and thickened interlobular septa[9].

When ICD-10 codes as J10 and J11 were employed, the authors were able to retrieve 32 cases diagnosed as influenza including six cases with influenza pneumonia between 1995 and 2005 at Siriraj Hospital. The number is too small since at a medium-sized private hospital there were at least two cases of influenza pneumonia during one year of active surveillance[3]. Surprisingly, neither one with influenza pneumonia at this hospital was given empiric neuraminidase inhibitor. Siriraj Hospital is tertiary and the biggest hospital in Thailand with 2,400 beds. From year 2002-2007, there were 30,086 cases discharged from general wards of the Department of Medicine and 9.9% of these had the diagnosis of pneumonia. From these, there were 1,714 cases with pneumonia whose ages were over 60 years old and mortality rate of pneumonia in this old age was 53.7%. Thus, 32 cases diagnosed as influenza were too small for this size of hospital and only six of whom had influenza pneumonia. Perhaps influenza is a greatly neglected disease in terms of recognition, diagnosis of its complication and antiviral treatment when indicated. Moreover, initial empiric antibacterial was preferably employed among these cases and oseltamivir was empirically used only in this reported case. The benefit of empiric treatment with oseltamivir or zanamivir within 48 hours of onset of influenza pneumonia has never been fully appreciated since no one has ever been through a case similar to this report and gained experience like the one the authors had from the presented case. In the authors opinion influenza is usually regarded as self-limited and neglected for its increased morbidity and mortality in certain high risk populations with underlying cardiovascular or pulmonary disease, diabetes mellitus, renal disease or old age. The authors propose that influenza pneumonia deserves first priority to be ruled out in the elderly with community-acquired pneumonia and respiratory failure, especially in those with a negative smear of sputum or tracheal secretion for bacteria. Obtaining an adequate sample of tracheal secretion is not a problem since most cases at this stage are intubated. When gram-stain of tracheal secretion reveals numerous leukocytes without bacteria, diagnosis of influenza pneumonia is more likely. Then laboratory identification of influenza virus should be sought for using direct antigen detection, virus isolation in cell culture, or detection of influenza-specific RNA by reverse transcriptase-polymerase chain reaction.

In recent years, commercial influenza rapid diagnostic tests have become available and are not expensive. These are mostly antigen detection tests, which can produce results within 30 minutes. They can provide results in a clinically relevant time frame to complement the use of neuraminidase inhibitors for treatment of influenza pneumonia with respiratory failure. In a study on the impact of access to rapid influenza test results on antibiotic prescribing for outpatients with influenza-like illness in a rural province in Thailand, patients with positive rapid test were less likely to be prescribed antibacterials than those with a negative result[10]. To be effective, antivirals must be

started within 2 days of symptom onset and delayed diagnosis must be avoided so that patients rapidly revert from full blown complications[11,12]. If rapid test for influenza virus is not available, then newer macrolide such as clarithromycin should be co-administered to cover other atypical pathogens such as *M. pneumoniae*, *C. pneumoniae*, and *L. longbeachae*, which were frequently associated with severe pneumonia in rural Thailand[13].

Recently, pathogenesis of influenza pneumonia involves inhibition of epithelial sodium-channel-mediated clearance of pulmonary fluid through a pathway involving phospholipase and protein kinase C[14-15]. As a consequence, pulmonary edema can develop and its severity varies among different influenza virus infections. Prompt hemodialysis on the first day of respiratory failure in this case gave us the impression that hemodialysis helped ameliorate severe influenza pneumonia. However, at present, it is premature to recommend hemodialysis or beta-agonist administration as an adjunctive therapy in a case with severe influenza pneumonia[16].

Influenza is a big burden for Thai elderly[17]. It is still under-diagnosed and poses the highest mortality in persons who have various chronic medical conditions. Interestingly, the incidence of treatment failure in community-acquired pneumonia was recently reported to be 10 to 15% and the mortality was increased nearly fivefold[18]. However, treatment failure in community-acquired pneumonia was reportedly lower in influenza vaccinated patients[18,19]. Moreover, the percentage of influenza-vaccinated patients was also found to be lower among those with early failure[20]. This evidence could be interpreted as influenza pneumonia being under-recognized or not treated with antiviral drug among some of the unvaccinated group who had community-acquired pneumonia. Hence, influenza vaccination in the elderly with comorbidity illness cannot be overemphasized and innovative procedures to improve vaccination rates among elderly must be searched for[2].

Conclusion

The authors reported an elderly patient presenting with near-fatal influenza pneumonia and pulmonary edema that led to respiratory failure. The presented case provides a unique sample to study the variables that contribute to influenza-related mortality. Hemodialysis, aggressive ventilatory support and empiric oseltamivir given at 48 hours of hospitalization aborted the infection and rapidly decreased the consequent inflammation that led to rapid recovery and decreased potentially superimposed infection and permanent damage. The authors emphasize that every elderly with a sudden onset of pneumonia and rapidly progressive into respiratory failure or pulmonary edema with preceding influenza-like illness must be screened for influenza virus infection. The present case illustrates the sequence of treatments for the dreadful complication and reminds physicians of influenza as a likely cause of fulminating pneumonia in the elderly with comorbid illnesses. Such a clinical suspicion can lead to appropriate testing and rapid initiation of proper antiviral therapy.

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ปอดอักเสบรุนแรงในผู้สูงอายุจากเชื้อไข้หวัดใหญ่: การสอนแสดงผู้ป่วย 1 ราย

อมร ลีลารัศมี, อุบลวรรณ จงวุฒิเวศย์, หัสญา ตันติพงศ, พิไลพันธุ์ พุธวัฒนะ, สนทนา ศิริตันติกร

ผู้ป่วยชายไทย อายุ 82 ปี อาศัยอยู่ในกรุงเทพมหานครและมีโรคประจำตัว คือ ความดันโลหิตสูง เบาหวาน โรคไตพิการระยะสุดท้ายและโรคหลอดเลือดหัวใจตีบ นานหลายปี รับไว้ในโรงพยาบาลเพราะมีไข้ น้ำมูกไหล ไอมีเสมหะสีขาว ปวดศีรษะมา 3 วันและหอบเหนื่อยแน่นหน้าอกและการหายใจล้มเหลว 1 วัน วัดความอิ่มตัวของ ออกซิเจนที่ห้องฉุกเฉินได้ร้อยละ 79 ภาพถ่ายรังสีทรวงอกพบเงาขึ้นทั้งสองข้าง ได้รักษาโดยใส่ท่อช่วยหายใจ และทำการฟอกไต การตรวจสภาพหลอดเลือดแดง coronary ที่หัวใจในวันแรกรับไม่พบว่ามีการตีบตัน การตรวจย้อม เสมหะพบเม็ดเลือดขาวจำนวนมากแต่ไม่พบแบคทีเรีย ผู้ป่วยได้รับยา oseltamivir และ clarithromycin ในวันที่สามของการอยู่ในโรงพยาบาล อาการผู้ป่วยทุเลาอย่างรวดเร็วใน 72 ชั่วโมงต่อมาและหายเป็นปกติใน 7 วัน การตรวจย้อม เสมหะด้วยเทคนิคสีเรืองแสงพบเชื้อไข้หวัดใหญ่ ชนิด เอ จำนวนปานกลางและการเพาะเชื้อจากเสมหะได้เชื้อ ไข้หวัดใหญ่ชนิด เอ subtype H_1N_1 (Influenza A virus subtype H_1N_1) การทบทวนเวชระเบียนในภาควิชา อายุรศาสตร์ ระหว่างปี พ.ศ. 2538 ถึง พ.ศ. 2548 พบ 32 รายที่ถูกวินิจฉัยว่า เป็นไข้หวัดใหญ่หรือปอดบวมจากไข้หวัดใหญ่ แต่รายนี้เป็นรายแรกที่มีผลการตรวจยืนยันจากห้องปฏิบัติการว่าเป็นปอดอักเสบจากไข้หวัดใหญ่และได้รับยา oseltamivir แบบ empiric รายนี้แสดงถึงความรวดเร็วและรุนแรงของการเกิดปอดอักเสบจากไข้หวัดใหญ่ในผู้สูงอายุ และพยาธิสภาพของการเกิดรอยโรคในปอดเพื่อให้แพทย์ได้รู้จักความรุนแรงของปอดอักเสบจากไข้หวัดใหญ่ในผู้ป่วยสูงอายุ และเพื่อให้ยาได้ทันกาล